Angiotensin II for the Treatment of Vasodilatory Shock

Khanna A, et al. *New England Journal of Medicine* 2017;377(5):419-430.

P: Adults with vasodilatory shock despite ≥25mL/kg of fluid resuscitation and high-dose vasopressors
I: Synthetic human angiotensin II (20ng/kg/min) and standard of care vasopressors
C: Saline placebo and standard of care vasopressors
O_1: Mean arterial pressure at hour 3 post administration (MAP ≥75mmHg, or a rise of ≥10mmHg)
O_2: 1) Mean change in cardiovascular sequential organ failure assessment (SOFA) scores
2) Total SOFA score between baseline measurement and hour 48
3) Safety assessment including evaluation of: serious adverse events, adverse event-related drug discontinuations, all adverse events, and all-cause mortality (7 and 28 days)
D: International, double-blind, placebo-controlled trial

What we already know:

- Vasodilatory shock is characterized by peripheral vasodilation and reduced blood pressure despite preserved cardiac output
- Refractory shock is associated with a very high mortality rate
- Current standard of care vasopressors are either sympathomimetic amines, or vasopressin
- The renin-angiotensin-aldosterone is a physiologic pathway which offers another theoretical avenue to combat hypotension

Methods:

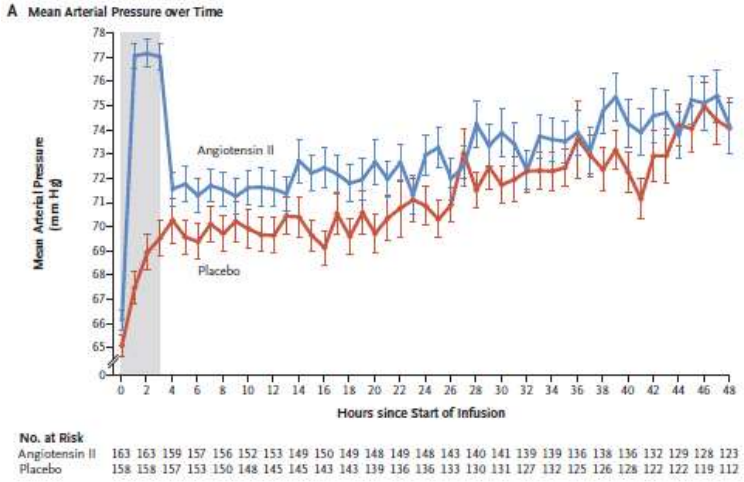
- International trial with 75 study locations in many developed nations, including Canada
- Randomization performed in blocks through a central web-based system
    - Stratified according to MAP at screening (either <65 or >65 mmHg) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score
- Angiotensin II infusions and placebo were prepared locally in identical saline bags by prespecified, unblinded study personnel
    - All other study personnel were blinded to the treatment assignments
- Baseline MAP determined by three measurements, each done in triplicate, at -30, -15 and 0 minutes
- Angiotensin II infusion started at 20ng/kg/min and titrated (to a max of 200ng/kg/min) over the first 3 hours to achieve MAP ≥75mmHg
    - Standard vasopressors were held constant during this period (except for safety reasons)
        - If doses were increased, the patient was designated as not having a response
    - After 3 hours, doses of angiotensin II (range 1.25-40ng/kg/min) and standard vasopressors were adjusted to maintain target MAP 65-75mmHg
        - Nonbinding adjustment scheme was provided to participating physicians
- After 48 hours the study infusion was discontinued via a protocol-specified taper
    - Could re-initiate the study drug (for up to 7 days) if the patient's condition became unstable
- Modified intention to treat analysis; excluded (23) patients who were randomized but did not receive either treatment or placebo
- Sample size based on hypothesized rate of 60% success in treatment group with an alpha level of 0.05 and a power of 90%
- Differences between treatment groups were analyzed with Wilcoxon rank-sum test or analysis of variance for continuous or ordinal variables
    - Chi square or Fisher's exact test for discrete variables
    - Two-tailed alpha level of 0.05
- Primary end-point was analyzed with logistic regression, adjusted for: dichotomized baseline MAP, APACHE II score, vasopressin use and vasopressor dose in 6 hours prior to randomization

