Top 4 Papers

Amy E. Lodolce, PharmD, BCPS
Assistant Director - UIC Drug Information Group

I have no actual or potential conflicts of interest in relation to this program.

Learning Objectives

- Discuss the key findings of the papers presented
- Critically evaluate the papers by identifying strengths and weaknesses
- Calculate the NNT or NNH if applicable
- Explain the clinical implications of each paper

Outline

- Pertinent background
- Study objective/hypothesis
- Methods
- Results
- Critique/clinical implications

Polling Question

Prior to reviewing the material for this presentation, had you heard/read anything about the 4 studies being presented?

A. Yes
B. No

Polling Questions

- Does your institution have a protocol for managing glucose in the ICU?
- If so, has it been revised within the last 6 to 7 months?

NICE-SUGAR

- Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation
- Why does hyperglycemia occur in the ICU?
  - stress hormone release
  - decreased activity
  - TPN, steroids
- What are the consequences?
  - decreased immune function
  - impaired wound healing
  - procoagulant state

N Engl J Med. 2009;360(13):1283-1297
N Engl J Med. 2006;355(18):1903-1911

NICE-SUGAR

	Van den Berghe 2001	Van den Berghe 2006
Patients	SICU	MICU
Target BG (mg/dL)	Strict: 80 to 110 Conventional: 180 to 200	
Results (mortality & morbidity)	⇩	Benefit for morbidity/not mortality

N Engl J Med. 2001;345(19):1359-1367
N Engl J Med. 2006;354(5):449-461

NICE-SUGAR

- Hypothesis: intensive glucose control will reduce mortality at 90 days
- Methods
  - randomized controlled trial, multicenter, open-label
  - 6104 medical and surgical ICU patients, expected to stay ≥3 days
  - stratified based on type of admission

N Engl J Med. 2009;360(13):1283-1297

NICE-SUGAR

- Intervention: IV insulin infusion
  - conventional: ≤180 mg/dL
  - intensive: 81 to 108 mg/dL
  - algorithm-guided treatment (https://studies.thegeorgeinstitute.org/nice/)
  - nutrition at discretion of treating clinician

N Engl J Med. 2009;360(13):1283-1297

NICE-SUGAR

- 1º endpoint: death from any cause within 90 days
- 2º endpoints (examples):
  - duration of mechanical ventilation
  - LOS (ICU & hospital)
  - cause-specific death
- Safety: BG ≤40 mg/dL

N Engl J Med. 2009;360(13):1283-1297

NICE-SUGAR

Main Results

	Conventional	Intensive
1º (death at 90 days)	24.9%	27.5% [OR 1.14 (95% CI 1.02 to 1.28) p=0.02]
Hypoglycemia (severe)	0.5%	6.8% [OR 14.7 (95% CI 9 to 25.9) p<0.001]

N Engl J Med. 2009;360(13):1283-1297

NICE-SUGAR

- What is the number-needed-to-harm (NNH) for intensive control?

The number of patients who would have to be treated with a specific intervention in order for 1 patient to have an unfavorable outcome

Equation: 1/ARR

Pharmacist's Letter. 2005;21:210610

NICE-SUGAR

- Absolute risk reduction: 27.5% - 24.9%= 2.6%
- NNH: 1/.026 = 38 (round to whole number)

For every 38 patients treated to intensive glucose control, 1 patient will die within 90 days

Audience Question

What is the NNH for causing an episode of severe hypoglycemia?

A. 15.8
B. 0.158
C. 15
D. Cannot calculate based on data in the paper.

NICE-SUGAR

Critical evaluation

- Strengths
  - large, well-designed study
  - multicenter (differs from Van den Berghe)
  - appropriate patient population
  - consistent use of insulin protocol (detailed)
  - clinically important endpoints

N Engl J Med. 2009;360(13):1283-1297
N Engl J Med. 2009;360(13):1346-1349

NICE-SUGAR

Critical evaluation

- Limitations
  - open-label?
  - method of determining conventional BG range
  - subjective inclusion criteria (3 day)
  - baseline difference in steroid use

N Engl J Med. 2009;360(13):1283-1297
N Engl J Med. 2009;360(13):1346-1349

Audience Question

What is the ideal target range for BG in critically ill patients?

