Curricular Track III: Clinical Controversies—Fast and Furious
Activity No. 0217-0000-14-102-L01-P, 1.5 contact hours; Knowledge-based activity.

Monday, October 13
9:15 a.m.–10:45 a.m.
Convention Center:
Grand Ballroom F

Moderator: Sandra L. Kane-Gill, Pharm.D., M.Sc., FCCP
Associate Professor, University of Pittsburgh, School of Pharmacy, Pittsburgh, Pennsylvania

Agenda

9:15 a.m.	Colchicine for the Heart *Kristen Bova Campbell, Pharm.D., BCPS (AQ-Cardiology), CPP* Clinical Pharmacist – Electrophysiology, Duke University Hospital Residency Director, PGY2 Cardiology Residency, Duke University Hospital, Durham, North Carolina
9:30 a.m.	Combination tPA and Dornase Alfa Therapy for Pleural Infection *Mitchell S. Buckley, Pharm.D., FCCP, FCCM, FASHP, BCPS* Clinical Pharmacy Specialist – Medical ICU, Director of PGY1 Pharmacy Residency, Banner Good Samaritan Medical Center, Phoenix, Arizona
9:45 a.m.	Should I Start This Septic Patient on a Statin? *Zachariah Thomas, Pharm.D., BCPS* Clinical Associate Professor, Rutgers University; Critical Care Pharmacist, Ernest Mario School of Pharmacy, Hackensack University Medical Center, Piscataway, New Jersey
10:00 a.m.	Crystalloids versus Colloids: Which One Is Safe? *Erin Nicole Frazee, Pharm.D.* Assistant Program Director, PGY2 Critical Care Residency Program, Mayo Clinic, Rochester, Minnesota
10:15 a.m.	When Is Factor VIIa Off-label Use Worth the Risk and Cost? *Emily M. Hutchison, Pharm.D., BCPS* Clinical Specialist, Trauma/Surgery Critical Care, Methodist Hospital, Clarian Health, Indianapolis, Indiana

10:30 a.m.	Male Testosterone Deficiency—Should This Be Treated? *Michael P. Kane, Pharm.D., FCCP, BCPS, BCACP* Professor, Albany College of Pharmacy and Health Sciences, Albany, New York

Faculty Conflict of Interest Disclosures

Kristen Bova Campbell: no conflicts to disclose.
Mitchell S. Buckley: no conflicts to disclose.
Erin Nicole Frazee: no conflicts to disclose.
Emily M. Hutchison: no conflicts to disclose.
Michael P. Kane: no conflicts to disclose.
Zachariah Thomas: no conflicts to disclose.

Learning Objectives

1. Interpret the current evidence for using colchicine in treating atrial fibrillation.
2. Examine the effect of colchicine in acute coronary syndromes.
3. Review the clinical data on intrapleural fibrinolytic therapy.
4. Compare and contrast clinical outcomes with combination t-PA and dornase alpha to monotherapy.
5. Recommend an evidence-based strategy for intrapleural therapy.
6. Explain the rationale behind using statins in septic patients.
7. Analyze recent literature on the use of statins in septic patients.
8. Provide recommendations for the use of statins in septic patients.
9. Assess the recent literature on crystalloids and colloids for resuscitation and effects on mortality.
10. Manage the adverse effects associated with crystalloids and colloids.
11. Identify measurable resuscitation targets for effectiveness.
12. Interpret the clinical evidence for off-label use with Factor VIIa.
13. Provide a risk-benefit profile of off-label use of Factor VIIa.
14. Consider the cost in the off-label use of Factor VIIa.
15. Describe male testosterone deficiency and the evidence available regarding treatment approaches.
16. Review the evidence available regarding treatment approaches.
17. Provide an algorithm for the treatment of testosterone deficiency.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am

Colchicine for the Heart

Kristen Bova Campbell, Pharm.D., CPP, BCPS (AQ-C)
Clinical Pharmacist, Electrophysiology
Duke University Hospital

Objectives

- Interpret the current evidence for using colchicine in treating atrial fibrillation
- Examine the effect of colchicine in acute coronary syndromes

Disclosures

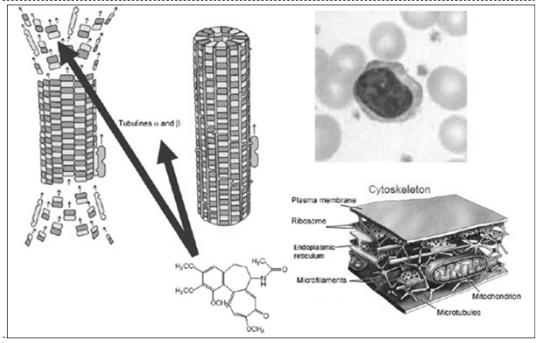
- I have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

Colchicine Crash Course

- Pharmacokinetics
  - Rapidly absorbed from GI tract
    - Peak 0.5 – 2 hrs
  - Distribution
    - Leukocytes, kidneys, liver, spleen, intestines
  - Half-life
    - 20 min in plasma; 60 hrs in leukocytes
  - Metabolism
    - Primarily hepatic (CYP3A4)
    - 10-20% excreted unchanged in urine
  - Cost
    - $164 / 30 tablets Colcrys

J Am Coll Cardiol 2013;62:1817. Circulation. 2011;124:2290

Anti-Inflammatory Mechanism



Eur Heart J (2009) 30 (5): 532-539.

Colchicine: Beyond Gout

- Multiple studies investigating treatment of recurrent pericarditis
  - Dose: 0.5-0.6 mg PO twice daily
- Evidence Summary

Study	Year	Design	Pts	Dose	Adjunct?	Follow-Up (mo)	Recurrence Rate
Imazio et al.	2005	NR	35	1.0	Yes	48-108	3/35 (8.6%)
COPE	2005	R	120	0.5-1.0	Yes	18	7/60 (11%)
CORE	2005	R	84	0.5-1.0	Yes	8-44	9/42 (21.0%)
CORP	2011	R	120	0.5-1.0	Yes	18	15/60 (24%)
ICAP	2013	R	240	0.5-1.0	Yes	18	20/120 (16.7%)

NR = not randomized; R = randomized

J Am Coll Cardiol 2013;62:1817

Atrial Fibrillation

- Post-Operative Atrial Fibrillation (POAF)
  - 10 – 65% of all cardiac surgery patients
  - Increased morbidity and length of stay
- Post Pulmonary Vein Isolation
  - Immediate (within 3 days): 25%
  - Early: 15-20%

J Am Coll Cardiol 2013;62:1817. Am J Cardiol 2009;103:1249

Colchicine: Post-Op Atrial Fibrillation

- Evidence Summary

Study	Year	Design	Pts	Dose	Endpoint	Recurrence Rate (%)
COPPS	2011	R, DB	336	0.5-1.0	Rate of POAF	12 vs. 22
COPPS-2	2014	R, DB	360	0.5-1.0	Rate of POAF (2°)	34 vs. 42

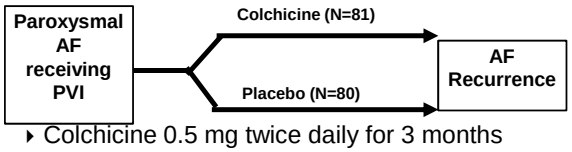
NR = not randomized; R = randomized

Circulation 2011;124:2290. JAMA 2014, online release 8/29/14

Pulmonary Vein Isolation

Colchicine: Post Ablation

- Randomized, double-blind trial



- Colchicine 0.5 mg twice daily for 3 months
- AF Recurrence:
  - 33.5% vs. 16%, NNT 5.6
- Decrease in inflammatory markers (CRP and IL-6)