- Also performed logistic regression analysis to identify baseline factors which could have influenced primary end-point results
- Safety assessment was analyzed with Kaplan-Meier estimates and hazard rates

Inclusion Criteria:
- Adult patients (≥18 years old)
- Vasodilatory shock despite ≥25mL/kg of fluid resuscitation and high-dose vasopressors
  - Vasodilatory shock defined as a cardiac index >2.3L/min/m^2 or as a central venous oxygen saturation >70% coupled with CVP >8mmHg, with a MAP between 55 and 70mmHg
  - High-dose vasopressors defined as >0.2µg/kg/min of norepinephrine (or equivalent dose in another vasopressor) for between 6 and 48 hours
- Arterial line and indwelling catheter

Exclusion Criteria:
- Burns with TBSA >20%
- Acute coronary syndrome
- Bronchospasm, liver failure, mesenteric ischemia, active bleeding, AAA, ANC <1000/mm^3
- Patients receiving ECMO or treatment with high-dose glucocorticoids

Results:
- 321 patients underwent randomization and received treatment between May 2015 – Jan 2017
  - 163 in the angiotensin group and 158 in the placebo
  - Sepsis was the cause of shock in 80% of included patients
- 69.9% of patients in the treatment group achieved a MAP of ≥75mmHg, or a rise of at least 10mmHg, within 3 hours compared to 23.4% in the placebo group
  - P<0.001; OR 7.95; 95% CI 4.76 to 13.3
- During first 3 hours, the angiotensin II group had a significantly higher increase in MAP
    - 12.5mmHg vs 2.9mmHg (P<0.001)
  - 67% of patients were titrated down from the starting dose (20ng/kg/min) of angiotensin II within 30 minutes due to rapid response
- Mean change in norepinephrine-equivalent dose from baseline to hour 3
  - -0.03±0.1 in the treatment group vs 0.03±0.23 in the placebo
  -
- Improvement in cardiovascular component of SOFA score was significantly greater in treatment group
  - -1.75±1.77 vs -1.28±1.65 (p=0.01)
- No significant differences between the other SOFA scores
- Multivariate analysis to adjust for age, sex, and prespecified stratification variables showed that treatment assignment was the most significant positive predictor of a MAP response
  - OR 12.4 (95% CI 6.7-22.8)(P<0.001)
  - Negative predictors included: hypoalbuminemia (OR 0.40 [0.22-0.72](P0.002)), elevated vasopressor dose (OR 0.40 [0.21-0.77](P=0.006))



- There were no identified safety concerns with angiotensin II administration; there were higher adverse events of any grade reported in the placebo group (87.1% vs. 91.8%)
    - Discontinuation for adverse events in 14.1% of treatment group and 21.5% of placebo
- All-cause mortality at day 7 was 28.8% in the treatment group and 34.8% in the placebo group (Hazard ration 0.78, P=0.22)
    - By day 28, mortality rates were 46% in the treatment group and 53.8% in the placebo (HR 0.78, P=0.12)
- Non-significant absolute reduction of 9% in mortality at 28 days.

Strengths:
- Multinational, double-blind, randomized RCT
- Published protocol in advance of study
- Comprehensive study drug titration scheme outlined for participating ICUs

Limitations:
- Funded by the company developing an angiotensin II treatment
- Relatively small sample size
- Follow-up limited to 28 days
- No discussion of why 75 mmHg was chosen as a target MAP. The 2016 Surviving Sepsis guidelines currently recommend a target MAP of 65 mmHg.
    - In addition, is this a clinically meaningful outcome?
        - Mortality differences at 7 and 28 days were not significant

Study Conclusions:
- Angiotensin II was effective in increasing blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors

Validity:
- Internal: very well-run study with all the following elements: allocation concealment, baseline balance, modified intention to treat analysis, block stratified randomization, blinding.
- External: Multi-centre distribution, including the University of Alberta, strengthens applicability to use here.

Presenter's Clinical Bottom Line:
- Angiotensin II administration, in combination with traditional vasopressors, in patients with refractory vasodilatory shock is an effective means to rapidly raise mean arterial pressure.

