TOP ARTICLES 2014

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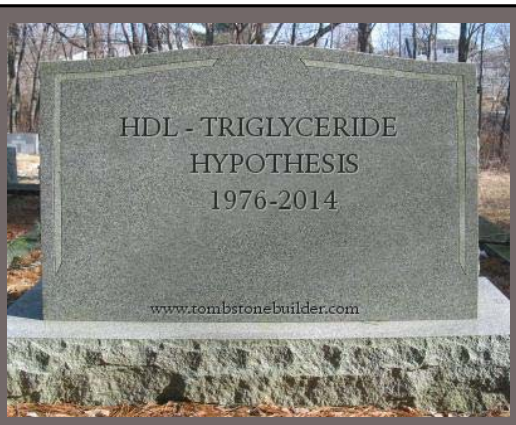
Disclosure

- Dr. Neil Skolnik has an financial relationship or interest with a commercial entity that may have a direct interest in the subject matter of this session. Dr. Skolnik sits as part of a consultant or advisory board partnership, a Speaker's Bureaus, and receives research grants or supports. Dr. Skolnik has a relationship with AstraZeneca, Sanofi, Lilly, Teva, and Amgen. No conflict of interest exists.

WHAT MAKES A TOP ARTICLE???

LIPIDS



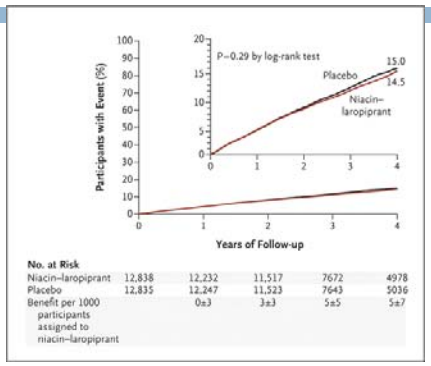
Stone N J et al. Circulation. 2014;129:S1-S45

Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients

- The HPS2-THRIVE Collaborative Group
- 25,673 adults with vascular disease randomized to 2 g of extended-release niacin and 40 mg of laropiprant or a matching placebo daily.
- Primary outcome: First major vascular event (nonfatal myocardial infarction, death from coronary causes, stroke, or arterial revascularization).

N Engl J Med 2014; 371:203-212July 17, 2014

Niacin as Add on HPS2-Thrive Study



N Engl J Med 2014; 371:203-212July 17, 2014

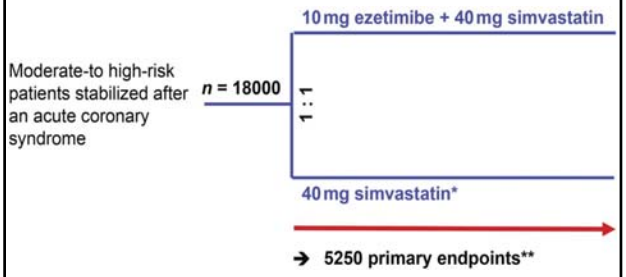
Ezetimibe –Improve IT Background

- LDL lowering with statins decreased CV outcomes in high-risk patients
- No lipid lowering therapy added to statins has been shown to have additional benefit
- Significant "residual risk" exists in high-risk patients treated with statins.
- Ezetimibe inhibits cholesterol absorption and decreases LDL-C by approx 20% when added to statins

Ezetimibe –Improve IT

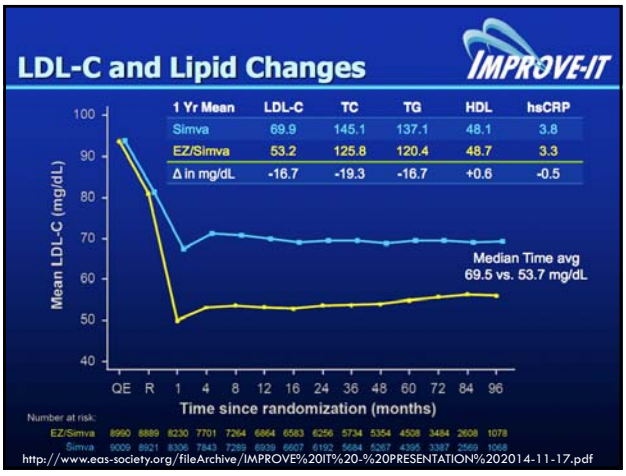
- Inclusion Criteria
  - Hospitalization for STEMI, NSTEMI/UA < 10 days
  - Age ≥ 50 years, and ≥ 1 high-risk feature:
    - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
  - LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)
- Major Exclusion Criteria:
  - CABG for treatment of qualifying ACS
  - Current statin Rx more potent than simva 40mg
  - Creat Cl < 30mL/min, active liver disease

Ezetimibe –Improve IT



Primary endpoint

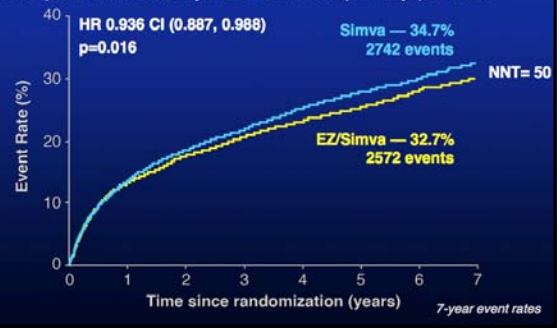
- Cardiovascular death, MI, hospital admission for unstable angina, coronary revascularization (≥ 30 days after randomization), or stroke.



