Top Articles of 2014:
Turning Evidence into Practice

Mel L. Anderson, MD, FACP
Associate Professor of Medicine
University of Colorado School of Medicine

Chief, Hospital Medicine Section
Denver VA Medical Center

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Roadmap

- Case based interactive format
- Multiple articles per case
- Quick hitters and Short takes
- Summary of suggested practice changes

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Learning Objectives

1. *Describe* the primary conclusions
2. *Identify* changes to your practice
3. *Implement* these practice changes

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Journals Reviewed…

- Jan 2014 – Dec 2014
  - N Engl J Med
  - JAMA; JAMA Intern Med
  - J Gen Intern Med
  - J Hospit Med
  - Lancet; Stroke; Ann Emerg Med
  - Am J Med; Am Heart J; Am J Cardiol
  - Ann Intern Med + ACP J Club
  - Crit Care Med; Am J Respir Crit Care Med
  - Circulation, J Am Coll Cardiol
  - BMJ, Chest, Clin J Am Soc Nephrol
  - ACP Plus, BMJ Online update, J Watch

Disclosures

- None relevant

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  University of Washington
- Brad Sharpe, MD

  UCSF School of Medicine

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2014 Notables

- **JNC 8** altered BP treatment targets
- **ACC/AHA Cholesterol Guidelines** change to risk based treatment:
  - High intensity
  - Moderate intensity

JAMA 2014;311:507-520.
Circulation 2014;129[suppl 2]:S1-S45.

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2014 Notables

- Updated **ACC/AHA Periop Guidelines**
- Algorithm largely the same
- Downgraded BB to IIb
- Periop Statin IIa vascular surgery
- Post-op troponin IIb

J Am Coll Cardiol 2014;64:2371.

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2014 Notables

- Updated **ACC/AHA NSTEMI Guidelines**

J Am Coll Cardiol 2014;64:e139-228.

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Case 1

71 y/o woman with 1 week increasing dyspnea, pleuritic chest pain, no cough

PMHx: Gold III COPD, HTN; pan inhalers and oxygen 2 lpm

Temp 99.2, HR 108, RR 24, BP 112/68, needing 6 lpm O2 sats 92%

Awake and alert, dec BS bilat, good air mvnt

CXR clear, creat 1.3; CT-PE + bilateral PEs

Case 1

She is started on UFH bolus and gtt and admitted to the ICU.

ECHO: + RV dilation and dysfunction

Troponin I: 0.158

You know what question is coming, right?...

Intermediate Risk Acute PE

A. IV tenecteplase ↓ all cause mortality
B. IV tenecteplase ↓ hemodynamic decompensation
C. IV tenecteplase ↑ length of stay
D. Consult Magic 8 ball…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*

N Engl J Med 2014;370:1402-11.

Pulmonary EmbolIsm THrombOlysis trial…

'PEITHO'

N Engl J Med 2014;370:1402-11.

"Pulmonary EmboLism Lysis with Tenecteplase – Intermediate risk Trial"…

'PELT-IT'

Mel's Magical Journal 2014.

"pulMonary Embolism Lysis with Tenecteplase – Intermediate risk Trial"…

'MELT-IT'!

Mel's Magical Journal 2014.

PEITHO Trial

Question:	What is the effect of IV tenecteplase in intermediate risk pulmonary embolism?
Design:	Double blind RCT
Patients:	1005 patients, PE<15 days, + RV dysfxn
1° Outcome:	Death or hemodynamic decompensation at 7 days; also recurrent PE, bleeding of all types

N Engl J Med 2014;370:1402-11.

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PEITHO Trial: Results

	Plac.	Lytics	ARR	p
Primary Endpoint				
Hemod. Decomp.				
All cause death				

N Engl J Med 2014;370:1402-11.

PEITHO Trial: Results

	Plac.	Lytics	ARR	p
Primary Endpoint	5.6%	2.6%	3.0%	0.02
Hemod. Decomp.				
All cause death				

N Engl J Med 2014;370:1402-11.

