# Top 4 Papers

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

## Learning Objectives

- Discuss the key findings of the papers presented
- Identify strengths and weaknesses of study design for each paper reviewed
- Explain the clinical implications of each paper

## Outline

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

## Audience Demographics

- Please select the response that best describes your status:
  A. Pharmacy Student
  B. Pharmacy Resident
  C. Pharmacist
  D. Pharmacy Technician

## 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
  C. There was material available about this session?

## Audience Question

- Does the boxed warning for rosiglitazone differ from that of pioglitazone?

  A. Yes
  B. No

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA See full prescribing information for complete boxed warning. • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.• AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)

***A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.***

Avandia [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2008.

## CV Events: Pioglitazone vs. Rosiglitazone

- Rosiglitazone controversy
- Senate report February 20, 2010
  - 2-year inquiry started after Nissen MA
  - GSK was aware of risks and failed to warn patients & FDA
  - "…any proposed head-to-head trial of rosiglitazone vs. pioglitazone would be unethical and exploitative."

United States Senate Committee on Finance: http://finance.senate.gov/press/Gpress/2010/prg022010.pdf
*N Engl J Med*. 2007;356(24):2457-2471.

## CV Events: Pioglitazone vs. Rosiglitazone

- Objective: to compare the risk of acute MI, HF, and death in patients with type 2 DM treated with pioglitazone or rosiglitazone
- Methods
  - Retrospective cohort study
  - Ontario Public Drug Benefit Program
  - >39,000 patients

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## CV Events: Pioglitazone vs. Rosiglitazone

- Inclusion criteria
  - TZD-naïve
  - 66 years of age or above
- Exclusion criteria
  - Concurrent insulin

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## CV Events: Pioglitazone vs. Rosiglitazone

- Primary outcome: composite of death from any cause, hospital visit for HF or MI
- Secondary outcomes: individual components of primary

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## CV Events: Pioglitazone vs. Rosiglitazone

- Demographic data
  - 22,785 (57.3%) rosiglitazone
  - 16,951 (42.7%) pioglitazone
  - Median follow-up ~300 days
  - ~80% of patients had DM >5 years

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## CV Events: Pioglitazone vs. Rosiglitazone

| | Events pioglitazone (n=16,951) | Events rosiglitazone (n=22,785) | Adjusted hazard ratio (95% CI) |
|---|---|---|---|
| Primary (composite) | 895 (5.3%) | 1563 (6.9%) | 0.83 (0.76 to 0.90) |
| Secondary | | | |
| HF | 461 (2.7%) | 869 (3.8%) | 0.77 (0.69 to 0.87) |
| MI | 273 (1.6%) | 425 (1.9%) | 0.95 (0.81 to 1.11) |
| Death | 377 (2.2%) | 645 (2.8%) | 0.86 (0.75 to 0.98) |

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## CV Events: Pioglitazone vs. Rosiglitazone

Conclusion

In this cohort of older patients with diabetes, pioglitazone was associated with a lower risk of HF and death compared to rosiglitazone.

Continued use of rosiglitazone may not be justified.

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## CV Events: Pioglitazone vs. Rosiglitazone

<u>Critical evaluation</u>

- Strengths
  - Large cohort
  - Robust analyses
- Limitations
  - Study design
  - Universal access to healthcare and Rx coverage
  - Age of cohort (ability to generalize results)

*BMJ*. 2009;339:doi:10.1136/bmj.b2942.

## Audience Question

Should rosiglitazone be removed from the US market based on the results of this paper?

A. Yes
B. No

## CV Events: Pioglitazone vs. Rosiglitazone

Clinical implications

- TIDE (TZD Intervention with Vitamin D Evaluation)
  - Ongoing trial (currently recruiting as of 2-18-10)
  - Test the CV effects of long-term TZD treatment
  - Ethical considerations?