Primary Endpoint — ITT

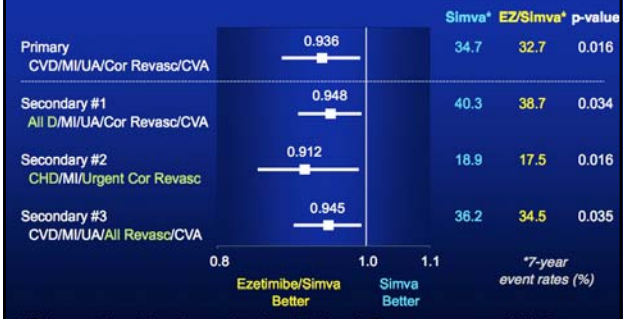
IMPROVE-IT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



Primary and 3 Prespecified Secondary Endpoints — ITT

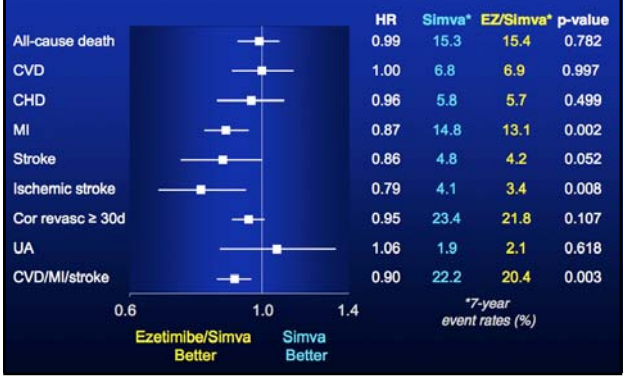
IMPROVE-IT



UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

Individual Cardiovascular Endpoints and CVD/MI/Stroke

IMPROVE-IT



Improve It - Summary

AHA lipid Guidelines Non-Statins

- The Expert Panel could find no data supporting the routine use of non-statin drugs combined with statin therapy to further reduce ASCVD events.

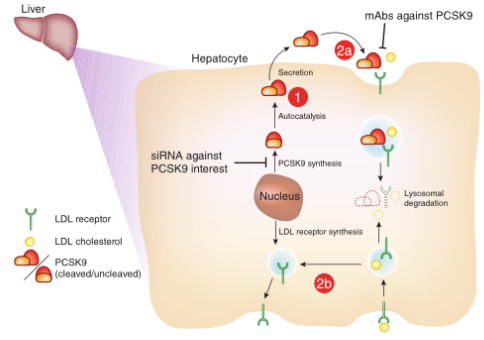
Stone N J et al. Circulation. 2014;129:S1-S45

EVOLOCUMAB IN HYPERLIPIDEMIA

Background

- Pro-protein convertase subtilisin/kexin type 9 (PCSK9) is produced predominantly in the liver
  - Plays a major role in regulating LDL by binding to hepatic LDL receptors → degradation
- Evolocumab
  - Monoclonal antibodies that inhibits PCSK9
  - Inhibition of PCSK9 increases LDL receptors
  - Reduces LDL levels in multiple studies including this study's Phase 2 trial

Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222



mAbs against PCSK9 reduce cholesterol by regulating LDL receptor levels. 1. The PCSK9 enzyme is synthesized in the liver. 2a. Secreted PCSK9 binds LDL receptors leading them to degradation, and preventing them from recycling to the surface where they continue to remove LDL cholesterol from the bloodstream. 2b. If no PCSK9 binding takes place, the LDL cholesterol receptors are free to remove LDL cholesterol from circulation. Image adapted from *Scibx* doi:10.1038/scibx.2009.895.

Garber, Ken. Biologics inch toward cholesterol lowering market. Nature Biotechology 30, 302-304 (2012). DOI 10.1038/nbt0412-302

Question

Is the use of Evolocumab, a monoclonal PCSK9 antibody, safe and efficacious in reducing LDL cholesterol in patients with hyperlipidemia over the course of 52 weeks?

