CUF1

Update In General Medicine

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Note: All copyrighted figures/tables have been removed. Please refer to the original articles for graphical presentations of methods and results. The titles of the articles that we plan to include in the oral presentation are highlighted in orange. The final oral presentation may differ from the handout.

Cardiovascular

Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial. Schierbeck LL, Rejnmark L, et al. *BMJ* 2012;345:e6409

Objective: To investigate the long term effect of hormone replacement therapy on cardiovascular outcomes in recently postmenopausal women.

Study Design: Open label randomized controlled trial

Participants: Number of subjects: 1006. Inclusion criteria: Healthy women aged 45-58 who were recently postmenopausal or had perimenopausal symptoms in combination with recorded postmenopausal FSH levels. Women aged 45-52 who had hysterctomy were included if they had elevated FSH. Exclusion criteria: History of bone disease, uncontrolled chronic disease, previous or current cancer or VTE, current or past glucocorticoid treatment for > 6 months, current or previous HRT within past 3 months, EtOH or drug dependence. Baseline characteristics: mean age 49.7, BMI 25.2, BP 130/81; mean time since menopause 7 months, 43% smokers; women in the control group were about 5.7 months older than those in the treatment group.

Intervention: HRT (n = 502) or no HRT (n = 504). Women in the treatment group with intact uterus received 2mg 17-B-estradiol for 12 days, 2mg 17-B-E2 + 1mg norethisterone for 10 days, and 1mg 17-B-E2 for 6 days. Women s/p hysterectomy first line treatment was 2mg 17-B-E2 daily.

Outcomes: Primary: Composite of death, admission to hospital for MI, or heart failure. Secondary: included death, MI, HF, stroke, venous thromboembolism (VTE), and cancer.

Results: Planned duration of study was 20 years, but women advised to stop HRT early after 10 years (Aug 2002) because of data from the Women's Health Initiative indicating adverse outcomes with the use of HRT. The women were followed for an additional 5.7 years for a total mean follow up time of 15.8 years. Groups did not differ for stroke, VTE, or cancer after 10 years of therapy or at 16 years.

After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint vs 33 in the control group (hazard ratio 0.48, 95% CI 0.26 to 0.87; P=0.015) and 15 died vs 26 (0.57, 0.30 to 1.08; P=0.084). The reduction in cardiovascular events was not associated with an increase in any cancer (36 in treated group vs 39 in control group, 0.92, 0.58 to 1.45; P=0.71) or in breast cancer (10 in treated group vs 17 in control group, 0.58, 0.27 to 1.27; P=0.17). The hazard ratio for deep vein thrombosis (2 in treated group *v* 1 in control group) was 2.01 (0.18 to 22.16) and for stroke (11 in treated group vs 14 in control group) was 0.77 (0.35 to 1.70).

After 16 years the reduction in the primary composite outcome was still present and not associated with an increase in any cancer.

Despite limitations, the results are consistent with secondary analysis of WHI data, which showed a nonsignificant reduction in coronary heart disease (CHD) (nonfatal MI, CHD-related death, or silent MI) in the estrogen-only group when HRT was initiated in younger, recently menopausal women

Hormone replacement therapy (HRT) vs no HRT in recently postmenopausal women

Outcomes	**Event rates**		**After 10 years of therapy**	
	HRT	**No HRT**	**RRR**	**NNT**
Death, MI, or HF*	3.2%	6.5%	50% (11 to 72)	31 (22 to 144)
			At 16 years	
Death, MI, or HF**	6.6%	11%	37% (4 to 59)	26 (17 to 251)

***Death (3.0% vs 5.2%, *P* = 0.08), MI (0.2% vs 0.8%, *P* = 0.21), HF (0.2% vs 1.4%, *P*= 0.07)**
****Death (5.4% vs 7.9%, *P* = 0.10), MI (1.0% vs 2.2%, *P* = 0.14), HF (0.6% vs 1.6%, *P*= 0.15)**

Limitations: (1) Open label, without placebo or blinding, (2) In regards to breast and other cancer rate, longer follow up may be necessary to draw definitive conclusions because of potential lag time, (3) healthier women may not develop adverse events as quickly, (4) number of events was low, (5) 1006 patients vs 27000 in WHI (younger 50 vs 64, avg time from menopause 0.7 vs 10 years).

Impact on Practice: HRT for the relief of symptoms early in menopause seems safe and may provide CV benefit depending on the dose, formulation, and route of administration.

Lipid modifying therapies and risk of pancreatitis. Preiss D, Tkkkanen MJ, Welsh, P, et al. JAMA. 2012;308:804-811.

Objective: to examine the association between statins or fibrates and the incidence of pancreatitis.

Study Design: meta-analysis

Selection of studies: Number included: 28 (21 statin, 7 fibrate). Inclusion criteria: randomized trials of statins or fibrates with >1000 subjects and mean follow up > 1 year; either published or unpublished data regarding incident pancreatitis. Exclusion criteria: studies including transplant or hemodialysis patients, comparing combination therapy, too small/short, data unavailable.

Outcomes: report of pancreatitis as an adverse event during a trial; cases identified by text word searches of event reports, self reported hospitalization data, Medical Dictionary for Regulatory Activities classifications, ICD-10 codes. All cases were included, regardless of potential etiology.

Results: All trials were high quality (Jadad score 5/5). There was minimal heterogeneity and no publication bias detected. The average duration of follow up in the statin trials was 4.2 years and in the fibrate trials was 5.3 years. Baseline average triglyceride levels were less than 200 in all trials (118-187 in the statin trials; 145-184 in the fibrate trials). Statin use was associated with a lower rate of pancreatitis:

	# participants	**RR for pancreatitis**	**NNT/(NNH)**
All statin trials	153,414	0.79 (0.65-0.95)	1187
Statin vs. placebo	113,800	0.77 (0.62-0.97)	1175
High dose vs. moderate dose statin	39,614	0.82 (0.59-1.12)	NA
Fibrate vs. placebo	40,162	1.39 (1.00-1.95)	(935)

Results were similar in all sensitivity analyses.

Limitations: (1) Pancreatitis was not a pre-specified endpoint in any of the trials; (2) the recording of pancreatitis was not standardized; (3) it was not possible to stratify the analysis by etiology of pancreatitis; (4) patient level data was not available; (5) participants with marked hypertriglyceridemia were excluded from the trials.

Impact on Practice: In patients with mild hypertriglyceridemia, statins are associated with a small decrease in the risk of pancreatitis. There is a trend toward increased risk with fibrates. This study does not address the relationship between these medications and pancreatitis in patients with moderate-severe increases in triglyceride levels.

Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Ridker PM, Pradhan A, MacFadyen JG, et al. Lancet 2012;380:565-71.

Objective: To assess the balance of vascular benefits and incident diabetes risk of statin use.

Study Design: Analysis of randomized, double-blind, placebo-controlled JUPITER trial participants, stratified on the basis of the presence or absence of any of four major risk factors for developing diabetes (metabolic syndrome, impaired fasting glucose, body-mass index 30 kg/m2 or higher, or A1c > 6%).

Participants: Number of subjects: 17603. Inclusion criteria: Men 50 years of age or older or women 60 years of age or older with an LDL <130, a high-sensitivity CRP of 2 or higher with no prior history of cardiovascular disease or diabetes. Exclusion criteria: Previous or current use of lipid-lowering therapy, current use of hormone-replacement therapy, evidence of hepatic dysfunction, a CK level > three times the upper limit of normal, sCr > 2, diabetes, uncontrolled hypertension (>190 SBP or >100 DBP), cancer within 5 years before enrollment, uncontrolled hypothyroidism, recent history of alcohol or drug abuse. Baseline characteristics: Median age 66, 41% women, 70% white, median BMI 30.7, median LDL 50, median A1c 5.8%.

Intervention: Participants were randomly assigned to rosuvastatin 20 mg or placebo and followed up for a median of 2 years.

Outcomes: Primary: Occurrence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes). Secondary: Protocol-prespecified secondary endpoints of VTE, all-cause mortality, and incident physician-reported diabetes.

Results: Trial participants with one or more major diabetes risk factor (n=11508) were at higher risk of developing diabetes than were those without a major risk factor (n=6095). In individuals with one or more risk factors, statin allocation was associated with a 39% relative risk reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47—0·79, p=0·0001) but an **absolute risk reduction of only 0.51%** (NNT = 196), and a 28% relative risk increase in diabetes (1·28, 1·07—1·54, p=0·01), but an **absolute risk increase of only 0.47%** (NNH = 212). For those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed.

For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33—0·68, p=0·0001), but an **absolute risk reduction of only 0.76%** (NNT = 131) and no increase in diabetes (0·99, 0·45—2·21, p=0·99). For such individuals, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed.

Analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin vs 216 on placebo; HR 1·25, 95% CI 1·05—1·49, p=0·01), demonstrated that in

comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5·4 weeks (84·3 [SD 47·8] weeks on rosuvastatin vs 89·7 [50·4] weeks on placebo).

Limitations: (1) All participants in the trial had elevated hsCRP, which is an independent risk marker for both incident T2DM and incident cardiovascular events; (2) rosuvastatin at only one dose (20 mg daily) was assessed vs placebo, which may be an incomplete assessment of its risk in light of the data about intensive-dose statin therapy conferring a higher risk incident diabetes than lower dose therapy; (3) median follow up within JUPITER was only 2 years, which is insufficient to assess long-term risks and benefits; (4) the trial was sponsored by AstraZeneca

Impact on Practice: In the absence of any major diabetes risk factors, statin therapy appears to have no significant risk for causing incident diabetes. Even for those patient with one or more major diabetes risk factors, the absolute risk increase of developing incident diabetes from starting statin therapy is small and should not deter the initiation of statin therapy when indicated.

Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events. Rizos EC, Ntzani EE, Bika E, et al. JAMA. 308:1024-1033.

Objective: to determine the association between omega-3 fatty acids and CV disease.

Study Design: meta-analysis

Selection of Studies: Number included: 20. Inclusion criteria: randomized controlled trials in adults of either dietary or supplemental omega-3s vs. another diet or placebo; primary or secondary prevention populations; reporting all cause mortality, cardiac death, sudden death, MI, or stroke. Exclusion criteria: treatment duration > 1 year.

Outcomes: All cause mortality in 19 trials (68,426 subjects), cardiac mortality in 15 (61,554 subjects), sudden death in 8 (44,865), MI in 14 (55908), stroke in 9 (52,589).

Results: 2/20 trials used dietary interventions; 18/20 used supplements with a mean dose 1.51 g/day. The median treatment duration was 2 years (range 1-6.2); 13/20 were secondary prevention populations. Most studies were considered high quality; 4 did not use intention to treat analysis, and 4 were not double blind. There was no publication bias. The two studies of diet showed opposite results. Results for the trials of supplements are as follows: There was no effect on all cause mortality (RR 0.96, 0.91-1.02), with benefit found in studies published before 2007 but not in studies published in 2007 or later (see figure 5 in the paper). There was no significant difference for cardiac death, sudden death, MI, or stroke. Sensitivity analyses using omega-3 dose, prevention setting, presence of an ICD, and blinding in the trial did not change the results.

Limitations: (1) duration of trials may have been too short to detect an effect; (2) patient level data not used; (3) significant heterogeneity for some results, although not for the all cause mortality endpoint (4) different doses/formulations of omega-3s used.

Impact on Practice: In mostly a high risk, secondary prevention population, omega-3 supplementation had no effect on cardiac events or all cause mortality. Although the study cannot determine causality, one could theorize that omega-3s add little to contemporary improved risk factor management with anti-platelet agents, statins, and ACE inhibitors.

Primary prevention of cardiovascular disease with a Mediterranean diet. Estruch R, Ros E, Salas-Salvado J, et al. NEJM. 2013;

Objective: to compare the effects of a Mediterranean diet and a low fat diet on primary CV prevention.

Study Design: Parallel group, multicenter, randomized trial in Spain.

Participants: Number of subjects: 7447. Inclusion criteria: men 55-80 and women 60-80 with no CV disease, with either DM or ≥ 3 risk factors (smoking, HTN, ↑ LDL, ↓ HDL, obesity or FH premature CVD). Exclusion criteria: documented CVD, BMI > 40, immunodeficiency, severe condition prohibiting participation or limiting life expectancy to < 1 yr, alcoholism, food allergies, low predicted likelihood to change dietary habits. Baseline characteristics: mean age 67 and BMI 30 (47% > 30); 55% female; 97% white from Europe; 48% DM; 82% HTN; 72% dyslipidemia; 22% FH, 14% current smokers/25% former smokers; 40% on statins; 49% ACEI; 21% diuretics; 20% anti-platelet agent; baseline adherence to Med. Diet 8.7 (0-14, higher more adherent).