ClinicalTrials.gov: TIDE
http://www.clinicaltrials.gov/ct2/show/NCT00879970?term=TIDE&rank=1

## ARBITER 6-HALTS

- Ezetimibe lacks outcome data
- ENHANCE trial
  - Spring 2008
  - Familial hypercholesterolemia
  - Simvastatin vs. simvastatin + ezetimibe
  - LDL reduced with combination, but no difference in intima-media thickness
- IMT– surrogate outcome?

*N Engl J Med*. 2008;358(14):1431-1443.

## ARBITER 6-HALTS

- Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies
- Objective: to compare the effects of niacin ER vs. ezetimibe when added to long-term statin therapy

*N Engl J Med.* 2009;361(22):2113-2122.

## ARBITER 6-HALTS

- Methods
  - Prospective, randomized, parallel-group, open-label study (evaluation blinded)
  - 2 centers
  - Comparative effectiveness
- Patients
  - 30 years and above
  - CVD or CHD risk equivalent
  - Statin monotherapy
  - LDL <100 mg/dL, HDL <50 mg/dL (men) or <55 mg/dL (women)

*N Engl J Med.* 2009;361(22):2113-2122.

## ARBITER 6-HALTS

- Intervention
  - Niacin ER 2000 mg/day (n=97), dose titrated
  - Ezetimibe 10 mg/day (n=111)

*N Engl J Med.* 2009;361(22):2113-2122.

## ARBITER 6-HALTS

- Primary endpoint: change in carotid intima-media thickness after 14 months
- Secondary:
  - change in lipid levels
  - composite (MI, revascularization, ACS admission, death due to CHD)
  - D/C study drug
  - Health-related quality of life

*N Engl J Med*. 2009;361(22):2113-2122.

## ARBITER 6-HALTS

- Demographic data (groups similar)
  - Mean age 65
  - 80% male
  - Simvastatin and atorvastatin accounted for 95% of statin use
  - Mean dose of statin 42 mg
  - Baseline LDL 82 mg/dL, HDL 42 mg/dL

*N Engl J Med*. 2009;361(22):2113-2122.

## ARBITER 6-HALTS

Results

- Trial terminated early based on efficacy CIMT at 8 & 14 months (niacin was superior)
- Primary endpoint: niacin superior in terms of CIMT reduction (p=0.003) at 14 months; ezetimibe no net changes

*N Engl J Med*. 2009;361(22):2113-2122.

## ARBITER 6-HALTS

Results – lipid parameters

| | Ezetimibe | Niacin ER | p-value |
|---|---|---|---|
| LDL (mg/dL) | -17 | -10 | 0.01 |
| HDL (mg/dL) | -2.8 | +7.5 | <0.001 |

*N Engl J Med.* 2009;361(22):2113-2122.

## ARBITER 6-HALTS

Results – secondary endpoints continued

- Adverse CV events (composite): 9 (5%) of 165 ezetimibe vs. 2 (1%) of 160 niacin ER (p=0.04)
- Discontinuation: 16 (9%) of 176 ezetimibe vs. 28 (15%) of 187 niacin ER (p=0.09)
- QOL: no difference

*N Engl J Med.* 2009;361(22):2113-2122.

## ARBITER 6-HALTS

Conclusion

Niacin ER was superior to ezetimibe in terms of reduction in CIMT and clinical CV events when added to statin therapy.

*N Engl J Med.* 2009;361(22):2113-2122.

## ARBITER 6-HALTS

Critical evaluation

- Strengths
  - Study design
  - Appropriate doses
- Limitations
  - Pre-treatment LDL of 83 mg/dL, high-risk patients
  - Early termination (only those with 14-month data included in analysis)
  - Open-label?
  - Surrogate endpoint?

*N Engl J Med*. 2009;361(22):2113-2122.
*N Engl J Med*. 2009;361(22):2178-2180.
*N Engl J Med*. 2009;361(22):2180-2183.

## Audience Question

- Does current literature suggest a role for ezetimibe as add-on therapy to statins?

A. Yes
B. No

## ARBITER 6-HALTS

- On-going trials with ezetimibe
  - IMPROVE-IT
  - SHARP

ClinicalTrials.gov: SHARP http://clinicaltrials.gov/show/NCT00125593.
ClinicalTrials.gov: IMPROVE-IT http://clinicaltrials.gov/show/NCT00202878.