Study Design and Patients

- Placebo controlled
- Conducted at 88 centers in 9 countries
- Participants eligible are ages 18-75 years
- Participants had to have LDL ≥ 75 mg/dL and a fasting triglyceride level ≤ 400 mg/dL

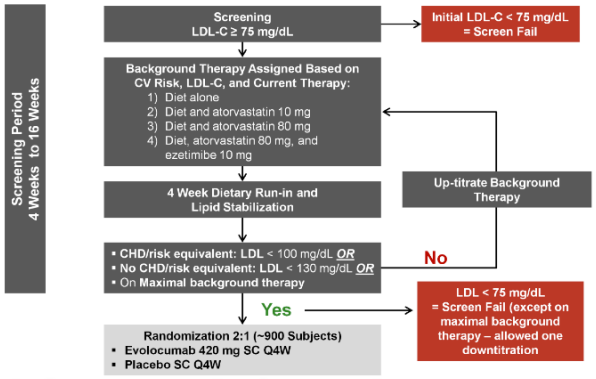
Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Study Method

- Participants assigned to one of four lipid lowering regimens for a "run-in period" of 4-12 weeks
- Stratified patients to risk categories per the Adult Treatment Panel III (ATP III)
  - Diet alone
  - Diet with 10mg Atorvastatin daily
  - Diet with 80mg Atorvastatin daily
  - Diet with 80mg Atorvastatin + 10mg Ezetimibe daily
- Patients with LDL ≥ 75mg/dL then assigned in a 2:1 ratio to receive either Evolocumab (420mg) or placebo every 4 weeks

Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Supplementary Figure S2. Flow diagram: Lipid stabilization and Titration Phase.



Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Primary End Point

- The percent change from baseline LDL at week 52 in patients receiving Evolocumab as compared with the change in those receiving placebo

Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Summary of Study Results

- Total patients:
  - Each group
- Overall, least squares mean (**±SE) reduction in LDL from baseline with the use of Evolocumab was 57.0±2.1% (p < 0.001**)
- Therapy reductions
  - **Diet alone: 55.7±4.2% (N=74)**
  - **Diet with 10mg Atorvastatin daily: 61.6±2.6% (N=254)**
  - **Diet with 80mg Atorvastatin daily: 56.8±5.3% (N=145)**
  - **Diet with 80mg Atorvastatin + 10mg Ezetimibe daily: 48.5±5.2% (N=126)**
- **P < 0.001** for all comparisons

Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Adverse Events

- Overall incidence of adverse events was similar in the evolocumab group and the placebo group
  - 74.8% vs. 74.2% respectively
- Most common adverse events in the Evolocumab group included:
  - Nasopharyngitis
  - URI infections
  - Influenza
  - Back pain

Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Conclusion Similar to Findings of Previous Studies

- Consistent with same Evolocumab regimen in the 12 week, phase 2 trial
- Also saw similar effects in PCSK9 levels in the ODYSSEY LONG TERM trial
  - Over 2,000 patients with HLD and high CV risk
  - Double blinded assignment of alirocumab 150mg every 2 weeks vs. placebo
  - Follow up for 52 weeks (still on-going)
  - Mean reduction in LDL was 61% for patients treated with alirocumab vs. an increase of 0.8% in patients treated with placebo
  - 79% received a target LDL < 70 after treatment with alirocumab

Blom, DJ, et.al. A 52 week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014: 370:1809-19. DOI 10.10156/NEJMoa1316222

Conclusion

In patients ages 18-75, with an elevated LDL and triglyceride, and receiving guideline recommended lipid lowering therapy, the monoclonal PCSK9 antibody Evolocumab reduced LDL by 57% vs. placebo at 52 weeks

ASPIRIN FOR PRIMARY PREVENTION

ASPIRIN FOR PRIMARY PREVENTION
THE FDA ANALYSIS

The Question

- Should we be recommending Aspirin to our patients for primary prevention of CV disease?

Background

- The recommendations have varied over the last twenty years with regard to Aspirin and primary prevention.
- USPSTF (2002) – Good evidence that aspirin decreases the incidence of CAD in adults who are at increased risk. Also good evidence that aspirin increases hemorrhagic strokes. Balance of risk and harm most favorable in patient at high CAD risk.

http://www.regulations.gov/contentStreamer?objectId=09000064816def58&disposition=attachment&contentType=pdf , accessed Sept 2014

Background

- USPSTF (2009) – Aspirin recommended for men 45-79 for MI prevention, women age 55-79 for stroke prevention.
  - Discussed increased risk of hemorrhagic stroke and major GI bleed

Background

- FDA response May 2, 2014 to Bayer for labeling for Aspirin 75 mg to 325 mg for primary prevention of MI in:
  - Patients with CHD risk of $\geq$ 10% over 10 years
  - Positive risk-benefit as assessed by their physician
- FDA generally requires the effectiveness of a drug to be supported by at least 2 well-controlled studies that show intended primary-endpoint effects.

Benefits

- Reviewed six studies – none achieved statistically significant positive results, and none shared a common endpoint that could be combined.
- Secondary endpoint analysis suggested that aspirin may reduce nonfatal MI, but results were inconsistent and not associated with improved mortality.

- In addition, studies of aspirin for primary prevention in patients with DM or PVD did not support use of aspirin for prevention of CV events.