Intervention: Patients were randomized to a Med. diet + 1 liter/week extra virgin olive oil (EVOO), a Med diet + 30 g/day of mixed nuts (15 g walnuts, 7.5 g hazelnuts, 7.5 g almonds), or a control low fat diet (see table below for general guidelines). The 2 Med. diet groups received individual and group instruction at baseline and quarterly throughout the study. The control group initially received just printed materials, but 3 years into the study (2006), the control group subjects were also given individual and group instruction.

Outcomes: Primary: composite of MI, CVA, or CV death. Secondary: CVA, MI, CV death, any cause death.

Results: The study was stopped in 2010, after a median of 4.8 years of follow up. 7% of patients were lost to follow-up (3.6% Med + EVOO, 6.3% Med + nuts, 11.3% control); they were younger, heavier, and less adherent than participants who remained in the trial. The Med diet groups had higher Med diet adherence scores (10.5 vs. 8.7) and diet history + urinary markers indicating significantly more intake of EVOO or nuts, as assigned. The Med. diet groups ate slightly more fish and legumes, but the primary differences in intake between treatment and control groups were in the intake of either EVOO or nuts. There was no difference in exercise or medications between the groups. There was a significant reduction in the primary endpoint and stroke in the Med. diet groups, with no difference in MI, CV death, or any cause death.

	Med EVOO*	**Med Nuts**	**Control**	**HR (both Med vs. control)**	**NNT**
Primary Endpoint	8.1	8.0	11.2	0.71 (0.56-0.90)	
Stroke	4.1	3.1	5.9	0.61 (0.44-0.86)	
MI	3.1	3.0	3.9	0.77 (0.52-1.15)	

* All event rates per 1000 person-yrs.

Limitations: (1) the control group did not receive intensive counseling for the first 3 yrs; (2) the patients lost to follow up were different from those who remained in the study; however, those lost to follow up were sicker and more were lost from the control group, biasing the study in favor of the control group; (3) there was missing data; however, sensitivity analyses using different

methods to account for this did not change the results; (4) at baseline participants ate more of a Mediterranean diet than most Americans; however, this also biases the study in favor of the control group.

Impact on Practice: A Mediterranean style diet, supplemented with EVOO or nuts, reduces CV events in a high risk, primary prevention population. It is not clear how to implement this diet in the much more heterogeneous American population.

Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate risk individuals. Yeboah J, McClelland RL, Polonsky TS, et al. JAMA. 2010;308:788-795

Objective: to assess the improvements in prediction accuracy and reclassification with additional testing in Framingham intermediate risk patients.

Study Design: prospective cohort study (MESA study)

Participants: Number of subjects: 1330/6814 Framingham (FRS) intermediate risk (> 5 to <20% 10 year risk) patients with complete data. Inclusion criteria: men and women aged 45-84 without known cardiovascular disease, recruited from Chicago, Baltimore, North Carolina, Los Angeles County, New York City, St. Paul, Minnesota. Baseline characteristics: mean age 64, BMI 28, FRS 8.8, cholesterol 197, HDL 46, LDL 122, BP 130/74; 33% female, 36% white, 17% Chinese, 22% black, 25% Hispanic, 46% never smokers, 14% statin use, 38% BP medication use.

Intervention: Each subject underwent measurement of (1) family history of CAD [asking whether immediate family members had a fatal or nonfatal MI], (2) ABIs, (3) coronary artery calcium [CAC] score by either gated electron beam or multidetector CT, centrally read (4) brachial flow-mediated dilation [FMD], (5) high sensitivity CRP, (6) carotid intima-media thickness [CIMT].

Outcomes: Primary: Net reclassification improvement (NRI)*, which represents the relative improvement in classification when an additional predictive variable is added to a baseline model consisting of the FRS + race/ethnicity. Secondary: ROC curve. An adjudicated committee determined incident CHD (MI, CHD death, resuscitated cardiac arrest, angina [if followed by revascularization] and incident CVD (addition of stroke and CVD death to other endpoints) during a median follow up period of 7.6 years.

**NRI = probability correct reclassification to higher risk category – probability incorrect reclassification to lower risk category + probability correct reclassification to lower risk category - probability incorrect reclassification to higher risk category*

Results: Brachial FMD and CIMT were not associated with CHD in a multivariate adjusted analysis. Addition of each additional risk marker improved the ROC curve, with the CAC having the biggest effect. Addition of CAC led to the greatest amount of correct reclassification (see figure in paper).

Limitations: (1) relatively small population (2) follow up did not extend to 10 years (3) frequency of screening with CAC not addressed (4) overall risk/benefit ratio of CAC unclear, considering radiation exposure (5) family history of premature CAD not specifically assessed.

Impact on Practice: Overall, this is a well done study suggesting that of the markers studied, CAC has the most significant impact on risk stratification for patients with FRS scores between 5 and 20%. Whether CAC should be done in all such patients is not yet clear.

Fasting time and lipid levels in a community-based population. Sidhu D, Naugler C. Arch Intern Med. 2012;172:1707-1710.

Objective: to investigate the association of fasting duration with lipid levels

Design: cross-sectional analysis

Participants: Number of subjects: 209180 individuals who had lipid panels performed by a single laboratory in Calgary. Baseline characteristics: 53% female; mean age 52.8, total cholesterol 183, HDL 55, calculated LDL 103, triglycerides 127.

Analysis: Time since the last meal was based on self report, and 4253 records with missing meal data were excluded. Men and women were analyzed separately, and results were adjusted for age.

Results: 1.5% of patients had triglyceride levels over 400. The mean total cholesterol and HDL levels varied by < 2%, the mean calculated LDL by <10%, and the mean triglycerides by < 20%. Triglyceride and calculated LDL levels were significantly different in patients with fasting times of ≤ 5 hours for women and ≤ 6 hours for men, compared to those in patients with > 8 hours of fasting.

	Men (≤ 6 hours)	Women (≤ 5 hours)
Triglycerides: ≤5- 6 hours fasting time	150-165 (mean 156)	124-134 (mean 128)
Triglycerides: > 8 hours fasting time	117-135 (mean 124)	107-114 (mean 110)
LDL: ≤ 5-6 hours fasting time	89-95 (mean 93)	90-95 (mean 92)
LDL: > 8 hours fasting time	93-102 (mean 97)	96-102 (mean 99)

Limitations: (1) Fasting times were based on self report and could have been erroneous; (2) whether or not a patient fasted could have been related to underlying medical conditions or treatment, leading to a self selected group of longer duration fasters (3) individual variation can be masked in such a large sample; (4) the statistical differences found may not be clinically significant

Impact on Practice: On average, fasting times do not significantly affect lipid panel results, and even the differences found may not affect clinical management. Therefore, many patients can be managed with non-fasting sample results. However, fasting may have a big impact on results in selected patients, particularly those with metabolic syndrome.

Meta-analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran, Rivaroxaban, Apixaban)* Versus *Warfarin* in Patients with Atrial Fibrillation. Miller CS, Grandi SM, Shimony A, et al. Am J Cardiol. 2012; 110: 453-460.

Objective: To examine with long-term efficacy and safety of the new oral anticoagulants (NOAC) compared to warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation (AF)

Study design: Meta-analysis of RCTs comparing NOACs to warfarin

Study selection: Number of subjects: 44,563. Inclusion: RCT (open-label or blinded), randomized subjects to warfarin or NOACs, atrial fibrillation patients, published in peer-reviewed journals, follow-up duration of >1 year. Exclusion: studies examining ximelogatran because no longer on the market. Baseline characteristics: Mean age 70-73 years; 35-40% women, mean CHADS2 score 2.1-3.5

Outcomes: Main efficacy outcome: composite end point of stroke and systemic embolism (SE); Main safety outcome: major bleeding; Other safety outcomes: Gastrointestinal bleeding, intracranial bleeding

Results: Three studies were identified (ARISTOTLE-apixaban, RE-LY-dabigatran, ROCKET AF-rivaroxaban); each was a noninferiority trial. Half of patients received NOACs and half warfarin. Mean length of follow-up 1.8 to 2.0 years; mean time in therapeutic range for warfarin 55%-64%. All trials found that the NOACs were noninferior to warfarin with respect to stroke and SE and ARISTOTLE and RE-LY found the NOACs to be superior to warfarin in this regard—pooled RR 0.78 (95% CI 0.67-0.92). All 3 drugs were associated with lower risk of hemorrhagic stroke – pooled RR 0.45 (95% CI 0.31-0.68). There was no significant difference in risk of major bleeding; lower risk of intracranial bleeding (RR 0.49, 95% CI 0.36-0.66) and no difference in GI bleeding.

Limitations: There was heterogeneity between the trials including study drugs and included populations. The ROCKET-AF trial performed a per-protocol analysis, which can introduce bias. Patients in the warfarin group were in therapeutic range 55-64% of the time but this is consistent with other clinical trials. While investigators found a significant difference, the studies were not powered to assess the bleeding risks.

Impact on practice: Clinicians should consider using these agents in patients with atrial fibrillation who require anticoagulation and are reluctant to start warfarin due to monitoring needs or patients who are having difficulty with maintaining therapeutic range.

Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization.
Roe MT, Armstrong PW, Fox KA, et al. NEJM. 2012; 367(14): 1297-1309.

Objective: To evaluate if combined aspirin and prasugrel therapy is superior to aspirin and clopidogrel therapy is for long-term therapy in patients younger than 75 years with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) who are medically managed.

Study design: Multicenter, international, randomized, double-blind, double-dummy, active control event-driven trial

Participants: Number of subjects: 7243. Inclusion: Patients with acute coronary syndrome (ACS) if selected for medical management within 10 days after the index event and had at least one of the following risk factors: at least 60 years of age; diabetes mellitus; previous MI; previous coronary revascularization. Exclusion: history of TIA or stroke, coronary revascularization within the previous 30 days; on hemodialysis; concomitant treatment with an anticoagulant. Baseline characteristics: Mean age 62 years, 1/3 female, 67% NSTEMI, 28% previous PCI and 15% previous CABG

Intervention: Randomized to either prasugrel or clopidogrel and all patients were also treated with aspirin (encouraged daily dose of 100mg); treatment was continued for at least 6 months and maximum of 30 months

Outcome: Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke in patients younger than 75 years

Results: Median duration of treatment was 14.8 months; median duration of follow-up was 17.1 months. During follow-up, 7.9% underwent revascularization. At 30 months, there was no significant difference in the primary end point: 13.9% in the prasugrel group and 16.0% in the clopidogrel group. There was no difference in major bleeding events at 30 months (1.1% patients in prasugrel vs. 0.8% in clopidogrel). A prespecified analysis of recurrent ischemic events suggested a lower risk among the prasugrel group (HR 0.85, 95% CI 0.72-1.00)which was more pronounced after 12 months of treatment (HR 0.64, 95% CI 0.48-0.86).

Limitations: This study is limited to patients in whom medical management was pursued so cannot be generalized to all patients with ACS and limited to younger patients. Four sites were found to have violated key protocol requirements but their enrolled patients were removed from the database before unblinding and data analysis.

Impact on practice: There does not seem to be superiority of prasugrel to clopidogrel in reducing cardiovascular events; this may be important now that clopidogrel is generic in the event insurance coverage or affordability of prasugrel is a concern for your patients.

Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Artery Disease. (FAME 2) De Bruyne B, Pijls NHJ, Kaalesan B et al. N Engl J Med 2012;367:991-1001.

Objective: To compare the effectiveness of PCA and optimal medical therapy (OMT) vs. optimal medical therapy alone in patients with functionally significant CAD (as evidence by limited fractional flow).

Study Design: multicenter international RCT

Participants: Number of subjects: 1220. Inclusion criteria: stable CAD, at least one stenosis > 50% reduction in diameter of one native vessel, eligible for PCI. Exclusion criteria: Patients in whom preferred treatment is CABG, left main disease requiring revascularization, patients w/i 1 week of MI, prior CABG, contraindication to dual anti-platelet therapy, LVEF < 30%, severe LVH, potential for non-compliance. Baseline characteristics: mean age 64, 20% tobacco use, 78% HTN, DM 27%, prior MI 37%, 68% class II to IV angina.

Intervention: Patients with stenoses thought to be significant underwent adenosine induced hyperemia. Those with a FFR of ≤ 80% were randomized to best medical therapy with or without PCA. Patients with FFR of > 80% received OMT and were not randomized. All patients received ASA (80 – 325 mg QD), metoprolol (with or without calcium channel blocker), ACEi or ARB and atorvastatin to lower LDL to < 70mg/dl. PCI patients received clopidogrel and drug eluting stents.

Outcomes: Primary: Composite of death from any cause, nonfatal myocardial infarction or unplanned hospitalization leading to urgent revascularization during the first two years. (Urgent revascularization was defined as patients admitted to the hospital with increasing or persistent chest pain with or without ST segment changes or elevations of biomarkers and the procedure was performed during the same hospitalization.)