PEITHO Trial: Results

	Plac.	Lytics	ARR	p
Primary Endpoint	5.6%	2.6%	3.0%	0.02
Hemod. Decomp.	5.0%	1.6%	3.4%	0.002
All cause death				

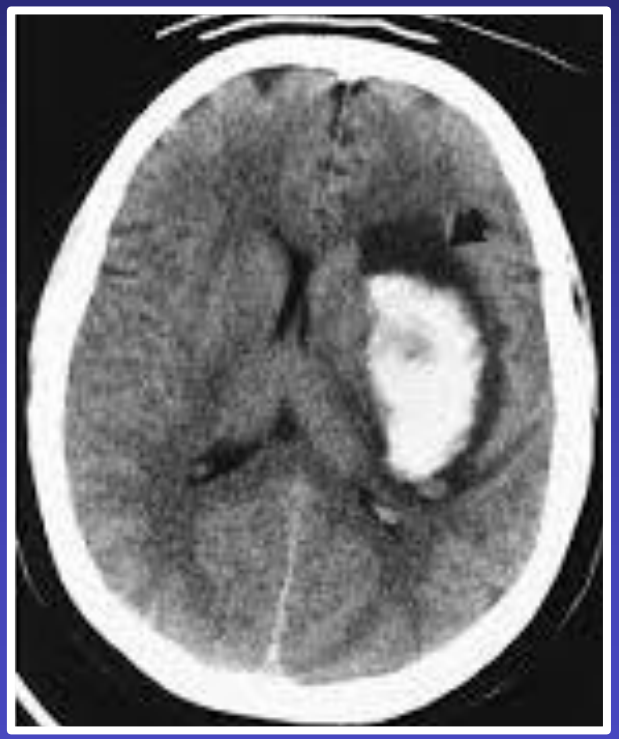
N Engl J Med 2014;370:1402-11.

PEITHO Trial: Results

	Plac.	Lytics	ARR	p
Primary Endpoint	5.6%	2.6%	3.0%	0.02
Hemod. Decomp.	5.0%	1.6%	3.4%	0.002
All cause death	1.8%	1.2%	0.6%	NS

N Engl J Med 2014;370:1402-11.

But what about bleeding…



PEITHO Trial: Results

	Plac.	Lytics	AR▲	p
Non CNS bleed				
Stroke				
30d bad events…				

N Engl J Med 2014;370:1402-11.

PEITHO Trial: Results

	Plac.	Lytics	AR▲	p
Non CNS bleed	1.2%	6.3%	5.1%	<0.001
Stroke				
30d bad events…				

N Engl J Med 2014;370:1402-11.

PEITHO Trial: Results

	Plac.	Lytics	AR▲	p
Non CNS bleed	1.2%	6.3%	5.1%	<0.001
Stroke	0.2%	2.4%	2.2%	0.003
30d bad events…				

N Engl J Med 2014;370:1402-11.

PEITHO Trial: Results

	Plac.	Lytics	AR▲	p
Non CNS bleed	1.2%	6.3%	5.1%	<0.001
Stroke	0.2%	2.4%	2.2%	0.003
30d bad events…	11.8%	10.8%	1.0%	NS

N Engl J Med 2014;370:1402-11.

PEITHO Trial

Question:	What is the effect of IV tenecteplase in intermediate risk pulmonary embolism?
Design:	Double blind RCT
Patients:	1005 patients, PE<15 days, + RV dysfxn
1° Outcome:	Death or hemodynamic decompensation at 7 days; also recurrent PE, bleeding of all types
Conclusion:	IV tenecteplase prevented hemodynamic decompensation but increased major hemorrhage

N Engl J Med 2014;370:1402-11.

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Bottom Line?

- Individualized decision-making
- Informed consent…

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Case 1

- Significant underlying COPD, uncertain pulmonary status after submassive PE
- Careful discussion pros/cons
- IV rt-PA 60 minutes
- Clinical response in hours
- Normal ECHO 2 days later! No serious bleeding

Intermediate Risk Acute PE

A. IV tenecteplase ↓ all cause mortality
B. IV tenecteplase ↓ hemodynamic decompensation
C. IV tenecteplase ↑ length of stay
D. Consult Magic 8 ball…

Quick hitter:

Research

Original Investigation

Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism

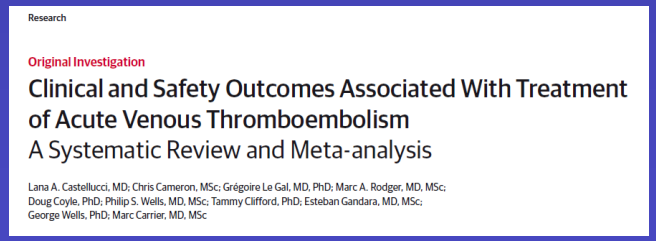
A Systematic Review and Meta-analysis

Lana A. Castellucci, MD; Chris Cameron, MSc; Grégoire Le Gal, MD, PhD; Marc A. Rodger, MD, MSc; Doug Coyle, PhD; Philip S. Wells, MD, MSc; Tammy Clifford, PhD; Esteban Gandara, MD, MSc; George Wells, PhD; Marc Carrier, MD, MSc

JAMA 2014;312(11):1122-1135.