## Glucose Control in the ICU

- NICE-SUGAR
  - Large, well-designed RCT
  - Increased mortality with tight control
- American Diabetes Association 2010
  - Initial target of <180 mg/dL
  - Maintain between 140 to 180 mg/dL
  - Targets <110 mg/dL NOT recommended

*N Engl J Med*. 2009;360(13):1283-1297
*Diabetes Care*. 2010;33(suppl 1):s11-s61.

## Audience Question

- Why do we need to look at a meta-analysis if there was already a well designed RCT (i.e. NICE-SUGAR)?

A. To increase power
B. To reduce bias
C. Previous literature is conflicting
D. NICE-SUGAR is definitive, no meta-analysis is needed

## Glucose Control in the ICU

- Objective: to provide an updated estimate of the effect of intensive insulin therapy on the risk of hypoglycemia and death in patients in the ICU
- Methods
  - Meta-analysis and systematic review
  - MEDLINE, EMBASE, Cochrane Central Register, manual searching
  - Variety of search terms

*CMAJ*. 2009;180(8):821-827.

## Glucose Control in the ICU

- Trial inclusion criteria
  - RCT
  - Adults in the ICU
  - Intensive therapy target BG of <150 mg/dL
  - Mortality documented
  - Published in full or as in abstract form in a journal
- Trial quality scored

*CMAJ*. 2009;180(8):821-827.

## Glucose Control in the ICU

- Primary outcome: 90-day mortality
  - Attempted to gather the data for day 90
  - Hospital mortality, 28-day mortality, ICU mortality
- Secondary outcome: hypoglycemia (BG <40 mg/dL)

*CMAJ*. 2009;180(8):821-827.

## Glucose Control in the ICU

Results

- Trial characteristics
  - 26 trials involving >13,000 critically ill adults
  - MICU (n=6), SICU (n=5), mixed (n=15)

Intensive vs. Conventional

- Primary: RR 0.93 (95% CI 0.83 to 1.04)
- Secondary: RR 6.0 (95% CI 4.5 to 8.0)

*CMAJ*. 2009;180(8):821-827.

## Glucose Control in the ICU

- Heterogeneity existed in the primary analysis
- Analyses by ICU type
  - SICU: RR 0.63 (95% CI 0.44 to 0.91)
  - MICU: RR 1.00 (95% CI 0.78 to 1.28)
  - Mixed: RR 0.99 (95% CI 0.86 to 1.12)

*CMAJ*. 2009;180(8):821-827.

## Glucose Control in the ICU

Conclusions

Intensive insulin therapy did not provide a mortality benefit and significantly increased the risk of hypoglycemia.

Intensive therapy may be beneficial in the SICU; however, this finding requires confirmation.

*CMAJ*. 2009;180(8):821-827.

## Glucose Control in the ICU

<u>Critical evaluation</u>

- Strengths
  - Search strategy
  - Inclusion/exclusion criteria
- Limitations
  - Cannot definitely prove cause/effect
  - Heterogeneity
  - Insulin infusion and glucose monitoring differed
  - Success in achieving BG control varied

*CMAJ*. 2009;180(8):821-827.
*CMAJ*. 2009;180(8):799-800.

## Audience Discussion

- What are the clinical implications of this meta-analysis, and where do we go from here?

## Acetaminophen & Vaccine Response

- Advisory Committee on Immunization Practices (ACIP)
  - Can consider acetaminophen (APAP) at the time of vaccination and q 4 to 6 hours for 48 to 72 hours for children at higher risk of seizures
  - Widespread practice to give acetaminophen prior to DT
  - Acellular pertussis improved tolerability

*MMWR Recomm Rep*. 1996;45(RR-12):1-35.
*MMWR Recomm Rep*. 2006;55(RR-15):1-48.
*Lancet*. 2009;374(9695):1305-1306.