Effect of Oral Prednisolone on Symptom Duration and Severity in Non Asthmatic Adults with Acute Lower Respiratory Tract Infection: A Randomized Clinical Trial

Hay, A.D. et all. *JAMA.* 2017;318(8):721–730. doi:10.1001/jama.2017.10572. Published online 22 August 2017.

P: Non asthmatic adult patients with lower respiratory tract infection
I: Moderate dose of oral corticosteroids (prednisolone 40mg/d x5 days)
C: Matched placebo
O_1: Duration of moderately bad or worse cough and mean severity of symptoms
O_2: Duration and severity of acute LRTI symptoms, duration of abnormal peak flow, antibiotic use, adverse events
D: Multicenter placebo controlled RCT

What we already know:

- Acute lower respiratory tract infection (cough with at least one symptom of sputum, chest pain, SOB, wheeze) is one of the most common conditions managed in the primary care setting internationally
- Many patients have been prescribed antibiotics in the past, despite good evidence that they do not reduce symptom duration or severity (estimated costs US 726M annually), and antimicrobial resistance is a challenge in many countries
- Symptoms of acute LRTI are similar to those of exacerbated asthma
- Oral and inhaled corticosteroids are effective for acute asthma, but no clear guidelines on whether steroids should be used for LRTI

Methods:

- Setting: 54 family practices in England
- Family physicians and nurses trained in study protocol by 4 university centers who assessed eligibility criteria and recruited patients same-day or day following their presentation between July 2013 and October 2014
- Intervention: packs contained either ten 20-mg oral prednisolone tabs or placebo tablets
    - Participants were asked to take 2 tabs once daily x 5 days, starting on the day of visit, if possible before starting any antibiotics
- Block randomization of variable size to prednisolone or placebo in a 1:1 ratio stratified by center; computer generated treatment allocation schedule by blinded statistician
- Participants, recruiting physicians, pharmacists and trial team were masked to treatment allocation until the data analyses completed
- Participants asked to report presence and severity of symptoms (0- no problem, 3- moderately bad, 6- as bad as could be) via web or paper diary daily and twice daily peak flows for 28d or until symptoms resolved; weekly telephone calls and £5 vouchers to encourage completion
- Two primary outcomes assessed: duration of moderately bad or worse cough (# of days from randomization to the last day with a score of at least 3 points, to a max of 28 days) and mean severity score (range 0-6) of 6 main symptoms
    - Cough, phlegm, shortness of breath, sleep disturbance, feeling unwell and activity disturbance
- Secondary outcomes (specified *a priori*): total duration and severity of each symptom (see list below) up to 28 days, duration of cough up to 56 days, antibiotic use, adverse events, re-presentation with evidence of illness deterioration, patient satisfaction and intention to use treatment again
    - Cough, phlegm, shortness of breath, wheeze, rhinorrhea, chest pain, fever, muscle aching, headache, sleep disturbance, feeling unwell, activity disturbance
- Estimated the minimally clinically importance difference to be 20% based on expert opinion
    - 3.79 days for duration of cough and 1.66 points for severity of symptoms
    - With 20% attrition →required sample size of 218 per group to retain 174 at follow up for 90% power and 2-sided alpha=0.05 for primary outcome
- Primary comparative analysis considered patients in groups they were randomized to, adjusted for center
    - Time to recovery used to analyze the duration of cough
    - Hazard ratios reported comparing instantaneous rate of resolution of cough between prednisolone and placebo groups, with 95% confidence and P values
- Absolute measures of effect for primary outcome calculated around day 7
- Mean severity score from days 2-4 considered in linear regression models

Inclusion Criteria:

- Age 18 years or older
- Presenting for an acute (≤28 days) cough as the main symptom with at least 1 lower respiratory tract symptom (phlegm, chest pain, wheezing, or shortness of breath) in the previous 24 hours

Exclusion Criteria:

- Any history of chronic pulmonary disease or use of asthma medication in the past 5 years

- Met criteria for severe infection/complications (National institute for Health and Clinical Excellence criteria)
- Required same day hospital admission or same day antibiotics

