disclosures

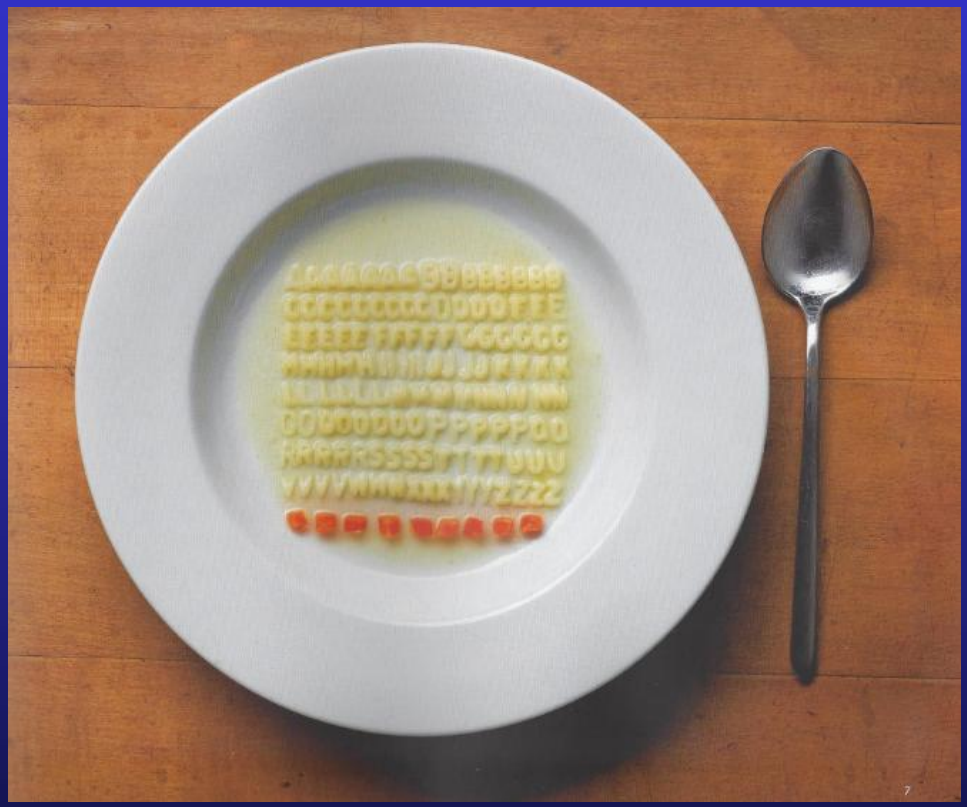
- ***Advisory board, lectures for AZ, MSD, Lilly, Boehringer, Genzyme***

…

De WCN in Cardiologisch Onderzoek

- *25 jaar*
- *Ordening in RCT's*

…



Ursus Wehrli 2012

De WCN in Cardiologisch Onderzoek

- *25 jaar*
- *Ordening in RCT's*
- *Naar indicaties, naar groepen medicamenten*
- *Naar inbreng*
- *Participaties in "game changing" trials*
- *Overwegingen*
- *Toekomst*

...

EMPHASIS-HF:

- *METHODS:*
  - *In this randomized, double-blind trial, we randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.*
- *CONCLUSIONS:*
  - *Eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms.*

NEJM 2011.. o.a Dunselman

COACH

- ***METHODS:***
  - ***The Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) was a multicenter, randomized, controlled trial in which 1023 patients were enrolled after hospitalization because of HF.***
- ***CONCLUSIONS:***
  - ***Neither moderate nor intensive disease management by a nurse specializing in management of patients with HF reduced the combined end points of death and hospitalization because of HF compared with standard follow-up. There was a nonsignificant, potentially relevant reduction in mortality, accompanied by a slight increase in the number of short hospitalizations in both intervention groups.***

Arch Int Med 2008: o.a. Lok, Dunselman ..

EASEGO

- ***OBJECTIVE:***
  - ***To assess the incremental low-density lipoprotein-cholesterol (LDL-C) lowering efficacy of doubling the statin dose or switching to the ezetimibe/simvastatin 10/20 mg combination tablet (EZE/SIMVA) in patients on simvastatin 20 mg or atorvastatin 10 mg not at LDL-C target < 2.5 mmol/L.***

- ***CONCLUSIONS:***
  - ***In CHD/DM2 patients treated with simvastatin or atorvastatin with LDL-C persistently > or = 2.5 mmol/L, switching to the EZE/SIMVA was more effective in attaining the LDL-C target of < 2.5 mmol/L than doubling the statin dose***

Curr Med Res Opinion 2008: Roeters van Lennep, Liem, Dunselman

ACTION:

- ***OBJECTIVE:***
  - ***Few trials report event-adjudication procedures in detail. Using data from the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study … ACTION randomized 7665 patients with stable angina to either nifedipine or placebo.***
- ***CONCLUSION:***
  - ***Both the diagnostic criteria used and the adjudication process determine event-rates and conclusions about treatment effects in clinical trials. Published trial reports should always state if event-adjudication was independent of the diagnoses of investigators, and if all events of interest were adjudicated or only the first one***

Contemp Clinical Trials 2007.. o.a Kragten, Dunselman

TIMI studies:

- *Vrijwel alle TIMI studies waaraan de WCN heeft geparticipeerd logistieke en wetenschappelijke input van vooral JanHein Cornel, Ton Oude Ophuis*
- *En samenwerking met de Yusuf groep door Ies Stoel*

RADAR:

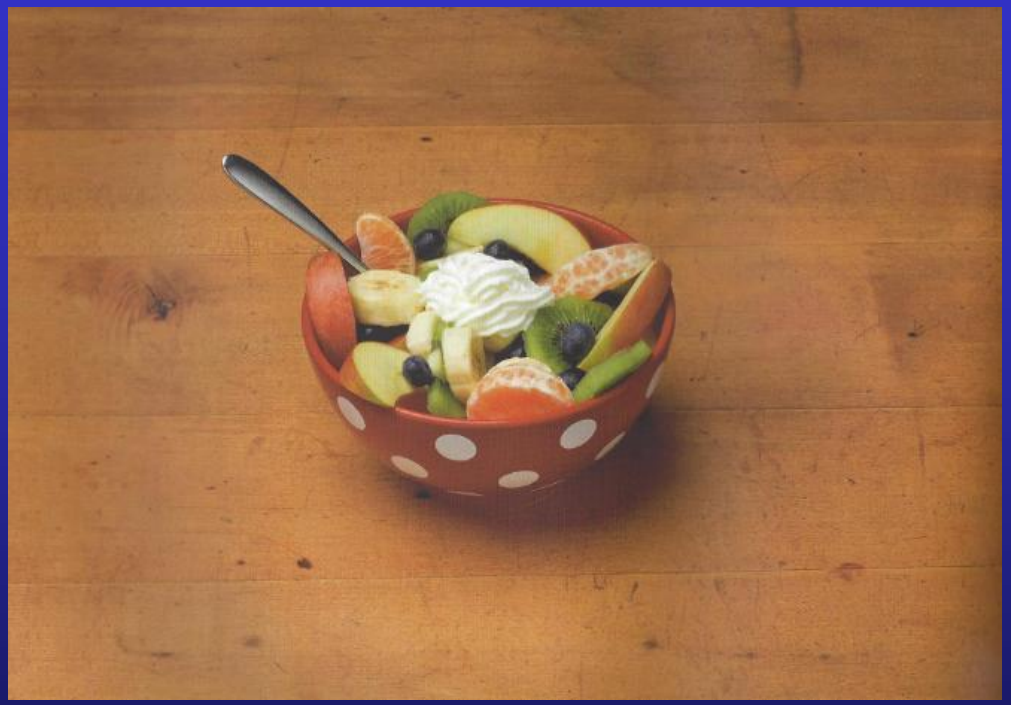
- ***OBJECTIVES:***
  - ***This study compared the effects of rosuvastatin and atorvastatin on the LDL-C/HDL-C.***
- ***CONCLUSIONS:***
  - ***Rosuvastatin 10, 20 and 40 mg is significantly more effective than atorvastatin 20, 40 and 80 mg, respectively, in improving the LDL-C/HDL-C ratio in patients with cardiovascular disease and low HDL-C. Further studies are required to clarify the benefits of rosuvastatin for reduction of cardiovascular risk.***

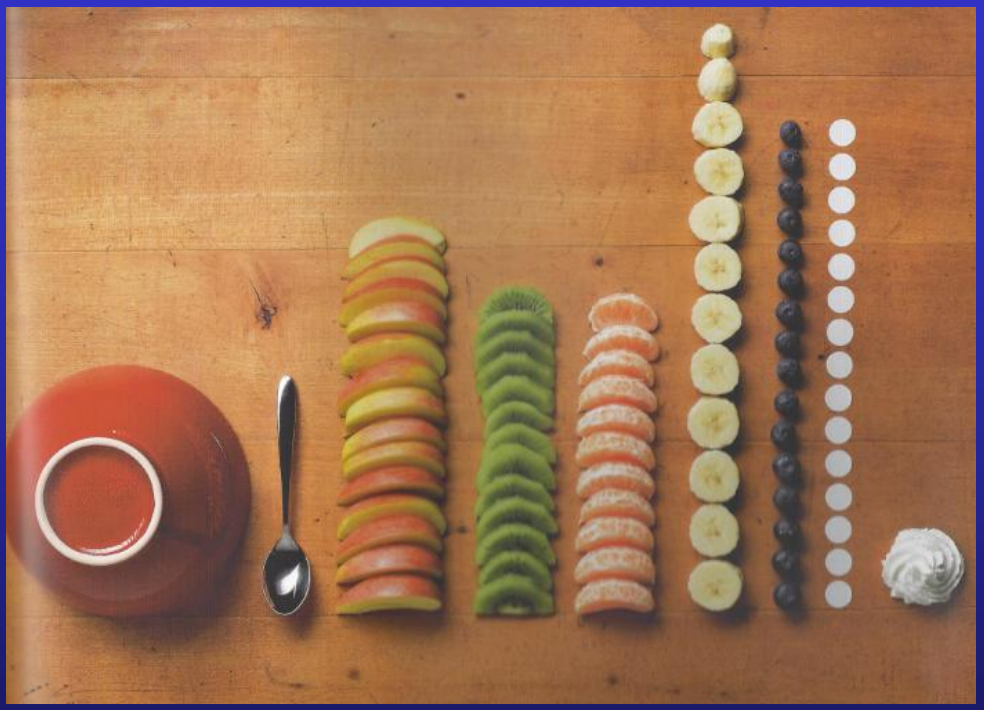
Curr Med Opin 2005: Liem, Dunselman, Lok (and other substudies)

ICTUS:

- ***METHODS:***
  - ***We randomly assigned 1200 patients with acute coronary syndrome without ST-segment elevation who had chest pain, an elevated cardiac troponin T level (> or =0.03 mug per liter), and either electrocardiographic evidence of ischemia at admission or a documented history of coronary disease to an early invasive strategy or to a more conservative (selectively invasive) strategy.***
- ***CONCLUSIONS:***
  - ***We could not demonstrate that, given optimized medical therapy, an early invasive strategy was superior to a selectively invasive strategy in patients with acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level***

NEJM 2005: o.a. Cornel, Dunselman. Oude Ophuis (and other sub-analysis)





Ursus Wehrli 2012

VAL-HEFT:

- ***BACKGROUND:***
  - ***Brain natriuretic peptide (BNP) and norepinephrine (NE) are strongly related to severity of and are independent predictors of outcome in heart failure. The long-term effects of angiotensin receptor blockers on BNP and NE in heart failure patients are not known.***
- ***CONCLUSIONS:***
  - ***In Val-HeFT, the largest neurohormone study (4284 pts) in patients with symptomatic chronic heart failure, BNP and NE rose over time in the placebo group. Valsartan caused sustained reduction in BNP and attenuated the increase in NE over the course of the study. These neurohormone effects of valsartan are consistent with the clinical benefits reported in Val-HeFT***

Circ 2002: ..o.a Holwerda ,Dunselman

MERIT:

- ***BACKGROUND:***
  - ***Results from recent studies on the effects of beta1-blockade in patients with heart failure demonstrated a 34% reduction in total mortality. However, the effect of beta1-blockade on the frequency of hospitalizations, symptoms, and quality of life in patients with heart failure has not been fully explored.***
- ***Conclusion:***
  - ***In this study of patients with symptomatic heartfailure, metoprolol CR/XL improved survival, reduced the need for hospitalizations due to worsening heart failure, improved NYHA functional class, and had beneficial effects on patient well-being***

JAMA 2000.. o.a Dunselman

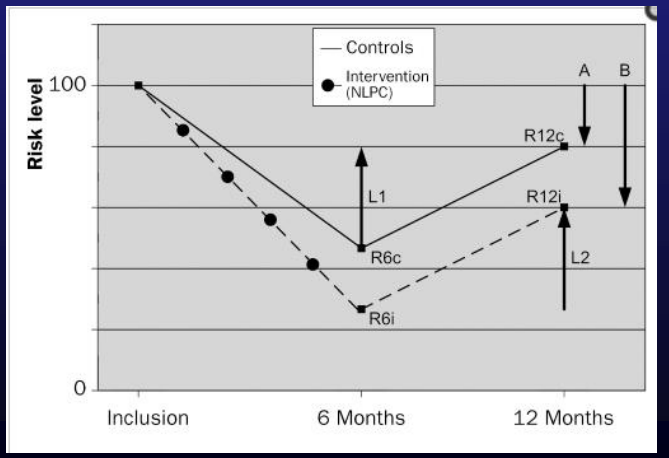
FEMINA:

- ***AIMS:***
  - ***The study aimed to compare the addition of felodipine to metoprolol, and of the replacement of metoprolol by felodipine, with continuation of metoprolol, in patients with angina pectoris despite optimal beta-blockade.***
- ***CONCLUSION:***
  - ***Combination of metoprolol and felodipine is to be preferred to felodipine monotherapy in patients who have signs and symptoms of myocardial ischaemia despite optimal beta-blockade.***

EHJ 1997.. o.a Kragten, Verdel, Liem, Bernink, Dunselman

RESPONSE:

- ***Objectives.***
  - ***The aim of the current study is to quantify the impact of NLPC on the risk of cardiovascular events in patients with established coronary artery disease.***
- ***Methods.***
  - ***A randomised, multicentre clinical trial of NLPC in addition to usual care or usual care alone in post-acute coronary syndrome patients***



Neth Heart J 2009 o.a Alings, Liem, Kragten

WARCEF:

- ***CONCLUSIONS:***
  - ***Among patients with reduced LVEF who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. The choice between warfarin and aspirin should be individualized.***

NEJM 2012: o.a. Lok

ORIGIN:

- ***BACKGROUND:***
  - ***To investigate whether the combination of HbA1c and fasting plasma glucose (FPG) can be used for the diagnosis of diabetes and impaired glucose tolerance (IGT) in people at high risk of cardiovascular disease (CVD).***
- ***Conclusion:***
  - ***Using FPG alone results in the underdiagnosis of glucometabolic abnormalities in people at high risk of CVD. Using an algorithm with both HbA1c and FPG improves the detection of diabetes, but not IGT, and could be easily implemented in patient care.***

J Diabetes 2011: Badings, Lok

SHIFT:

- *Aims*
  - *We explored the effect of treatment with ivabradine, a pure heart rate-slowing agent, on recurrent hospitalizations for worsening heart failure (HF) in the SHIFT*
- *Conclusion*
  - *Treatment with ivabradine, on a background of guidelines-based HF therapy, is associated with a substantial reduction in the likelihood of recurrent hospitalizations for worsening HF. This benefit can be expected to improve the quality of life and to substantially reduce health-care costs*

EHJ 2012: o.a. Alings

ARISTOTLE:

- ***BACKGROUND:***
  - ***In the ARISTOTLE trial, the rate of stroke or systemic embolism was reduced by apixaban compared with warfarin in patients with atrial fibrillation (AF). Patients with AF and previous stroke or transient ischaemic attack (TIA) have a high risk of stroke. We therefore aimed to assess the efficacy and safety of apixaban compared with warfarin in prespecified subgroups of patients with and without previous stroke or TIA.***
- ***CONCLUSION:***
  - ***The effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA. Owing to the higher risk of these outcomes in patients with previous stroke or TIA, the absolute benefits of apixaban might be greater in this population***

Lancet Neurology 2012 : o.a. Alings

RE-LY:

- ***Results (subanalysis):***
  - ***Rates of stroke or systemic embolism, major and intracranial bleeding, and vascular and total mortality each increased in the warfarin and dabigatran groups as CHADS(2) score increased. The rates of stroke or systemic embolism with dabigatran, 150 mg twice daily, and of intracranial bleeding with dabigatran, 150 mg or 110 mg twice daily, were lower than those with warfarin; there was no significant heterogeneity in subgroups defined by CHADS(2) scores.***
  - ***Higher CHADS(2) scores were associated with increased risks for stroke or systemic embolism, bleeding, and death in patients with atrial fibrillation receiving oral anticoagulants.***

Annals int Med: 2011 o.a. Alings (also main paper NEJM 2009)

PALLAS:

- ***BACKGROUND:***
  - ***Dronedarone restores sinus rhythm and reduces hospitalization or death in intermittent atrial fibrillation. It also lowers heart rate and blood pressure and has antiadrenergic and potential ventricular antiarrhythmic effects. We hypothesized that dronedarone would reduce major vascular events in high-risk permanent atrial fibrillation.***
- ***CONCLUSIONS:***
  - ***Dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events. Our data show that this drug should not be used in such patients..***