Adverse Effects

Table 4: Major Bleeding Events from Six Trials

	Aspirin Events in 330,000 person-years	Control/Placebo Events in 330,000 persons-years	Odd Ratios (95% CI)
Hemorrhagic strokes	116	89	1.32 (1.00-1.75)
Major extracranial bleed	335	219	1.54 (1.30-1.82)

Low-Dose Aspirin for Primary Prevention of CV Events in Patients ≥ 60 Years Atherosclerotic Risk Factors

- 14,464 patients 60 to 85 years, with hypertension, dyslipidemia, or diabetes recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007, and followed up for up to 6.5 years.

JAMA. 2014;312(23):2510-2520.
doi:10.1001/jama.2014.15690

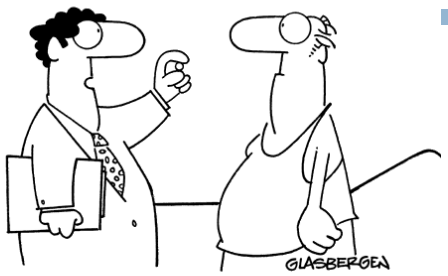
Results

- Study terminated early after median follow-up of 5.02 years based on likely futility.
- In both the aspirin and no aspirin groups, 56 fatal events occurred.
- **CONCLUSIONS AND RELEVANCE** Once-daily,low-dose aspirin did not significantly reducethe risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

JAMA. 2014;312(23):2510-2520.
doi:10.1001/jama.2014.15690

Conclusion

- FDA supports the use of aspirin for secondary prevention of recurrent MI, unstable angina, chronic stable angina, stroke, or TIA.
- Did not approve label change to support the use of aspirin for primary prevention.



"To prevent a heart attack, take one aspirin every day. Take it out for a jog, then take it to the gym, then take it for a bike ride..."

Conclusion

- "What to do in clinical practice in the face of uncertainty is often not…easy…The data considered by USPSTF, together with the expectation that people with a high risk of heart attach or stroke may behave more like a secondary prevention population, could support the view that the benefits of aspirin for primary prevention outweigh the risks in certain subgroups, even if the FDA does not find such data to be sufficient for labeling."

http://www.regulations.gov/contentStreamer?objectId=09000064816def58&disposition=attachment&contentType=pdf , accessed Sept 2014

CONCUSSION UPDATE

Mild Traumatic Brain Injury (mTBI): Background

- What do we already know?
  - 1.6-3.8 million sports and recreation related TBIs occur in the U.S. each year
    - Most of these are mTBIs that are treated at the patient's primary care office
  - The CDC recommends rest post-injury with a stepwise return to activity
    - Motivated by re-injury during recovery

http://www.cdc.gov/concussion/headsup/pdf/Facts_for_Physicians_booklet-a.pdf

How Much Rest Do We Need?

- Most data recommends a minimum of 24-48 hours before initiating activity
  - Many clinicians recommend much longer times
    - "Cocoon therapy" - patients are restricted to several days in a darkened room with minimal activity or screen time
- No study has determined an *optimal* period of rest post-injury
  - Strict rest vs. usual care

Thomas, Danny George, et.al. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics peds.2014-0966; published ahead of print January 5, 2015, doi:10.1542/peds.2014-0966

The Question

Does recommending strict rest improve concussion recovery and outcome in adolescents after discharge from the pediatric ED?

Study Participants and Interventions

- Randomized, control study
- Recruited participants aged 11-22 years that presented to a pediatric ED within 24 hours of concussion
  - 99 recruited, 88 completed
- Randomized to strict rest vs. usual care
  - Strict rest: 5 days at home, no school, work or physical activity followed by stepwise return to activity
  - Usual care: 1-2 days of rest followed by stepwise return to activity

Thomas, Danny George, et.al. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics peds.2014-0966; published ahead of print January 5, 2015, doi:10.1542/peds.2014-0966

Study Method and Outcome Measures

- Patients completed a diary used to record physical and mental activity levels, energy exerted and daily post-concussive symptoms
  - Measured by the Three Day Activity Diary and Post Concussive Symptoms Scale (PCSS)
- Neurocognitive and balance symptoms were performed 3 and 10 days post-injury
  - Measured by the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) and the Balance Error Scoring System

Thomas, Danny George, et.al. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics peds.2014-0966; published ahead of print January 5, 2015, doi:10.1542/peds.2014-0966

Results: Activity Levels

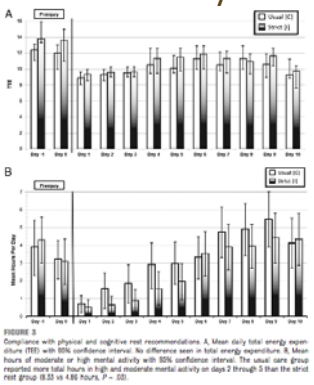


FIGURE 3
Compliance with physical and cognitive rest recommendations A, Mean daily total energy expenditure (TEE) with 95% confidence interval. No difference seen in total energy expenditure. B, Mean hours of moderate or high mental activity with 95% confidence interval. The usual care group reported more total hours in high and moderate mental activity on days 2 through 5 than the strict rest group (8.33 vs 4.86 hours, $P = .02$).