Results:
- 525 patients assessed for suitability, 401 were eligible, consented and randomized
- 199 in prednisolone group and 202 in placebo group
- Baseline characteristics similar between groups, with the exception prednisolone group more likely to be male/older/had flu vaccine; adjustment for factors demonstrating possible imbalance at baseline and smoking had no effect
- Median duration of bad or worse cough: 5d (IQR 3-8d) in prednisolone group and 5d (IQR 3-10) in placebo group
    - Kaplan-Meier survival curves were similar for both groups
    - Weibull accelerated failure time model ratio was 0.91 (95%CI, 0.76-1.10)- time to resolution reduced by 9% (0.45 days)
- Mean symptom severity scores: 1.99 (SD 0.99) for prednisolone and 2.16 (SD 1.09) for placebo groups
    - Mean severity difference was 0.20 points (95% CI -0.4 to 0.00, *P* = 0.05) equates to relative reduction of 9.3% (less than 20% reduction used in sample size calculation)
- No significant effects on any symptom duration up to 28 days, or cough duration up to 56 days
- No significant effects observed for antibiotic use, patient satisfaction or intention to use the same treatment, non serious adverse events
- Sensitivity analyses did not have any effect on primary comparisons

Strengths:
- Multicenter RCT, fully blinded, with low rates or missing baseline and follow up data
- Eligibility criteria are generalizable to most populations seen in primary care
- Clinically relevant outcomes
- Investigates oral, rather than inhaled steroids in an adult population- no previous studies

Limitations:
- Higher than expected number of participants with zero duration of moderately bad or worse cough
- Practice variation in clinicians also prescribing antibiotics in addition to steroids
- Other baseline biomarkers were not measured (bloodwork, chest X rays) – possible that patients with more severe, inflammatory or microbiological etiology could have entered the trial
- Based on eligibility criteria- some patients could have been recruited with chronic or post infectious cough rather than acute lower respiratory tract infection
- Patient reported outcomes and no way to monitor treatment adherence

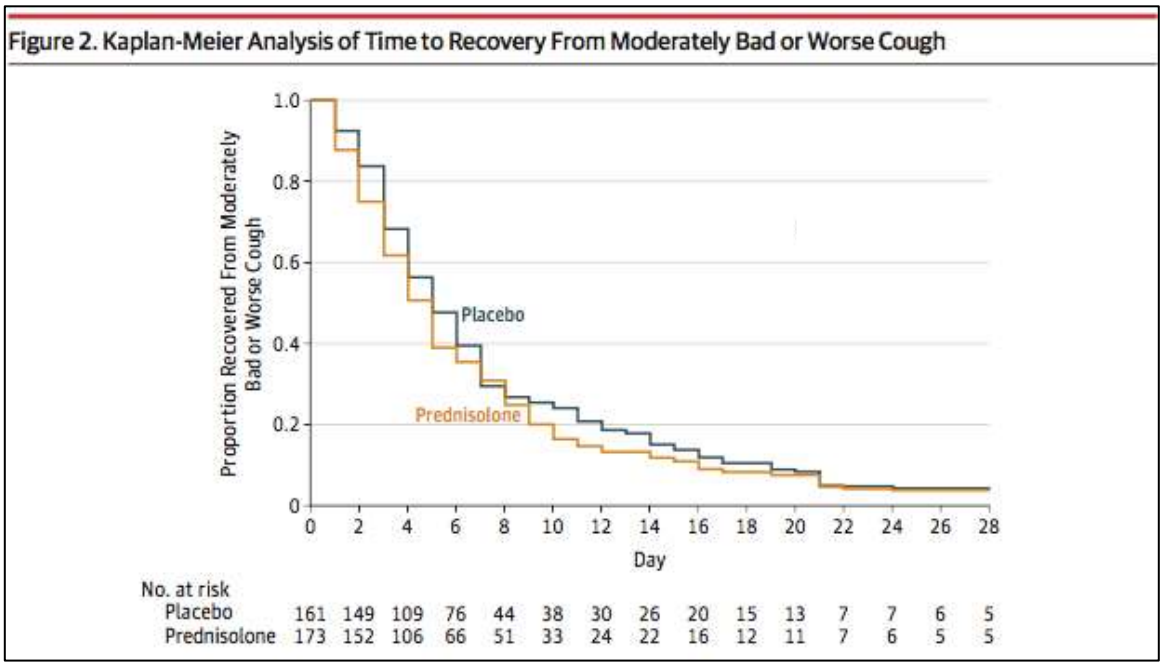
Study Conclusions:
- Oral steroids should not be used in adult primary care patients without asthma or chronic pulmonary disease who do not require treatment with an immediate antibiotic