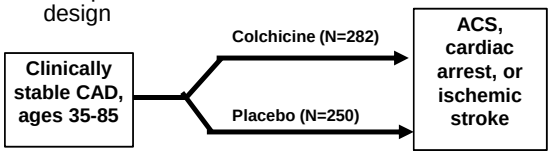
J Am Coll Cardiol 2012;60:1790

ACS

- Inflammation during plaque formation and after rupture

LoDoCo Trial

- Prospective, randomized, observer-blinded design



- Colchicine 0.5 mg daily (plus standard treatment)
- Median follow up: 3 years
- Outcome: 5.3% vs. 16%, NNT 11
  - Largely driven by reduction in ACS

J Am Coll Cardiol 2013;61:404

Other Considerations

- Side effects
  - Gastrointestinal (often severe enough to cause discontinuation)
  - Rare: liver failure, bone marrow depression, rhabdomyolysis)
- DDI
  - CYP3A4 Substrate
    - Metabolism affected by inducers or inhibitors
    - Diltiazem/Verapamil
    - Azole antifungals
    - Amiodarone
    - Etc

Conclusions

- Colchicine has potent anti-inflammatory actions
- Benefit has been seen in prevention of pericarditis, post-operative atrial fibrillation, and secondary ACS
- Further data is needed to confirm the role of colchicine in cardiovascular disease

Combination t-PA and Dornase alpha Therapy for Pleural Infection

Mitchell Buckley, Pharm.D., FASHP, FCCM, FCCP, BCPS

Clinical Pharmacy Specialist
Banner Good Samaritan Medical Center
Phoenix, AZ

October 13, 2014

Disclosures

- Dr. Buckley has no financial disclosures to report

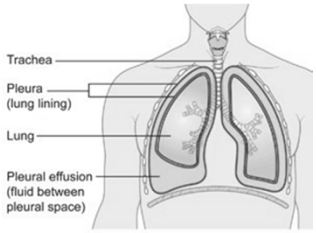
2

Objectives

- Review the clinical data on intrapleural fibrinolytic therapy
- Compare and contrast clinical outcomes with combination t-PA and dornase alpha to monotherapy
- Recommend an evidence-based strategy for intrapleural therapy

3

Pleural Effusion



Etiology
- Heart failure
- Pneumonia
- Tuberculosis
- Pulmonary embolism
- Liver disease
- Kidney disease
- Autoimmune disorders
- Cancer

4

Pleural Fluid Analysis

Characteristic	Uncomplicated Parapneumonic effusion	Exudate: Complicated Parapneumonic Effusion	Exudate: Empyema
Appearance	Clear	Cloudy	Pus
Biochemistry Values			
pH	≥7.3	<7.2	N/A
Glucose, mg/dL	>60	<40	N/A
Pleural Fluid: Serum Glucose Ratio	>0.5	<0.5	N/A
LDH, IU/L	<700	>1000	N/A
PMN count, cell/mL	<15,000	>25,000	N/A
Microbiology Results	Negative	Negative/Positive	Negative/Positive

Sahn SA. Clin Infect Dis 2007;45:1480-6

5

Management Strategies

Medical
- Antibiotics
- Thoracentesis
- Tube thoracostomy
- Suction drainage
- Intrapleural fibrinolytics
- Medical thoracoscopy

Surgical
- Video-assisted thoracoscopic surgery (VATS)
- Thoracotomy
- Open drainage

6

Thrombolytic Use in PPE / Empyema

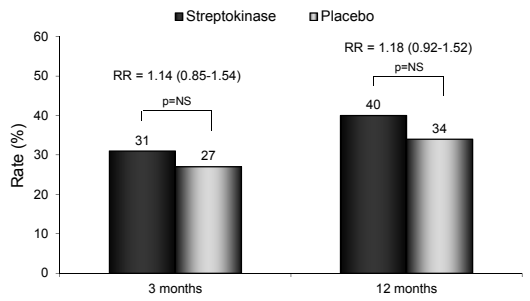
MIST1 Trial

- Objective
  - Evaluate the impact of fibrinolytics on mortality and requiring surgical drainage in patients with parapneumonic effusion / empyema
- Study design
  - Multicenter, randomized, double-blind, placebo-controlled
- Study population
  - n=454
  - Any cause of pleural infection (pleural effusion with positive bacterial cultures, pus, or biochemical features)
  - Chest tube drainage and antibiotics
- Intervention
  - Streptokinase 250,000 units (30mL NS) with 1 hour clamping q12h via chest tube x 6 doses

Maskell NA. NEJM 2005;352:865-74

8

Combined Death and Surgical Referral Rates



Maskell NA. NEJM 2005;352:865-74

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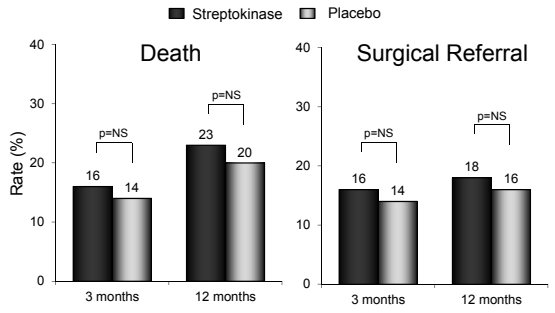
Death and Surgical Referral Rates



Maskell NA. NEJM 2005;352:865-74

10

Secondary Endpoints

Variable	Streptokinase	Placebo	P value
Median (IQR) duration of hospitalization (days)	13 (1 – 271)	12 (2-152)	0.16
Residual pleural thickening at lateral chest wall (mm)	12 ± 14	15 ± 19	0.20
Vertical height of thorax on infected side (mm)	209 ± 30	221 ± 33	0.003

Maskell NA. NEJM 2005;352:865-74

11

MIST2 Trial

- Objective
  - Evaluate the impact of thrombolytics/DNase on chest radiographic improvement
- Study design
  - Multicenter, randomized, double-blind, double-dummy
- Study population
  - n=210
  - Positive bacterial cultures or clinical features of pleural infection
- Intervention (via chest tube w/ 1 hour clamping q12h x 3 days)
  1) t-PA 10mg + dornase 5mg
  2) t-PA 10mg
  3) Dornase 5mg
  4) Placebo

Rahman NM. N Engl J Med 2011;365:518-26

12

Primary & Secondary Outcomes

Outcome	t-PA	DNase	t-PA–DNase	Placebo
Change from baseline in hemithorax area occupied by effusion (primary outcome) — %	−17.2±24.3	−14.7±16.3	−29.5±23.3	−17.2±19.6
Percent difference vs. placebo (95% CI)	2.0 (−4.6 to 8.6)	4.5 (−1.5 to 10.5)	−7.9 (−13.4 to −2.4)	NA
P value	0.55	0.14	0.005	NA
Surgical referral — no. referred/total no. (%)	3/48 (6)	18/46 (39)	2/48 (4)	8/51 (16)
Odds ratio vs. placebo (95% CI)	0.29 (0.07 to 1.25)	3.56 (1.30 to 9.75)	0.17 (0.03 to 0.87)	NA
P value	0.10	0.01	0.03	NA
Hospital stay — no. of days	16.5±22.8	28.2±61.4	11.8±9.4	24.8±56.1
Percent difference vs. placebo (95% CI)	−8.6 (−40.8 to 3.3)	3.6 (−19.0 to 30.8)	−14.8 (−53.7 to −4.6)	NA
P value	0.21	0.73	<0.001	NA

Rahman NM. N Engl J Med 2011;365:518-26

13

Guidelines

- American College of Chest Physicians (2000)
  - Tube thoracotomy and therapeutic thoracentesis not recommended
  - Thrombolytics, VATS, or surgery recommended for adequate pleural fluid drainage
- British Thoracic Society (2010)
  - No specifics recommendations on role or timing of thrombolytics

Colice GL. Chest 2000;18:1158-1171
Davies HE. Thorax 2010;65(Suppl 2):ii41-ii53

14

Conclusions

- Most simple parapneumonic effusions resolve after adequate antibiotics
- Intrapleural thrombolytics alone are NOT recommended
- Patients with persistent complicated PPE / empyema may benefit from concomitant intrapleural t-PA / dornase alpha
- Role as salvage therapy in non-surgical candidates or considered high-risk for surgical complications

15

Questions

16

Should I Start This Septic Patient on a Statin?

