New Drug Update 2013-2014

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Faculty Disclaimer

- I am a consultant for Merck in the area of outcomes research.
Acetaminophen Update

January 13, 2011 FDA Drug Safety Communication: **Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit** - The FDA is asking drug manufacturers to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids. This action will limit the amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients.

- Drug companies will have three years from the date of publication of the Federal Register Notice (January 14, 2011) to limit the amount of acetaminophen in their oral prescription drug products to 325 mg per dosage unit (see the Federal Register Notice2 Docket number FDA-2011-N-0021-0001).

- In addition, a Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (e.g., swelling of the face, mouth, and throat, difficulty breathing, itching, or rash) are being added to the label of all prescription drug products that contain acetaminophen.
Abbott Announces New Reformulated Vicodin (hydrocodone/acetaminophen)

• May 29, 2012 Abbott is discontinuing manufacturing and distribution of current formulations of Vicodin
  – Vicodin (hydrocodone bitartrate 5mg / acetaminophen 500mg) will be 5mg/300mg
  – Vicodin ES (hydrocodone bitartrate 7.5mg / acetaminophen 750mg) will be 7.5mg/300mg
  – Vicodin HP (hydrocodone bitartrate 10mg / acetaminophen 660mg) will be 10mg/300mg
• Norco by Watson is converting to 325 mg acetaminophen per tablet
FDA recommends against prescribing and dispensing prescription combination drug products with more than 325 mg of acetaminophen

• More than half of manufacturers have voluntarily complied with our request. However, some prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit remain available.

• In the near future we intend to institute proceedings to withdraw approval of prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit that remain on the market.
  
  — FDA Jan 14, 2014
<table>
<thead>
<tr>
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<tr>
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<td>51.7</td>
<td>45.3</td>
<td>43.3</td>
<td>54.9</td>
</tr>
</tbody>
</table>

# of Rx’s (30 and 90 day supply) in millions
March 22, 2013 by IMS
FDA Announces Plan to Move Hydrocodone to Schedule II

• By early December, FDA plans to submit our formal recommendation package to HHS to reclassify hydrocodone combination products into Schedule II. We anticipate that the National Institute on Drug Abuse (NIDA) will concur with our recommendation. This will begin a process that will lead to a final decision by the DEA on the appropriate scheduling of these products.

– FDA Drug Safety and Availability: October 24, 2013
The Drug Enforcement Administration (DEA) proposes to reschedule hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act. This proposed action is based on a rescheduling recommendation from the Assistant Secretary for Health of the Department of Health and Human Services and an evaluation of all other relevant data by the DEA. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule II controlled substances.

The DEA will receive comments until April 28, 2014.
FDA Approves Zohydro ER C-II

• 10/26/2013 The U.S. Food and Drug Administration today approved Zohydro ER (hydrocodone bitartrate extended-release capsules) by Zogenix for the management of pain severe enough to require daily, around-the-clock, long-term treatment and for which alternative treatment options are inadequate.

  – The first FDA-approved single-entity (not combined with an analgesic such as acetaminophen) and extended-release hydrocodone product.
Hydrocodone bitartrate extended-release capsules – Zohydro ER

- ER/LA opioid formulations like Zohydro ER should be reserved for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. **Zohydro ER is not approved for as-needed pain relief.**
  - The approved labeling for Zohydro ER conforms to updated labeling requirements for all ER/LA opioid analgesics announced by the FDA on Sept. 10, 2013.
Hydrocodone bitartrate extended-release capsules – Zohydro ER

- Extended-release capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg and 50 mg
  - Capsules must be swallowed whole and are not to be chewed, crushed or dissolved.

- For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg capsules orally every 12 h. To convert to Zohydro ER from another opioid, use available conversion factors to obtain estimated dose.