## Acetaminophen & Vaccine Response

- Objective: to assess the effect of prophylactic APAP at vaccination on febrile reactions and vaccine response
- Methods
  - 2, randomized, controlled, open-label trials (primary series and booster)
  - 456 healthy infants (9 to 16 weeks of age) in primary series, 414 for booster phase (12 to 15 months of age)

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

- Methods (cont.) - routine vaccination
  - 10-valent *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV)
  - Hexavalent diptheria-tetanus-3-component acellular pertussis with hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b (DTPa-HBV-IPV/Hib)
  - Oral rotavirus
- Booster: as above without rotavirus

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

- Intervention
  - APAP suppositories weight-based dosing, given immediately after vaccination, and q 6 to 8 hours x 2 additional doses (additional dose at booster for those weighing at least 9 kg)
  - Placebo
  - Concurrent antipyretics allowed at MD discretion (some restrictions)

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

- Outcome measures
  - Primary: reduction in febrile reactions (100.4° F or above) on days 0 to 3
  - Secondary: immune response to vaccine (per protocol)
- Protocol amendment to stop APAP with booster doses based on immune response (complicated the booster phase results)

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

- Result: fever >103.1° F was rare (<1% to 2%)

| Series | APAP % with fever | No APAP % with fever | Difference (95% CI) |
|---|---|---|---|
| Primary | 94 (42%) of 226 | 154 (66%) of 233 | 24.5% (15.49 to 33.11) |
| Booster | 64 (36%) of 178 | 100 (58%) of 172 | 22.18% (11.78 to 32.11) |

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

- APAP effect most pronounced after 1st dose

Immune response

- 1 month after primary series: ~96% of patients had sufficient antipneumococcal antibody (robust response)
- Higher % in APAP group who failed to reach desired response

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

- Immune response (cont.)
  - Mean antibody concentration was lower in the APAP group for all 10 pneumococcal serotypes
  - APAP recipients had lower antibody concentrations to Hib, diptheria, tetanus, & pertactin (pertussis)

*Lancet*. 2009;374(9698):1339-1350.

## Acetaminophen & Vaccine Response

Conclusions

Prophylactic APAP at time of vaccination should not be routine practice due to reduced antibody response to several vaccines.

The overall effect is probably small for an individual patient based on high rate of seropositive conversion.

*Lancet*. 2009;374(9698):1339-1350.
*Lancet*. 2009;374(9698):1305-1306.

## Acetaminophen & Vaccine Response

- Critical evaluation
- Strengths
  - APAP dosing appropriate
  - Detailed randomization procedure, especially after protocol amendment
  - Questions a long standing practice
- Limitations
  - Clinical importance largely unknown
  - Conducted in the Czech Republic

*Lancet*. 2009;374(9698):1339-1350.
*Lancet*. 2009;374(9698):1305-1306.

## Audience Question

- Should the practice of giving APAP prophylactically to patients at risk for febrile seizures be stopped?

A. Yes
B. No

# References


CV Events: Pioglitazone vs. Rosiglitazone

1. Avandia [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2008.
2. United States Senate Committee on Finance. Baucus, Grassley release finance committee report on diabetes drug Avandia, express concern about FDA's role in protecting patients in ongoing Avandia Study. http://finance.senate.gov/press/Gpress/2010/prg022010.pdf. Accessed February 28, 2010.
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4. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ*. 2009;339:b2942. doi:10.1136/bmj.b2942.
5. ClinicalTrials.gov. Thiazolidinedione intervention with vitamin D evaulation (TIDE). http://www.clinicaltrials.gov/ct2/show/NCT00879970?term=TIDE&rank=1. Accessed February 28, 2010.