Zachariah Thomas, PharmD, BCPS
Rutgers, the State University of New Jersey
Hackensack University Medical Center
Email: zthomas@rci.rutgers.edu

No disclosures

Objectives

- Explain the rational behind using statins in septic patients
- Analyze recent literature on the use of statins in septic patients
- Provide recommendations for the use of statins in septic patients

Statins in Sepsis: Possible Mechanisms

- Reduced leukocyte migration and recruitment
- Reduced inflammatory response
  - IL-6, IL-8, TNF-α, MCP–1, CRP
- Anticoagulant properties
  - Decreased: platelet aggregation, tissue factor, conversion of prothrombin to thrombin
  - Enhanced fibrinolysis
- Direct antibiotic and antifungal effects

Gao F, Br J Anaesth. 2008;100:288-98.
Welsh AM, Pathology. 2009;41:689-91.
Forrest G, BMC Infect Dis. 2010;10:152.

Animal Models

- Statins have been shown to improve outcomes in animal models of sepsis
  - Cecal ligation and puncture
  - Lipopolysaccharide
- Improved survival, decreased inflammation, immunomodulation

Merx MW, Circulation. 2004;109:2560-5.
Ando H, J Pharmacol Exp Ther. 2000;294:1043-6.

Statins seem to have a lot in common with steroids, EXCEPT the anti-inflammatory is delayed 7 – 14 days in humans

Ann Intensive Care. 2012;2:19.

The Highest Quality Evidence, Circa 2010

Study	Included Studies	Outcomes	OR (95% CI)
Janda et al., J Crit Care. 2010 ; 25:656.e7-22.	Total = 20 12 retrospective cohorts 6 prospective cohorts 1 matched cohort/ case control 1 RCT N= 265,558	15 (+) 1 (-) 4 (No effect)	⇩ Mortality 0.61 (0.48 - 0.73) I^2 = 77% 60% reduction in septic patients

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Björkhem-Bergman et al., PLoS One. 2010;5:e10702.	Total = 15 11 retrospective cohorts 3 prospective cohorts 1matched cohort/ case control N = 113,910	12 (+) 3 (No effect)	⇩ Mortality 0.52 (0.42–0.66)* I^2 = 60%

* After adjusting for publication bias: 0.79 (0.58–1.07)

Healthy User Bias

- Patients who adhere to a medication schedule also engage in a healthy lifestyle, which may result in better overall health
- Statin treated patients
  - See a primary care physician more often
  - Have regular mammography
  - Former smoker
  - Have insurance coverage

Dormuth CR, Circulation. 2009;119:2051-7
Beattie WS, Anesth Analg. 2010;111:261-3
Yende S, Crit Care Med. 2011;39:1871-8

Healthy User Bias

- Statin treated patients
  - Have higher socioeconomic status
  - Better baseline functional status
  - More likely to be white
  - Better dental hygiene
  - Less drug dependency
  - Fewer workplace accidents
  - Fewer falls
  - Fewer automobile accidents
  - Receive influenza and pneumococcal vaccination
  - Less likely to be admitted from a nursing home
  - Take daily aspirin

Thomsen RW, Br J Clin Pharmacol. 2005;60:534-42.
Dormuth CR, Circulation. 2009;119:2051-7.
Yende S, Crit Care Med. 2011;39:1871-8
Beattie WS, Anesth Analg. 2010;111:261-3.

A Multicenter Randomized Trial of Atorvastatin Therapy in Intensive Care Patients with Severe Sepsis

Peter Kruger[1,2,3], Michael Bailey[3], Rinaldo Bellomo[3,4], David James Cooper[3,5], Meg Harward[1], Alisa Higgins[3], Belinda Howe[3], Darryl Jones[3,4], Chris Joyce[1,6], Karam Kostner[6,7], John McNeil[3], Alistair Nichol[3], Michael S. Roberts[8,9], Gillian Syres[3], and Bala Venkatesh[1,4,10]; for the ANZ-STATInS Investigators-ANZICS Clinical Trials Group*

Am J Respir Crit Care Med. 2013;187:743-50.

ANZ-STATInS Trial (N=250)

- Multicenter, prospective, randomized, double blind, placebo controlled, **phase II**, clinical trial
- Atorvastatin 20 mg daily or placebo until day 14 (or death or discharge from ICU)
- **July 2007- August 2010**

ANZ-STATInS Trial

INCLUSION

- Critically ill
- Age 18- 90
- At 3 out 4 SIRS criteria
- Organ dysfunction of less than 24 hours

EXCLUSION

- Moribund
- Fatal disease
- Pregnant/breast feeding
- Statin intolerant
- Severe liver disease
- Recent statin start or stop
- No enteral medications

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- No enteral medications

PRIMARY ENDPOINT: CHANGES IN IL-6

Study Population

- APACHE II ~ 23
- Mechanical ventilation: ~ 60%
- Vasopressors: ~78%
- Statin PTA: 30%
- Higher age in placebo arm: 64 vs. 58
- Overall "moderate" severity

Results

- No difference in IL-6 over time
  - Lower at baseline in statin PTA group
- No difference in mortality
  - ICU, hospital, 28-day, 90-day
- No difference in length of stay
- No safety signals

Silver Lining?

- Continued atorvastatin therapy in prior statin users was associated with improved mortality: 5% vs 28%, P=0.01
- **NO difference at 90-days (P=0.1 after adjustment for age)**

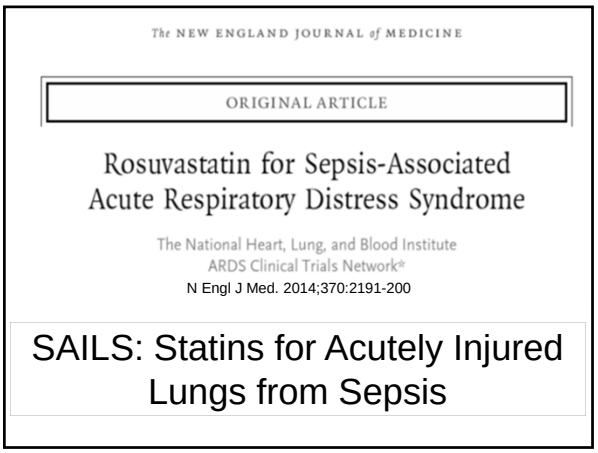
Rose Colored Conclusions

- Atorvastatin therapy in severe sepsis did not affect IL-6 levels
- "***Prior statin use was associated with a lower baseline IL-6 concentration and continuation of atorvastatin in this cohort was associated with improved survival***"