Results:
1. The study was terminated early due to a highly significant difference in the primary endpoint after a mean f/u of 213 days. Among those with low FFR the authors found:

Outcome	OMT & PCI	OMT	HR	NNT
Primary outcome	4.3%	12.7%	0.32 (0.19 – 0.53)	12
Death from any cause	0.2%	0.7%	0.33 (0.03 – 3.17)	NS
Myocardial infarction	3.4%	3.2%	1.05 0.51 – 2.19)	NS
Urgent revascularization[1]	1.6%	11.1%	0.13 (0.06 – 0.3)	10

2. Patients with FFR > 80% had a low rate of events on optimal medical therapy (primary outcome 3%, death 0%. MI 1.8%), urgent revascularization 1.8%

Limitations: (1) Follow-up was short and re-stenoses may not yet have emerged. (2). The awareness of stents may have influenced decisions re revascularization. (3) The primary end point includes urgent revascularization which improved markedly, but MI and death did not. (4) Only the PCI group received dual platelet therapy.

Impact on Practice: The study improves our understanding of who may benefit from PCI with stable CAD. Patients with good hemodynamic function (and high FFR) had low event rates with just OMT. Among those with limited flow, PCI decreased urgent revascularizations but not MI or death.

[1] 50% of these patients had ST segment depression, biomarker elevations or both.

Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomized, clinical SUNTAX trial. Mohr FW, Morice MC, et al. Lancet 2013;381:629-38

Objective: to compare the effectiveness of CABG vs. paclitaxel-eluting PCI in patients with triple vessel or left main CAD disease

Study Design: multicenter randomized controlled trial

Participants: Number of subjects: 1800 Inclusion criteria: patients with de-novo three vessel or left main disease. Baseline characteristics: Mean age 65, 78% male, 25% medically treated DM. There was a mean of more than 4 treatable lesions per patient and an average baseline SYNTAX score 29 (a measure of disease severity incorporating the number of lesions, their complexity and location). Angiograms were reviewed and patients included who had vascular disease felt equally amenable to CABG or PCI by a cardiac surgeon and interventional cardiologist.

Intervention: PCI or CABG with the goal of achieving complete revascularization. PCI was accomplished using paclitaxel-eluting stents and followed by the use of a minimum of 6 months of thienopyridine (i.e. clopidogrel) and aspirin indefinitely. Arterial conduits were encouraged in patients undergoing CABG. Minimally invasive direct CABG was not permitted. Three study groups were pre-specified: 1. Left main disease (with or without other disease) 2. Triple vessel disease without left main disease 3. Diabetic patients

Outcomes: Primary: Major adverse cardiac and cerebrovascular events (MACCE). This included all cause mortality, stroke, myocardial infarction, and repeat vascularization. Secondary outcomes: MACCE rates at 1 mo, 6 mos, 3 and 5 years and rates of individual components and rates of stent thrombosis or graft occlusions.

Results at 5 years:

All patients

Outcome	CABG %	PCI %	p	NNT
MACCE	26.9	37.3	< 0.0001	9.6
Myocardial infarction	3.8	9.7	< 0.0001	16.9
Death, stroke or MI	16.7	20.8	0.03	24.4
Cardiac death	5.3	9	0.003	21.3
Revascularization	13.7	25.9	< 0.0001	8.2

MACCE Outcome by Patient Category

Patient category	CABG %	PCI %	p	NNT
Left main disease	31	36.9	0.12	NS
Three vessel disease	24.2	37.5	< 0.0001	7.5
Diabetes	29	46.5	0.0002	5.7
SYNTAX score 0 - 22	28.6	32.1	0.43	NS
SYNTAX score 23 - 32	25.8	36	0.008	9.8
SYNTAX score ≥ 32	26.8	44	< 0.0001	5.8

- In patients with scores of 0 – 22 the rate of death stroke or MI was very similar in the two groups (14.9% in the CABG group, 16.1% in the PCI group)
- The absolute rate of MI was lower by 6.2 – 7.4% in the CABG groups with Syntax scores above 22.
- In the highest syntax group all cause death was lower in the CABG group 11.4% vs. 19.2% p = 0.005 NNT 12.8

Limitations: Blinding is not possible in this study. An independent committee adjudicated events and mortality is impervious to bias. Significantly more patients in the PCI group were on dual anti-platelet therapy than the CABG group (27.4% vs. 9.1%) & on a thienopyridine (32% vs. 12.1%)

Impact on Practice: Patients with high or moderate SYNTAX scores should be treated with CABG. Those with low scores PCI.

Comparative risk for angioedema associated with the use of drugs that target the rennin-angiotensin-aldosterone system. Toh S, Reichman ME, Houstoun M et al. Arch Intern Med. 2012;172:1582-1589.

Objective: to assess the risk for angioedema associated with the use of ACEIs, ARBs, and aliskiren.

Study Design: Cohort

Participants: Number of subjects: 3,909,596. Inclusion criteria: 18 years or older with an outpatient dispensing of an ACEI, ARB, aliskiren, or beta-blocker between 2001 and 2010; pharmacy benefits for at least 183 days prior to the index dispensing; no prescription for any other study drug; no previous diagnosis of angioedema. Baseline characteristics: ~50% female, ~21% > age 65, ~24% < age 45, ~12% diabetic, ~15% using NSAIDs.

Outcomes: Primary: angioedema recorded in any outpatient, inpatient, or ED encounter. Secondary: serious angioedema (with airway obstruction requiring inpatient care. All outcomes were identified by ICD-9 codes (positive predictive value 90-95%). The follow-up period began on the index date and ended at the earliest occurrence of the following: first angioedema diagnosis, death, disenrollment, 365 follow-up days, December 31, 2010, cessation of use of study drug (> 14 days without the drug), or initiation of another study drug of a different class (except for individual ARB analyses, for which censoring also occurred with initiation of a different ARB).

Analysis: Data submitted by 17 health plans were abstracted from the Mini-Sentinel Distributed Database, an FDA database. Beta-blocker users were the reference group; hazard ratios were adjusted for age, sex, history of allergic reactions, DM, heart failure or ischemic heart disease, and use of NSAIDs. Information on race/ethnicity was not available.

Results: ACEI (n = 1,845,138), ARB (467,313), and aliskiren (4867) users were more likely to be male and have diabetes, and were less likely to have ischemic heart disease than were beta-blocker users (1,592,278). The risk of angioedema was highest in ACEI users:

	Incidence rate per 1000 person-years		**Adjusted HR**	
	Angioedema	**Serious angioedema**	**Angioedema**	**Serious**
ACEIs	4.38	0.43	3.04 (2.81-3.27)	4.91 (3.6-6.6)
ARBs	1.66	0.06	1.16 (1.00-1.34)	0.56 (0.28-1.1)
Aliskiren	4.67	0.67	2.85 (1.34-6.04)	1.14 (0.46-2.8)
Beta-blockers	1.67	0.09	1	1

There were only 7 events in aliskiren users, compared to 3301 in ACEI users, 288 in ARB users, and 915 in beta-blocker users. The rate for ACEI was higher in users > 65 than in younger users. 66% of angioedema events occurred during the first 90 days of use. Losartan users had a higher risk of angioedema than users of other ARBs (HR = 1.53, 1.23-1.9 for losartan; HR not significant for others).

Limitations: (1) not able to look for differences based on race/ethnicity; (2) might have missed mild angioedema that was not coded as a diagnosis; (3) inherent risk of selection bias in cohort studies.

Impact on Practice: The absolute rates of angioedema in patients on these medications are low. However, users of ACEI do have a higher risk. Although this information should not changes general prescribing patterns, it may be useful in selected patients with a history of angioedema or drug allergies.

Effects of body size and hypertension treatments on cardiovacular event rates: sub-analysis of the ACCOMPLISH randomized controlled trial. Weber MA, Jamerson K, Bakris GI et al. Lancet 2013;381:537-45.

Objective: to compare the effectiveness of benazepril/HCTZ vs. benazepril/amlodipine in normal, overweight and obese patients.
Study Design: pre-specified analysis of the ACCOMPLISH trial, a multicenter randomized double blind, controlled trial, to evaluate drug effects as a function of BMI.

Participants: Number of subjects: 11,482. Inclusion criteria: Patients ≥ 55 y.o. with previously treated or untreated hypertension, 2 CV risk factors or target organ damage from 2 systems of if > 60 evidence of one CV disease or target organ damage. (CV events due to concomitant CAD, MI, revascularization procedures, stroke, PAD, LVH, impaired renal function or DM). Duration 35.7 months. Exclusion criteria: drug allergy to meds used in trial, current angina, secondary hypertension, refractory hypertension, MI or revascularization within one month of visit, stroke or TIA within 3 months of visit. Creatinine > 2.5 mg/dl, baseline serum potassium > 5.2 meq/L not on potassium supplements. Baseline characteristics: Mean age 71 y.o. (normal weight patients); 69 y.o. (overweight patients) and 67 y.o. (obese patients)

Intervention: Patients stratified by body weight: normal BMI < 25, overweight BMI ≥ 25 – 30, obese ≥ 30. Patients randomized to benazepril/HCTZ 20/12.5 or benazepril/amlodipine 20/5 which was increased to 40/12.5 and 40/5 at visit 2. Thereafter the HCTZ & amlodipine could be increased to 25 mg and 10 mg respectively to achieve a target BP < 140/90. (target was < 130/80 for patients with diabetes or CKD). If necessary β blockers, clonidine, alpha blockers & spirono-lactone could be added for BP control or loop diuretics if necessary for volume management.
Outcomes: Primary: reduction of a composite of cardiovascular death, non-fatal MI, or non-fatal CVA. Secondary: Cardiovascular death, total myocardial infarction and total stroke.

Results:

- BP control was virtually identical between the benazepril/HCTZ group and the benazepril/amlodipine group and across the BMI categories
- Event rates **were higher** in normal weight individuals compared with obese individuals. (Figure) However note that the differences are small over the course of the study (3 years) The event rate was 9% in normal weight group, 7% in obese patients and 5% in the obese group. (p=0.0034)
- The study was terminated early due to meeting pre-specified differences in clinical outcomes. The increase in events in normal weight individuals compared with obese patients was almost eliminated in the benazepril/amlodipine group (but not the benazepril/HCTZ group). (Figure)
- The data shows a 4% reduction in primary endpoints in normal weight individuals treated with benazepril/amlodipine vs. benazepril/HCTZ and a 2% reduction in overweight patients. No difference is seen in obese patients.

Limitations: In addition to the different BMI, these groups had other differences.

- More obese patients were Black (9% of the normal weight vs. 16% of overweight pts)
- More obese patients had DM (71%) vs. 53% of overweight & 41% of the normal patients
- Age: Obese patients were younger

This raises the possibility that the benefit of amlodipine over HCTZ was modified by race, DM or age, rather than weight. That is, amlodipine may be more beneficial in young patients, black patients or diabetic patients. The authors note that they too noticed other differences in the patients' baseline characteristics but that adjusting for these did not make a major difference to their findings. They do not show that data.
Impact on Practice: The data suggests that diuretics and ACI are reasonable choices in obese patients but may not be ideal in lean and overweight patients where ACEI and calcium channel blockers may be superior

Endocrine

A Pooled Analysis of Vitamin D Dose Requirements for Fracture Prevention. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. NEJM 2012; 367(1):40-49.

Objective: to estimate the effects of vitamin D supplementation according to the actual intake on hip and non-vertebral fractures
Study Design: meta-analysis of 11 double-blind randomized controlled trials

Participants: Number of subjects: 31,022. Inclusion criteria: double-blind randomized controlled trials with persons aged 65 or older that evaluated oral vitamin D alone or with calcium vs. control (placebo or calcium alone) with data on low-trauma fractures and that were published before 8/31/11 Exclusion criteria: not fitting above criteria Baseline characteristics: mean age 76, 91% women, 11 trials were included.

Intervention: participants were randomly assigned to receive vitamin D with or without calcium or placebo (calcium alone or placebo) daily, weekly or every 4 months.
Outcomes: primary: incidence of hip and any non-vertebral fractures with adjustment for age group, sex, type of dwelling and study.

Results: Those assigned to take vitamin D had a 7% reduction in risk of non-vertebral fracture HR 0.93, CI 0.87-0.99, the reduction in risk of hip fracture was not significant. At the highest quartile of vitamin D intake (792-2000 IU/day) there was a 30% reduction in risk of hip fracture HR 0.70, CI 0.58-0.86 ($p<0.001$) and a 14% reduction in risk of non-vertebral fracture HR 0.86, CI 0.76-0.96 ($p=0.007$). There was not a significant reduction of fracture risk in any other quartile of actual vitamin D intake. There was no change with adjustment for age group, sex, type of dwelling or study. This finding was independent of the assigned treatment dose of vitamin D.

Limitations: (1) They authors did not have trial source data from 2 out of 14 qualifying trials although the estimated the effect of this (2) this is a meta-analysis and thus there may be small differences in the trials affecting the data (3) they could not assess the intake of higher levels of vitamin D alone without calcium as in the trials that used higher doses, they were given together

Impact on Practice: Vitamin D intake at or over 800 IU per day may reduce fracture risk in the elderly. This is similar to current guideline recommendations.