A. 140 to 180 mg/dL
B. 80 to 110 mg/dL
C. 81 to 108 mg/dL
D. Anyone's guess

Clopidogrel + PPIs

- Proton pump inhibitors (PPIs) often prescribed for gastroprotection in patients receiving antiplatelet therapy
- Reports surfacing about a potential drug-drug interaction between PPIs and clopidogrel

Circulation. 2008;118(18):1894-1909
U.S. Food and Drug Administration Early Communication

Clopidogrel + PPIs

- Objective: assess outcomes in patients taking clopidogrel with or without a PPI
- Methods
  - retrospective cohort study (VA data)
  - 8205 patients following discharge for acute coronary syndrome (ACS)
  - refill data to determine concurrent use

JAMA. 2009;301(9):937-944

Clopidogrel + PPIs

- 1º outcome: all-cause mortality or rehospitalization for ACS (combined)
- 2º outcomes:
  - incidence of each 1º outcome
  - revascularization procedures

JAMA. 2009;301(9):937-944

Clopidogrel + PPIs

- Results
  - 5244 (63.9%) of 8205 had PPI Rx at discharge, follow-up, or both vs. 2961 (36.1%) who did not
  - omeprazole (59.7%) was most frequently used PPI followed by rabeprazole (2.9%)
  - nearly 40% had more than 1 type of PPI

JAMA. 2009;301(9):937-944

Clopidogrel + PPIs

- Results
  - 1561 (29.8%) of 5244 patients receiving PPIs experienced 1º outcome vs. 615 (20.8%) of 2961 of those not receiving a PPI
  - Any PPI use increased the risk of a 1º endpoint (adjusted OR 1.25, 95% CI 1.11 to 1.41)

JAMA. 2009;301(9):937-944

2º Outcomes

	Clopidogrel + PPI	Clopidogrel without PPI*
Death	19.9%	16.6%
Revascularization	15.5%	11.9%
Rehospitalization	14.6%	6.9%

p<0.001 for all outcomes

JAMA. 2009;301(9):937-944

Clopidogrel + PPIs

Critical evaluation

- Strengths
  - clinically relevant endpoints
  - various types of sensitivity analyses on the data found similar results
  - VA database

JAMA. 2009;301(9):937-944

Clopidogrel + PPIs

Critical evaluation

- Limitations
  - results largely apply to omeprazole
  - 99% male
  - genetic polymorphisms (CYP2C19)?
  - Observational design does not allow for true determination of cause-effect

JAMA. 2009;301(9):937-944

Audience Question

Which of the following is the most appropriate clinical implication of this study?

A. Concurrent use of PPIs + clopidogrel should be avoided
B. Carefully consider the need for a PPI in patients receiving clopidogrel
C. Further data from RCTs are warranted
D. The specific PPI prescribed may make a difference in terms of the potential interaction

Early vs. Deferred Antiretroviral Therapy

- HIV practice guidelines (11/3/2008)

Panel's Recommendations:
• Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 T-cell count <350 cells/mm3. The data supporting this recommendation are stronger for those with a CD4 T-cell count <200 cells/mm3 and with a history of AIDS (AI) than for those with CD4 T-cell counts between 200 and 350 cells/mm3 (AII).
• Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count:
a. Pregnant women (AI);
b. Patients with HIV-associated nephropathy (AI); and
c. Patients coinfected with HBV when treatment is indicated (BIII).

Antiretroviral therapy may be considered in some patients with CD4 T-cell counts >350 cells/mm3.

HIV Practice Guidelines - Department of Health & Human Services

Early vs. Deferred Antiretroviral Therapy

- Objective: to determine if early initiation of antiretroviral therapy is associated with improved survival
- Methods
  - observational, cohort study
  - North American AIDS Cohort Collaboration

N Engl J Med. 2009;360(18):1815-1826

Early vs. Deferred Antiretroviral Therapy

- Methods (cont.)
  - >17,000 patients with HIV (asymptomatic and antiretroviral naïve)
  - stratified according to CD4+ count prior to initiation of therapy
    - 351 to 500 cells/mm^3
    - >500 cells/mm^3
  - compared survival of those starting therapy while in the stratum vs. those who waited

N Engl J Med. 2009;360(18):1815-1826

Early vs. Deferred Antiretroviral Therapy

	CD4+ (cells/mm^3)	
	351 to 500 (n=8362)	>500 (n=9155)
Initiated therapy within 6 months	2084 (25%)	2220 (24%)
Deferred therapy	6278 (75%)	6935 (76%)

N Engl J Med. 2009;360(18):1815-1826

Early vs. Deferred Antiretroviral Therapy

Results

- Survival: 351 to 500 cells/mm^3
  - 137 deaths early-therapy vs. 238 deferred
  - RR 1.69 (95% CI 1.26 to 2.26, p<0.001)
- Survival: >500 cells/mm^3
  - 113 deaths early-therapy vs. 198 deferred
  - RR 1.94 (95% CI 1.37 to 2.79, p<0.001)
- Results in both CD4+ groups remained significant with additional analyses