More Pragmatic Conclusions

- The play of chance
- Multiple comparisons lead to false positives
- Statistically significant findings in subgroups are always subject to be spurious **ESPECIALLY** if the primary outcome is negative
  - Apha-spending

BMJ. 2001;322:989-91.
Control Clin Trials. 1999;20:40-9.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*

N Engl J Med. 2014;370:2191-200

SAILS: Statins for Acutely Injured Lungs from Sepsis

SAILS Trial (N=745/1000)

- Multicenter, prospective, randomized, double blind, placebo controlled, phase III, clinical trial
- Rosuvastatin 40 mg load followed by 20 mg daily or placebo until day 14 (or death or discharge from ICU)
- **January 2010 – November 2013**

SAILS Trial

INCLUSION

- Mechanical ventilation
- P:F ratio < 300
- Bilateral infiltrates w/out evidence of left atrial hypertension
- Known/suspected infection
- One of the following
  - Fever/hypothermia
  - Leukocytosis /leukopenia

EXCLUSION

- ARDS > 48 hours
- Chronic conditions that would affect survival
- AST/ALT > 5x ULN
- Statin ingestion within 48-hours of randomization

SAILS Trial

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- ARDS > 48 hours
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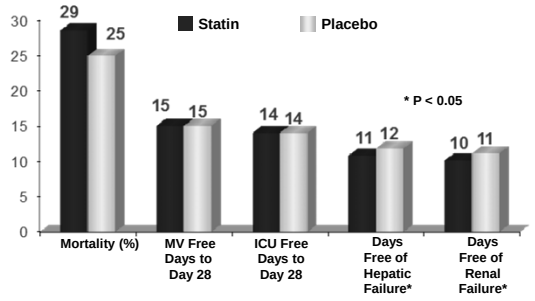
- AST/ALT > 5x ULN
- Statin ingestion within 48-hours of randomization

PRIMARY ENDPOINT: HOSPITAL/60 DAY MORTALITY

SAILS Study Population

- APACHE III ~ 93
- Mechanical ventilation: 100%
- P:F ratio: 170
- Shock: ~ 45%
- Age: 54
- Pneumonia: 70%
- Overall "moderate-severe" illness

Results – Trial Stopped Early for Futility



Patients Previously on Statins

- NO benefit
  - There were 17 deaths among 54 prior statin users who received rosuvastatin (31%) and 11 deaths among 55 prior statin users who received placebo (20%) (95% CI, −4.8 to 27.8 %, P=0.14)
  - This is consistent with a previously conducted clinical trial: PMID: 20959555

Conclusions

- No benefit in sepsis-associated ARDS and may have contributed to hepatic and renal organ dysfunction
- These data do not provide support for initiating or continuing statin therapy for the treatment of sepsis-associated ARDS
- The lack of effect of statins in pulmonary infection is consistent (PMID: 24108510)

Statins Have Been Linked to Serious Adverse Effects in Acute Illness

- Rhabdomyolysis in community acquired bacterial sepsis--a retrospective cohort study. PLoS One. 2009;4:e7182.
- Systemic infections can decrease the threshold of statin-induced muscle injury. South Med J 2006 ; 99 : 403-4.
- Rhabdomyolysis from simvastatin triggered by infection and muscle exertion. South Med J 2005; 98: 827-9
- Rhabdomyolysis triggered by CMV infection in a heart transplant patient on concomitant cyclosporine and atorvastatin therapy. J Gastroenterol Hepatol 2004 ; 19: 952-3.

Statin Prescribing Information

Lovastatin PI: Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

ZOCOR (simvastatin) Tablets
Initial U.S. Approval: 1991

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Summary

- There are no compelling indications for statins in the treatment of sepsis
- There are no compelling indications to continue PTA statins while critically ill
  - Reconciliation upon ICU discharge

Final Thoughts

We should abandon randomized controlled trials in the intensive care unit

Jean-Louis Vincent, MD, PhD, FCCM

Crit Care Med. 2010;38:S534-8

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Do the observational studies using propensity score analysis agree with randomized controlled trials in the area of sepsis?☆

J Crit Care. 2014. Epub

Final Thoughts

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J Crit Care. 2014. Epub

DISCREPANCIES BETWEEN META-ANALYSES AND SUBSEQUENT LARGE RANDOMIZED, CONTROLLED TRIALS

Jacques LeLorier, M.D., Ph.D., Geneviève Grégoire, M.D., Abdeltif Benhaddad, M.D., Julie Lapierre, M.D., and François Derderian, M.Sc.

N Engl J Med. 1997;337:536-42.

Final Thoughts

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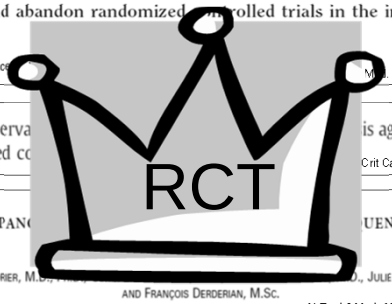
Jean-Louis Vinc… M… 2010;38:S534-8

Do the observa… is agree with randomized co… Crit Care. 2014. Epub

DISCREPAN… UENT LARGE

Jacques LeLorier, M.… D., Julie Lapierre, M.D., and François Derderian, M.Sc.

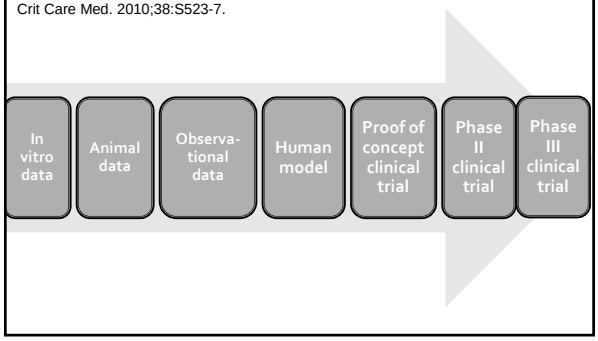
N Engl J Med. 1997;337:536-42.



A stepwise approach to justify phase III randomized clinical trials and enhance the likelihood of a positive result

Daniel F. McAuley, MD, FRCP; Cecilia O'Kane, PhD, MRCP; Mark J. D. Griffiths, PhD, MRCP

Crit Care Med. 2010;38:S523-7.



A stepwise approach to justify phase III randomized clinical trials and enhance the likelihood of a positive result

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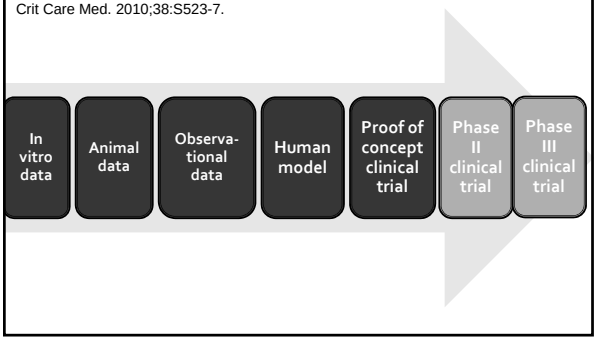

The Abstracts That Launched a Multi-million Dollar Trial?

"The study was conceived in 2004 and revised in 2009 by the ARDS Clinical Trials Network steering committee"

23 Choi H, Park M, Kang H, et al. Statin Use in Sepsis Due to Pneumonia. American Journal of Respiratory and Critical Care Medicine 2008:A580

24 Montoya C ME, Sanchez C, Poblano M, Aguirre C, Olivera J, Marinez J, Franco J. Anti-inflammatory therapy with statins for septic patients. ECICS abstract 2008

Crystalloids versus Colloids: Which one is safe?