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ARBITER 6-HALTS

1. Kastelein JJ, Akdim F, Stroes ES. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358(14):1431-1443.
2. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009;361(22):2113-2122.
3. Blumenthal RS, Michos ED. The HALTS trial – halting atherosclerosis or halted too early? *N Engl J Med*. 2009;361(22):2178-2180.
4. Kastelein JJP, Bots ML. Statin therapy with ezetimibe or niacin in high-risk patients. *N Engl J Med*. 2009;361(22):2180-2183.
5. ClinicalTrials.gov. SHARP: study of heart and renal protection. http://clinicaltrials.gov/show/NCT00125593. Accessed February 28, 2010.
6. ClinicalTrials.gov. IMPROVE-IT: examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe/simvastatin) vs simvastatin (Study P04103AM3). http://clinicaltrials.gov/show/NCT00202878. Accessed February 28, 2010.


# References


Glucose Control in the ICU

1. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
2. American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care*. 2010;33(suppl 1):s11-s61.
3. Griesdale DEG, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009;180(8):821-827.
4. Van den Berghe G, Messotten D, Vanhorebeek I. Intensive insulin therapy in the intensive care unit. *CMAJ*. 2009;180(8):799-800.


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Acetaminophen and Vaccine Response

1. Centers for Disease Control and Prevention. Update: vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1996;45(RR-12):1-35.
2. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). *MMWR Recomm Rep*. 2006;55(RR-15):1-48.
3. Chen RT, Clark TA, Halperin SA. The yin and yang of paracetamol and paediatric immunisations. *Lancet*. 2009;374(9695):1305-1306.
4. Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009;374(9698):1339-1350.

ICHP Spring Meeting 2010
Lodolce – Top 4 Papers
121-000-10-012-L01-P

PubMed Results
Items 1 -4 of 4

1. Lancet. 2009 Oct 17;374(9698):1339-50.

**Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials.**

Prymula R, Siegrist CA, Chlibek R, Zemlickova H, Vackova M, Smetana J, Lommel P, Kaliskova E, Borys D, Schuerman L.
Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic. prymula@pmfhk.cz
Comment in:

- Lancet. 2009 Oct 17;374(9698):1305-6.

BACKGROUND: Although fever is part of the normal inflammatory process after immunisation, prophylactic antipyretic drugs are sometimes recommended to allay concerns of high fever and febrile convulsion. We assessed the effect of prophylactic administration of paracetamol at vaccination on infant febrile reaction rates and vaccine responses. METHODS: In two consecutive (primary and booster) randomised, controlled, open-label vaccination studies, 459 healthy infants were enrolled from ten centres in the Czech Republic. Infants were randomly assigned with a computer-generated randomisation list to receive three prophylactic paracetamol doses every 6-8 h in the first 24 h (n=226) or no prophylactic paracetamol (n=233) after each vaccination with a ten-valent pneumococcal non-typeable Haemophilus influenzae protein D-conjugate vaccine (PHiD-CV) co-administered with the hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenzae type b (DTPa-HBV-IPV/Hib) and oral human rotavirus vaccines. The primary objective in both studies was the reduction in febrile reactions of 38.0 degrees C or greater in the total vaccinated cohort. The second objective was assessment of immunogenicity in the according-to-protocol cohort. These studies are registered with ClinicalTrials.gov, numbers NCT00370318 and NCT00496015. FINDINGS: Fever greater than 39.5 degrees C was uncommon in both groups (after primary: one of 226 participants [<1%] in prophylactic paracetamol group vs three of 233 [1%] in no prophylactic paracetamol group; after booster: three of 178 [2%] vs two of 172 [1%]). The percentage of children with temperature of 38 degrees C or greater after at least one dose was significantly lower in the prophylactic paracetamol group (94/226 [42%] after primary vaccination and 64/178 [36%] after booster vaccination) than in the no prophylactic paracetamol group (154/233 [66%] after primary vaccination and 100/172 [58%] after booster vaccination). Antibody geometric mean concentrations (GMCs) were significantly lower in the prophylactic paracetamol group than in the no prophylactic paracetamol group after primary vaccination for all ten pneumococcal vaccine serotypes, protein D, antipolyribosyl-ribitol phosphate, antidiphtheria, antitetanus, and antipertactin. After boosting, lower antibody GMCs persisted in the prophylactic paracetamol group for antitetanus, protein D, and all pneumococcal serotypes apart

from 19F. INTERPRETATION: Although febrile reactions significantly decreased, prophylactic administration of antipyretic drugs at the time of vaccination should not be routinely recommended since antibody responses to several vaccine antigens were reduced. FUNDING: GlaxoSmithKline Biologicals (Belgium).