Results: Post-Concussive Symptoms

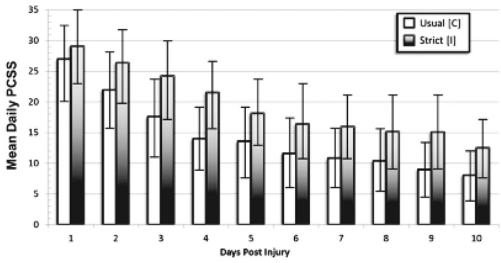


FIGURE 5
Mean PCSS with 95% confidence interval over time. Patients in the intervention group experienced higher total symptoms over the course of follow-up with the greatest difference in mean symptoms on day 4 (13.95 [C] vs 21.51 [I], $P < .03$).

Thomas, Danny George, et.al. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics peds.2014-0966; published ahead of print January 5, 2015, doi:10.1542/peds.2014-0966

Results: Symptom Resolution

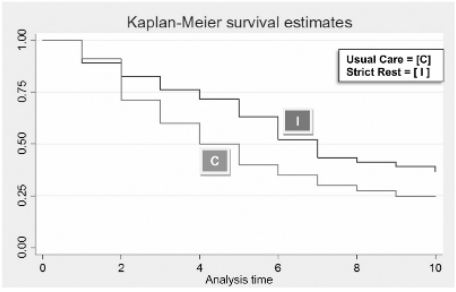


FIGURE 4
Proportion of patients reporting symptom resolution (PCSS ≤7) over time. It took longer for 50% the intervention group to report symptom resolution. However, the difference in overall proportion of patient reporting symptom resolution did not meet statistical significance ($P = .06$).

Thomas, Danny George, et.al. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics peds.2014-0966; published ahead of print January 5, 2015, doi:10.1542/peds.2014-0966

Results

- **Both groups** reported a **20% decrease in energy** and physical activity level
- The **intervention group** reported **less school and after school attendance** for days 2-5 post-concussion
  - 3.8 vs. 6.7 hours total, $p < 0.05$
- The **intervention group reported more daily post-concussive symptoms and slower resolution** over 10 days
  - 187.9 vs. 131.9, $p < 0.03$
- No clinically significant difference in neurocognitive or balance outcomes

Thomas, Danny George, et.al. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics peds.2014-0966; published ahead of print January 5, 2015, doi:10.1542/peds.2014-0966

Conclusion

Recommending strict rest for adolescents immediately after concussion offered no health benefit over the usual care

CHF

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure - Background

- Neprilysin, a endopeptidase, degrades endogenous vasoactive peptides, natriuretic peptides, bradykinin, and adrenomedullin.
- Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.

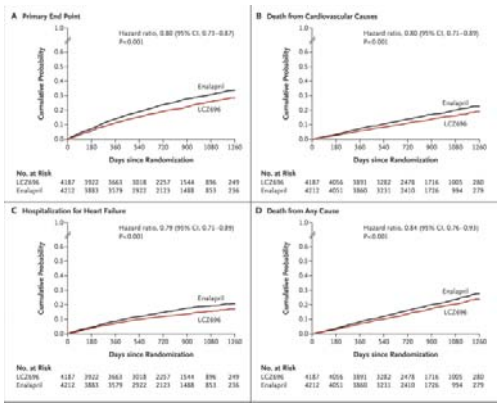
Mechanism

- Combined inhibition of the renin–angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies, but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema.
- LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema.
- In small trials involving patients who had hypertension or heart failure with a preserved ejection fraction, LCZ696 had hemodynamic and neurohormonal effects that were greater than those of an ARB alone.

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

- 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less randomly assigned to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy.
- The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure,
  - the trial was designed to detect a difference in the rates of death from cardiovascular causes.

N Engl J Med 2014; 371:993-1004September 11, 2014



Significance

- 20% change in all areas in patients with EF below 40%
- No impact with preserved EF

Conclusion

Atrial Fibrillation and Cryptogenic Stroke

- Do we need to do workup in addition to 24 hours of monitoring to look for atrial fibrillation in patients who have had a TIA or stroke with no clear etiology?

Background

- Over 25% of strokes have no clear cause detected after standard evaluation.
- Antiplatelet therapy is then recommended

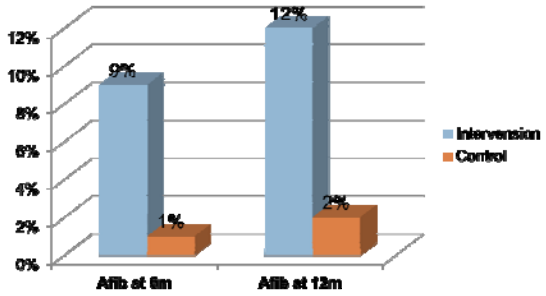
N Engl J Med 2014;370:2467-77.

Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial - Methods

- 441 patients > 40 years old with cryptogenic stroke and no afib on 24 hour monitoring randomized within 3 months of stroke.
- Long-term monitoring with an insertable cardiac monitor (ICM) vs conventional follow-up (control)
- The primary end point was time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months; secondary end points within 12 months.