Validity:
- Study done in the UK, in primary care physician offices instead of the ED

Presenter's Clinical Bottom Line:
- Among adults without asthma who develop acute LRTI, the use of oral steroids did not reduce symptom duration or severity
- Further studies around the same may be needed in an ED patient population

EBM Pearl: Kaplan-Meier Survival Curves:

- One of the most frequently used methods of survival analysis
- Often interested in the time until participants in a study present a specific event or endpoint
  - ex) measure the fraction of patients living for a certain amount of time after treatment; tie to resolution of a cough
- Does not require normally distributed data
- Able to accommodate "censored" data points (people lost to follow-up)



http://www.bmj.com/about-bmj/resources-readers/publications/statistics-square-one/12-survival-analysis

Push-Alert Notification of Troponin Results to Physician Smartphones Reduces the Time to Discharge Emergency Department Patients: A Randomized Controlled Trial

Verma A, Wang AS, Feldman MJ, Hefferon DA, Kiss A, Lee JS. *Annals of Emergency Medicine* 2017;70(3):348-356.

P: Patients presenting to tertiary care ED with primary complaint of chest pain, discharged from ED to usual residence

I: Push-notification of troponin results sent directly to most responsible physician's smartphone

C: Standard troponin reporting on electronic database

O_1: Time from last troponin reported to discharge decision

O_2: Total ED length of stay (triage to actual discharge); Total time to discharge decision (triage to discharge decision)

D: Randomized controlled trial from Sunnybrook Hospital in Toronto

Journal Club – September 27, 2017

-Drs. Hill, Lam, and Fletcher

What we already know:

- Time spent waiting for laboratory results can delay disposition decisions and ED efficiency
- Smartphones with automatic notifications can be a valuable tool for cognitive offloading
- People look at their phones a lot ☺

Methods:

- Cluster-randomization control trial conducted in a single academic tertiary emergency department at Sunnybrook Health Science Centre from February 1, 2014 to October 15, 2014
- Physicians were recruited via email, in-office mailboxes, departmental meetings
- Of 34 eligible physicians, 26 consented to participate and were randomized to either receive emailed troponin push alerts on hospital-issued smartphone (13 physicians) or required to look up results on electronic database on hospital desktop computers (13 physicians)
- Physician phones are automatically linked to patients via EDIS
- 1554 patients met the inclusion criteria
    - 554 patients were assessed by intervention physicians and 551 patients were assessed by control group physicians
    - 448 patients were assessed by physicians not participating in the study;
- Time stamps for troponin results obtained from Electronic Patient Record, time stamps for admission and discharge decision ("ready for discharge" and "actually discharged") obtained from EDIS
- All patients were analyzed with intension to treat protocol
- Sample size powered to detect 30min or more time difference with alpha of 0.05 and 80% power
- Data presented with mean/SD for continuous measures, median/IQR for skewed data, and counts/percentages for categorical measures.
- Employed a linear mixed model to account for clustering of physicians when examining the primary outcome
- Time to discharge decision (O_1) was highly skewed, so values were log transformed prior to analysis

Inclusion Criteria:

- All patients who were treated by a participating physician and discharged from the ED with a final diagnosis of chest pain
- Chest pain diagnosis defined by EDIS diagnosis of "chronic chest pain", "chest pain NYD", "angina-stable", "pain- chest NYD", "chest wall pain (MSK)", "noncardiac chest pain (MSK)", "atypical chest pain (cardiac)"

Exclusion Criteria:

- Admission to hospital
- Referral to specialist service before discharge
- Treatment by non-participating physician
- Diagnosis of acute coronary syndrome

Results:

- 1,105 total patients enrolled with 26 participating physicians
- Relatively similar demographics between groups (age, gender)
- Predominantly CTAS 2 patients (70.8%)

Group	Troponin to Discharge Decision, Median (IQR), Minutes	Triage to Discharge Decision, Median (IQR), Minutes	Total ED LOS, Median (IQR), Minutes
Control group (N=551)	94.3 (36.2–177.8)	340.0 (261.0–413.0)	345.0 (261.0–419.0)
Intervention group (N=554)	68.4 (30.5–157.2)	323.0 (248.0–402.0)	328.0 (250.0–408.0)

LOS, Length of stay.