PMID: 19837254 [PubMed - indexed for MEDLINE]Related articles

**Publication Types:**

- Clinical Trial, Phase III
- Multicenter Study
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

**MeSH Terms:**

- Acetaminophen/administration & dosage*
- Analgesics, Non-Narcotic/administration & dosage*
- Antibody Formation/drug effects*
- Chemoprevention
- Female
- Fever/etiology
- Fever/prevention & control*
- Humans
- Infant
- Male
- Vaccination/adverse effects*

**Substances:**

- Analgesics, Non-Narcotic
- Acetaminophen

**Secondary Source ID:**

- ClinicalTrials.gov/NCT00370318
- ClinicalTrials.gov/NCT00496015

2. N Engl J Med. 2009 Nov 26;361(22):2113-22. Epub 2009 Nov 15.

**Extended-release niacin or ezetimibe and carotid intima-media thickness.**

Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M.
Cardiology Service, Walter Reed Army Medical Center, Washington, DC, USA. allen.taylor@medstar.net

Comment in:

- NEngl J Med. 2009 Nov 26;361(22):2180-3.
- NEngl J Med. 2009 Nov 26;361(22):2178-80.

BACKGROUND: Treatment added to statin monotherapy to further modify the lipid profile may include combination therapy to either raise the high-density lipoprotein (HDL) cholesterol level or further lower the low-density lipoprotein (LDL) cholesterol level. METHODS: We enrolled patients who had coronary heart disease or a coronary heart disease risk equivalent, who were receiving long-term statin therapy, and in whom an LDL cholesterol level under 100 mg per deciliter (2.6 mmol per liter) and an HDL cholesterol level under 50 mg per deciliter for men or 55 mg per deciliter for women (1.3 or 1.4 mmol per liter, respectively) had been achieved. The patients were randomly assigned to receive extended-release niacin (target dose, 2000 mg per day) or ezetimibe (10 mg per day). The primary end point was the between-group difference in the change from baseline in the mean common carotid intima-media thickness after 14 months. The trial was terminated early, on the basis of efficacy, according to a prespecified analysis conducted after 208 patients had completed the trial. RESULTS: The mean HDL cholesterol level in the niacin group increased by 18.4% over the 14-month study period, to 50 mg per deciliter ($P < 0.001$), and the mean LDL cholesterol level in the ezetimibe group decreased by 19.2%, to 66 mg per deciliter (1.7 mmol per liter) ($P < 0.001$). Niacin therapy significantly reduced LDL cholesterol and triglyceride levels; ezetimibe reduced the HDL cholesterol and triglyceride levels. As compared with ezetimibe, niacin had greater efficacy regarding the change in mean carotid intima-media thickness over 14 months ($P = 0.003$), leading to significant reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P <$ or $= 0.001$ for all comparisons). Paradoxically, greater reductions in the LDL cholesterol level in association with ezetimibe were significantly associated with an increase in the carotid intima-media thickness ($R = -0.31$, $P < 0.001$). The incidence of major cardiovascular events was lower in the niacin group than in the ezetimibe group (1% vs. 5%, $P = 0.04$ by the chi-square test). CONCLUSIONS: This comparative-effectiveness trial shows that the use of extended-release niacin causes a significant regression of carotid intima-media thickness when combined with a statin and that niacin is superior to ezetimibe. (ClinicalTrials.gov number, NCT00397657.) 2009 Massachusetts Medical Society