Quick hitter:

1. Overall no significant differences across *most* comparisons…
2. UFH + warfarin may be the least effective regimen
3. Rivaroxaban and apixaban may be associated w/ lower bleeding risk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JAMA 2014;312(11):1122-1135.

PE Short Takes

ADJUST-PE: Another study showing age-adjusted D-dimer retains sensitivity but improves specificity (negative = age x 10 ng/mL). *JAMA* 2014;311(11):1117-1124.

Retrospective review of IVC filter placement (n=758) across three centers. Complications were common and only 36% had them removed at 4.5 months f/u. Don't forget about them! *Am J Cardiol* 2014;113:389-394.

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Case Report

Chronic subdural haematoma secondary to headbanging

Ariyan Pirayesh Islamian, Manolis Polemikos, Joachim K Krauss

"Headbanging is a contemporary dance form…abrupt flexion-extension…"

Lancet 2014;384:102.

Case 2

A 63 y/o woman presents to the ER with 4 days of dysuria, flank pain, and chills.

PMHx: Osteoporosis, episodic UTIs

Exam: 101.2, HR 102, RR 20, 88/55, SaO2 95% on room air. BP no better after 1 L NS.

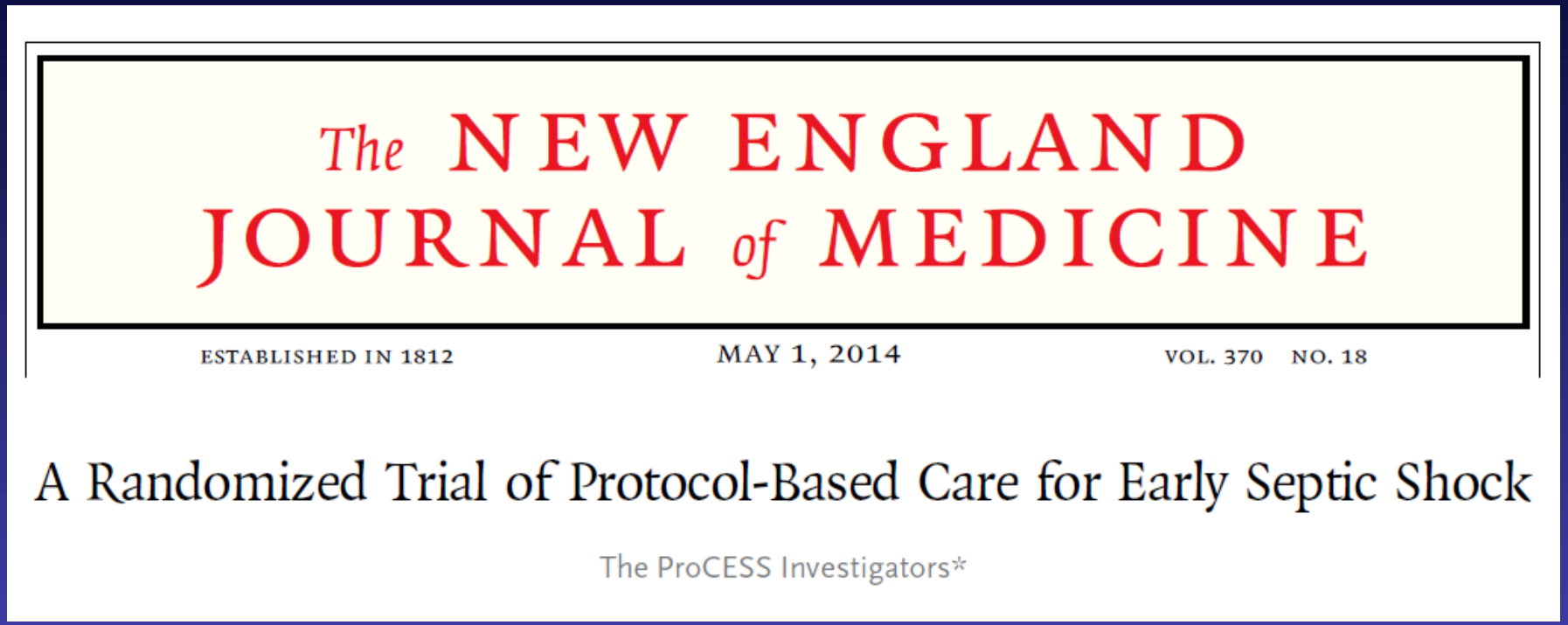
Ill-appearing but alert; warm; percussion tenderness to R flank, otherwise non-focal.