Fracture Risk and Zolendronic Acid Therapy in Men with Osteoporosis. Boonen S, Reginster JY, Kaufman JM, et al. NEJM. 2012; 367: 1714-23.

Objective: To assess the effect of zolendronic acid on the risk of vertebral fracture among men with osteoporosis

Study design: Multicenter, randomized, double-blind, placebo-controlled, parallel group study

Participants: Number of participants: 1199. Inclusion: Men aged 50-85 years with primary osteoporosis or osteoporosis due to low testosterone levels and 1-3 prevalent vertebral fractures [osteoporosis was defined as having T score of -1.5 or less] OR men with T score of -2.5 or less without fractures; Exclusion: 4 or more prevalent vertebral fractures, 25-hydroxyvitamin D level of 15 or less, creatinine clearance <30mL/min, abnormal liver function tests, hyper- or hypocalcemia, use of testosterone within 1 year before randomization, and many others. Baseline characteristics: median age 66, 94% white, 67% without previous vertebral fractures, average T-score in femoral neck -2.23 and -1.71 in total hip

Intervention: Men were randomized to receive either zolendronic acid 5mg or placebo intravenously at baseline and at month 12; all received daily calcium at 1000 to 1500mg daily and vitamin D at 800 to 1200 IU daily.

Outcomes: Primary end point: proportion of men with one or more new morphometric vertebral fractures over 24 months; Secondary end points included: the time to first clinical fracture, changes in bone mineral density

Results: Modified intention-to-treat analysis revealed that 9 of 553(1.6%) men in the zolendronic acid group developed one or more morphmetric vertebral fractures over 24 months compared to 28 of 574 (4.9%) in the placebo group with relative risk of 0.33 (95% CI 0.16-0.70). Similar pattern was seen at the 12 month mark. There was no difference in the rates of clinical vertebral fractures or nonvertebral fractures (1.0% zolendronic acid vs 1.8% placebo). Zolendronic acid was associated with improvement in bone mineral density over the study period. No significant differences in severe adverse events were seen except in myocardial infarction (1.5% in the zolendronic acid group and 0.3% in placebo group, P=0.03) but the investigator did not feel it was related to the study. Men in the zolendronic acid group experienced significantly more pyrexia, myalgia, arthralgia and headache.

Limitations: The study was analyzed as a modified intention-to-treat and 10% of men who enrolled were not included in the analysis which limits the interpretation. Results may not be generalizable as the majority of the men were white. The study is also limited to reduction in vertebral fractures and not other fractures such as hip. Mild side effects were significantly higher in the zolendronic acid group. The myocardial infarction finding is unexpected but investigators felt it was not associated. The study was sponsored by the drug company and the manuscript edited by a group paid by them.

Impact on practice: Zolendronic acid seems effective and safe for preventing vertebral fractures in men with osteoporosis. Physicians should remember to screen at risk men.

Effect of Testosterone Replacement on Response to Sildenafil Citrate in Men with Erectile Dysfunction. Spitzer M, Basaria S, et al. Ann Intern Med 2012; 157:681-691

Objective: to determine whether the addition of testosterone to sildenafil therapy improves ED in men with low testosterone and ED.

Study Design: randomized controlled trial

Participants: Number of subjects: 140. Inclusion criteria: aged 40-70 with ED (indicated by erectile function domain EFD score of 25 or less on the International Index of Erectile Function IIEF), a sexual partner and total testosterone <330ng/dl or free testosterone<50 pg/ml. Exclusion criteria: prostate ca, breast ca, structural penis abnormality, untreated OSA, major psych disease, lower urinary tract symptom scores > 21, Hct>0.5, Cr>2, PSA>4, A1c>8.5, bp>160/100, uncontrolled HF, MI or CVA in past 6 mo or androgen use. Baseline characteristics: mean age 55, 50% white, 43% black; mean BMI 32; mean total testosterone 250, mean free testosterone level 46.

Intervention: Patients were optimized on sildenafil dose then randomized to either 14 weeks of 10 g testosterone transdermal gel daily or placebo

Outcomes: primary: change in EFD score of the IIEF from randomization to the end of 14 week treatment. secondary: other domains of sexual function on the IIEF

Results: There were no baseline differences between groups. 10 in the testosterone group and 12 in the placebo group did not complete the study. Both groups had increases in EFD score with sildenafil (mean change 7.7 CI 6.5-8.8). Change in EFD score after randomization was not different between groups (difference between mean change 2.2 CI -0.8-5.1, p=0.150). Postrandomization changes in other domains (sexual desire, intercourse satisfaction, overall satisfaction, and orgasmic function, composite IIEF score) were not different between groups. Adverse events were similar for both placebo and testosterone gel. Hct increased significantly more in the testosterone group. Testosterone levels were in the target range with therapy in the testosterone group. The study was powered to detect a 4 point difference in EFD score between the two groups.

Limitations: (1) the trial length may not have been long enough to see the full effect of testosterone supplementation

Impact on Practice: In men with low testosterone levels, testosterone replacement with sildenafil is not superior to sildenafil alone.

Intensive and Standard Blood Pressure Targets in Patients With Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis. McBrien K, Rabi DM, Campbell N, et al. Arch Intern Med. 2012;172(17):1296-1303.

Objective: To determine the effectiveness and safety of treating BP to intensive targets (upper limit of 130 mm Hg systolic and 80 mm Hg diastolic) compared with standard targets (upper limit of 140-160 mm Hg systolic and 85-100 mm Hg diastolic) in patients with type 2 DM.

Study Design: Systematic review and meta-analysis

Included Trials: Number of patients: 7312 patients with DM from 5 included studies. Inclusion criteria: Parallel, randomized, or quasi-randomized controlled trials (1) enrolling adults diagnosed as having type 2 DM as the primary population or subgroup, (2) comparing an intervention of antihypertensive therapy to achieve prespecified BP targets, and (3) assessing at least 1 end point of mortality, myocardial infarction, or stroke. Exclusion criteria: Studies that tested multifactorial interventions in which the effect of BP lowering could not be analyzed separately from other treatments.

Intervention: Blood pressure targets were defined as intensive or standard. Intensive BP targets were defined as a systolic target up to 130 mm Hg or a diastolic target up to 80 mm Hg. Standard BP targets were defined as a systolic target up to between 140 and 160 mm Hg or a diastolic target up to between 85 and 100 mm Hg.

Outcomes: All-cause mortality, myocardial infarction, and stroke.

Results: The use of intensive BP targets was not associated with a significant decrease in the risk for mortality (relative risk difference, 0.76; 95% CI, 0.55-1.05) or myocardial infarction (relative risk difference, 0.93; 95% CI, 0.80-1.08) but was associated with a decrease in the risk for stroke (relative risk, 0.65; 95% CI, 0.48-0.86). The pooled analysis of risk differences associated with the use of intensive BP targets demonstrated a small absolute decrease in the risk for stroke (absolute risk difference, −0.01; 95% CI, −0.02 to −0.00) but no statistically significant difference in the risk for mortality or myocardial infarction.

Limitations: (1) Significant heterogeneity existed across studies and data were limited; (2) few trials (only 5) tested BP targets in patients with DM; (3) due to the dearth of data, the authors included data from subgroup analyses and combined trials of systolic targets with trials of diastolic targets; (4) divergence of the achieved BPs from the target BPs in the standard BP arms of the meta-analysis makes it impossible to draw conclusions about any specific target BP level, only on the comparative effectiveness of the level of BP lowering; (5) the ACCORD-BP study, accounting for 64.7% of included patients, had a significant influence on the meta-analysis and had an achieved BP of 134/70 in the standard BP arm.

Impact on Practice: Together with the results of previous prospective trials, the data do not support lower, more aggressive target BP levels for overall CV risk reduction in patients with diabetes. Future evidence based guidelines for BP goals in patients with diabetes are likely to suggest a goal of <140/90.

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes. Parving HH, Brenner BM, McMurray JJ, et al. NEJM. 2012; 367: 2204-13.

Objective: To determine the effectiveness and safety of treatment with aliskiren (renin inhibitor) in patients with type 2 diabetes mellitus who are at high risk of fatal and nonfatal renal and cardiovascular events and already taking an ACE inhibitor or ARB

Study design: Multicenter, international , randomized, double-blind, placebo-controlled trial

Participants: Number of subjects: 8606. Inclusion criteria: Patients aged 35 years and old with type 2 diabetes mellitus (DM) and evidence of microalbuminuria, macroalbuminuria or cardiovascular disease. Baseline characteristics: mean age 64 years; 1/3 female; mean HbA1c 7.8%; 42% known cardiovascular disease

Intervention: Aliskiren or placebo plus standard treatment for median of 32.9 months

Outcomes: Primary outcome: composite of death from cardiovascular causes or first occurrence of cardiac arrest with resuscitation, nonfatal MI, nonfatal stroke, unplanned hospitalization for heart failure, ESRD, death attributable to renal failure, need for renal-replacement therapy, or serum creatinine that was at least double the baseline creatinine level and that exceeded the upper limit of normal; Secondary cardiovascular outcome: composite of all 5 cardiovascular components of the primary composite outcome; Secondary renal outcome: composite of renal components of the primary composite endpoint

Results: There was no difference in the rate of the primary outcome (18.3% aliskerin and 17.1% placebo) or secondary cardiovascular composite outcome (13.8% aliskerin and 12.6% placebo) or secondary renal composite outcome (6.0% aliskerin vs. 5.9% placebo). Rate of death was no different. The overall urinary albumin-to-creatinine ratio decreased more with aliskerin compared with placebo (16% vs 5%, $P<0.0001$). A significantly higher proportion of patients in the aliskerin group discontinued the medication due to adverse event with hyperkalemia being the most common reason and renal impairment and hypotension second and third reasons. There was also a higher risk of stroke in the aliskerin group (HR 1.34, 95% CI 1.01-1.77). A similar number of patients in both groups stopped taking the medications by the end of the study period (25.9% aliskerin vs. 21.35%).

Limitations: This study was stopped early because of a higher rate of adverse events in patients taking aliskiren compared to placebo but no reduction in the rate of cardiovascular or renal outcomes.

Impact on practice: Evidence suggests there is no benefit and may be harm in starting aliskiren in patients with diabetes who are at risk for cardiovascular events. While it is unclear what to do in your patients who are taking aliskiren and tolerating it, you should reconsider starting aliskiren in this patient population.

Geriatrics/Neurology

Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease. Devanand DP, Mintzer J, Schultz SK, et al. NEJM. 2012; 367: 1497-507.

Objective: To assess the risk of relapse in patients with Alzheimer's disease (AD) who had psychosis or acute agitation who initially responded with risperidone and then stopped taking the medication

Study design: Randomized, double-blind, placebo controlled trial of patients initially enrolled in an open-label trial

Study participants: Number of subjects: 180 phase 1, 100 phase 2. Inclusion: Patients with AD aged 50-95 years of age with psychosis or acute agitation who responded to risperidone therapy in the initial phase. Exclusion: history of stroke, TIA, uncontrolled atrial fibrillation. Baseline characteristics of phase 2 group: Mean age 79.6 years, 59% female, ~50% living in assisted living or nursing homes

Intervention: Patients were initially enrolled in an open-label trial received risperidone (dose 0.25mg up to 3mg by end of 16-week study period) [phase 1]; following this patients who responded to the treatment were enrolled into one of 3 groups: continued risperidone for 32 weeks; received risperidone for 16 weeks then placebo for 16 weeks; placebo for 16 weeks [phase 2]. In each group, patients who relapsed at 16-week time interval did not move to the 17-32 week phase

Outcomes: Primary end point: Time to relapse during weeks 0-16; Secondary end point: Time to relapse 17 to 32 weeks; Secondary outcomes: extrapyramidal signs, tardive dyskinesia, change in cognitive status or physical function and others

Results: A total of 180 patients were enrolled in the initial phase and 112 (62.2%) responded to therapy; 110 (61.1%) moved on to the second phase: 32 (29%) to risperidone, 38 (34.5%) to risperidone + placebo; 40 (36.4%) to placebo. There was no significant difference in demographic and efficacy and side-effect variables at the start of phase 2. Patients who initially responded had significantly higher MMSE scores, lower scores on somatic symptom scale and lower scores on scale assessing extrapyramidal symptoms. See table below for relapse rates. There were no significant differences in rate of adverse events among the groups: overall 17% with extrapyramidal symptoms, 11% sedation, 2% death, 3% cardiac event.

Randomization group (N 0-16 wk; N 17-32)	Relapse at 16 weeks N (%)*	Relapse from 17-32 weeks N (%)^
Risperidone (32, 13)	14 (44%)	1 (8%)
Risperidone + placebo (38, 27)	8 (21%)	13 (48%)
Placebo (40, 13)	23 (56%)	13 (15%)

*OR relapse placebo vs risperidone 1.94 (95% CI 1.09-3.45)

^ OR relapse group changed to placebo vs risperidone 4.88 (95% CI 1.08-21.98)

Limitations: A large proportion of patients withdrew from each phase of the study due to relapse or dropping out (38% phase 1 and 68% phase 2). The sample size was small so unable to evaluate between-group differences in adverse events and mortality.