- Increase the dose of Zohydro ER in increments of 10 mg every 12 hours every 3 to 7 days as needed to achieve adequate analgesia.
FDA Drug Safety Communication - Olmesartan

• 7-3-2013 FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil (Benicar, Azor, Tribenzor)
  – Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization.
  – Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.
  
    • In June 2012, Mayo Clinic researchers published a case series of sprue-like enteropathy associated with olmesartan in 22 patients (Mayo Clin Proc 2012;87:732-8)
Fluoroquinolones may cause disabling peripheral neuropathy symptoms in the arms or legs such as pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature. These symptoms can occur early in treatment and may be permanent.

It can occur at any time during treatment with fluoroquinolones and can last for months to years after the drug is stopped or be permanent. Patients using fluoroquinolones who develop any symptoms of peripheral neuropathy should tell their health care professionals right away.
Class IIA

- Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (Level of Evidence: B)
  - Digoxin Intervention Group Trial (N Engl J Med 1997;336:525-33)
  - Doses of digoxin that achieve a plasma concentration of drug in the range of 0.5 to 0.9 ng/mL are suggested, given the limited evidence currently available
    - Circulation. published online June 5, 2013
Digoxin and Outcomes?

- New digoxin use and risks of death and HF hospitalization, controlling for medical history, laboratory results, medications, HF disease severity, and the propensity for digoxin use. We also conducted analyses stratified by sex and concurrent β-blocker use. Among 2891 newly diagnosed patients with systolic HF, 529 (18%) received digoxin.

- During a median 2.5 years of follow-up, incident digoxin use was associated with higher rates of death (14.2 versus 11.3 per 100 person-years) and HF hospitalization (28.2 versus 24.4 per 100 person-years). In multivariable analysis,

- incident digoxin use was associated with higher mortality (hazard ratio, 1.72; 95% confidence interval, 1.25–2.36) but no significant difference in the risk of HF hospitalization (hazard ratio, 1.05; 95% confidence interval, 0.82–1.34).
  - Results were similar in analyses stratified by sex and β-blocker use.
Digoxin after 230 years?

• The Editorial by Dr. Opie entitled “Digitalis, Yesterday and Today, But Not Forever” concludes: “This conclusion is the opposite of what the earlier studies favoring digoxin use in the bygone era of imperfect therapy for HF had found, with the new conclusion that therapy for HF that includes β-blockade and full angiotensin-II modulation dispenses with the need for taking the risks of adding digoxin therapy. The data at our disposal, taking into account the current study, allow us to seriously question the advice on digoxin given by both the current and influential guidelines, European and American.”

Aspirin in Patients with Heart Failure

• A retrospective cohort study of 1476 patients (mean age 70.4±12.4 years, 63% male) attending a HF disease management program examined aspirin use at baseline and its association with mortality and HF hospitalization. 892 (60.4%) were prescribed aspirin (75mg/day in 92.8%). Median follow-up time was 2.6 [0.8:4.5] years.
  - Over the follow-up period, 464 (31.4%) patients died. In adjusted analysis, low-dose aspirin use was associated with reduced mortality risk compared to non-aspirin use (HR=0.58, 95% CI 0.46–0.74).
  - Low-dose aspirin use was associated with reduced risk of HF hospitalization compared to non-aspirin use in the total population (adjusted HR=0.70, 95% CI 0.54–0.90).

• 10.1161/CIRCHEARTFAILURE.113.000132 (on-line 2-5-2014)
Aspirin in Patients with Heart Failure

• In adjusted analysis, there was no difference in mortality or HF hospitalization between high-dose aspirin users (>75mg/day) and non-aspirin users.

• Conclusions— In this study low-dose aspirin therapy was associated with a significant reduction in mortality and morbidity risk over long-term follow-up.

– 10.1161/CIRCHEARTFAILURE.113.000132 (on-line 2-5-2014)
OTC Nasacort Allergy 24hr Nasal Spray

• Sanofi/Chattem announced that **Nasacort** (triamcinolone acetonide) Allergy 24hr Nasal Spray is now available over-the-counter (OTC) to relieve a range of seasonal and year-round nasal allergy symptoms, including nasal congestion, in adults and children >2 years of age.
  