UA pyuria, creat 1.9, WBC 18,000, lactate 4.2

Cultures are obtained and IV abx given in ER

What would you do next?

A. Place central line, begin protocol-guided Early Goal Directed Therapy (Rivers)
B. Skip central line if PIV ok, give IVF and pressors to keep SBP > 100 mm Hg
C. Begin IV hydrocortisone 100mg Q 8 hours
D. Calculate APACHE II score to guide APC treatment
E. I like them all except B…



Protocolized Care for Early Septic Shock

N Engl J Med 2014;370:1683-93.

ProCESS

Question:	Is protocolized care of severe sepsis / septic shock superior to usual care?
Design:	Multicenter randomized trial comparing 1. "Protocol based EGDT" 2. "Protocol based standard care" 3. "Standard care"
Patients:	1341 patients, 60% in septic shock, average lactate about 5 mmol/L
1° Outcome:	60 day mortality

N Engl J Med 2014;370:1683-93.

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"Protocol based EGDT"

1. Central line w/ oximetric port
2. 500 cc fluid bolus until CVP 8-12 cm H2O
3. Vasoactive agents until MAP 65-90 mm Hg
4. Measure ScvO2; if $\leq$ 70%,

   --Transfuse PRBC to Hct 30% or greater

   --Inotropes until goal reached

N Engl J Med 2014;370:1683-93.

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"Protocol based Standard care"

1. 18g PIV x ii
2. 500-1000 cc fluid bolus within 20 minutes
3. 2 liters IVF in first hour
4. IVF at 250-500 cc/hr until replete
5. Vasoactive agents to keep SBP $\geq$ 100 mm Hg

N Engl J Med 2014;370:1683-93.

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"Standard care"

1. Manage as you see fit, my friend.

N Engl J Med 2014;370:1683-93.

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Differences among groups

	EGDT	PBSc	Sc	p
Central Line				
IVF at 6 hours				
Vasopressors				
Dobutamine				
PRBC transf.				

Differences among groups

	EGDT	PBSc	Sc	p
Central Line	93.6%	56.5%	57.9%	<0.001
IVF at 6 hours				
Vasopressors				
Dobutamine				
PRBC transf.				

Differences among groups

	EGDT	PBSc	Sc	p
Central Line	93.6%	56.5%	57.9%	<0.001
IVF at 6 hours	2.8 L	3.3 L	2.3 L	<0.001
Vasopressors				
Dobutamine				
PRBC transf.				

Differences among groups

	EGDT	PBSc	Sc	p
Central Line	93.6%	56.5%	57.9%	<0.001
IVF at 6 hours	2.8 L	3.3 L	2.3 L	<0.001
Vasopressors	54.9%	52.2%	44.1%	0.003
Dobutamine				
PRBC transf.				

Differences among groups

	EGDT	PBSc	Sc	p
Central Line	93.6%	56.5%	57.9%	<0.001
IVF at 6 hours	2.8 L	3.3 L	2.3 L	<0.001
Vasopressors	54.9%	52.2%	44.1%	0.003
Dobutamine	8.0%	1.1%	0.9%	<0.001
PRBC transf.				

Differences among groups

	EGDT	PBSc	Sc	p
Central Line	93.6%	56.5%	57.9%	<0.001
IVF at 6 hours	2.8 L	3.3 L	2.3 L	<0.001
Vasopressors	54.9%	52.2%	44.1%	0.003
Dobutamine	8.0%	1.1%	0.9%	<0.001
PRBC transf.	14.4%	8.3%	7.5%	0.001

Primary Endpoint

	EGDT	PBSc	Sc	p
60 day death				

N Engl J Med 2014;370:1683-93.

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Primary Endpoint

	EGDT	PBSc	Sc	p
60 day death	21.0%	18.2%	18.9%	

N Engl J Med 2014;370:1683-93.

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Primary Endpoint

	EGDT	PBSc	Sc	p
60 day death	21.0%	18.2%	18.9%	**NS**

N Engl J Med 2014;370:1683-93.