NEJM 2011 o.a. Alings

Ursus Wehrli 2012

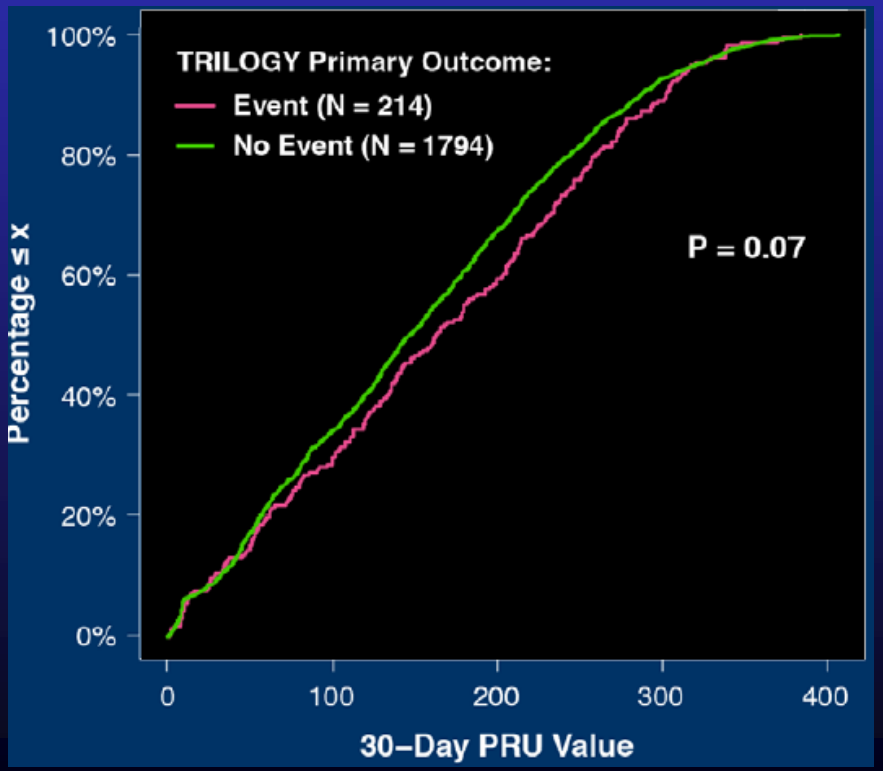
RACE 2:

- ***BACKGROUND:***
  - ***Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.***
- ***CONCLUSIONS:***
  - ***In patients with permanent atrial fibrillation, lenient rate control is as effective as strict rate control and is easier to achieve***

NEJM 2010 o.a. Cornel, Alings, Bosker

TRILOGY substudy:

.. Among those in the platelet substudy, no significant differences existed between prasugrel vs clopidogrel in the occurence of the primary efficacy end point through 30 months and no significant association existed between platelet reactivity and occurrence of ischemic outcomes



JAMA 2012: o.a. Cornel

PLATO sub-study:

- ***BACKGROUND:***
  - ***Habitual smoking has been associated with increased platelet reactivity, increased risk of thrombotic complications and greater efficacy of clopidogrel therapy over placebo. In the PLATO trial, ticagrelor compared to clopidogrel in patients with acute coronary syndromes (ACS) reduced the primary composite end point of vascular death, myocardial infarction and stroke, without increasing overall rates of major bleeding. We evaluated the results in relation to smoking habits.***
- ***CONCLUSIONS:***
  - ***In patients hospitalized with ACS, habitual smoking is associated with a greater risk of subsequent stent thrombosis. The reduction of vascular death, myocardial infarction, stroke, and stent thrombosis by ticagrelor compared to clopidogrel is consistent regardless of smoking habits.***

AHJ 2012: o.a. Cornel (also main paper NEJM 2012 and other substudies)

TRACER:

- ***BACKGROUND:***
  - ***Vorapaxar is a new oral protease-activated-receptor 1 (PAR-1) antagonist that inhibits thrombin-induced platelet activation…tinvestigated in NSTE-ACS pts***
- ***CONCLUSIONS:***
  - ***In patients with acute coronary syndromes, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point but significantly increased the risk of major bleeding, including intracranial hemorrhage***

..NEJM 2012: o.a. Cornel

APPRAISE-2:

- ***BACKGROUND:***
  - ***Apixaban, an oral, direct factor Xa inhibitor, may reduce the risk of recurrent ischemic events when added to antiplatelet therapy after an acute coronary syndrome.***
- ***CONCLUSIONS:***
  - ***The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events.***

NEJM 2011: o.a. Cornel

Back to the Drawing Board!

CORONA substudy:

- ***Patients in the lowest tertile of NT-proBNP had the <u>best</u> prognosis and, if assigned to rosuvastatin rather than placebo, had a greater reduction in the primary end point (HR: 0.65; 95% CI: 0.47 to 0.88) than patients in the other tertiles (heterogeneity test, p = 0.0192). This reflected fewer atherothrombotic events and sudden deaths with rosuvastatin.***

JACC 2009: o.a. Dunselman, Cornel (main paper NEJM 2007; and other sub-analysis)

RUTH:

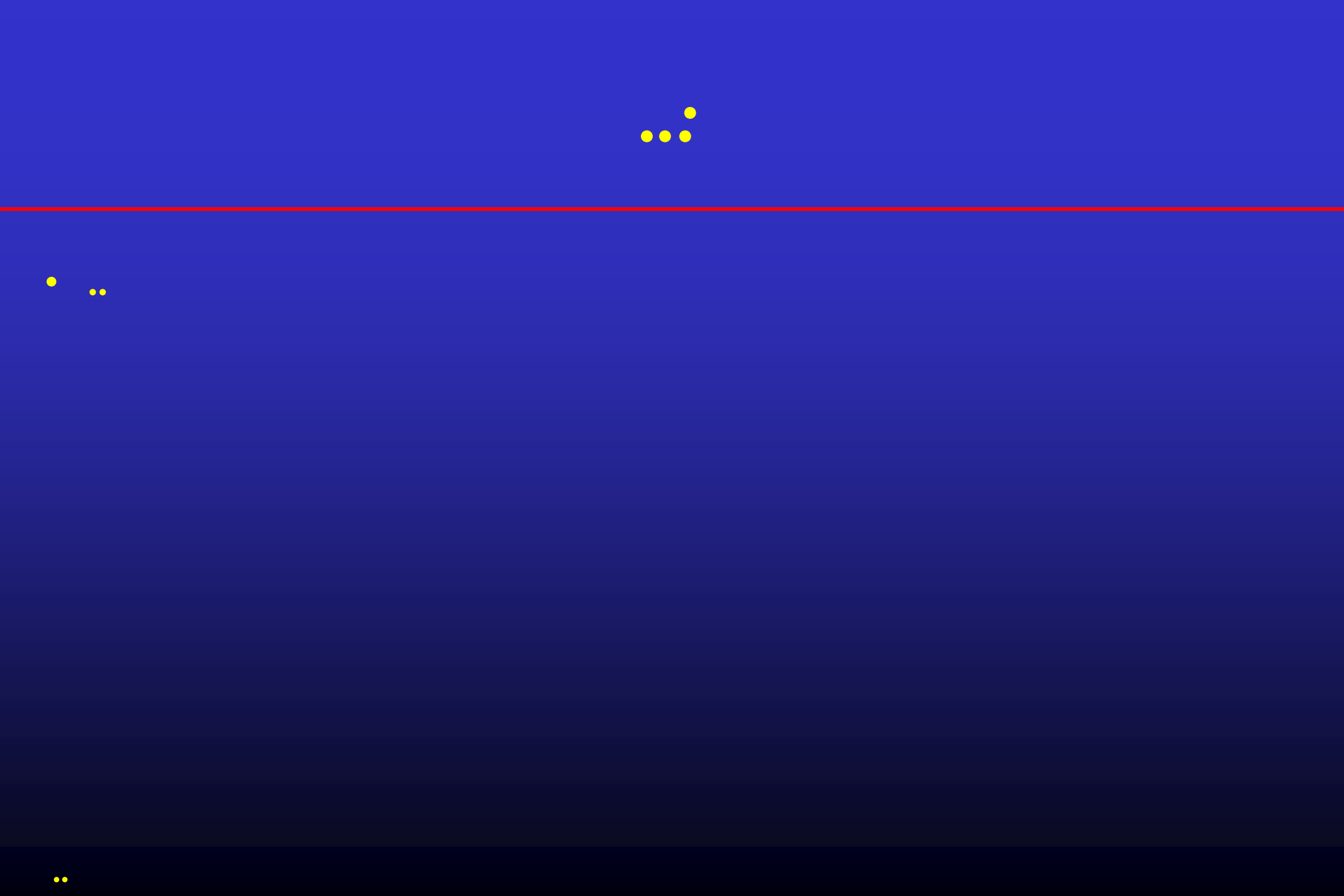
- ***Early harmful effects of hormone replacement therapy and lack of beneficial effects on coronary heart disease event rates in high-risk women have challenged the beneficial results gleaned from observational studies in the past.***
- ***The current available data indicate that estrogens are beneficial to healthy endothelium but are harmful once atherosclerotic disease has developed.***

Semin Vasc Med 2004: AH Maas

Ursus Wehrli 2012

De WCN in Cardiologisch Onderzoek

- *25 jaar onderzoek: verleden, heden en toekomst*
- *Niet alleen een "vlees machine" gedreven door "Big Pharma"*
- *Ook gerandomiseerd onderzoek naar behandel strategieën (bijv ICTUS, RACE, RESPONSE, COACH etc)*
- *Participatie in steeringcie en auteurschappen: punt van aandacht ..*
- *Eigen protocollen (bijv RADAR, EASEGO, FEMINA, FLORIDA, FOLARDA etc): kan meer …*
- *Deelname aan mechanistische studies (bijv BIOMARCS): kan meer ..*
- *Substudies genesteld in grote studies (bijv ORIGIN): kan veel meer ..*
- *De tijd van "blockbuster" studies ligt achter ons. Wat volgt zijn lastige studies (veel fase II) in "niches" (FH, PCSK9, acuut HF etc)*
- *Aandacht voor studies bij pat met DM*



19 september 2012

Afgeraden DPP-4-remmers toch vaak gebruikt

DPP-4-remmers moeten niet voorgeschreven worden volgens het NHG, zijn duurder dan bestaande middelen en zijn niet bewezen veilig en effectief. Toch zijn er volgens KRO's Brandpunt 30.000 diabetespatiënten die het middel gebruiken.

'Er is wel veel onderzoek aan vooraf gegaan, er worden strenge eisen gesteld voordat een middel tot de markt wordt toegelaten. Maar de lange termijn effecten van DPP-4-remmers zijn onbekend', zegt Jako Burgers van het NHG.

Strengere toelatingseisen

Om dit soort situaties te voorkomen wil het NHG dat er strengere eisen worden gesteld aan het toelaten van nieuwe geneesmiddelen. 'De eis moet zijn dat het aantoonbare meerwaarde heeft op het gebied van effectiviteit en veiligheid ten opzichte van de bestaande middelen', zegt Burgers.

Daarnaast kunnen artsen beter de richtlijnen volgen en moeten patiënten beter weten wat ze slikken, vindt Burgers.

Onderzoek vergeleken

Het Geneesmiddelenbulletin vergeleek onderzoek over DPP-4-remmers. 'We hebben geconcludeerd dat het middel niet beter werkt dan de al op de markt zijnde middelen', zegt hoofdredacteur Dick Bijl. 'Het middel is tien keer zo duur als bestaande middelen en het onduidelijk is wat de bijwerkingen op de lange termijn zijn. Ook de werkzaamheid op de lange termijn is niet aangetoond. Onze conclusie is dat het niet voorgeschreven moet worden.'

Van der Linde

Internist Frank van Berkum schrijft in zijn blog over de discussie die hij met huisarts Van der Linde heeft over de DPP-4-remmers.