- Fluid resuscitation is the most widespread intervention administered to critically ill patients (Myburgh, *N Engl J Med* 2013)
    - Typically broken into two groups
        - Crystalloids: Ion containing solutions whose tonicity is determined by their concentrations of sodium and chloride
            - 0.9% Sodium chloride
            - "Balanced solutions": Lactated ringers, PlasmaLyte
        - Colloids: Suspensions of relatively high molecular weight molecules in a carrier solution which, at least temporarily, remain in the intravascular space to generate oncotic pressure
            - Human albumin
            - Hydroxyethylstarch
            - Gelatin
    - For patient outcomes and adverse effects, however, it may be more advantageous to consider specific agents rather than assigning them to conceptual groups
- Albumin
    - Saline versus Albumin Fluid Evaluation study (SAFE; *N Engl J Med* 2007)
        - Design: Multicenter trial of 6997 critically ill adults, randomized in a blinded fashion to either 4% Albumin or 0.9% Sodium Chloride
        - Primary outcome: 28-day all-cause mortality not different between groups (20.9% in the albumin group; 21.1% in the saline group)
        - Subgroup analyses
            - Greater risk of mortality among patients with traumatic brain injury treated with albumin (RR 1.63; 95% CI 1.17-2.26) (*N Engl J Med* 2007)
            - Reduced adjusted risk of mortality among 1218 patients with severe sepsis treated with albumin (Adjusted OR 0.71; 95%CI 0.52-0.97) (*Intensive Care Med* 2011)
            - No difference in risk among hypoalbuminemic patients
    - Albumin Italian Outcome Sepsis Study (ALBIOS; *N Engl J Med* 2014)
        - Rationale: Septic subpopulation in SAFE showed potential benefit for albumin; other purported mechanisms by which albumin could be beneficial outside of intravascular oncotic pressure
            - Antioxidant and anti-inflammatory properties
            - Reactive oxygen and nitrogen species scavenging
            - Buffer in acid/base equilibrium
            - Carrier for endogenous and exogenous compounds
        - Design: Multicenter open label trial of 1806 adults with severe sepsis or septic shock, randomized to administration of crystalloid with 20% albumin to achieve a serum albumin of at least 3g/dL or crystalloid alone
        - Primary outcome: 28-day all-cause mortality no difference (Albumin-inclusive resuscitation: 31.8%, Crystalloid-alone resuscitation: 32%)
        - Subgroup analysis
            - Patients with septic shock: RR for 28-day all cause mortality 0.87 (95% CI 0.77-0.99)

    - Primary messages: Noninferiority of the albumin containing resuscitation relative to crystalloid, “normal” serum albumin should not be used as a resuscitation target; possible subpopulations with unique outcomes (TBI, septic shock); primary driving factors for use remain clinician preference and cost
- Hydroxyethylstarch: Semisynthetic colloid which comes from manipulation of sorghum, maize, or potatoes; Cross-sectional analysis of resuscitation fluids internationally showed hydroxyethylstarch to be the most frequently used colloid as of 2010 (*Crit Care* 2010)
    - Concerns have arisen about the adverse effects of starches
        - Alterations in coagulation parameters, and accumulation in reticuloendothelial tissues which may precipitate pruritis, liver injury, acute kidney injury (AKI)
        - Recent studies test starch solutions with reduced concentrations, lower molecular weight, and reduced molar substitution which has improved the safety profile
        - Total day limits may also reduce the risk for these adverse effects
    - Crystalloid versus hydroxyethylstarch trial (CHEST; *N Engl J Med* 2012)
        - Design: Multicenter, randomized, blinded trial in 6742 mixed medical/surgical ICU patients requiring volume resuscitation
        - Primary outcome 90-day all-cause mortality no difference [18% HES, 17% normal saline; RR 1.06 (95% CI 0.96-1.18)]
        - Safety considerations
            - AKI occurred more commonly in saline versus HES (RIFLE-I 34.6% HES vs 38% Placebo; P = 0.005)
            - Use of renal replacement therapy higher in the HES group (HES 7% vs normal saline 5.8%; P = 0.04), although not a clearly outlined protocol for use
            - Other adverse events (e.g. pruritis, skin rash) more come in the starch group (HES 5.3% vs Saline 2.8%; P < 0.001)
    - Scandinavian Starch for Severe Sepsis and Septic Shock trial (6S; *N Engl J Med* 2012)
        - Design: Multicenter, randomized, blinded trial of 798 patients with severe sepsis or septic shock who were given either 6% HES 130/0.42 or lactated ringers
        - Primary outcome: Composite of death or dependence on dialysis at 90 days was significantly more common in the HES group (51%) versus the lactated ringers group (43%; RR 1.17, 95% CI 1.01-1.36; P = 0.03; endpoint driven almost exclusively by death, not dialysis)
        - Secondary endpoints for safety: Use of renal replacement therapy was more common in the starch patients (22% HES vs 16% lactated ringers; P = 0.04) although it was a nonprotocolized intervention
    - CRISTAL (*JAMA* 2013)
        - Design: Multicenter, randomized, open label trial of 2857 critically ill patients needing fluid resuscitation for sepsis or hypovolemia primarily; patients were randomized to crystalloids or colloids, but the type and amount of fluid administered was per provider discretion

                - Primary fluids used in 60-70% of patients were normal saline and hydroxyethylstarch
            - Primary outcome: 28-day all cause mortality no difference (25.4% colloid, 27% crystalloid)
                - At 90-days, mortality was lower in the colloid group (30.7% vs 34.2%)
            - Safety endpoints: No difference in RRT
    - Primary messages: In high quality trials, starches have shown no benefit on all-cause mortality relative to crystalloid for resuscitation in all-comers, and in septic patients mortality may be higher with HES use; recent advances to use low molar, low molecular weight, low concentration solutions has reduced many of the adverse effects, but AKI and need for RRT is still more common with these agents than crystalloids and therefore there isn't a clear place in therapy for their routine use
- Chloride-containing IV fluids
    - Supraphysiologic concentrations of chloride in exogenously administered solutions may result in metabolic acidosis as well as renal vasoconstriction and a reduced GFR
    - Chloride concentrations: 4% albumin 120 mmol/L, 6% HES 130/0.4 110-154 mmol/L, 0.9% sodium chloride 154 mmol/L, lactated ringers 111 mmol/L, PlasmaLyte 98 mmol/L
    - Yunos, et al (*JAMA* 2012)
        - Design: Prospective, single center, sequential study wherein a chloride liberal strategy was changed in the ICU to a chloride restrictive strategy; essentially it was a shift from stocking/using normal saline in the ICU to stocking/using lactated ringers
        - Results: Reduced incidence of both AKI and renal replacement therapy in the chloride-restrictive strategy
    - McCluskey, et al (*Anesth Analg* 2013)
        - Design: 5-year large retrospective cohort study at a single center which used propensity matching to evaluate clinical outcomes between patients with acute postoperative hyperchloremia and those without
        - Results: Association with higher mortality, longer length of stay, and more frequent renal dysfunction in the hyperchloremic group
- Take home points
    - Well designed studies of resuscitation for critically ill patients, show no difference in mortality between albumin and crystalloid solutions
    - Starches do not provide a mortality benefit for resuscitation in critically ill patients relative to crystalloid and may be associated with worse renal adverse effects
    - "Balanced solute solutions" with an attention to the chloride content of products is key when considering the evidence and the future crystalloid of choice

Indiana University Health

When is Factor VIIa Off Label Use Worth the Risk and Cost?