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ProCESS

Question:	Is protocolized care of severe sepsis / septic shock superior to usual care?
Design:	Multicenter randomized trial comparing 1. "Protocol based EGDT" 2. "Protocol based standard care" 3. "Standard care"
Patients:	1341 patients, 60% in septic shock, average lactate about 5 mmol/L
1° Outcome:	60 day mortality
Conclusion:	Protocol-based resuscitation did not improve outcomes

What??

"Standard care" has changed the last decade + since Rivers trial published – more IVF, greater attention to early abx.

An opportunity to avoid CVC and complications

N Engl J Med 2014;370:1683-93.

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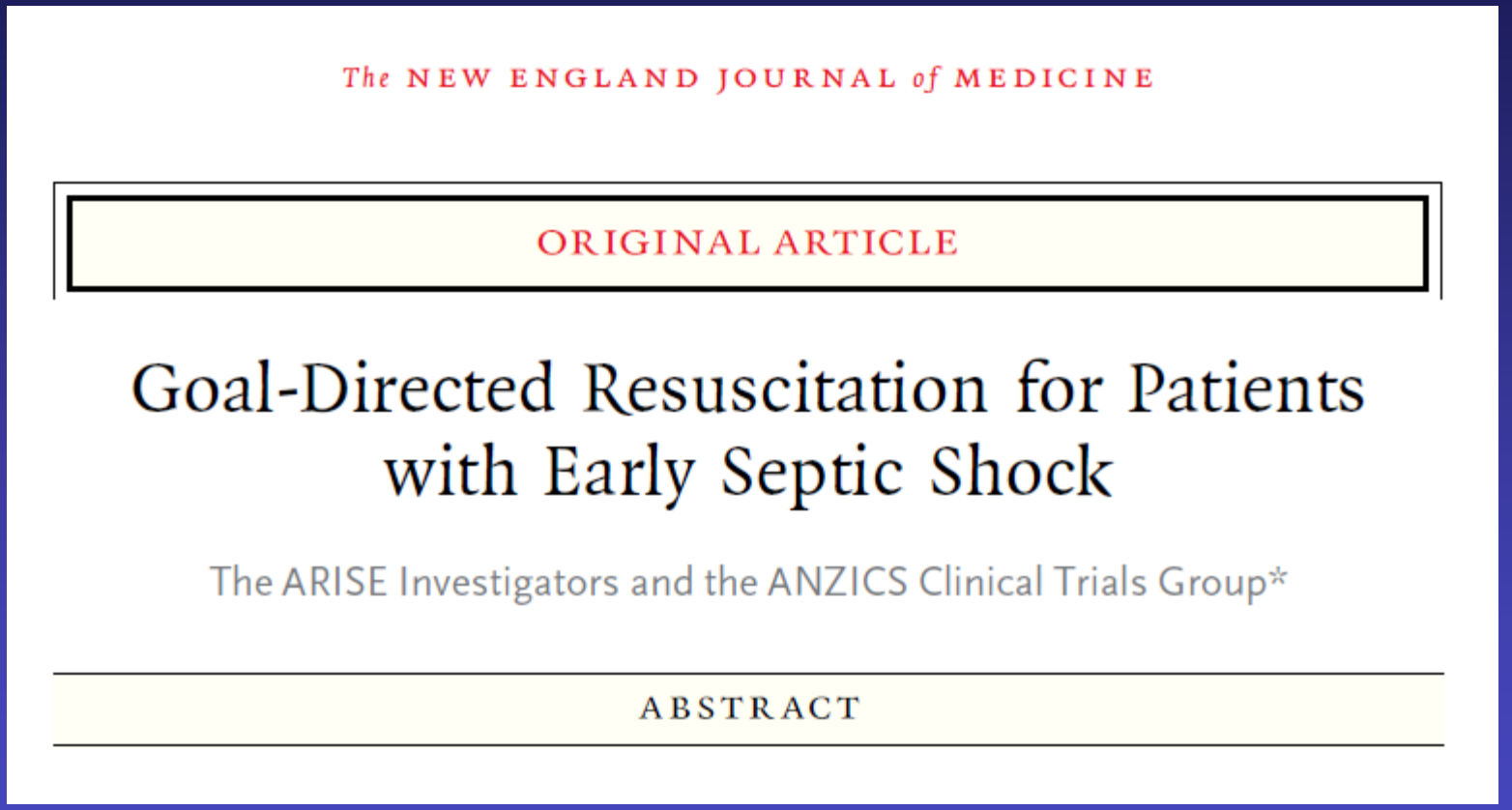
And there is another…