» NHG ontraadt nieuwe diabetesmiddelen (2010)

» Reactie farmaceut MSD

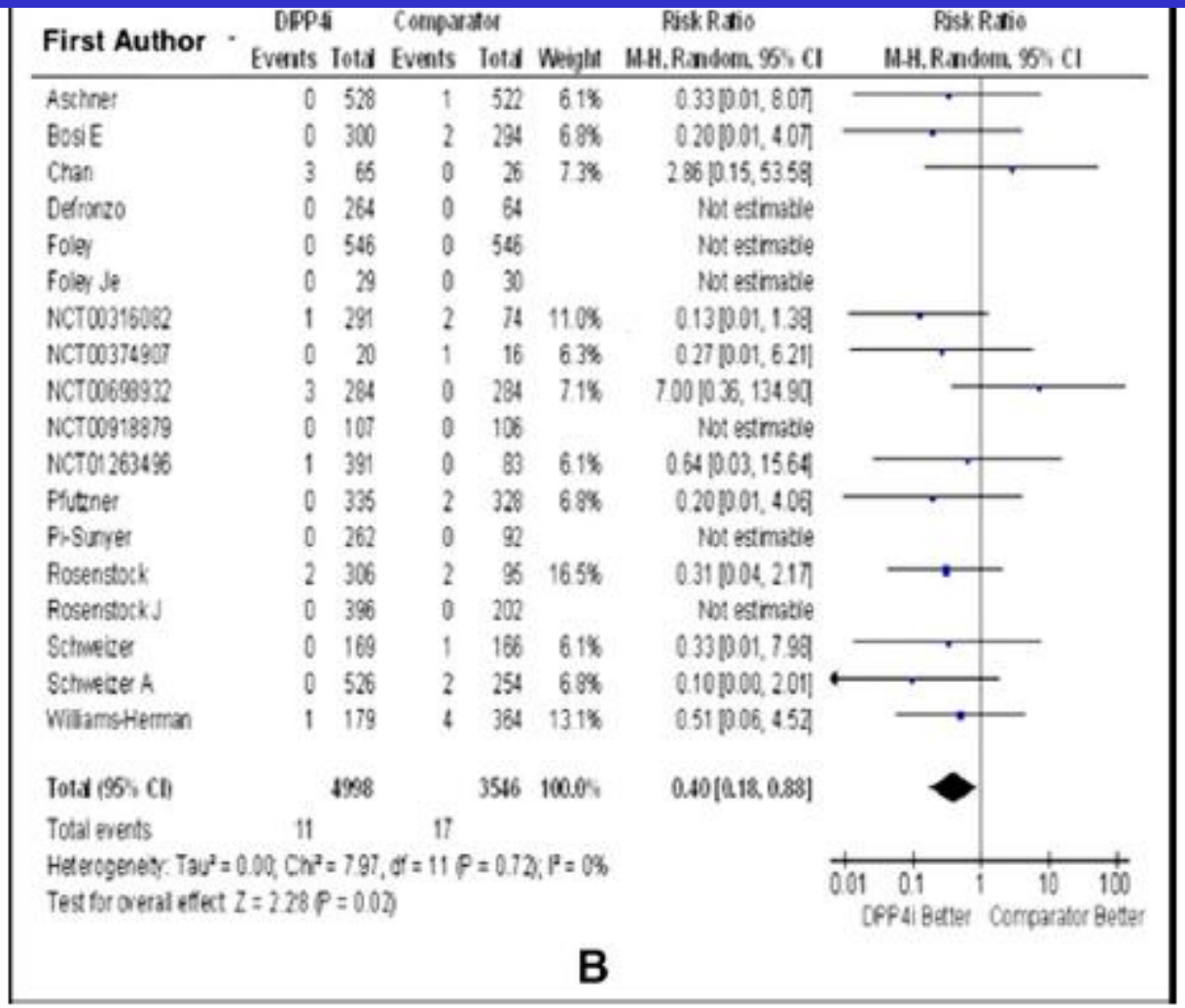


Figure 3. Risks of *(A)* adverse cardiovascular events and *(B)* acute coronary syndrome with dipeptidyl peptidase-4 inhibitors. M-H = Mantel–Haenszel. Other abbreviation as in Figure 1.

A meta-analysis is like a sausage. .

Only God and the butcher know what goes in it and neither would ever eat any!

Bangalore and Messerli. BMJ 2009.
http://www.bmj.com/cgi/eletters/338/may19_1/b1665#214447

SPECIAL ARTICLE

A Randomized Study of How Physicians Interpret Research Funding Disclosures

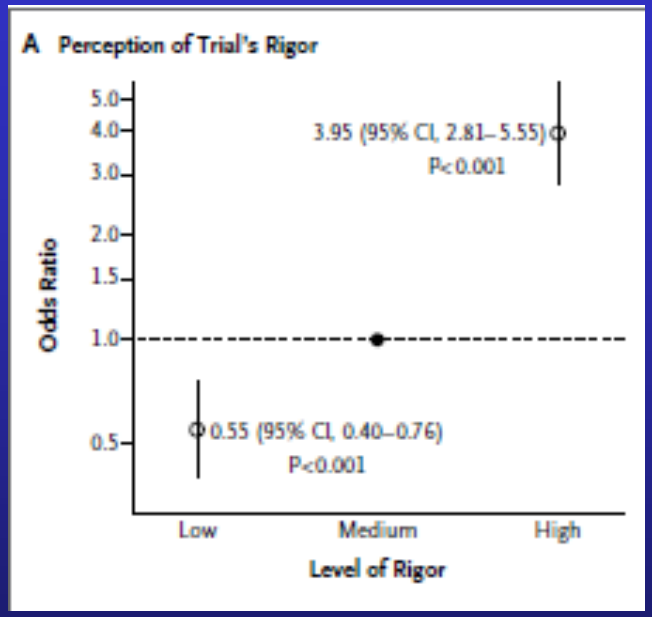
"Lampytinib" would be used for dyslipidemia in patients who had unacceptable side effects from statins,