N Engl J Med. 2009;360(18):1815-1826

Early vs. Deferred Antiretroviral Therapy

Critical evaluation

- Strengths
  - nature/size of the cohort
  - statistical analysis
  - clinically meaningful endpoint

N Engl J Med. 2009;360(18):1815-1826
N Engl J Med. 2009;360(18):1897-1899

Early vs. Deferred Antiretroviral Therapy

Critical evaluation

- Limitations
  - cannot prove true cause-effect
  - unable to evaluate safety of prolonged therapy
  - regimens differ from current SOC
  - incomplete cause of death information
  - a number of patients never initiated therapy

N Engl J Med. 2009;360(18):1815-1826
N Engl J Med. 2009;360(18):1897-1899

Audience Question

Which of the following is/are the most appropriate clinical implication(s) of this study?

A. The practice guidelines should be updated to recommend therapy be initiated for asymptomatic patients with CD4+ >350 cells/mm^3
B. Data from RCTs are needed to validate these findings
C. Clinicians should consider this study when discussing treatment options with individual patients
D. B & C
E. All of the above

Vitamin K vs. Placebo

- Management of supratherapeutic INRs in absence of significant bleeding

Chest guideline summary

For INRs above therapeutic range, but <5.0: lower dose ± omit a dose

INR ≥5 but <9.0: Omit 1 to 2 doses or omit a dose + give vitamin K 1 to 2.5 mg orally

Chest. 2008;133(6 suppl):160s-198s
Br J Haematol. 2008;101(2):374-387
Med J Aust. 2004;181(9):492-497

Vitamin K vs. Placebo

- Objective: to evaluate whether or not low-dose vitamin K reduces bleeding events over 90 days

- Methods
  - randomized, double-blind, placebo-controlled, multicenter
  - patients with INR of 4.5 to 10 without bleeding

Ann Intern Med. 2009;150(5):293-300

Vitamin K vs. Placebo

- Methods (cont.)
  - oral vitamin K 1.25 mg (n=355) vs. placebo (n=365)
  - warfarin held x 1 day, re-initiation by clinicians
  - 1º outcome: bleeding events during 90 days
    - major: fatal, requiring transfusion, bleed into an enclosed space, bleed requiring intervention
    - minor: does not meet above criteria
    - trivial: patient-reported/no assessment by MD

Ann Intern Med. 2009;150(5):293-300

Vitamin K vs. placebo

- Methods (cont.)
  - 2º endpoints:
    - frequency of major bleeds
    - thromboembolism
    - death during the 90 days
  - INR response

Ann Intern Med. 2009;150(5):293-300

Vitamin K vs. Placebo

Results

- 1º endpoint: 56 (15.8%) of 355 vitamin K recipients vs. 60 (16.3%) of 369 in the placebo group (-0.5% difference, 95% CI -6.1 to 5.1)
- 2º endpoints: no significant differences
- INR favors vitamin K: ⇩ 2.8 vs. 1.4 ($p<0.001$)

Ann Intern Med. 2009;150(5):293-300

Vitamin K vs. Placebo

Critical evaluation

- Strengths
  - study design
  - adequately powered
  - incorporates clinical effectiveness
  - clinically meaningful endpoints

Ann Intern Med. 2009;150(5):293-300

Vitamin K vs. Placebo

Critical evaluation

- Limitations
  - combination of bleeding events
  - not powered to detect difference in major bleeding events
  - majority of patients had INRs ≤6

Ann Intern Med. 2009;150(5):293-300
Ann Intern Med. 2009;150(12):JC6-9

Audience Question

Should we calculate the NNT for the primary endpoint?

A. Yes
B. No

Audience Question

Do the results of this study warrant a change in clinical practice?

A. Yes
B. No

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NICE-SUGAR

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Clopidogrel + PPIs

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2. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med*. 2009;360(18):1815-1826.
3. Sax PE, Baden LR. When to start antiretroviral therapy - ready when you are? *N Engl J Med*. 2009;360(18):1897-1899.

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Vitamin K vs. Placebo

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4. Crowther MA, Ageno W, Garcia D. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin. *Ann Intern Med*. 2009;150(5):293-300.
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Top 4 Papers
121-000-09-036-L01-P

Citations:

Article:
From *Annals of Internal Medicine*

http://www.annals.org/cgi/content/abstract/150/5/293

Crowther MA et.al. Oral vitamin k versus placebo to correct excessive anticoagulation in patients receiving warfarin. *Annals of Internal Medicine,* 2009,150 (5): 293-300.