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

Incidence of Afib at 6 and 12 months



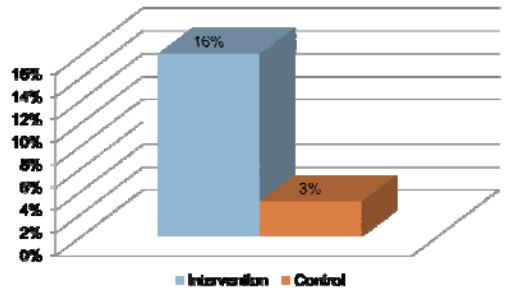
N Engl J Med 2014;370:2478-86.

Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) Trial - Methods

- 572 patients > 55 years of age, without known atrial fibrillation, who had had a cryptogenic ischemic stroke or TIA within the previous 6 months
- Cause undetermined after standard tests, including 24-hour electrocardiography [ECG])
- Randomized to ECG monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-hour monitor (control group).

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

Atrial Fibrillation Lasting ≥ 30 secs



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

Conclusion

- Noninvasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of atrial fibrillation by a factor of more than five

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

Putting it together

- Editorial: "The results of two studies published in this issue of the *Journal* indicate that prolonged monitoring of heart rhythm should now become part of the standard care of patients with cryptogenic stroke."

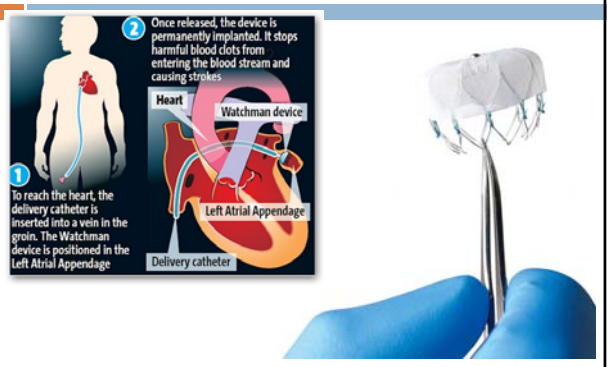
N Engl J Med 2014;370:2532-3.

Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation

- **Participants:** 707 patients with nonvalvular AF and at least 1 additional stroke risk factor (CHADS2 score ≥1).
- **Interventions:** Left atrial appendage closure with the device (n = 463) or warfarin (n = 244; target international normalized ratio, 2-3).

JAMA. 2014.;312(19):1988-98. doi: 10.1001/jama.2014.15192.

Watchman Atrial Device



- At a mean follow-up of 3.8 years:
  - Mechanical Closure:
    - Primary Events – 8%
    - Primary event rate -2.3 events per 100 patient-years
  - Warfarin
    - Primary Events - 14%
    - Primary event rate – 3.8 events per 100 patient-years
  - Rate ratio - 0.60 - met prespecified criteria for both noninferiority and superiority

Conclusion

AN UPDATE ON HYPOGLYCEMIA AND ADVERSE MACROVASCULAR EVENTS

Hypoglycemia: Background

- Associated with significant morbidity and mortality
- Can provoke acute cardiovascular and cerebrovascular events
- Previous studies have tried to decrease severity and frequency of microvascular and macrovascular disease but at the risk of tight glycemic control

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

Macrovascular Events: Background

- Associated with chronic inflammation
  - See increments in specific inflammatory markers, especially IL-6
- Insulin resistance and diabetes increases risk of events

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

The Question

Is there a prospective association between severe hypoglycemia and macrovascular outcomes in patients with T2DM and is this association mediated by inflammatory mechanisms?

Study Design and Patients

- Prospective study design
- 1,066 men and women between the ages of 60-75 years old, with established T2DM, living in the Lothian region of Scotland
  - Selected from the Lothian Diabetes Register
- Participants had to be receiving treatment with insulin and/or oral agents, or with diet alone but have a HbA1c > 6.5%
- Baseline h/o hypoglycemia and plasma inflammatory markers were recorded
  - Their association with macrovascular events after 4 years was followed and assessed

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

Study Outcome Definitions

- Definitions
  - Macrovascular disease
    - Included h/o MI, angina, stroke and TIA
  - Macrovascular outcomes vs. composite disease
    - Macrovascular outcomes included MI, angina, TIA or stroke
    - Composite disease was defined as one or more episodes of MI, angina, TIA or stroke
  - Hypoglycemia
    - Defined as having any episodes of hypoglycemia that required external assistance for recovery

Overview of Study Results

- At baseline, 87 participants (8.2%) reported one or more episodes of hypoglycemia
- **At follow-up, 99 participants (9.3%) had suffered a new macro-vascular event**
- **Hypoglycemia was associated increased odds of macrovascular events (OR 2.11, p = 0.035)**
  - Coronary events (OR 2.44, p = 0.023)
    - **Largely due to MI (OR 4.02, p = 0.004)**