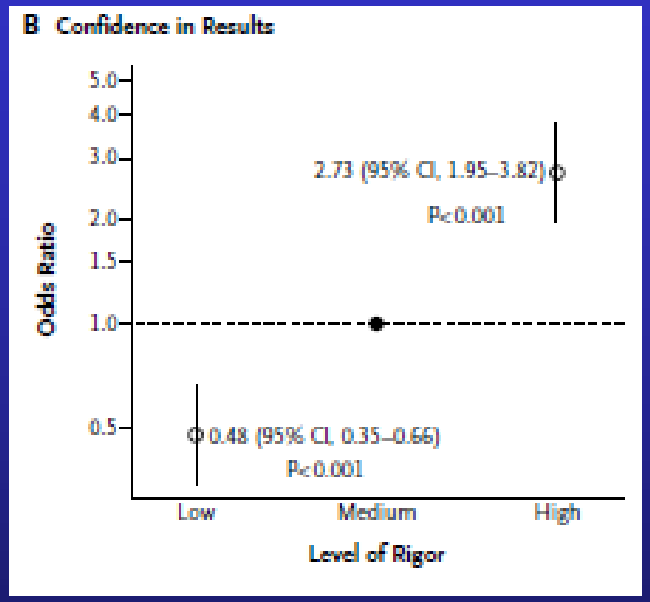
"bondaglutaraz" would be used for diabetes and low levels of high-density lipoprotein cholesterol in patients who were taking metformin and a sulfonylurea and who were unwilling or unable to add insulin,

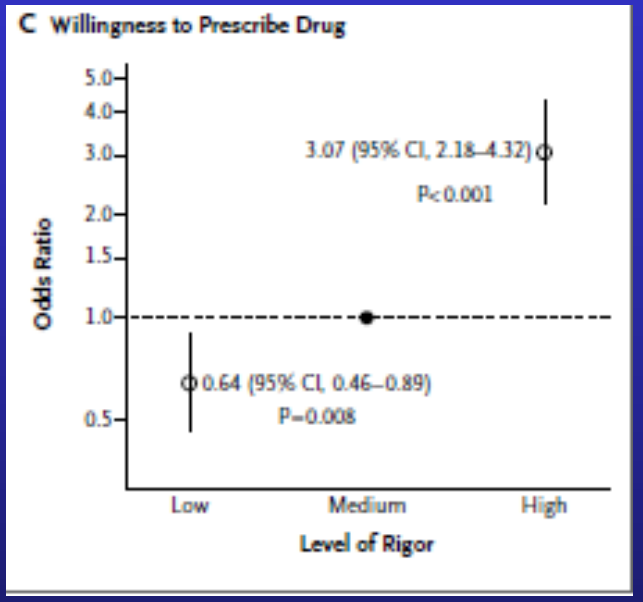
"provasinab" would be used for angina in patients with untreatable multivessel coronary disease who were taking maximal doses of beta-blockers

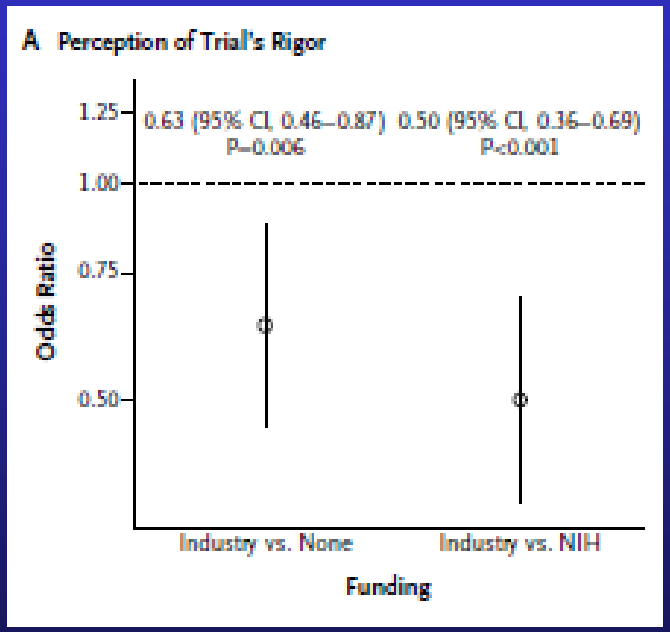
Table 1. Characteristics Used to Differentiate Trials of Hypothetical New Drugs, According to Methodologic Rigor.

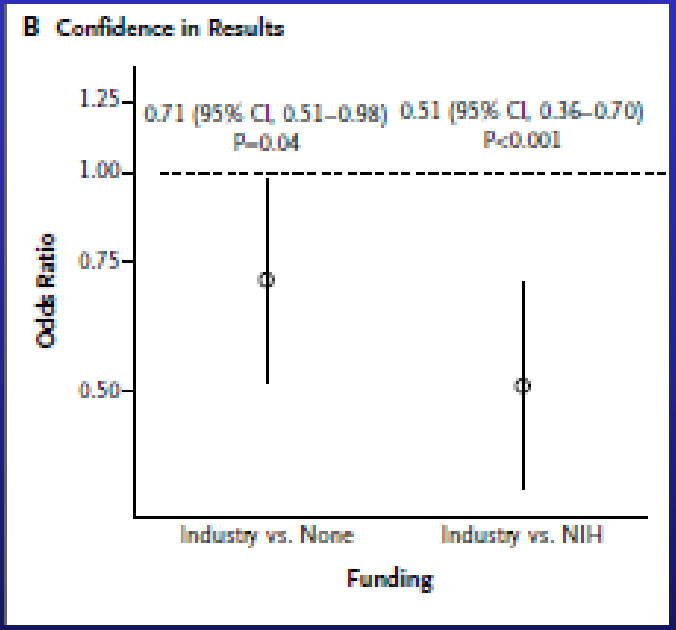
Characteristic	Level of Rigor		
	High	Medium	Low
Randomization	Randomized	Randomized	Randomized
Blinding	Double-blind	Single-blind	Open-label
Comparator	Active	Active	Usual care
Dropout rate (%)	<9	13	19
Sample size (no. of patients)	5322	964	483
End point	Mortality	Surrogate	Surrogate
Patient population	Representative	Representative	Not representative
Length of follow-up (mo)	36	12	4
Report of safety	Drug appears to be safe	Drug appears to be safe	No report