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IU Health Methodist Hospital
October 13, 2014

1

Conflict of Interest Disclosures

- Nothing to disclose

2

Learning Objectives

- Interpret the clinical evidence for off-label use with Factor VIIa
- Provide a risk-benefit profile of off-label use of Factor VIIa
- Consider cost in the off-label use of Factor VIIa

3

Use of Factor VIIa

- Frequency of off label use
- Common off label uses:
  - Cardiovascular (CV) Surgery
  - Intracerebral hemorrhage (ICH)
  - Trauma
- Safety concerns

Yank. Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. 290-02-0017. Rockville, MD: Agency for Healthcare Research and Quality. May 2010.
Zatta. *Blood Transfus* DOI 10.2450/2014.0260-13.Access Aug 2014.
Levi. *New Engl J Med* 2010;363(19):1791-800.

4

Factor VIIa Use in CV Surgery

Study, Methods	N (FVIIa, UC) Dose	Key Findings	Adverse Events
Diprose 2005, A	19 (9, 10) 90 mcg/kg (prophylactic)	↓ transfusions, ↓INR	1 MI and 1 stroke
Gill 2009, A	172 (104,68) 40 mcg/kg (n=35) 80 mcg/kg (n=69)	↓ transfusions, ↓ in re-operations	1 MI in usual care group
Romagnoli 2006, B	30 (15, 15) 1.2 mg	↓ blood loss, transfusion requirements, and ICU stay	2 postoperative strokes
Karkouti 2005, C	102 (51, 51) 2.4 or 4.8 mg	↓ blood loss, transfusions ↑ ICU/hospital LOS	↑ renal dysfunction
Von Heymann 2005, C	48 (24, 24) 60 mcg/kg	No difference in blood loss, transfusion requirements, or 6 mo survival	No TE events
Gelsomino 2008, C	80 (40, 40) 1.2 mg	No mortality difference ↓ blood loss and transfusions	No significant difference in overall complications

UC: usual care; A: prospective double blind randomized placebo control trial; B: prospective cohort study with case matched historical control trial; C: retrospective cohort study with case matched historical control trial; MI: myocardial infarction; TE: thromboembolic

Diprose. *Br J Anaesth* 2005;95:596-602.
Gill. *Circulation* 2009;120:21-7.
Romagnoli. *Anesth Analg* 2006;102:1320-6
Karkouti. *Transfusion* 2005;45:26-34.
Von Heymann. *Crit Care Med* 2005;33:2241-6.
Gelsomino. *Eur J Cardiothorac Surg* 2008;33(1):64-71.
Warren. *Ann Thorac Surg* 2007;83:707-14.

5

Considerations for Use in CV Surgery

- No difference in mortality
- May decrease transfusion requirements
- May increase risk of arterial thromboembolic events
- Primary use as adjunct in post-operative bleeding

Diprose. *Br J Anaesth* 2005;95:596-602.
Gill. *Circulation* 2009;120:21-7.
Romagnoli. *Anesth Analg* 2006;102:1320-6
Karkouti. *Transfusion* 2005;45:26-34.
Von Heymann. *Crit Care Med* 2005;33:2241-6.
Gelsomino. *Eur J Cardiothorac Surg* 2008;33(1):64-71.
Warren. *Ann Thorac Surg* 2007;83:707-14.

6

Factor VIIa Use for Spontaneous ICH

Study, Methods	N (FVIIa, UC) Dose (mcg/kg)	Key Findings	Adverse Events
Mayer 2005, A	399 (303, 96) 40 (n=108) 80 (n=92) 160 (n=103)	Increase in volume of ICH was significantly ↑ in the placebo vs 160 mcg/kg ↓ in mortality and improved outcomes at 90 day	16 vs 0 serious arterial thromboembolic events in Factor VIIa group
Mayer 2006, A	40 (32, 8) 5 (n=8) 20 (n=8) 40 (n=8) 80 (n=8)	No significant difference in adverse events between groups	N/A
Mayer 2008, A	841 (573, 268) 20 (n=276) 80 (n=297)	No difference in mortality or mRS Increase in volume of ICH was less in 80 mcg/kg group	Significant ↑ in arterial thrombosis in 80 mcg/kg group

UC: usual care; A: prospective double blind randomized placebo control trial; mRS: modified Rankin Scale

Mayer. *New Engl J Med* 2005;352(8):777-85.
Mayer. *Neurocrit Care* 2006;4(3):206-14.
Mayer. *New Engl J Med* 2008;358:2127-37.

7

Considerations for Use in Spontaneous ICH

- No difference in mortality
- No difference in mRS or other long term outcome evaluations
- Dose-related decrease in hematoma expansion
- May increase risk of arterial thromboembolic events (esp. with doses > 40 mcg/kg)

Mayer. *New Engl J Med* 2005;352(8):777-85.
Mayer. *Neurocrit Care* 2006;4(3):206-14.
Mayer. *New Engl J Med* 2008;358:2127-37.

8

Factor VIIa Use for Trauma

Study, Methods	N (FVIIa, UC) Dose (mcg/kg)	Key Findings	Adverse Events
CONTROL trial collaborators (blunt) 2010, A	468 (221, 247) 200 mcg/kg x1; 100 mcg/kg 1 hr later; 100 mcg/kg 3 hrs later	No difference in morbidity or mortality ↓ FFP/RBC transfusions in the first 24 and 48 hrs	No significant difference reported
CONTROL trial collaborators (penetrating) 2010, A	86 (46, 40) 200 mcg/kg x1; 100 mcg/kg 1 hr later; 100 mcg/kg 3 hrs later	No difference in morbidity or mortality ↓ FFP transfusions in first 24 and 48 hrs	No significant difference reported

UC: usual care; A: prospective double blind randomized placebo control trial

Hauser. *J Trauma* 2010;69:489-500.
Rizoli. *J Trauma* 2006;61(6):1419-25.
Dutton. *J Trauma* 2004;57(4):709-18.
Harrison. *J Trauma* 2005;59(1):150-4.
Spinella. *J Trauma* 2008;64(2):286-93.
Fox. *J Trauma* 2009;66(4 Suppl):S112-9.

9

Considerations for Use in Trauma

- Many studies exclude patients who die within 24 or 48 hrs
- No difference in mortality
- May decrease transfusions in blunt trauma
- Significant change in hemorrhagic resuscitation
- Surgical control of hemorrhage necessary
- Many studies exclude patients with pH < 7

Hauser. *J Trauma* 2010;69:489-500.
Rizoli. *J Trauma* 2006;61(6):1419-25.
Dutton. *J Trauma* 2004;57(4):709-18.
Harrison. *J Trauma* 2005;59(1):150-4.
Spinella. *J Trauma* 2008;64(2):286-93.
Fox. *J Trauma* 2009;66(4 Suppl):S112-9.