Impact on practice: While this study was small, results do show that patients who initially respond to therapy have lower rates of relapse. Providers should weigh this benefit against the side effect risks.

GI

Surgical vs. conventional therapy for weight loss treatment of obstructive sleep apnea.
Dixon JB, Schachter LM, O'Brien PE, et al. JAMA. 2012;308:1142-1149

Objective: to compare the effects of laparascopic adjustable gastric banding (LAGB) with conventional weight loss on moderate to severe OSA.

Study Design: randomized controlled trial

Participants: Number of subjects: 60. Inclusion criteria: aged 18-60 with BMI 35-55, AHI ≥ 20 (within previous 6 months), ≥ 3 unsuccessful weight loss attempts. Exclusion criteria: previous bariatric surgery, obesity hypoventilation syndrome, contraindications to surgery. Baseline characteristics: mean age 48, BMI 45, AHI 60; 58% men, 33% DM, 38% depression, 53% HTN.

Intervention: Conventional program (individualized dietary, physical activity and behavioral programs; goals of 200 minutes of structured activity/week and a daily deficit of 500 kcal; variable use of very low energy diet) vs. surgical program (2 wks of a very low energy diet followed by LAGB surgery). All patients had access to bariatric and sleep physicians and a dietician.

Outcomes: Primary: change in AHI at 2 yrs measured by laboratory PSG, scored by blinded staff. Secondary: CPAP adherence, cardiometabolic factors, functional status measures.

Results: There were no baseline differences between groups. 4/30 patients assigned to surgery did not have a procedure; 1/30 assigned to conventional treatment had surgery outside the study. The surgical group lost a mean of 27.8 kg (20.6% of initial body weight; mean BMI 43.6 $\rightarrow$ 36.6) compared to a mean of 5.1 kg (2.9% of initial weight; mean BMI 43.8 $\rightarrow$ 42.3) in the conventional group. The surgical group mean AHI decreased from 65 to 39.5 (31% $\downarrow$), and the conventional group mean AHI decreased from 57.2 to 43.2 (13.5% $\downarrow$). The between group difference was not significant (-11.5, 95% CI: -28.3 to 5.3). 27% of surgical patients and 7% of conventional patients achieved an AHI <15 (RR = 3.85; NNT = 5). Results were similar in a per protocol analysis. There were no differences in a variety of metabolic factors; the surgical group reported greater quality of life improvements on several scales. There was notable individual variability in the amount of weight loss and change in AHI (see figures in paper).

Limitations: (1) The study could have been underpowered to detect a difference; (2) the relatively modest weight loss seen with LAGB might not be enough to affect AHI; (3) there was missing data (see table 2; note that 10% of the AHI change data was missing).

Impact on Practice: Some patients will have substantial improvement in their AHI after bariatric surgery, but the effect is variable and often not enough to stop CPAP treatment. Patients who wish to stop CPAP should undergo reassessment with PSG, even if they have lost a substantial amount of weight.

Health benefits of gastric bypass surgery after 6 years. Adam TD, Davidson LE, Litwin SE, et al. JAMA. 2012;308:1122-1131.

Objective: to compare long term weight loss and cardiometabolic factors in obese patients undergoing or not undergoing Roux-en-Y gastric bypass surgery (RYGB).

Study Design: single center prospective cohort study

Participants: Number of subjects: 418 in surgery group, 417 in control group 1 (sought surgery but did not have it), 321 in control group 2 (randomly recruited obese patients). Baseline characteristics: 82% women and 96% white; mean age 45 (range 18-72), BMI 45.9, AIC 5.9, LDL 109, BP 127/72.

Outcomes: 6 year follow up: weight change; incidence of diabetes, hypertension, and dyslipidemia in subjects without baseline disease, and remission in those with baseline disease. Both propensity scores and covariate analyses were performed to adjust for baseline differences between the groups, with detailed sensitivity analyses to test model assumptions.

Results: Follow up rates at 6 years were 92.6% in the surgical group, 72.9% in group 1, and 96.9% in group 2. 101 patients in the control groups underwent bariatric surgery, and were analyzed by intention to treat. Patients in control group 1 were similar to the surgery group, while those in group 2 were older (49 vs. 42) and less obese (BMI 44 vs. 47), with high QOL scores. Patients in the surgery group lost more weight, had less incident disease, and had more remissions:

	Weight change from baseline		Incidence DM		Remission DM	
	2 years	6 years	Rate	Adjusted OR*	Rate	Adjusted OR*
Surgery	- 34.9%	- 27.7%	2%	0.11, 0.21	62%	16.5, 21.5
Control 1	NA	+ 0.2%	17%		8%	
Control 2	NA	0%	15%		6%	

*Surgery group compared to control group 1, control group 2

For incident hypertension, the OR was 0.4-0.47, and for remission of hypertension was 2.9-5; for incident high LDL, the OR was 0.12-0.14, and for remission was 4.4-6.8. At 6 years, 96% of surgical patients had maintained more than a 10% weight loss, and 76% more than a 20% weight loss. There were 29 deaths overall, 12 (3%) in the surgical group, 14(3%) in control group 1, and 3 (1%) in control group 2. No deaths were within 30 days of surgery; however, 4/4 suicides and 2/3 poisonings of undetermined intention occurred in the surgical group (OR=18, CI 1-385)

Limitations: (1) Despite the detailed analyses, there is still potential selection bias in any cohort study; (2) follow up was incomplete in control group 1.

Impact on Practice: Patients who have undergone bariatric surgery maintain a significant weight at 6 years, with significant improvement in their cardiovascular risk profile. The small, but notable, rate of suicide in the surgery group merits further study, and support careful pre-operative psychological assessment.

Related Article

Health care use during 20 years following bariatric surgery. Neovius M, Narbro K, Keating C, et al. JAMA. 2012;308:1132-1141.

In 2007, the Swedish Obese Subjects study, a prospective, matched cohort study of 4047 patients choosing or not choosing bariatric surgery, showed a reduction in all cause mortality in the surgical patients after a mean follow up 10.9 years (adjusted HR - 0.73, 0.56 - 0.95; NNT = 80). The current article assesses the amount of health care used by the surgical patients compared to the nonsurgical patients over 20 years, obtaining data from national databases. At baseline, 71% were female, and the mean BMI was 41. 13% underwent gastric bypass, 19% gastric banding, and 68% vertical banded gastroplasty. Overall, the surgery patients used fewer cumulative hospitals days (54 vs. 40, p=0.03), although surgery patients had slightly more days in years 2-6 (1.7 vs. 1.2, p<0.001). Surgical patients also had more nonprimary care outpatient visits in years 2-6 (1.3 vs. 1.1, p=0.003), but similar numbers of visits in years 7-20. From year 7-20, mean annual drug costs were less in the surgery group ($930 vs. $1123), due at least in part to reduced use of diabetes and cardiovascular medications.

Impact on Practice: Although somewhat limited by its cohort design, this study supports the use of bariatric surgery to treat obese patients.

Probiotics for the Prevention of Clostridium difficile-Associated Diarrhea. A Systematic Review and Meta-analysis. Johnston BC, Ma SSY, et al. Ann Intern Med. 2012;157:878-888.

Objective: to assess the efficacy and safety of probiotics for the prevention of Clostridium difficle associated diarrhea (CDAD) in adults and children receiving antibiotics.

Study Design: meta-analysis of 20 randomized controlled trials

Participants: Number of subjects: 3818 Inclusion criteria: RCT's with adults or children treated with antibiotics that compared the effect of any dose of a specified probiotic of any strain with placebo or no treatment and reported the incidence of CDAD with positive stool toxin assay or culture for c.diff Exclusion criteria: not fitting above Baseline characteristics: reported for each separate trial but not pooled data

Intervention: participants treated with antibiotics were randomly assigned to receive probiotics of any strain or placebo/no treatment

Outcomes: primary: incidence of CDAD as diagnosed by stool toxin assay or culture secondary: adverse effects

Results: Probiotics reduced the incidence of CDAD by 66% (40/1974, 0.020 CDAD events in probiotic group vs. 108/1844, 0.059 events in the control group) with RR of 0.34, CI 0.24-0.49. This gives a NNT of 26 to prevent one episode of CDAD. Overall, 9.3% of probiotic patients experienced adverse effects vs. 12.6% of control patients (RR 0.82, CI 0.65-1.05). The most common adverse effects were abdominal cramping, nausea, fever, soft stools, flatulence and taste disturbance.

Limitations: (1) Several low quality articles were included. (2) In 13 trials, CDAD data was missing for 5-45% of patients. However, the authors performed sensitivity analysis with worst-plausible-case assumptions regarding missing outcome data and the results were still robust. (3) Probiotics used included a variety of strains (4) 4 trials did not report adverse events

Impact on Practice: Probiotic prophylaxis decreases the incidence of antibiotic associated CDAD and is not harmful.

Duodenal infusion of donor feces for recurrent *Clostridium difficile*. Van Nood E, Vrieze A, Nieuwdorp M, et al. NEJM. 2013;368: 407-415.

Objective: to compare donor feces infusion with vancomycin ± bowel lavage in the treatment of patients with recurrent *C. difficile* infection (CDI).

Study Design: open-label, randomized controlled trial

Participants: Number of subjects: 43. Inclusion criteria: >18 years of age, life expectancy ≥ 3 months, relapse after ≥ 1 course of adequate therapy (≥ 10 days of 125 mg qid of vancomycin or 500 mg tid metronidazole), + PCR for C. difficile toxin with ≥3 episodes of diarrhea for ≥ 2 days or ≥ 8 in 48 hours. Exclusion criteria: immunocompromise due to chemotherapy, HIV infection with CD4 < 240, prolonged steroid use; pregnancy; use of antibiotics for any other infection; ICU admission; need for vasopressors. Baseline characteristics: mean age 71; 41% female; Karnofsky status 50 (0-100, higher score = better function); median recurrences = 3 (range 1-9); previous failure tapered vancomycin therapy 52%; 49-63 days of antibiotic use for CDI.

Intervention: (1) vancomycin 500 mg qid for four or five days, followed by bowel lavage with 4 liters macrogol solution (Klean-Prep®) on the last day of antibiotic treatment and infusion of fresh donor feces suspension through a nasoduodenal tube the next day; or (2) vancomycin 500 mg qid for 14 days; or (3) vancomycin 500 mg q.i.d. for 14 days with bowel lavage at day four or five. Patients who developed recurrent *C. difficile* infection following the first fecal infusion with were given a second infusion with donor feces solution from a different donor. Patients who failed on antibiotic therapy were offered treatment with donor feces infusion off protocol. Donors were screened extensively for infections. Feces were diluted with 500 ml normal saline and infused within 6 hrs of collection.

Outcomes: Primary: cure without relapse within 10 weeks, defined as the absence of diarrhea or diarrhea due to another cause with 3 negative tests for *C. difficile* toxin. Secondary: cure without relapse within 5 weeks. A blinded adjudication committee determined cure.

Results: The trial was stopped early based on high relapse rates in the control groups. 41/43 patients completed the study (1 in the vancomycin only group stopped all therapies and died; he was considered a failure in the intention to treat analysis. 1 in the infusion group was not treated due to medical complications; he was excluded from the analysis). 94% (15/16) of infusion patients were cured (13 after 1 infusion, and 2 after a second infusion). 31% of the vancomycin alone group and 23% of the vancomycin + lavage groups were cured (RR cure infusion vs. vancomycin alone 3.05, 99% CI 1.08-290, NNT = 2). 18 patients who relapsed after antibiotic treatment received off-protocol infusions; 83% were cured. Nearly all patients had diarrhea immediately after the infusion, with 31% having abdominal cramping and 19% belching; all symptoms resolved within 3 hours. Fecal diversity was low in patients prior to infusion and became indistinguishable from donor diversity by 2 weeks.

Limitations: (1) Immunocomprised patients, ICU patients, and those requiring concomitant antibiotics were excluded. (2) the trial was small (3) newer agents, such as fidaxomycin were not included in the study; nor was a comparison to a long vancomycin taper

Impact on Practice: Donor fecal infusions can be considered for patients with recurrent CDI not responsive to other treatments.

Kwok CS, et al. Risk of *Clostridium difficile* Infection with Acid Suppressing Drugs and Antibiotics: Meta-Analysis. Am J Gastroenterol 2012; 107: 1011-19.