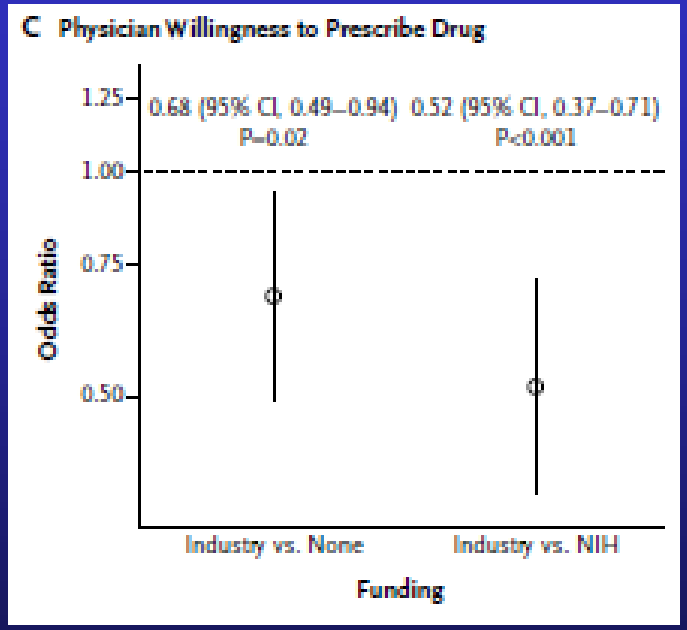

A Perception of Trial's Rigor
5.0
4.0
3.0
2.0
1.5
1.0
0.5
Odds Ratio
3.95 (95% CI, 2.81–5.55)
P<0.001
0.55 (95% CI, 0.40–0.76)
P<0.001
Low
Medium
High
Level of Rigor


B Confidence in Results
5.0
4.0
3.0
2.0
1.5
1.0
0.5
Odds Ratio
2.73 (95% CI, 1.95–3.82)
P<0.001
0.48 (95% CI, 0.35–0.66)
P<0.001
Low
Medium
High
Level of Rigor


C Willingness to Prescribe Drug
5.0
4.0
3.0
2.0
1.5
1.0
0.5
Odds Ratio
3.07 (95% CI, 2.18–4.32)
P<0.001
0.64 (95% CI, 0.46–0.89)
P=0.008
Low
Medium
High
Level of Rigor



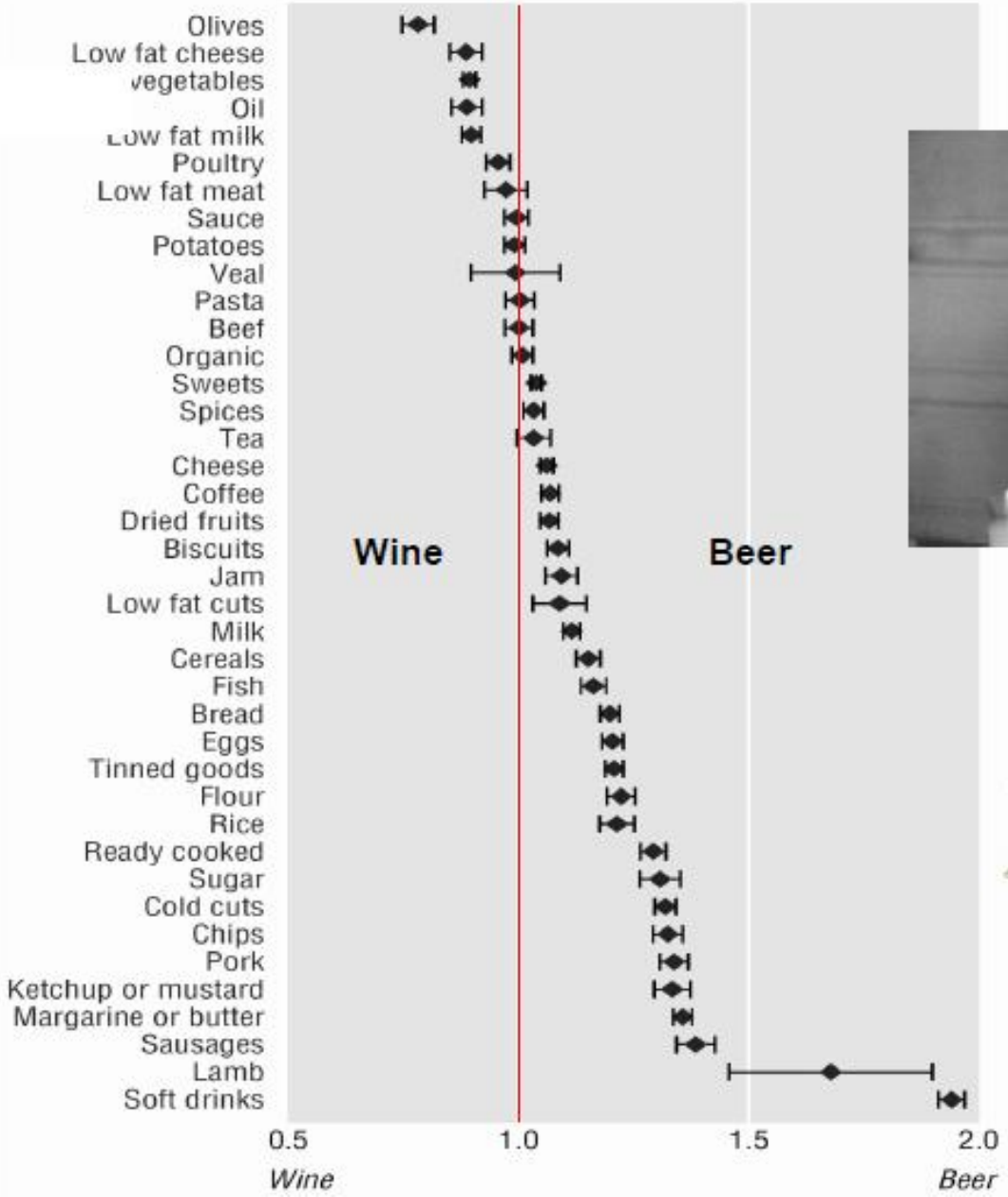




CONCLUSIONS

Physicians discriminate among trials of varying degrees of rigor, but industry sponsorship negatively influences their perception of methodologic quality and reduces their willingness to believe and act on trial findings, independently of the trial's quality. These effects may influence the translation of clinical research into practice.

Food buying habits of people who buy wine or beer: cross sectional study



Johansen et al., BMJ 2006; 332:519-24