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

Table 2—Effects of history of severe hypoglycemia at baseline on macrovascular events at 4-year follow-up

	Unadjusted		Age/sex adjusted		CV risk factor adjusted*		Adjusted†	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Macrovascular disease events	2.43 (1.35, 4.38)	0.003	2.63 (1.45, 4.78)	0.001	2.26 (1.17, 4.36)	0.015	2.11 (1.06, 4.21)	0.035
Coronary heart disease event	3.20 (1.66, 6.14)	<0.001	3.27 (1.69, 6.33)	<0.001	2.59 (1.24, 5.41)	0.011	2.44 (1.13, 5.26)	0.023
Cerebrovascular disease event	1.19 (0.42, 3.43)	0.742	1.39 (0.48, 4.03)	0.550	1.16 (0.36, 3.78)	0.804	1.01 (0.29, 3.61)	0.983
MI	4.76 (2.21, 10.23)	<0.001	4.98 (2.29, 10.84)	<0.001	3.67 (1.48, 9.07)	0.005	4.02 (1.54, 10.48)	0.004
Stroke	1.17 (0.35, 3.92)	0.799	1.37 (0.40, 4.64)	0.616	1.02 (0.27, 3.84)	0.978	0.86 (0.21, 3.56)	0.836

Sample size: unadjusted $n = 1,066$; adjusted $n = 978$. CV, cardiovascular. *Logistic regression adjusted for baseline age, sex, smoking, blood pressure, HbA_{1c} level, cholesterol level, HDL level, BMI, eGFR, microalbuminuria, use of lipid-lowering and blood pressure–lowering medications; and prevalent (baseline) composite macrovascular events, CV disease events, cerebrovascular disease events, MI, and stroke. †Logistic regression model adjusted for same variables as CV risk factor–adjusted model, with the addition of baseline diabetes treatment and duration.

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

Overview of Study Results (cont'd)

- Increased levels of plasma inflammatory markers were noted in those that experienced a hypoglycemic event, but results statistically insignificant.

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

Conclusion Similar to Findings of Previous Studies

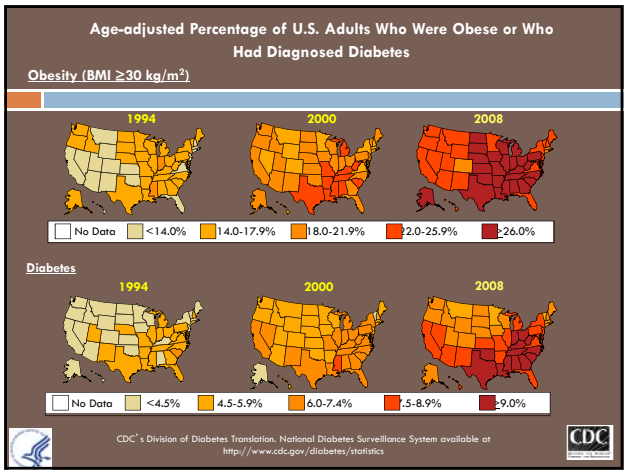
- ADVANCE Trial
  - Showed a strong association between severe hypoglycemia and macrovascular events with a hazard ratio (HR) of 2.88
- ORIGIN Trial
  - Showed that the risk of composite CV death, nonfatal MI or stroke was increased when people had experienced severe hypoglycemia
    - HR 1.58

Bedenis, Rachel, et.al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. September 2, 2014. DOI: 10.2337/dc14-0908

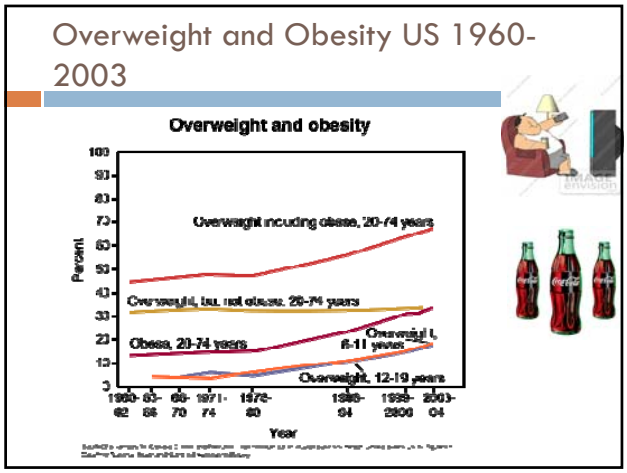
The odds of suffering a macrovascular event were higher in patients with T2DM who had a h/o severe hypoglycemia. Evidence not clear that a pro-inflammatory state had a major role in mediating this association.