10

Effect of acidosis

- Retrospective evaluations of Factor VIIa failure
- Decrease in pH from 7.4 to 7 → reduced activity of FVIIa by over 90%

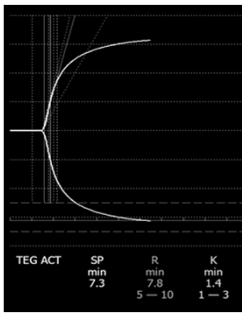
Maximize patient conditions prior to administration

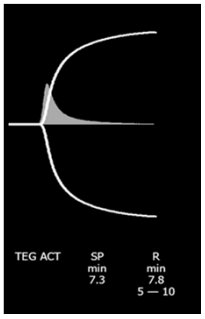
- Correct acidosis
- Replace calcium
- Correct hypothermia
- Maximize fibrinogen/platelet activity

Zatta. *Blood Transfus* DOI 10.2450/2014.0260-13. Accessed Aug 2014.
Knudson. *J Am Coll Surg* 2011;212(1):87-95.
Stein. *J of Trauma* 2005;59:609-15.
Meng. *J of Trauma* 2003;55(5):886-91.

11

Application of Viscoelastic Laboratory Tests





Tromboelastography or Rotational Thromboelastometry

12

Safety of Factor VIIa

- 26 R, PC trials (n=4119)
- 9 R, PC trials in healthy volunteers (n=349)
- Various indications and dosing

Thromboembolic Event	rFVIIa , n(%) (n=2583)	Placebo , n(%) (n=1536)	Odds Ratio (95% CI)	P Value
All	264 (10.2)	134 (8.7)	1.17 (0.94-1.47)	0.16
Arterial	141 (5.5)	49 (3.2)	1.68 (1.20-2.36)	0.003
Venous	137 (5.3)	88 (5.7)	0.93 (0.70-1.23)	0.61

Levi M. *N Engl J Med* 2010;363(19):1791-1800.

13

Cost Considerations

NovoSeven RT® AWP: $2.20/mcg

70 kg at 40 mCg/kg	• $6,160	$616,000
70 kg at 80 mCg/kg	• $12,320	$1.23 million
70 kg at 400 mCg/kg	• $61,600	$3.08 million

Total cost based on 100 CV surgery cases/yr and 50 trauma cases/yr
Thomson Reuters Micromedex Clinical Evidence Solutions [Internet]. Thomson Reuters; c2011. RED BOOK Drug References; c2011 [cited 2014 Aug 14].

14

American College of Clinical Pharmacy

Clinical Controversies: Fast and Furious
Male testosterone deficiency: should it be treated?

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Albany, NY

Conflict of Interest Disclosures

- I have no relevant conflicts of interest to report.

Learning Objectives

- Describe male testosterone deficiency and the evidence available regarding treatment approaches.
- Review the evidence available regarding treatment approaches.
- Provide an algorithm for the treatment of testosterone deficiency.

Patient Case

- Terry is an overweight 63 yo white male with a history of HTN who presents for annual physical exam. Complains of fatigue, ED, depression, and decreased ability to concentrate.
- BMI 29.8 kg/m2; BP 140/90 mmHg; TC 280 mg/dL; FPG 118 mg/dL. Total testosterone level is 235 ng/dL.
- The patient wishes to begin testosterone replacement therapy.

How Should We Proceed?

A. The patient should be worked up for hypogonadism and treated if warranted.
B. Give him what he wants; what's the harm?
C. Under no circumstances should he receive TRT; it's too dangerous!
D. Refer the patient to a specialist (e.g., urologist or endocrinologist).

Male Testosterone Deficiency

- Affects an estimated 13 million men in the U.S.
- Prevalence increases with age.
- More common in men with obesity, diabetes, AIDS.
- Average decline in T levels in aging men is 1–2% per year.
- Annual Rx's for T have increased 5-fold from 2000-2011.
- Low T in older men
  - Does it need to be treated?
  - Is it just part of the natural aging process?

Male testosterone deficiency- should it be treated?

- Background
  - Late-onset hypogonadism is associated with central obesity, insulin resistance, low HDL, low cholesterol, and high LDL, triglyceride, and fibrinogen levels.
  - T replacement therapy is associated with improved sexual function, sense of well-being, muscle strength and BMD.
  - T therapy has been in use for more than 70 years for the treatment of T deficiency.
  - Are there hidden issues?????

Wang C et al. J Androl 2009;30:1-9.
Ruige JB et al. J Clin Endocrinol Metab 2013;98:4300-10.

Male testosterone deficiency- should it be treated?

- Background
  - Multiple meta-analyses and systemic reviews previously have not identified TRT as causing CV events (though insufficient size and duration).
  - Numerous studies demonstrate increased CV events in men with T deficiency, and improvement in a variety of CV risk factors and some CV outcomes with T therapy.
  - Recently, one randomized and two epidemiologic studies have suggested an increase in CV risk in hypogonadal men receiving T replacement Rx.

Toma M et al. Circ Heart Fail 2012;5:315-21.
Isidori AM et al. Clin Endocrinol (Oxf) 2005;63:280-93.
Whitsel EA et al. Am J Med 2001;111:261-9
Calof OM et al. J Gerontol A Biol Sci Med Sci 2005;60:1451-7.
Haddad RM et al. Mayo Clin Proc 2007;82,29-39.
Fernandez-Balsells MM et al. J Clin Endocrinol Metab 2010;95:2560-75.

Male Testosterone Deficiency Signs and Symptoms

- Fatigue/Loss of vigor
- Reduced libido
- Diminished AM erections/erectile dysfunction
- Depression
- Loss of body hair/decreased shaving
- Gynecomastia
- Decreased muscle formation (lean body mass) and muscle strength/ Visceral obesity
- Decreased bone mineralization/low trauma fx's

Bhasin S et al. J Clin Endocrinol Metab 2010;95:2536-59.

Male Hypogonadism - Diagnosis

- Symptoms of androgen deficiency
- Signs of androgen deficiency
- Consistently low serum testosterone levels (< 300 ng/dL; 10.4 nmol/L); reliable assay.
  - If close to lower normal range, get free T level
  - If suspected or known abnormal SHBG levels, get free T level
- No reliable diagnostic questionnaires are available (e.g. Androgen Deficiency in Aging Males - Adam)
- Rule out secondary causes

Bhasin S et al. J Clin Endocrinol Metab 2010;95:2536-59.
Dohle GR et al. Eur Assoc Urol 2012.

The Testosterone in Older Men with Mobility Limitations (TOM) trial

- Funded by the National Institute on Aging
- Prospective, randomized, PC trial
- Age 65 years or older, limitations in mobility, community-dwelling men; total serum testosterone level of 100-350 ng/dL
- Designed to investigate whether T therapy (transdermal gel) provides greater muscular and functional benefits over placebo in an older, frail population of men.

Basaria S et al. N Engl J Med. 2010;363:109-22.

The Testosterone in Older Men with Mobility Limitations (TOM) trial

- 209 men enrolled; mean age 74 years; BMI 30 kg/m^2; mean T level of 243 ng/dL.
- Target T level of 500-1000 ng/dL.
- Study terminated early after 6 months of therapy due to an observation of increased adverse events.
- Testosterone provided muscular and functional benefits over placebo. Mean T levels 574 vs 292.
- "CV-related events" reported in 23/106 (22%) on 1% gel vs. 5/103 (5%) receiving placebo.

Basaria S et al. N Engl J Med. 2010;363:109-22.

Critique

- Patients were not symptomatically hypogonadal
- Study was not designed to investigate CV events; none of the reported events were 1º or 2º endpoints
- Majority of reported "events" were subjective or noted incidentally
- "CV-related events" included palpitations, peripheral edema, syncope, elevated BP, and PVC's noted incidentally on EKG.
- Mean T levels were mid-nl range for young men.
- As authors state, "there is a clear possibility that the results are due to chance".