Objective: To determine the associated risk of *Clostridium difficile* infection with proton pump inhibitor (PPI) use with and without concurrent antibiotic use

Study design: Meta-analysis of controlled observational studies

Outcomes: Primary: Odds of development of CDI in the setting of PPI use; Secondary: Relative impact on the odds of developing CDI in the setting of concurrent antibiotic use as well as H2-blockers

Results: Forty-two studies were identified giving a study population of 310,000; most studies focused on inpatients and were single-center. Pooled analysis showed an increased risk of CDI with PPI use (OR 1.74, 95% CI 1.47-2.05) and this remained consistent when limiting the analysis to studies that provided adjusted data. In the 3 studies evaluating risk of recurrent CDI and PPI use, the pooled OR was 2.51 (95% CI 1.26-5.44). Concurrent use of antibiotics with a PPI was also associated with an increased risk of CDI (OR 1.96, 95% CI 1.03-3.70) when compared to PPI alone. H2 blockers were also found to be associated with an increased risk of CDI (OR 1.50, 95% CI 1.23-1.83) and when compared to PPI there was an associated 29% reduction in the risk of CDI (OR 0.71, 95% CI 0.53-0.97).

Limitations: The type, dose and duration of treatment with a PPI as well as antibiotic type were unknown. There was also significant statistical heterogeneity in the meta-analysis but analyses performed to better evaluate this fact suggested that despite heterogeneity the findings are consistent. The studies are all observational so assessing causality is not possible. Authors were also unable to adjust for unmeasured confounding variables such as indication for PPI and other comorbid conditions.

Impact on practice: Exposure to PPIs is associated with increased risk of CDI both with and without concurrent antibiotic use. While causality cannot be determined based on this study, clinicians should prescribe PPIs judiciously and stop PPIs when not indicated.

Transfusion strategies for acute upper gastrointestinal bleeding. Villanueva C, Colomo A, bosch A, et al. NEJM. 2013;368:11-21.

Objective: to compare restrictive and liberal transfusion strategies.

Study Design: open-label randomized controlled trial

Participants: Number of subjects: 899 admitted to a single hospital for upper GI bleeding. Inclusion criteria: >18 years of age with hematemesis, bloody nasogastric aspirate, or melena. Exclusion criteria: refusal of blood transfusion, massive exsanguinating bleeding, ACS, symptomatic peripheral vasculopathy, stroke, TIA, transfusion within the previous 90 days, recent history of trauma or surgery; lower gastrointestinal bleeding, and a clinical Rockall score (0-11 scale; higher score = higher risk of further bleeding or death) of 0 with a hemoglobin ≥ 12. Baseline characteristics: Mean age 64 + Rockall score 5.3; 67% men, 30% shock at admission; source of bleeding-PUD 50% (63% duodenal; 56% visible vessel, 15% active bleeding), varices 23%, esophagitis 8%; cirrhosis 31% (alcoholic 45%, Child-Pugh A 27%, B 57%, C 21%).

Intervention: Randomized to restrictive (transfusion threshold = 7, post transfusion target 7-9) vs. liberal (transfusion threshold = 9, post transfusion target 9-11) strategy stratified by presence of absence of cirrhosis. One unit of blood was transfused, the Hgb reassessed, and an additional unit given if the Hgb was below target. Transfusions were also given if symptoms of anemia developed, massive bleeding occurred, or surgical intervention was required. All patients underwent EGD within 6 hours with indicated endoscopic + medical treatment (PPI for patients with PUD; somatostatin + antibiotics for patients with portal hypertension)

Outcomes: Primary: any cause death with 45 days. Secondary: further bleeding (additional hematemesis or melena associated with hemodynamic instability, or a 2 gram fall in Hgb) and in-hospital complications.

Results: The mean Hgb at admission in both groups was 9.5. The restrictive therapy group had lower hemoglobins, received fewer units of blood and overall had better outcomes:

	Restrictive	Liberal	HR	NNT (NNH)
Lowest Hgb during admission	7.3	8.0		
% with lowest Hgb < 7	45%	18%		
Any transfusion	49%	86%		
Units transfused (total)	671	1638		
Mean/patient	1.5	3.7		
Transfusion for sx, bleeding	8%	3%		
Protocol violation	9%	3%		
Death from any cause	5%	9%	0.55 (0.33-0.92)	25
Further bleeding (all)	10%	16%	0.62 (0.43-0.91)	17
Further bleeding (varices)	11%	22%	0.5 (0.23-0.99)	9
Further bleeding (PUD)	10%	16%	0.63 (0.37-1.07)	17
Adverse events (any)	40%	48%	0.73 (0.56-0.95)	12
Cardiac complications	11%	16%	0.64 (0.43-0.97)	20

For the endpoint death, the HR was adjusted for age, in-hospital bleeding, presence or absence of cirrhosis and Rockall score.
For the endpoint further bleeding, the HR was adjusted for age, in-hospital bleeding, presence of cirrhosis, Rockall score, shock at admission and baseline hemoglobin.

Limitations: (1) There were more protocol violations in the restrictive group (meaning the patients received transfusions), biasing the results against the liberal strategy; (2) The criteria for when non-Hgb based transfusions could be given were unclear; i.e., the definition of “anemia signs and symptoms” was not clear; (3) all patients underwent EGD within 6 hours, which is not always accomplished in practice; (4) the study was not blinded; however, the outcomes were relatively objective and not subject to bias.

Impact on Practice: In a substantial proportion of patients with acute upper GI bleed, a more restrictive transfusion strategy, with a hemoglobin target of 7 g/dL, is not only safe but potentially beneficial.

Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomized. Liou M, Chen CC, Chen MJ et al. Lancet 2013;381: 205-13.

Objective: to compare the efficacy of sequential therapy vs. triple therapy for H. pylori infection

Study Design: open label, multicenter, open label, RCT in Taiwan

Participants: Number of subjects: 60. Inclusion criteria: Patients < 20 with documented H pylori infection[2]. Exclusion criteria: Previous eradication treatment for H pylori, history of gastrectomy, allergic reaction to study drugs, pregnant or lactating women, use of antibiotics in prior 4 weeks, severe concurrent diseases or malignancy. Baseline characteristics: mean age 53, 22% tobacco, PUD 64%-70% (64% in S-14 group, 70% in S-10 group, 66% in T-14 group)

Intervention: Sequential treatment for 10 & 14 d (S-10 and S014) was compared with triple therapy for 14 d (T-14). Sequential therapy: lansoprazole 30mg BID & amoxicillin 1 gm BID for 7 d followed by lansoprazole 30mg BID, clarithromycin 500mg BID & metronidazole 500mg BID for 7 d. Triple therapy utilized lansoprazole 30mg BID, amoxicillin 1 gm BID & clarithromycin 500mg BID. Patients positive after initial treatment were retreated with a modified sequential treatment for 14 days (MS-14) (Lansoprazole 30mg BID, amoxicillin 1gm BID for 7 days, followed by lansoprazole 30mg BID, metronidazole 500mg BID and levofloxacin 250 mg BID)

Outcomes: Primary: Eradication rate by ITT and per protocol analysis. Secondary: adverse events and compliance rates.

Results:

- Eradication[3] after first line treatment (%)

	S-14	S-10	T-14	P*	NNT
ITT analysis	90.7	87	82.3	0.011	11.9
PP analysis	94.4	90.5	87.1	0.012	13.7

*S14 vs. T 14

- Treatment efficacy of patients who failed first line therapy was 80% effective for all groups (using MS-14)
- Adverse event rates were not significantly different 54% S-14, 55% T-14. Abnormal taste and diarrhea were the most common side effects
- Clarithromycin resistance occurred= in 10% and markedly decreased the efficacy of all regiments (67% in S-14 and 55% T-14)
- Amoxicillin resistance was rare (<3%) but also markedly decreased the efficacy of all regiments (50% in S-14 and 20% T-14)
- Metronidazole resistance decreased the effectiveness of sequential but not triple therapy (88% S-14, 73% S-10, 89% T-14)

Limitations: The study takes place on Taiwan potentially limiting its generalizability

Impact on Practice: Sequential therapy is superior to triple therapy for first line treatment except in regions were metronidazole resistance is high (>80%) and clarithromycin resistance is low. In areas with high clarithromycin resistance (> 40%) alternative treatments should be chosen. Second line therapy with MS-14 is 80% effective.

[2] H pylori infection defined as positive results to at least 2 of the following: rapid urease test, histology, culture and serology. Carriers with a positive urea breath test were also eligible.
[3] Ascertained by a post treatment urea breath test at least 6 weeks after completing therapy

Infectious Disease

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial.
Sandberg T, Skoog G, Hermansson A, et al. Lancet. 2012; 380: 484-90.

Objective: To compare the efficacy of ciprofloxacin for 7 days and 14 days in women with community-acquired acute pyelonephritis

Study Design: Prospective, randomized, double-blind non-inferiority trial

Participants: Number of subjects: 248. Inclusion criteria: At least 18 years old, fever of at least 38 degrees C, and at least one symptom or sign relating to urinary tract (flank pain, CVA tenderness, dysuria, urgency, frequency). Exclusion criteria: Pregnancy or lactation, inadequate contraception for women of childbearing age, known fluoroquinolone allergy, antibiotic treatment in preceding 72h, presence of indwelling catheter or clean intermittent catheterization of the bladder, CrCl < 0.5 mL/s. Baseline characteristics: median age 46, temperature 39.2 degrees C, 3% diabetic, 5% complicated UTI, 95% CVA tenderness, 22% positive blood culture.

Intervention: Patients were randomly assigned to oral treatment with ciprofloxacin 500 mg twice daily for 7 days or 14 days. The first week was open label. The study was double-blind and placebo-controlled during the second week of treatment, which was either continuation of ciprofloxacin 500 mg or placebo tablets twice daily.

Outcomes: Primary: Short-term clinical and bacteriological efficacy 10–14 days after completion of treatment with ciprofloxacin. Secondary: Long-term cumulative efficacy of ciprofloxacin (at day 17-21 in the group treated for 7 days; at day 24-28 in the group treated for 14 days).

Results: Both treatment regimens resulted in high clinical cure rates at short-term follow-up. 126 of 248 patients were randomly assigned to 7 days and 122 to 14 days of ciprofloxacin. 73 and 83 patients, respectively, were analyzed. Short-term clinical cure occurred in 71 (97%) patients treated with ciprofloxacin for 7 days and 80 (96%) treated for 14 days (difference −0·9%; 90% CI −6·5 to 4·8; p=0·004; non-inferiority test). Cumulative efficacy at long-term follow-up was 93% in each group (68 of 73 *vs* 78 of 84; −0·3%; −7·4 to 7·2; p=0·015). Both regimens were well tolerated. Two patients discontinued ciprofloxacin because of myalgia with 7 days of treatment and itching exanthema with 14 days. Four (5%) of 86 patients assigned to 7 days of treatment who complied with study criteria and six (6%) of 93 assigned to 14 days reported an adverse event after the first week of treatment that was possibly or probably related to the study drug. In those assigned to 7 days, no patient had mucosal candida infection after the first week versus five treated for 14 days (p=0·036).

	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	Difference (90% CI)	Non-inferiority test p-value
Short term efficacy	73	83		
Cure	71 (97%)	80 (96%)	-0.9% (-6.5-4.8)	0.004

Clinical failure or recurrent symptomatic UTI	2 (3%)	3 (4%)	--	
Cumulative efficacy	73	84		
Cure	68 (93%)	78 (93%)	-0.3% (-7.4-7.2)	0.015
Clinical failure or recurrent symptomatic UTI	5 (7%)	6 (7%)		

Limitations: (1) Analysis was per protocol, not intention to treat; (2) while 14 women with community-acquired complicated pyelonephritis (most of whom were designated as complicated because of diabetes) were enrolled, only 4 of these women were treated for 7 days, limiting confidence of non-inferiority of the shorter regimen for complicated pyelonephritis; (3) the study was done in Sweden, which is known globally for a low prevalence of antimicrobial resistance.

Impact on Practice: Seven days of twice daily ciprofloxacin therapy is as effective as 14 days for the treatment of women with acute uncomplicated pyelonephritis with ciprofloxacin-sensitive organisms. As resistance rates continue to rise, the shortest effective duration of antimicrobial therapy should be used.

Azithromycin and the Risk of Cardiovascular Death. Ray, WA., et al. *N Engl J Med* 2012; 366:1881-1890

Objective: To determine if exposure to azithromycin increases the risk of cardiovascular death.

Study Design: Cohort study utilizing propensity matching.

Participants: Participants were included from a cohort of Tennessee Medicaid patients who had been prescribed azithromycin between 1992 and 2006. Eligibility criteria excluded people at high risk for death from causes unrelated to a short-term effect of proarrhythmic medications, thus participants were between 30 and 74 years of age, had no life-threatening noncardiovascular illness, had not received a diagnosis of drug abuse or resided in a nursing home in the previous year, and had not been hospitalized in the prior 30 days. Participants were matched to people taking no antibiotics or courses of amoxicillin, ciprofloxacin, and levofloxacin.

Outcomes: The primary study end points were cardiovascular death and death from any cause.