PHARMACOLOGICAL MANAGEMENT OF OBESITY: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE

J Clin Endocrinol Metab 2015; 100(2):342-362
(http://dx.doi.org/10.1210/jc.2014-3415)



Overweight and Obesity US 1960-2003



VeiwPoint - David

Medications – FDA Approved 2012

- Lorcaserin (Belviq)
  - approx 4% weight loss compared to placebo
- Phentermine/ Topiramate ER (Qysimia)
  - Approx 10-12% weight loss compared to placebo
- FDA approval as adjuncts to lifestyle modification for the treatment of:
  - overweight patients (body mass index [BMI] ≥27 kg/m2 but <30 kg/m2) with comorbidities such as T2DM, hypertension, and dyslipidemia,
  - obese patients (BMI ≥30 kg/m2) regardless of whether comorbidities are present

Medications – FDA Approved fall/Winder 2014

- Naltrexone HCl/bupropion HCl (Contrave) extended release
  - 2% to 4% more body weight on average than placebo group
- Liraglutide (Saxenda)
  - average weight loss of approximately 4% compared to placebo

Endocrine Society Recommendations

- Lifestyle modification as a component of all approaches to obesity.
  - "Just as increasing the dose of medication increases weight loss, increasing the intensity of behavioral modification increases weight loss"
- Pharmacotherapy (BMI $\geq$ 27 kg/m2 with comorbidity or BMI over 30 kg/m2)
  - Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications.

Pharmacotherapy for Obesity

- Assessment of efficacy and safety at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight loss medications.
- If response to weight loss medication is effective (weight loss $\geq$ 5% of body weight at 3 mo) and safe, we recommend that the medication be continued. If deemed ineffective (weight loss < 5% at 3 mo) or if there are safety or tolerability issues at any time, we recommend that the medication be discontinued

- In patients with T2DM who are overweight or obese, use of antidiabetic medications that have additional actions to promote weight loss (GLP-1 analogs or SGLT-2 inhibitors), in addition to metformin
  - in obese patients with T2DM requiring insulin therapy, suggest adding at least one of the following: metformin or GLP-1 agonist to mitigate associated weight gain due to insulin
- In patients with CV disease who seek pharmacological treatment for weight loss, avoid sympathomimetics

Bariatric surgery

- BMI $\geq$ 35 kg/m2 with comorbidity or BMI over 40 kg/m2 as adjuncts to behavioral modification

Conclusion

Effect of Citalopram on Agitation in Alzheimer Disease

- Intermittent agitation is common with dementia.
- Antipsychotic drugs are used widely have significant dangers including increased mortality, and are of uncertain efficacy

JAMA. 2014;311(7):682-691.

The Question

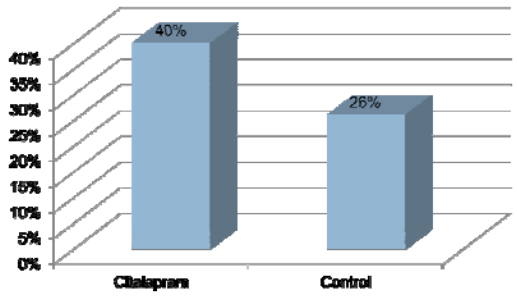
- Do SSRIs have a place in the treatment of agitated dementia?

Methods

- DBRT 186 patients with probable Alzheimer disease and clinically significant agitation
- Intervention: psychosocial intervention plus either citalopram (n = 94) or placebo (n = 92) for 9 weeks.
  - Dosage began at 10 mg per day with planned titration to 30 mg per day over 3 weeks based on response and tolerability.

JAMA. 2014;311(7):682-691.

Moderate or marked improvement from baseline



P=0.01

JAMA. 2014;311(7):682-691.

- Worsening of cognition (−1.05 points*P* = .03) and QT interval ,prolongation (18.1 ms;; *P* = .01) were seen in the citalopram group.

JAMA. 2014;311(7):682-691.

Conclusion

Epidurals in Spinal Stenosis

- 400 pts with lumbar central spinal stenosis and moderate-to-severe leg pain and disability
- Randomly assigned to receive epidural injections of glucocorticoids plus lidocaine or lidocaine alone.
- The patients received one or two injections before the primary outcome evaluation, performed 6 weeks after randomization and the first injection.
- The primary outcomes were the score on the Roland–Morris Disability Questionnaire (RMDQ, in which scores range from 0 to 24, with higher scores indicating greater physical disability) and the rating of the intensity of leg pain (on a scale from 0 to 10, with 0 indicating no pain and 10 indicating "pain as bad as you can imagine").

N Engl J Med 2014; 371:11-21July 3, 2014

Results

- No significant between-group differences in the RMDQ score

Beneficial Effect of Pistachio Consumption on Glucose Metabolism, Insulin Resistance

- 54 pts with prediabetes consumed two diets, each for 4 months with 2-week crossover washout: a pistachio-supplemented diet (PD) and a control diet (CD)
- Diets were isocaloric and matched for protein, fiber, and saturated fatty acids.

Diabetes Care 2014;37:1–8

Results

- Fasting glucose, insulin, and insulin resistance decreased significantly after the PD compared with the control diet.
- Other cardiometabolic risk markers including fibrinogen and oxidized LDL significantly decreased under the PD compared with the control diet ($P < 0.05$),

Diabetes Care 2014;37:1–8

Conclusion

- Eat more pistachios