PMID: 19915217 [PubMed - indexed for MEDLINE]Related articles

**Publication Types:**

- Multicenter Study
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

**MeSH Terms:**

- Aged
- Anticholesteremic Agents/pharmacology
- Anticholesteremic Agents/therapeutic use*
- Azetidines/pharmacology
- Azetidines/therapeutic use*
- Carotid Arteries/drug effects*
- Carotid Arteries/pathology
- Carotid Arteries/ultrasonography
- Cholesterol, HDL/blood
- Cholesterol, LDL/blood
- Coronary Disease/drug therapy*
- Coronary Disease/pathology
- Delayed-Action Preparations
- Drug Therapy, Combination
- Female
- Humans
- Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use
- Kaplan-Meiers Estimate
- Male
- Middle Aged
- Niacin/pharmacology
- Niacin/therapeutic use*
- Risk Factors
- Single-Blind Method
- Triglycerides/blood
- Tunica Intima/drug effects
- Tunica Intima/pathology
- Tunica Media/drug effects
- Tunica Media/pathology

**Substances:**

- Anticholesteremic Agents
- Azetidines
- Cholesterol, HDL
- Cholesterol, LDL

- Delayed-Action Preparations
- Hydroxymethylglutaryl-CoA Reductase Inhibitors
- Triglycerides
- ezetimibe
- Niacin

**Secondary Source ID:**

- ClinicalTrials.gov/NCT00397657

3. CMAJ. 2009 Apr 14;180(8):821-7. Epub 2009 Mar 24.

**Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data.**

Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D.
Department of Medicine, University of British Columbia, Vancouver, Canada.

Comment in:

- Ann Intern Med. 2009 Aug 18;151(4):JC2-4, JC2-5.
- CMAJ. 2009 Apr 14;180(8):799-800.

BACKGROUND: Hyperglycemia is associated with increased mortality in critically ill patients. Randomized trials of intensive insulin therapy have reported inconsistent effects on mortality and increased rates of severe hypoglycemia. We conducted a meta-analysis to update the totality of evidence regarding the influence of intensive insulin therapy compared with conventional insulin therapy on mortality and severe hypoglycemia in the intensive care unit (ICU). METHODS: We conducted searches of electronic databases, abstracts from scientific conferences and bibliographies of relevant articles. We included published randomized controlled trials conducted in the ICU that directly compared intensive insulin therapy with conventional glucose management and that documented mortality. We included in our meta-analysis the data from the recent NICE-SUGAR (Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation) study. RESULTS: We included 26 trials involving a total of 13 567 patients in our meta-analysis. Among the 26 trials that reported mortality, the pooled relative risk (RR) of death with intensive insulin therapy compared with conventional therapy was 0.93 (95% confidence interval [CI] 0.83-1.04). Among the 14 trials that reported hypoglycemia, the pooled RR with intensive insulin therapy was 6.0 (95% CI 4.5-8.0). The ICU setting was a contributing factor, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44-0.91); patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78-1.28; mixed ICU: RR 0.99, 95% CI 0.86-1.12). The different targets of intensive insulin therapy (glucose level < or = 6.1 mmol/L v. < or = 8.3 mmol/L) did not influence either mortality or risk of hypoglycemia. INTERPRETATION: Intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients. However, this therapy may be beneficial to patients admitted to a surgical ICU.

PMCID: PMC2665940
PMID: 19318387 [PubMed - indexed for MEDLINE]Related articles Free article

**Publication Types:**

- Meta-Analysis
- Review

**MeSH Terms:**

- Cause of Death*
- Critical Illness/mortality*
- Critical Illness/therapy
- Dose-Response Relationship, Drug
- Female
- Hospital Mortality/trends
- Humans
- Hypoglycemia/chemically induced*
- Hypoglycemia/mortality*
- Insulin/administration & dosage
- Insulin/adverse effects*
- Intensive Care Units
- Male
- Maximum Tolerated Dose
- Randomized Controlled Trials as Topic
- Risk Assessment
- Risk Management
- Survival Analysis

**Substances:**

- Insulin

4. BMJ. 2009 Aug 18;339:b2942. doi: 10.1136/bmj.b2942.

**Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study.**

Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM.
Division of Clinical Pharmacology and Toxicology, Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON, Canada M4N 3M5.
dnj@ices.on.ca

Comment in:

- Ann Intern Med. 2010 Feb 16;152(4):JC-213.
- BMJ. 2009;339:b3076.
- BMJ. 2009;339:b3957.