Results: The cohort included patients who took azithromycin (347,795 prescriptions), propensity-score–matched persons who took no antibiotics (1,391,180 control periods), and patients who took amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), or levofloxacin (193,906 prescriptions). The characteristics of patients receiving azithromycin prescriptions and the propensity-score matched controls were very similar but patients who were prescribed ciprofloxacin or levofloxacin were generally more likely to have complications of diabetes, incontinence, and wheelchair or walker use. The mean summary cardiovascular risk scores for patients taking amoxicillin (9.5), ciprofloxacin (10.3), and levofloxacin (10.6) were higher than the scores for those taking azithromycin (9.3). The table below shows the cumulative incidence of death/1million antibiotic courses, with hazard ratios and confidence intervals from various causes during courses of amoxicillin and azithromycin. These are compared to matched controls who were not taking antibiotics.

	Antibiotic		
Cause of Death	No Abx	Azithromycin	Amoxicillin
CV Death	29.8	85.2, 2.88 (1.79–4.63)	31.5, 0.95 (0.55–1.63)
Sudden Death	21.8	64.6, 2.71 (1.58–4.64)	24, 0.85 (0.45–1.60)
All Cause	57.4	105.9, 1.85 (1.25–2.75)	52.6, 1.85 (1.25–2.75)

The absolute excess risk of cardiovascular death for patients who took azithromycin, as compared with those who took amoxicillin, varied according to the baseline risk score for cardiovascular disease. For patients in the 1st to 6th deciles of risk there were only 9 excess deaths per 1 million courses of antibiotics. For patients in the highest decile of risk, there were 245 additional cardiovascular deaths per 1 million 5-day courses of azithromycin therapy.

Limitations: The obvious concern in this observational study was confounding by factors associated with both azithromycin use and an increased risk of cardiovascular death. The authors did extensive work to minimize confounding with use of propensity scores, comparison to other antibiotics, and delineation of cardiovascular risk.

Impact on Practice: Use of azithromycin should probably be limited in patients at the highest cardiovascular risk.

Oncology

Radical Prostatectomy versus Observation for Localized Prostate Cancer. Wilt, TJ, Brawer MK, Jones KM et al. N Engl J Med 2012;367:203-13.

Objective: to compare the effectiveness of surgery versus observation for men with localized prostate cancer detected by means of PSA testing.

Study Design: multicenter RCT at 44 Department of Veterans Affairs sites and 8 National Cancer Institute sites.

Participants: Number of subjects: 731 men. Inclusion criteria: Age < 75 (mean age 67), deemed medically fit for radical prostatectomy with histologically confirmed, bone scan negative, clinically localized prostate cancer (stage T1-T2NxM0) of any grade diagnosed within prior 12 months with a life expectancy of ≥ 10 years. Exclusion criteria: PSA > 50 ng/ml Baseline characteristics: mean age 48, 32% Black men. Mean PSA 7.8 ng/ml. 49% of men had stage T1c disease. The patient's tumor Gleason score was Grade 2- 4, 22.2%; Grade 5 – 6, 50%; Gleason score 7, 20.2%, Gleason score 8 – 10, 6.1%;

Intervention: Radical prostatectomy versus watchful waiting. Men in the observation group were offered palliate therapy or chemotherapy for symptomatic or metastatic progression.

Outcomes: Primary: all cause mortality. Secondary: Prostate specific mortality

Results:

	Radical Prostatectomy	Observation	HR
All Men			
All cause mortality	47%	49.8%	0.88 (0.71 – 1.08)
Prostate cancer mortality	5.8%	8.4%	0.63 (0.36 – 1.09)
Bone Metastases	4.7%	10.6%	0.4 (0.22 – 0.7)[4]

Surgical morbidity
Complications in the first 30 days occurred in 21.4% of men including 4.3% wound infection, 1.1% myocardial infarction and death 0.4%. The absolute increase in urinary incontinence in the surgical group was 10.8% (NNH 9.3) and erectile dysfunction 37% NNH 2.7

Subgroup analysis:
All cause mortality

Subgroup	Definition	ARR	HR
Low risk	PSA ≤ 10 Gleason score ≤ 6 T1a-c or T2a	(5.4%)	1.15 (0.8 – 1.66)
Intermediate or high risk	PSA > 10 or Gleason score ≥ 7 or ≥ T2b	10.5%	0.71 (0.54 – 0.92)

Prostate Cancer Mortality				
	Radical Prostatectomy	Observation	ARR %	RR
All men	5.8	8.4	2.6	0.68 (0.4 – 1.17)
PSA ≤ 10	5.9	6.2	0.3	0.95 (0.47 – 1.91)
PSA > 10	5.6	12.8	7.2	0.43 (0.18 – 1.02)

[4] No statistical decrease in men with PSA values of ≤ 10ng/ml

Limitations: (1) Median follow-up for prostate cancer was 10 years. This may limit the apparent impact of intervention. Prior observational studies of men without treatment have documented that significant mortality from prostate cancer accrues after 15 years[5]. Cause specific survival with observation has been shown to fall from 85% at 10 years to 55% at 20 years. (2) The study was fatally underpowered having originally aimed for 2000 men but limited to 731 due to difficulty in recruitment. The study closed with a 91% power to detect a 25% relative reduction in all cause morality. However, using all cause mortality as a primary outcome limits the power as well. Since prostate cancer typically accounts for only a small fraction of death among men with prostate cancer, reductions in total mortality are difficult to demonstrate. (The lifetime risk of prostate cancer is 17% but the risk of death is only 3% suggesting, that only 1/6 men die with prostate cancer die from it.) Consider that the overall mortality in the observation group was 50%. To reduce this by 25% would have required that all cause mortality fall to 37.5% or by an absolute reduction of 12.5%. Prostate cancer mortality was only 8.4% in the observation group so that even had ever single patient been saved by the intervention the reduction in mortality would have been from 50% to 41.6% (50% - 8.4%) or a 17% reduction in all cause mortality. (3)The power was further limited by the crossover in the study; Only 79% of men assigned to radical prostatectomy underwent attempted surgery and only 85% received definitive therapy; 10% of men assigned to observation underwent attempted radical prostatectomy and 20% definitive therapy. (4) Only 10% of men were < 60 y.o., the group of men most likely to benefit from intervention due to longer life expectancies and low competing mortalities.

Impact on Practice: The authors conclude that RP did not reduce prostate cancer mortality compared with observation. However, definitive conclusions are difficult to reach given the study's limited power. If one assumes that the power was insufficient to demonstrate an impact but that the point estimates are correct, for every 100 patients treated, 2.6 deaths and 5.9 patients with bony metastases will be averted, and an additional 11 patients will suffer from urinary incontinence ad 37 from erectile dysfunction. The benefit may be limited to men with PSAs > 10 and men < 65 y.o. and those with intermediate to high risk disease (PSA > 10 or Gleason score ≥ 7 or ≥ T2b)

[5] **Natural History of Early, Localized Prostate Cancer.** Johansson JE, Andren O et al. *JAMA.* 2004;291:2713-9

Rothwell PM, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 2012; 379: 1602-12.

Objective: To study the effects of daily aspirin use over the short and long-term, the risk of mortality, cancer incidence, and risk vs benefit in primary prevention.

Study design: Meta-analysis of RCTs comparing daily aspirin to placebo and no other antiplatelet agent and where the treatment course was 90 days or longer.

Results: Fifty-one RCTs were identified giving 77,549 patients (40.269 aspirin, 37,280 placebo). Death: Aspirin reduced the risk of non-vascular death by 12 % (OR 0.88, 95% CI 0.78-0.96) and cancer death by 15% (OR 0.85, 95% CI 0.76-0.96). The most benefit from cancer death occurred after 5 years' follow up (OR 0.63, 95% CI 0.49-0.82) and in the first 3 years in trials studying high-dose aspirin (OR 0.69, 95% CI 0.51-0.92). There was no difference in all-cause mortality. Cancer incidence: In trials studying aspirin for primary prevention, aspirin reduced the risk of cancer by 12% (HR 0.88, 95% CI 0.80-0.98) with the increasing benefit with longer follow-up (nonsignificant in the first 2.9 years but HR 0.71, 95% CI 0.57-0.89, at 5 or more years). Risk vs benefit: Reduced the risk of the composite outcome of major vascular events, cancer or fatal extracranial bleeds (HR 0.88, 95% CI 0.82-0.94).

Limitations: Results are limited to daily aspirin use and the trials were not designed to focus on cancer outcomes and some trials relied on patient reporting of cancer incidence and type.

Impact on practice: This study supports that daily aspirin use for primary prevention reduces the incidence of cancer and cancer death when prescribed for primary or secondary prevention. At this point, the reason for this unknown and it is not clear which patient population benefits the most. More evidence is needed before aspirin is specifically prescribed for cancer prevention but could be a point of emphasis for patients asking about the benefits of aspirin or patients who wish to stop aspirin when it is indicated for other reasons.

Pulmonary

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy. Kerstjens HAM, Engel M, Dahl R, et al. NEJM 2012; 367(13):1198-1207

Objective: to compare the effects of tiotropium vs. placebo added to standard therapy on lung function and exacerbation frequency in poorly controlled asthma

Study Design: two replicated randomized controlled trials

Participants: Number of subjects: 912. Inclusion criteria: aged 18-75 with 5 year or longer asthma history starting before age 40, symptomatic (score of >1.5 on Asthma Control Questionnaire (ACQ-7)), and persistent airflow limitation by PFTs after bronchodilator despite use of inhaled steroids and LABAs. Exclusion criteria: COPD, use of anticholinergic bronchodilators, serious coexisting illness. Baseline characteristics: mean age 53, 83% white; 60% women, mean ACQ-7 2.6, mean percent predicted FEV1 after bronchodilator 62%, 80% less than 3 exacerbations in past yr

Intervention: Placebo vs. tiotropium 5 micrograms daily by soft-mist inhaler for 48 weeks. All patients were taking inhaled glucocorticoids and LABAs. Continued use of other therapies was permitted if the doses were stable 4 weeks before and during the trial. Rescue medication salbutamol or albuterol were provided for patients.

Outcomes: primary: peak FEV1 (3 hours after administration of the placebo or tiotropium) change from baseline, the trough FEV1(pre-dose) change from baseline at week 24 third, and time to first severe asthma exacerbation. secondary: peak and trough FEV1 at each treatment visitTime to the first worsening of asthma.

Results: There were no baseline differences between groups. 20/222 discontinued placebo and 26/237 discontinued tiotropium in trial 1. 31/234 discontinued placebo and 21/219 discontinued tiotropium in trial 2. The mean change in peak FEV1 from baseline was greater with tiotropium compared with placebo in trial 1 with a difference or 86 ml $p=0.01$ from placebo and was a difference of 154 $p<0.001$ from placebo in trial 2. The mean change in trough FEV1 from baseline was greater with tiotropium in trial 1 with a difference of 88 ml $p=0.01$ from placebo in trial 1 and was 111 ml $p<0.0001$ for trial 2. Tiotropium increased the time to first severe exacerbation from 282 days as opposed to 226 days with placebo with 21% reduction in risk of severe exacerbation HR 0.79 $p=0.03$. Adverse events were similar for both placebo and tiotropium.

Limitations: (1) The clinical significance of change in peak FEV1 from baseline after receiving placebo vs. tiotropium is small (2) there was a higher placebo response in trial 1 and diversity between the two trials (3) it is an odd design to have two replicate trials instead of one larger trial.

Impact on Practice: Tiotropium may offer additional benefit for patient with poorly controlled asthma already treated with maximal inhaled corticosteroids and LABAs.

Aspirin for Preventing the Recurrence of Venous Thromboembolism. Becattini, C., et al. *N Engl J Med* 2012; 366:1959-1967.

Objective: To determine if daily aspirin therapy decreases the risk of recurrent venous thromboembolism (VTE) in patients who have completed 6 to 18 months of oral anticoagulant treatment for a first, unprovoked, VTE.

Study Design: Multicenter, double-blind randomized controlled trial.

Participants: Adult patients were included if they had been treated for 6 to 18 months with vitamin K antagonists for a first-ever, objectively confirmed, symptomatic, unprovoked VTE. The main exclusion criteria were known cancer, major thrombophilic state or an indication for long-term anticoagulant therapy.

Intervention: Patients were randomly assigned to aspirin,100 mg once daily, or placebo for 2 years within 2 weeks after vitamin K antagonists had been withdrawn.

Outcomes: The primary efficacy outcome was symptomatic, objectively confirmed recurrence of VTE, defined as the composite of deep-vein thrombosis and nonfatal or fatal pulmonary embolism.

Results: 403 patients were randomly assigned to either ASA or placebo. The median follow-up was just over 2 years. A recurrence of VTE occurred in 71 patients (8.6% patients per year). Interestingly, a recurrence in the form of pulmonary embolism was more common among the patients who entered the study because of prior PE than among those who entered because of DVT (12.7% vs. 3.2%)

The primary outcome, recurrence of VTE, occurred in 28 of the 205 patients who received aspirin, as compared with 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 0.36 - 0.93). Twenty three patients in the aspirin group had a recurrence, as compared with 39 patients in the placebo group (5.9% vs. 11.0% per year; hazard ratio, 0.55; 0.33 - 0.92). Mortality between the two groups was identical as was adverse effects (including minor and major bleeding events).