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

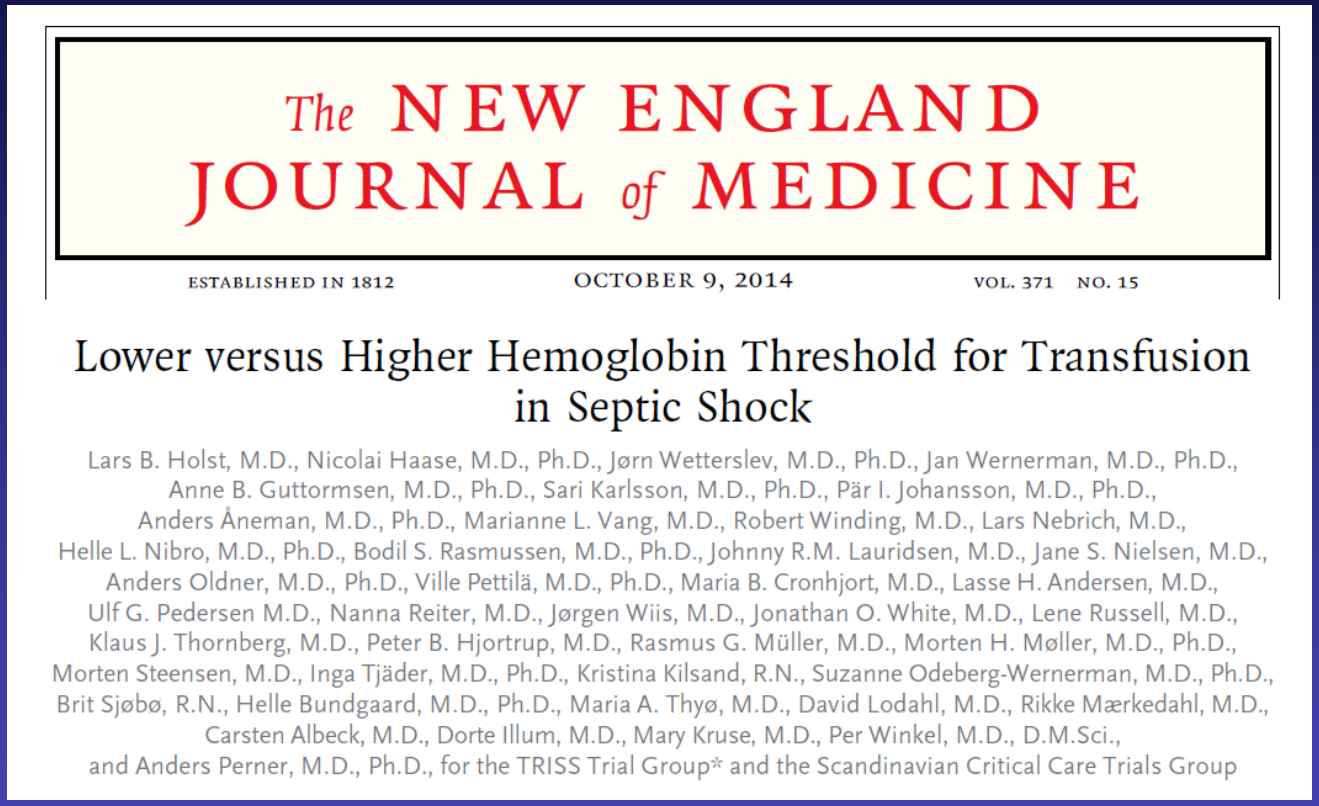
ABSTRACT

N Engl J Med 2014;371:1496-506.

What would you do next?

A. Place central line, begin protocol-guided Early Goal Directed Therapy (Rivers)
B. Skip central line if PIV ok, give IVF and pressors to keep SBP > 100 mm Hg
C. Begin IV hydrocortisone 100mg Q 8 hours
D. Calculate APACHE II score to guide APC treatment
E. I like them all except B…

Quick hitter:



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2014 VOL. 371 NO. 15

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D., Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D., Anders Åneman, M.D., Ph.D., Marianne L. Vang, M.D., Robert Winding, M.D., Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D., Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D., Ville Pettilä, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D., Ulf G. Pedersen M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D., Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Møller, M.D., Ph.D., Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N., Suzanne Odeberg-Wernerman, M.D., Ph.D., Brit Sjøbø, R.N., Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D., Rikke Mærkedahl, M.D., Carsten Albeck, M.D., Dorte Illum, M.D., Mary Kruse, M.D., Per Winkel, M.D., D.M.Sci., and Anders Perner, M.D., Ph.D., for the TRISS Trial Group* and the Scandinavian Critical Care Trials Group