- Statistically significant decrease in time to disposition decision between groups
    - 25.8-minute difference between median times
- Non-significant decrease in median ED length of stay (neither triage to discharge decision or total ED time)
- Median ED LoS for all patients (including those excluded from this study) receiving at least one troponin test in the ED was 444.5 minutes
    - 729.5 minutes for those referred to a consultant

Strengths:
- RCT design
- Electronic order system enables acquisition of robust data set
- Two measures for discharge time, one by study physicians ("discharge ready"), and one by nursing staff ("actual discharge")
    - Used to validate the physician timings and ensure no pre-emptive labelling of patients

Limitations:
- Nonblinded
- Unable to monitor whether physicians in the intervention group were using the push notifications, or checking their smartphones regularly
- Self-selection bias of recruited physicians
- No measurement of any detrimental effect on length of ED stay/delay in discharge decisions for patients with other chief complaints
- No follow-up with patients to track any increase in negative outcomes associated with the intervention
- Not powered to detect time difference under 30min

Study Conclusions:
- Smartphone push-alert notifications of troponin results in ED patients presenting with chest pain significantly decreased the time to discharge decision, but had a non-significant impact on total ED length of stay.

Validity:
- May not be generalizable:
    - Sunnybrook provides hospital-issued iPhones to be signed out at the onset of each shift.
    - Pre-existing sophisticated EMR which allows orders to be made digitally
- Physicians in the control group may have become reliant on the push-notifications during the period of 2011-2014, and subsequently were not used to checking troponin results without prompting

Presenter's Clinical Bottom Line:
- In an ED which has the capacity to integrate smartphones into the EMR, adding push notifications may improve ED flow and efficiency.

Predicting Short-Term Risk of Arrhythmia among Patients with Syncope: The Canadian Syncope Arrhythmia Risk Score

Thiruganasambandamoorthy, V. Stiell, I.G. et al. Acad Emerg Med 2017. PMID: 28791782.

P: Patients >16 yo who presented with syncope within 24 hours of the event

I: Observational (no patient intervention)

C: -
O_1: Death or dysrhythmia (including procedural interventions for dysrhythmia within 30 days)
O_2: Procedural interventions to treat arrhythmias within 30 days of ED discharge
D: Multicenter prospective cohort study

What we already know:
- Syncope (sudden transient loss of consciousness followed by spontaneous recovery) constitutes 1-3% of ED visits and 3% of hospitalizations from the ED
- Concern for serious underlying conditions leads to longer monitoring of patients in the ED
- Several tools have been developed to identify patients at risk for serious outcomes, and one tool to predict long term risk of arrhythmias but no risk tools that would identify adult patients at risk for arrhythmias or death within 30 days of ED disposition

Methods:
- Setting: six large EDs in Canada
- On duty ED staff screened patients with presenting complaints related to syncope
- Variables collected prospectively during ED visit included time and date of syncope, event characteristics, history of CV disease, family history of sudden death of congenital heart disease, and final ED diagnosis
    - Chart review variables: age, sex, all vital signs, all lab results and ECG variables
    - ECG variables: LBBB, left axis deviation, right axis deviation, QRS duration, QRS axis, corrected QT interval
- All ECGs performed were reviewed by a cardiologist
- From variables collected- candidate predictors for tests of association with outcome, followed by multivariate analysis were completed
    - Interobserver agreement reported as a proportion of agreement using the kappa coefficient
    - Predictors were excluded if <5 expected events, exceeded threshold of 2.5 for variance inflation, >25% missing values and lower inter-observer agreement (kappa <0.4)
- Outcomes selected and defined based on previous studies and consensus guidelines- 39 candidate predictors were selected at first
    - Bivariate tests of association for 35 remaining predictors after 4 had sparse distribution, and excluded 12 for failure to reach significance on testing
    - The remaining continuous predictors were dichotomized, and the results were combined across multiple datasets using Rubin's rules
- Sample size calculated based on sensitivity required of the tool, and achieved significance
- Outcomes confirmed by structured review of documents in medical records related to index and subsequent ED visits and scripted telephone follow up 30 days after discharge
- Internal validation performed using bootstrapping samples, and data was translated into a point scoring system via shrinkage corrected model