The VA Study

- Retrospective national cohort study
- Male veterans who underwent coronary angiography between 2005 and 2011 and who had a total testosterone level checked.
- No T therapy prior to angiography.
- Total testosterone level <300 ng/dL.
- VA Clinical Assessment Reporting and Tracking (CART) Program utilized.
- Primary outcome: composite of all-cause mortality, MI, and ischemic stroke.

Vigen R, et al. JAMA 2013; 310:1829-36.

The VA Study - Results

- 8709 men with a total testosterone level lower than 300 ng/dL.
  - 20% with prior hx of MI; 50% had DM; >80% had hx of CAD
  - 1223 patients started T therapy after a median of 531 days; mean age 60.6 yrs; average f/u 27.5 mos
  - 7486 patients not receiving testosterone therapy; mean age 63.8 yrs
  - 1710 outcome events
    - T Group: 67 men died, 23 had MIs, and 33 had strokes.
    - Non-T Group: 681 died, 420 had MIs, and 486 had strokes.
  - 14% of the population had 7% of the events (T group)
  - Authors concluded that T use was associated with increased risk of adverse outcomes

Vigen R, et al. JAMA 2013; 310:1829-36.

Critique

- Retrospective analysis of dataset obtained for other purposes.
  - Design cannot show cause and effect relationship (Results should be regarded as hypothesis-generating rather than conclusive)
- The article has already undergone two official corrections
  - Misreporting results as absolute risk (1/15/14)
  - Exclusion errors in non-T group (4/5/14)
- Petition sent to JAMA for article retraction; cites "gross data mismanagement and contamination" that rendered the study "no longer credible."

The Finkle Study

- Observational cohort study of a health insurance database; minimum of 22 months of continuous enrollment.
- Compared the rates of acute MI within the 1st 90 days following an initial T prescription (N = 55,593) with the rates of MI for the 12 previous months.
- Rate ratio of MI post-prescription to pre-prescription was 1.36.
- Rate in men older than 65 years was 2.19.
- In men < 65 years, risk only seen in those with prior history of heart disease.

Finkle WD et al. PLOS ONE 2014;9:e85805.

Critique

- Available information was limited to diagnosis and procedure codes, and prescriptions.
- No information regarding CV risk factors (obesity, BP, smoking history) or blood tests (T or lipid levels).
- Methodologically, is inappropriate to compare post-treatment rates of MI to pre-treatment rates, as these rates measure different things.
- Was the increased risk due to T therapy or a new diagnosis of hypogonadism (the condition of T deficiency).
- Absence of a control group.
- Inclusion of nonfatal MIs only.

Medicare Study

- Sought to assess the influence of treatment with IM testosterone therapy on myocardial infarction in a population of older male Medicare beneficiaries
- Retrospective Cohort study; compared 6355 Medicare beneficiaries 66 years or older treated with testosterone with a matched comparison cohort of 19,065 who were not.
- Therapy administered between January 1997 and December 2005.

Baillargeon J et al. Ann Pharmacother. 2014;48:1138-44.

Medicare Study - Results

- Use of intramuscular testosterone therapy was not associated with an increased risk of MI.
- A dose-response analysis demonstrated no increased risk in MI according to estimated cumulative dose of testosterone.
- T use was associated with a possible protective effect: a reduced risk of heart attack in patients with the highest prognostic risk index for MI (HR, 0.69; 95% CI, 0.53 – 0.92).

Baillargeon J et al. Ann Pharmacother. 2014;48:1138-44.

Critique

- Retrospective study design prevents proof of a direct cause and effect relationship (undetected selection bias).
- Addresses parenteral T therapy only.
- Claims data do not capture medications purchased outside the plan.
- Information on baseline T levels were not available (low T and CV risk).

Baillargeon J et al. Ann Pharmacother. 2014;48:1138-44.

- The US Food and Drug Administration announced Jan 31, 2014 it is officially investigating the potential that FDA-approved testosterone products increase the risk of serious adverse cardiovascular outcomes. [Food and Drug Administration. FDA Drug Safety Communications: FDA evaluating risk of stroke, heart attack, and death with FDA-approved testosterone products. January 31, 2014.]

Patient Case

- Terry is an overweight 63 yo white male with a history of HTN who presents for annual physical exam. Complains of fatigue, ED, depression, and decreased ability to concentrate.
- BMI 29.8 kg/m2; BP 140/90 mmHg; TC 280 mg/dL; FPG 118 mg/dL. Total testosterone level is 235 ng/dL.
- The patient wishes to begin testosterone replacement therapy.

Management

- Verify low T level (AM)
- Treat CV risk factors (HTN, pre-diabetes, cholesterol).
- Lose weight
- Consider stress test
- Check TFT's, FSH/LH, prolactin, all meds
- Consider DXA
- R/O contraindications of T therapy

Contraindications to Testosterone

- Prostate Cancer
- Male breast cancer
- PSA > 4 ng/mL
- Severe sleep apnea
- Male infertility
- Hematocrit > 50%
- Symptomatic benign prostatic hyperplasia (AUA/IPSS > 19)
- Class III or IV heart failure

Management

- Start at low testosterone replacement dose and titrate to mid-normal T range (500-700 ng/dL).
- Product selection is based on patient/prescriber preferences and insurance coverage.
- F/U in three months: symptoms, T level, LFT's, CBC, PSA, prostate exam

Conclusions

- There is little scientific basis for the suggestion that T therapy increases CV risk.
- T therapy has not unequivocally been proven to decrease CV risk.
- Large, long-term prospective randomized controlled trials of T therapy are necessary to determine the risk benefit ratio of TRT.
- Only symptomatic men with low T levels and without contraindication to therapy warrant consideration of TRT.

Helpful Resources

- Bhasin S et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536-59.
- Dohle GR et al. Guidelines on Male Hypogonadism. Eur Assoc Urol 2012:1-27.
- Wang C et al. Investigation, treatment and monitoring of late-onset hypogonadism in males; ISA, ISSAM, EAU, EAA and ASA recommendations. J Androl 2009;30:1-9.
- www.aace.com
- www.hormone.org

Questions?

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Increase in T replacement treatment

- Increases in direct-to-consumer marketing
- Expansion of clinics specializing in the treatment of low testosterone
- Development of new drugs and improved delivery mechanisms particularly dermal gels
- Greater diagnostic awareness of primary and secondary hypogonadism

Treatment goals

- Maintain secondary sex characteristics.
- Improve sexual function.
- Improve sense of well-being (energy, concentration, mood).
- Improve bone mineral density (BMD).
- Normalize serum T levels (low end of normal range for age).

T Adverse effects

- Edema (especially if underlying cardiac, renal, or hepatic disease)
- Acne
- Gynecomastia (aromatization of T to estradiol)
- Polycythemia (more likely with injections)
- Dyslipidemia
- Worsened sleep apnea
- Increased BP
- Hair loss/balding (increased production of DHT from T)
- Infertility (high doses decrease spermatogen)

Biologic Plausibility of CV Protection

- Decrease fat mass
- Increase insulin sensitivity
- Improve lipid profile
- testosterone may possess anti-inflammatory and anticoagulant properties that may reduce carotid intima media thickness
- Reduces peripheral vascular resistance

Biologic Plausibility of CV Events

- Exogenous testosterone is associated with physiologic changes:
  - Predispose to clotting and thrombotic disorders
  - Increased blood pressure
  - Polycythemia
  - Reductions in HDL cholesterol
  - Hyperviscosity of the blood and platelet aggregation
  - Testosterone therapy increases circulating estrogen levels