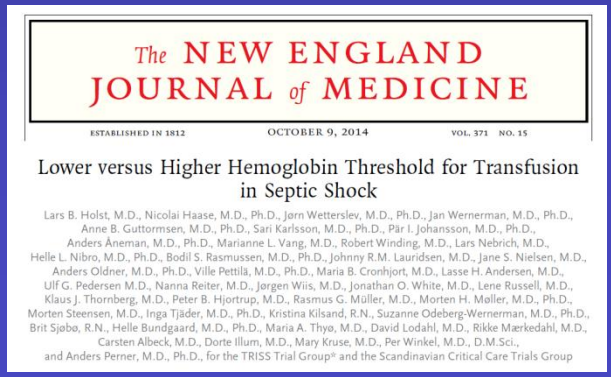
Transfusion Requirements in Septic Shock: TRISS

N Engl J Med 2014;371:1381-91.

Quick hitter:

1. Septic shock PRBC transfusion threshold of <7 g/dL and < 9 g/dL no different (1 unit vs. 4 units, on avg).

2. Fits with ProCESS, TRICC, recent GIB lit.



N Engl J Med 2014;371:1381-91.

ICU Short Take

Meta-analysis: restrictive transfusion strategy is associated with lower rates of HCA infection. *JAMA* 2014;311:1317-1326.

Case 3

A 67 y/o man presents with new substernal chest pain, diaphoresis, and dyspnea x 2 hrs.

PMHx: DM, HTN, tobacco, obesity + OSA

Exam: BMI 35, 162/92, 92, 20, afeb. No CHF. + diagonal earlobe creases bilat.

EKG: atrial fibrillation, no ST segment changes

ER: ASA, nitro → CP free.

Troponin: 0.012 → 0.109 → 0.325

Which are true regarding ACS?

A. Clopidogrel is indicated even without PCI
B. High potency statin unlikely to be rx
C. Prescribing generic statin inc. adherence
D. Lifestyle changes can be life-changing…
E. I like them all

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Comparative Effectiveness of Clopidogrel in Medically Managed Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Matthew D. Solomon, MD, PhD,*† Alan S. Go, MD,*†‡ David Shilane, PhD,†
Derek B. Boothroyd, PhD,† Thomas K. Leong, MPH,* Dhruv S. Kazi, MD, MSc, MS,‡§
Tara I. Chang, MD, MS,† Mark A. Hlatky, MD†

Oakland, Stanford, and San Francisco, California

J Am Coll Cardiol 2014;63:2249-57.

The New England Journal of Medicine

EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*

MACE dec from 11.4% to 9.3% w/ 9 m clopid.

N Engl J Med 2001;345:494-502.

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Modern clopidogrel use…

Question:	What is the real-world effectiveness of clopidogrel in ACS patients managed medically?
Design:	Retrospective cohort study Kaiser N. CA
Patients:	16,365 patients w/ USA/NSTEMI managed medically, i.e. without PCI/CABG
1° Outcome:	2 year all-cause mortality, hospital stay for MI, adjusted composite of death/MI

J Am Coll Cardiol 2014;63:2249-57.

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Modern clopidogrel use…

USA 35% and NSTEMI 65%

Discharged on clopidogrel: only 36%

Mortality dec from 13.0% to 8.3%

Composite dec from 17.4% to 13.5%

J Am Coll Cardiol 2014;63:2249-57.

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Question:	What is the real-world effectiveness of clopidogrel in ACS patients managed medically?
Design:	Retrospective cohort study Kaiser N. CA
Patients:	16,365 patients w/ USA/NSTEMI managed medically, i.e. without PCI/CABG
1° Outcome:	2 year all-cause mortality, hospital stay for MI, adjusted composite of death/MI
Conclusion:	Clopidogrel (underutilized) associated with lower risk of death or MI, esp if NSTEMI

J Am Coll Cardiol 2014;63:2249-57.