Inclusion Criteria:
- Adults (≥ 16 years) with syncope who presented within 2- 4 hours of the event

Exclusion Criteria:
- Prolonged loss of consciousness (>5 minutes)
- Change in mental status after syncope
- Witnessed seizure
- Head trauma causing loss of consciousness
- Patients unable to provide proper history due to alcohol or drug intoxication

- Language barrier

Results:

- Enrolled patients: 5, 358
- Incomplete outcomes assessment: 348/ 5358 (6.5%)
- Inter-rater reliability assessment: 204 patients (4.1%)
- Admission rate: 9.5%
- Co morbid conditions: hypertension (31.6%), diabetes (10%), CAD (11.6%), CHF (3.6%)
- Primary outcome at 30 days (death or dysrhythmia)
    - 2.1% (106/5010), with 95%CI, 1.7-2.5%
    - 0.9% (45/5010) had a primary outcome after being discharged from the hospital
    - 0.57% (29/5010) had a pacemaker placement performed
- Decision tool: researchers identified 39 candidate predictors initially, and came to 8 for their final rule

Figure 2. Canadian Syncope Arrhythmia Risk Score to Identify Patients at Risk for Serious Arrhythmias within 30 Days of Emergency Department Disposition

Canadian Syncope Arrhythmia Risk Score

Items	Points
1. Clinical Evaluation	
a) Vasovagal predisposition*	**-1**
b) History of heart disease†	**+1**
c) Any ED systolic blood pressure < 90 or >180 mmHg‡	**+1**
2. Investigations	
a) Troponin elevated (> 99%ile normal population)	**+1**
b) QRS duration >130 milliseconds	**+2**
c) Corrected QT interval >480 milliseconds	**+1**
3. Final ED Diagnosis	
a) ED diagnosis of vasovagal syncope	**-1**
b) ED diagnosis of cardiac syncope	**+2**
Total Score (-2 to 8):	____

ED = Emergency Department
*Warm-crowded place, prolonged standing, fear, emotion or pain
†Includes history of coronary or valvular heart disease, cardiomyopathy, congestive heart failure or non-sinus rhythm (ECG evidence during the index visit or documented history of ventricular or atrial arrhythmias, or device implantation)
‡Includes blood pressure values from triage until ED disposition

Risk Categories for Arrhythmias/Death

Total Score	Risk[§]	Category
-2	0.2%	Very Low
-1	0.5%	Very Low
0	0.9%	Very Low
1	1.9%	Low
2	3.8%	Medium
3	7.5%	Medium
4	14.3%	High
5	25.4%	High
6	41.1%	Very High
7	58.8%	Very High
8	74.5%	Very High

[§]Shrinkage-Adjusted Expected Risk

Strengths:
- Large, prospective study addressing an important clinical question that is common in the ED
- First study to look at short term outcomes
- Primary outcome is patient centered
- Extensive patient follow up and review in terms of medical records and follow up

Limitations:
- Single country
- Excluded non English speaking patients
- Requires external validation before implementation
- 20% of eligible patients not enrolled in the study
- Criteria are subjective- vasovagal predisposition, or diagnosis of cardiac syncope, though they did attempt to mitigate this with kappa values
- Incomplete data on parts of the decision tool (only 54.2% of the patients had troponin performed)

Study Conclusions:
- The Canadian Syncope Arrhythmia Risk Score can improve patient safety by identification of those at risk for arrhythmias and aid in acute management decisions. Once validated, the score can identify low risk patients who will require no further investigations

Validity:
- Mostly young, healthy patients- affects the generalizability of the tool

Presenter's Clinical Bottom Line:
- This decision tool may be helpful in stratifying syncopal patients in the ED that are at risk for death or dysrhythmia but needs external validation before widespread implementation