Article:
From *The New England Journal of Medicine*

http://content.nejm.org/cgi/content/full/360/18/1815

Kitahata MM. et.al. Effect of early versus deffered antiretroviral therapy for HIV on survival. *The New England Journal of Medicine, 2009,* 360(18):1815-1826.

Article:
From *The New England Journal of Medicine*

http://content.nejm.org/cgi/content/full/360/13/1283?ijkey=Wv3jfbmzqEkqQ&keytype=ref&siteid=nejm

NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *The New England Journal of Medicine,* 2009, 360(13):1283-1297.

Article:
From *JAMA*

http://jama.ama-assn.org/cgi/content/full/301/9/937

Ho MP, Maddox TM, Wang L. et.al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*, 2009, 301 (9):937-944 (doi:10-.1001/jama.2009.261)

ARTICLE

Oral Vitamin K Versus Placebo to Correct Excessive Anticoagulation in Patients Receiving Warfarin

A Randomized Trial

Mark A. Crowther, MD, MSc; Walter Ageno, MD; David Garcia, MD; Luqi Wang, PhD; Dan M. Witt, PharmD; Nathan P. Clark, PharmD; Mark D. Blostein, MD; Susan R. Kahn, MD, MSc; Sara K. Vesely, PhD; Sam Schulman, MD; Michael J. Kovacs, MD; Marc A. Rodger, MD, MSc; Phillip Wells, MD, MSc; David Anderson, MD, MSc; Jeffery Ginsberg, MD; Rita Selby, MD, MSc; Sergio Siragusa, MD; Mauro Silingardi, MD; Mary Beth Dowd, PharmD; and Clive Kearon, MD, PhD

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Background: Low-dose oral vitamin K decreases the international normalized ratio (INR) in overanticoagulated patients who receive warfarin therapy. Its effects on bleeding events are uncertain.

Objective: To see whether low-dose oral vitamin K reduces bleeding events over 90 days in patients with warfarin-associated coagulopathy.

Design: Multicenter, randomized, placebo-controlled trial. Randomization was computer-generated, and participants were allocated to trial groups by using sequentially numbered study drug containers. Patients, caregivers, and those who assessed outcomes were blinded to treatment assignment.

Setting: 14 anticoagulant therapy clinics in Canada, the United States, and Italy.

Patients: Nonbleeding patients with INR values of 4.5 to 10.0.

Intervention: Oral vitamin K, 1.25 mg (355 patients randomly assigned; 347 analyzed), or matching placebo (369 patients randomly assigned; 365 analyzed).

Measurements: Bleeding events (primary outcome), thromboembolism, and death (secondary outcomes).

Results: 56 patients (15.8%) in the vitamin K group and 60 patients (16.3%) in the placebo group had at least 1 bleeding complication (absolute difference, –0.5 percentage point [95% CI, –6.1 to 5.1 percentage points]); major bleeding events occurred in 9 patients (2.5%) in the vitamin K group and 4 patients (1.1%) in the placebo group (absolute difference, 1.5 percentage points [CI, –0.8 to 3.7 percentage points]). Thromboembolism occurred in 4 patients (1.1%) in the vitamin K group and 3 patients (0.8%) in the placebo group (absolute difference, 0.3 percentage point [CI, –1.4 to 2.0 percentage points]). Other adverse effects were not assessed. The day after treatment, the INR had decreased by a mean of 1.4 in the placebo group and 2.8 in the vitamin K group ($P < 0.001$).

Limitation: Patients who were actively bleeding were not included, and warfarin dosing after enrollment was not mandated or followed.

Conclusion: Low-dose oral vitamin K did not reduce bleeding in warfarin recipients with INRs of 4.5 to 10.0.

Funding: Canadian Institutes of Health Research and Italian Ministry of Universities and Research.

Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome

P. Michael Ho, MD, PhD; Thomas M. Maddox, MD, MSc; Li Wang, MS; Stephan D. Fihn, MD, MPH; Robert L. Jesse, MD, PhD; Eric D. Peterson, MD, MPH; John S. Rumsfeld, MD, PhD

JAMA. 2009;301(9):937-944.

Context Prior mechanistic studies reported that omeprazole decreases the platelet inhibitory effects of clopidogrel, yet the clinical significance of these findings is not clear.

Objective To assess outcomes of patients taking clopidogrel with or without a proton pump inhibitor (PPI) after hospitalization for acute coronary syndrome (ACS).

Design, Setting, and Patients Retrospective cohort study of 8205 patients with ACS taking clopidogrel after discharge from 127 Veterans Affairs hospitals between October 1, 2003, and January 31, 2006. Vital status information was available for all patients through September 30, 2006.