Limitations: This was a relatively small study, It is thus probably underpowered to define adverse effects so it is likely that in larger populations there will be more adverse events in the ASA group.

Impact on Practice: Pending further studies, patients who have completed 6 to 18 months of oral anticoagulant treatment for a first, unprovoked, VTE should receive low dose ASA.

Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism. Brighton TA, Eikelboom JW, Mann K, et al. NEJM. 2012; 367: 1979-87.

Objective: Evaluate the efficacy of low-dose aspirin in preventing recurrence of venous thromboembolism (VTE) in patients who have completed initial course of warfarin for treatment of an unprovoked VTE

Study design: Multicenter, international, double-blind, placebo-controlled randomized study

Participants: Number of subjects: 822. Inclusion: At least 18 years of age with a first unprovoked VTE and completed therapy with warfarin or effective alternative agent for at least 6 weeks to 24 months. Exclusion: If event had occurred more than 2 years before enrollment; had an alternative indication for aspirin or intolerance to aspirin; indication for needing continued anticoagulation therapy. Baseline characteristics: mean age 55 year; 55% male; 55% proximal DVT and 25% PE, 14% combined DVT and PE

Intervention: Randomized to aspirin 100mg daily or placebo and stratified by duration of initial anticoagulation therapy (<=26 weeks or >=26 weeks) for a minimum of 2 years

Outcome: Primary: Recurrence of symptomatic VTE; Secondary: composite of VTE, MI, stroke or cardiovascular death; Primary safety outcome: Major or clinically relevant nonmajor bleeding

Results: Median duration of follow-up was 37.2 months. There was no difference in rate of recurrence between the 2 treatment groups (18% overall, 6.5%/year in placebo group vs 14% overall, 4.8%/year in aspirin group). There was a significantly lower rate of the composite outcome of VTE, MI, stroke or cardiovascular death in the placebo group (8.0%/year in placebo group vs 5.2%/year in aspirin group; HR 0.66, 95% CI 0.48-0.92). There was no difference in rate of bleeding. A total of 132 patients (15.1%/year) in the placebo group and 117 patients (11.9%/year) in the aspirin group stopped therapy during the study period; there was no difference in rate of discontinuation.

Limitations: This study was underpowered to determine the effects on the primary outcome due to under-enrollment and the study was stopped prematurely due to slow progress.

Impact on practice: This study was underpowered to determine the benefits of aspirin in prevention of recurrent VTE.

Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. Schulman S, Kearon C, Kakkar AK, et al. NEJM. 2013;368: 709-718.

Objective: to compare dabigatran with warfarin or placebo for secondary VTE prevention.

Study Design: 2 randomized, double blind, placebo controlled trials (dabigatran vs. warfarin; dabigatran vs. placebo)

Participants: Number of subjects: 2856 in warfarin trial; 1343 in placebo trial. Inclusion criteria: ≥ 18 year of age, with confirmed, symptomatic proximal DVT or PE anticoagulated with warfarin (or dabigatran in a previous trial) for 3-12 months in the warfarin trial and 6-18 months for the placebo trial. Exclusion criteria: excessive bleeding risk, IVC filter use, Hgb < 10, cr cl < 30, active liver disease, uncontrolled CV disease. Baseline characteristics: mean age 55, weight 86 kg; 40-45% female; 90% white; cr cl 100; 65% DVT; 23% PE; 7-12% both; 7% CV disease; 38% HTN; warfarin trial-4% active cancer, 18% thrombophilia, 17% previous trial participants; placebo trial-11% thrombophilia, no active cancer

Intervention: Dabigatran 150 mg twice daily + warfarin placebo vs. warfarin + dabigatran placebo for 6-36 months OR dabigatran 150 mg twice daily vs. placebo for 12 months. Both warfarin and warfarin placebo were adjusted to an INR of 2-3.

Outcomes: Primary efficacy: recurrent confirmed, symptomatic VTE or VTE death. Primary safety: major and clinically relevant nonmajor bleeding. The dabigatran vs. warfarin trial was a noninferiority analysis with noninferiority margin for the hazard ratio defined as 2.85.

Results: The INR was therapeutic 65% of the time and supra-therapeutic 12% of the time. IN the warfarin trial, the study drug was stopped early in 19% of each group; in the placebo trial, 10% of dabigatran patients and 15% of placebo patients stopped early. In the warfarin trial, the dabigatran group had more patients with HTN and CVD. All patients who took at least one dose of the study drug were included in the analysis. Dabigatran met the inferiority criterion, and was associated with less bleeding but more ACS:

	Dabigatran	**Warfarin**	**HR**	**NNT (NNH)**
Primary endpoint	1.8%	1.3%	1.44 (0.78-2.64)	
Major or clinically relevant bleeding	5.6%	10.2%	0.54 (0.41-0.71)	22
ACS during treatment	0.9%	0.2%	4.5	(142)

In the placebo trial, dabigatran prevented recurrent VTE (6.9% vs. 10.7%; HR 0.61, 0.42-0.88) and caused more bleeding (5.3% vs. 1.8%; HR 2.92, 1.52-5.6).

Limitations: (1) The noninferiority margin of 2.85 is too high, allowing for a 3-fold increase in events in the dabigatran group; (2) dabigatran is again associated with increased cardiovascular events.

Impact on Practice: Warfarin is still preferred for long term secondary prevention of VTE.

Selective D-Dimer Testing for Diagnosis of a First Suspected Episode of Deep Venous Thrombosis: A Randomized Trial Linkins LA, Bates SM, et al
Ann Intern Med. 15 January 2013;158(2):93-100

Objective: To determine whether using a selective D-dimer testing strategy based on clinical pretest probability (C-PTP) for DVT is safe and reduces diagnostic testing compared with using a single D-dimer threshold for all patients.

Study Design: Randomized, multicenter, controlled trial.

Participants: Number of subjects: 1723. Inclusion criteria: Adults aged 18 years or older presenting to outpatient clinic, ED, or inpatient ward with first symptomatic DVT. Exclusion criteria: Those who had received full-dose heparin for 24 hours or more before study entry; on whom other tests for DVT had already been done; requiring ongoing anticoagulation; with symptoms consistent with PE; asymptomatic over previous 7 days; expected survival < 3 months; pregnant. Baseline characteristics: Age 61.5, 37% men, 89% outpatient, 7% with cancer, 17.5% with recent surgery/bedridden, 2.5% with recent paralysis/paresis or casting of a limb.

Intervention: Physicians used the 9-point Wells score to assess whether patients' clinical pretest probability of DVT was low, moderate or high. Patients were randomized to one group in which all patients were uniformly given D-dimer tests (and given ultrasonography based on those results) or one in which pretest probability determined testing.

In the intervention group, patients who had a low pretest probability and a D-dimer level <1.0 µg/mL had DVT excluded as their diagnosis. For patients with a moderate pretest probability, the D-dimer cutoff was 0.5 µg/mL. Patients who scored below either of these levels did not receive ultrasonography. Outpatients with high pretest probability and all inpatients were not given D-dimer tests and instead all received ultrasonography. Patients were followed for three months.

Outcomes: Primary: Proportion of patients not diagnosed with DVT during initial testing who had objectively confirmed symptomatic VTE (proximal DVT or PE) during 3-month follow-up; proportion of patients undergoing D-dimer testing and ultrasonography. Secondary: Suspected major bleeding events and deaths.

Results: At three months, the selective and uniform testing groups had equal incidence of symptomatic VTE: 0.5% (difference between groups, 0 percentage points; 95% CI, −0.8 to 0.8 percentage point). Selective testing reduced the proportion of patients getting D-dimer tests by 21.8 percentage points (95% CI, 19.1 to 24.8 percentage points) and ultrasonography by 7.6 percentage points (95% CI, 2.9 to 12.2 percentage points). Outpatients with low pretest probability had a particularly steep drop in ultrasonography: 21 percentage points (95% CI, 14.2 to 27.6 percentage points).

Limitations: (1) Patients and study personnel were not blinded to trial interventions, (2) Results may not be generalizable to patients with a history of DVT or to other D-dimer tests.

Impact on Practice: For first suspected episodes of DVT, these results support basing testing choices on pretest probability, strategy that is as safe and more efficient than testing everyone.

Rheumatology/Orthopedics

Epidural Corticosteroid Injections in the Management of Sciatica. A Systematic Review and Meta-analsysis. Zambelli Pinto R, Maher CG, et al. Ann Intern Med. 2012;157:865-877

Objective: to determine the efficacy of epidural corticosteroid injections for sciatica compared with placebo for short term (>2 weeks and <3 mos) and long term (>12 months) end points.

Study Design: meta-analysis of 23 randomized controlled trials

Participants: Number of subjects: 1316 for short-term efficacy data and 714 patients for long-term efficacy data. Inclusion criteria: randomized controlled trials evaluating epidural corticosteroid injections compared with placebo delivered in three anatomical approaches (caudal, interlaminar, and transforaminal) for sciatica only. Placebo was defined as injection of an inert or innocuous substance or local anesthetic with short duration of action into the epidural space or adjacent spinal tissue. Studies had to report overall pain intensity, back pain intensity, or disability status. Exclusion criteria: trials with patients who previously had surgery or with spinal canal stenosis Baseline characteristics: not specified

Intervention: participants were randomly assigned to receive epidural corticosteroid injections or placebo injection of an inert or innocuous substance or short-acting local anesthetic into the epidural or adjacent spinal tissue.

Outcomes: primary: leg pain, back pain and disability as assessed by a converted common scale from 0 to 100

Results: Epidural corticosteroids improved leg pain in the short term studies (mean difference of -6.2 (CI -9.4 to -3.0)) and disability (mean difference -3.1 (CI -5.0 to -1.2)). Epidural corticosteroids did not significantly improve any of the long term outcomes. The quality of the evidence by the GRADE classification was high.

Limitations: (1) The outcomes were small and did not reach the thresholds of clinically important change of 10 to 30 previously proposed (2) this is a meta-analysis and thus there may be small differences in the trials affecting the data (3) the inclusion of studies with short-acting anesthetic as placebo may have affected the short term outcomes seen.

Impact on Practice: There is little evidence to support the use of epidural steroid injections even for short term improvement in sciatica.

Effect of Corticosteroid Injection, Physiotherapy, or Both on Clinical Outcomes in Patients With Unilateral Lateral Epicondylalgia Coombes BK, Bisset L, et al. JAMA 2013; 309:461-469

Objective: to determine whether corticosteroid injection, multimodal physical therapy or both improve unilateral lateral epicondylalgia.
Study Design: randomized controlled trial

Participants: Number of subjects: 165. Inclusion criteria: age >18 with unilateral lateral epicondylalgia for longer than 6 weeks, defined as pain over the lateral epicondyle with pain severity of greater than 30 mm on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following: gripping, palpation, resisted wrist or middle finger extension, or stretching of forearm extensor muscles with reduced pain-free grip. Exclusion criteria: PT in the past 3 months, injection or concomitant neck/arm pain requiring treatment or preventing usual activities in the past 6 months, pregnancy/breastfeeding, contraindication to injection, or symptoms suggesting a radicular, neurologic or systemic arthritic etiology. Baseline characteristics: mean age 50; 38% female; median duration of symptoms 16 weeks, resting pain 7.5; mean worst pain 61.7

Intervention: Patients were randomized to corticosteroid injection, placebo injection (saline), corticosteroid injection with physiotherapy or placebo injection with physiotherapy
Outcomes: primary: global rating of change scores (based on 6 point likert scale from much worse to complete recovery) for complete recovery or much improvement after 1 year and recurrence after 1 year (defined as complete recovery or much improvement at 4 or 8 weeks) secondary: complete recovery or much improvement at 4 and 26 weeks, severity of current resting pain and worst pain over the preceding week on a 100-mm VAS

Results: There were no baseline differences between groups. The corticosteroid injection group had lower complete recovery or much improvement at 1 year vs. placebo (83% vs. 96% RR 0.86, 0.75-0.99; NNT-7.5) and higher 1 year recurrence (54% vs. 12% RR 0.23, 0.1-0.51; NNT -2.4). There was no difference in the physiotherapy and no physiotherapy groups in complete recovery or much improvement at 1 year (91% vs. 88% RR 1.04, 0.9-1.19) and 1 year recurrence (29% vs. 38% RR 1.31, 0.73-2.35). At 4 weeks there was a greater improvement in those receiving corticosteroid injection vs. placebo and the group receiving placebo with physiotherapy had greater complete recovery or much improvement vs. those with no physiotherapy (39% vs. 10% RR 4.00, 1.07-15.00)

Limitations: (1) patients were not blinded to treatment but were blinded to the type of injection (researchers were blinded however).

Impact on Practice: Corticosteroid injections improve chronic unilateral lateral epicondylalgia in the short-term (4 weeks) but lead to worse clinical outcomes after 1 year. Physical therapy did not significantly improve symptoms compared to no physical therapy after 1 year.