NDC 0591-3777-19
Atorvastatin
Calcium
Tablets
80 mg*
Watson
90 Tablets Rx only

Health Services and Outcomes Research

Patterns of Statin Initiation, Intensification, and Maximization Among Patients Hospitalized With an Acute Myocardial Infarction

Suzanne V. Arnold, MD, MHA; Mikhail Kosiborod, MD; Fengming Tang, MS; Zhenxiang Zhao, PhD; Thomas M. Maddox, MD, MSc; Patrick L. McCollam, PharmD; Julie Birt, PharmD; John A. Spertus, MD, MPH

Among 4340 acute MI patients:
Nearly 90% discharged on a statin, but…
Only 23% were prescribed high potency, e.g. atorvastatin 80mg

Circulation 2014;129:1303-1309.

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ORIGINAL RESEARCH | Annals of Internal Medicine

Comparative Effectiveness of Generic and Brand-Name Statins on Patient Outcomes

A Cohort Study

Joshua J. Gagne, PharmD, ScD; Niteesh K. Choudhry, MD, PhD; Aaron S. Kesselheim, MD, JD, MPH; Jennifer M. Polinski, ScD, MPH; David Hutchins, MBA, MHSA; Olga S. Matlin, PhD; Troyen A. Brennan, MD; Jerry Avorn, MD; and William H. Shrank, MD, MSHS

Among 90,111 Medicare patients starting a statin
If generic, more likely to be taking it and
Lower rates of clinical events! (NNT about 65)

Ann Intern Med 2014;161:400-407.

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Original Investigation

Different Time Trends of Caloric and Fat Intake Between Statin Users and Nonusers Among US Adults

Gluttony in the Time of Statins?

Takehiro Sugiyama, MD, MSHS; Yusuke Tsugawa, MD, MPH; Chi-Hong Tseng, PhD; Yasuki Kobayashi, MD, PhD; Martin F. Shapiro, MD, PhD

Among 27,866 adults in NHANES rx a statin
Over time, statin users consume more fat and increased BMI more than non-users
Are we sending a clear message?

JAMA Intern Med 2014;174:1038-1045.

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Effect of Sustaining Lifestyle Modifications (Nonsmoking, Weight Reduction, Physical Activity, and Mediterranean Diet) After Healing of Myocardial Infarction, Percutaneous Intervention, or Coronary Bypass (from the REasons for Geographic and Racial Differences in Stroke Study)

Among 4174 acute MI patients, HR for another MI

0: 1.0 (reference)

1: 0.60 (0.44 – 0.81)

2: 0.49 (0.36 – 0.67)

3: 0.38 (0.21 – 0.67)

Am J Cardiol 2014;113:1933-1940.

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Which are true regarding ACS?

A. Clopidogrel is indicated even without PCI
B. High potency statin unlikely to be rx
C. Prescribing generic statin inc. adherence
D. Lifestyle changes can be life-changing…
E. I like them all

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Misc. Short Takes

Look for atrial fibrillation in cryptogenic stroke: think 30 days or even longer. The yield is surprisingly high.

CRYSTAL-AF: *N Engl J Med* 2014;370:2478-86.

EMBRACE: *N Engl J Med* 2014;370:2467-77.

Meta-Analysis: Stroke 2014;45:520-526.

CAM-S is a new, validated tool to assess delirium severity in hospitalized patients. *Ann Intern Med* 2014;160:526-533.

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Misc. Short Takes

Increased sudden death when combining tmp/smx and ACEI/ARB. Don't do it. *BMJ* 2014;349:g6196.

NSAIDS and Anticoagulants: more bleeding, more thromboembolism. *Ann Intern Med* 2014;161:690-698.

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Practice Summary

Things to Do:

1. Screen for RV dysfunction in acute PE if lytics a consideration
2. If not giving lytics, consider LMWH vs. NOAC as more effective regimens (vs. UFH)
3. Use age-adjusted D-dimer in eval VTE
4. Don’t forget the ‘CURE-indication’ clopidogrel
5. Prescribe generic high-potency statins in ACS

Practice Summary

Things to Do, cont.:

6. Emphasize lifestyle changes in secondary prevention CAD: what to eat, how active to be, tobacco cessation
7. Look for atrial fibrillation in cryptogenic CVA
8. Limit transfusion to Hgb < 7.0 g/dL

Practice Summary

Things to Consider:

1. Limiting CVC placement by pursuing non-EGDT protocol resuscitation in severe sepsis / shock

Practice Summary

Things to Not Do:

1. Assume the IVC filter will be removed by well meaning future clinicians…make plans!
2. Vigorous head-banging

Thank you!

Melver.Anderson@va.gov

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