Main Outcome Measures All-cause mortality or rehospitalization for ACS.

Results Of 8205 patients taking clopidogrel after discharge, 63.9% (n = 5244) were prescribed PPI at discharge, during follow-up, or both and 36.1% (n = 2961) were not prescribed PPI. Death or rehospitalization for ACS occurred in 20.8% (n = 615) of patients taking clopidogrel without PPI and 29.8% (n = 1561) of patients taking clopidogrel plus PPI. In multivariable analyses, use of clopidogrel plus PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel without PPI (adjusted odds ratio [AOR], 1.25; 95% confidence interval [CI], 1.11-1.41). Among patients taking clopidogrel after hospital discharge and prescribed PPI at any point during follow-up (n = 5244), periods of use of clopidogrel plus PPI (compared with periods of use of clopidogrel without PPI) were associated with a higher risk of death or rehospitalization for ACS (adjusted hazard ratio, 1.27; 95% CI, 1.10-1.46). In analyses of secondary outcomes, patients taking clopidogrel plus PPI had a higher risk of hospitalizations for recurrent ACS compared with patients taking clopidogrel without PPI (14.6% vs 6.9%; AOR, 1.86 [95% CI, 1.57-2.20]) and revascularization procedures (15.5% vs 11.9%; AOR, 1.49 [95% CI, 1.30-1.71]), but not for all-cause mortality (19.9% vs 16.6%; AOR, 0.91 [95% CI, 0.80-1.05]). The association between use of clopidogrel plus PPI and increased risk of adverse outcomes also was consistent using a nested case-control study design (AOR, 1.32; 95% CI, 1.14-1.54). In addition, use of PPI without clopidogrel was not associated with death or rehospitalization for ACS among patients not taking clopidogrel after hospital discharge (n = 6450) (AOR, 0.98; 95% CI, 0.85-1.13).

Conclusion Concomitant use of clopidogrel and PPI after hospital discharge for ACS was associated with an increased risk of adverse outcomes than use of clopidogrel without PPI, suggesting that use of PPI may be associated with attenuation of benefits of clopidogrel after ACS.

Author Affiliations: Denver VA Medical Center, Denver, Colorado (Drs Ho, Maddox, and Rumsfeld); University of Colorado Health Sciences Center, Denver (Drs Ho, Maddox, and Rumsfeld); VA Puget Sound Health Care System, Seattle, Washington (Ms Wang and Dr Fihn); VA Central Office, Washington, DC (Drs Fihn and Jesse); Richmond VA Medical Center, Richmond, Virginia (Dr Jesse); and Duke Clinical Research Institute, Durham, North Carolina (Dr Peterson).

Top 4 Papers

Amy Lodolce
121-000-09-036-L01-P

Post-test questions

1. Which of the following statements best summarizes the results of the vitamin K vs. placebo trial (*Ann Intern Med*. 2009;150:293-300)?

    a. Vitamin K is superior to placebo in reducing the incidence of bleeding complications associated with supratherapeutic INR values.
    b. There is no difference between vitamin K and placebo in terms of incidence of bleeding.
    c. There is no significant difference between vitamin K and placebo in terms of rate of decrease in INR.
    d. The incidence of major bleeding was reduced with adminstration of vitamin K.

2. What is the number-needed-to-harm (NNH) for causing an episode of severe hypoglycemia based on the NICE-SUGAR (*N Engl J Med*. 2009;360(13):1283-1297)?

    a. 15. 8
    b. 0.158
    c. 15
    d. Cannot calculate based on data in the paper

3. Which of the following is a limitation shared by the early vs. deferred antiretroviral therapy (*N Engl J Med*. 2009;360(18):1815-1826) and the clopidogrel + PPIs (*JAMA*. 2009;301(9):937-944)?

    a. Neither trial can determine cause-effect.
    b. The studies are not powered adequately to find a difference among groups.
    c. They involve small numbers of patients.
    d. The endpoints are surrogate markers.

4. Which of the following is the most appropriate clinical implication of the clopidogrel + PPIs (*JAMA*. 2009;301(9):937-944) study?

    a. Concurrent use of PPIs + clopidogrel should be avoided.
    b. Carefully consider the need for a PPI in patients receiving clopidogrel.
    c. Further data from RCTs are warranted.
    d. The specific PPI prescribed may make a difference in terms of the potential interaction.

5. True/false. Early antiretroviral therapy appears to reduce the risk of death in patients with HIV and CD4+ counts of 351 to >500 cells/mm^3.

    a. True
    b. False