OBJECTIVE: To compare the risk of acute myocardial infarction, heart failure, and death in patients with type 2 diabetes treated with rosiglitazone and pioglitazone. DESIGN: Retrospective cohort study. SETTING: Ontario, Canada. PARTICIPANTS: Outpatients aged 66 years and older who were started on rosiglitazone or pioglitazone between 1 April 2002 and 31 March 2008. MAIN OUTCOME MEASURE: Composite of death or hospital admission for either acute myocardial infarction or heart failure. In a secondary analysis, each outcome was also examined individually. RESULTS: 39 736 patients who started on either pioglitazone or rosiglitazone were identified. During the six year study period, the composite outcome was reached in 895 (5.3%) of patients taking pioglitazone and 1563 (6.9%) of patients taking rosiglitazone. After extensive adjustment for demographic and clinical factors and drug doses, pioglitazone treated patients had a lower risk of developing the primary outcome than did patients treated with rosiglitazone (adjusted hazard ratio 0.83, 95% confidence interval 0.76 to 0.90). Secondary analyses revealed a lower risk of death (adjusted hazard ratio 0.86, 0.75 to 0.98) and heart failure (0.77, 0.69 to 0.87) with pioglitazone but no significant difference in the risk of acute myocardial infarction (0.95, 0.81 to 1.11). One additional composite outcome would be predicted to occur annually for every 93 patients treated with rosiglitazone rather than pioglitazone. CONCLUSIONS: Among older patients with diabetes, pioglitazone is associated with a significantly lower risk of heart failure and death than is rosiglitazone. Given that rosiglitazone lacks a distinct clinical advantage over pioglitazone, continued use of rosiglitazone may not be justified.

PMCID: PMC2728804
PMID: 19690342 [PubMed - indexed for MEDLINE]Related articles Free article

**Publication Types:**

- Research Support, Non-U.S. Gov't

**MeSH Terms:**

- Aged
- Cohort Studies
- Diabetes Mellitus, Type 2/drug therapy*
- Female
- Heart Failure/chemically induced*
- Humans
- Hypoglycemic Agents/adverse effects*
- Male
- Myocardial Infarction/chemically induced*
- Retrospective Studies
- Risk Factors
- Thiazolidinediones/adverse effects*
- Treatment Outcome

**Substances:**

- Hypoglycemic Agents
- Thiazolidinediones
- pioglitazone
- rosiglitazone

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Post-test Questions

1. In the cohort study by Juurlink and colleagues, outcomes are compared among a cohort of patients treated with either rosiglitazone or pioglitazone. Which of the following best summarizes the findings of this paper?

    a. Rosiglitazone appears to be more effective than pioglitazone.
    b. Pioglitazone was associated with a lower risk of heart failure and death compared to rosiglitazone.
    c. Both rosiglitazone and pioglitazone are associated with death.
    d. The paper proves that pioglitazone is the safer choice when compared to rosiglitazone.

2. Which of the following best summarizes the findings of ARBITER 6-HALTS (comparison of niacin ER to ezetimibe added on to statin therapy)?

    a. Niacin ER resulted in superior reduction in LDL compared to ezetimibe.
    b. Ezetimibe was superior to niacin in reducing carotid artery intima-media thickness.
    c. Niacin ER increased HDL more than ezetimibe.
    d. A and C

3. Why do we need to look at a meta-analysis if there was already a well designed randomized, controlled trial evaluating intensive insulin therapy in the ICU (i.e. NICE-SUGAR)?

    a. Previous literature is conflicting
    b. To increase power
    c. To reduce bias
    d. NICE-SUGAR is definitive, no meta-analysis needed

4. True/false. Based on the results of the meta-analysis by Griesdale and colleagues, intensive insulin therapy should be recommended to manage patients in the ICU.

    a. True
    b. False

5. True/false. Despite the findings of Prymula and colleagues, it may be still appropriate to administer prophylactic acetaminophen to infants receiving a vaccine.

    a. True
    b. False