  – Nasacort spray in 60 (~$12) and 120 (~$18) metered dose sprays. (55mcg/spray which is the same as the prescription (vs ~$58.00 for the generic Rx)
  
  – Nasacort was approved for the switch from prescription to OTC by the FDA on October 11, 2013.
FDA Joint Panel to Probe NSAID Safety

• A joint meeting of the agency’s Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee will is scheduled for Feb. 10-11, 2014 at the FDA to discuss literature published since 2005, with a specific focus on:
  – Whether the data show that naproxen has a lower CV thromboembolic risk compared to other nonselective NSAIDs and what this might mean for physicians;
  – Whether the published findings indicate a differential risk for non-naproxen NSAIDs;
  – Whether there is likely to be a latency period for increased risk for NSAIDs;
  – Whether there should be restrictions or specific warnings for higher-risk patients;
  – Whether NSAIDs should remain OTC in light of new findings; and
  – Whether the Precision trial should be altered in accordance with recent literature.
FDA Joint Panel on NSAID Safety

• The FDA Arthritis Advisory Committee (AAC) and Drug Safety and Risk Management (DSARM) Advisory Committee, just nine panel members said they believed naproxen has a lower risk of cardiovascular thrombotic events than other available nonsteroidal anti-inflammatory drugs (NSAIDs) while 16 others thought the data was insufficient to say that naproxen was safer than other NSAIDs.

• The current label implies that cardiovascular thrombotic risk is not "substantial" with short treatment courses, but 14 panel members said this advice should be reconsidered and that there was no latency period with the NSAID class.
PRECISION Trial

- Relative risks of major adverse CV events between celecoxib 100-200 mg BID, naproxen 375-500 mg BID and ibuprofen 600-800 mg TID
- Relative risks for gastrointestinal, renal, and other safety events between celecoxib, naproxen and ibuprofen in higher CV risk patients with OA and RA;
The PRECISION study is ongoing, with patient enrollment having achieved 22,278 as of 12/5/2013. Based on information as of December 2013, we know that the required 580 APTC events have not been accrued. The Sponsor also knows that there has not been a sufficient imbalance in primary composite events between treatments to require stopping the study.
FDA Drug Safety Communication
Testosterone Products

• Jan 31, 2014 The FDA is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products.
  – Testosterone products are FDA-approved only for use in men who lack or have low testosterone levels (<300ng/dl) in conjunction with an associated medical condition. Examples include failure of the testicles to produce testosterone, because of reasons such as genetic problems or chemotherapy. Other examples include problems with the hypothalamus and pituitary that control the production of testosterone by the testicles.
  – None of the FDA-approved testosterone products are approved for use in men with low testosterone levels who lack an associated medical condition. FDA-approved testosterone formulations include the topical gel, transdermal patch, buccal system (applied to upper gum or inner cheek), and injection.
FDA Drug Safety Communication-Testosterone Products

• An observational study of older men in the U.S. Veteran Affairs health system
  – The population was a very specific group of men who had coronary heart disease based upon coronary angiography and had their testosterone levels measured (<300 ng/dL) before they had a myocardial infarction, rather than after. These men received an appropriate prescription and filled it at least once to see what would happen. The investigators ended up with approximately 8700 men, about 1275 of whom had been given testosterone, and they examined the outcomes.
  – They looked at all-cause mortality, strokes, and heart attacks. They found that giving testosterone at recommended levels to men who were candidates for it actually raised their testosterone levels, as might be expected.
  • JAMA. 2013;310:1829-1836
The absolute rate of events (all-cause mortality, MI, and ischemic stroke) were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI, -1.4% to 13.1%) (NNH = 18) at 3 years after coronary angiography.

In Cox proportional hazards models adjusting for the presence of coronary artery disease, testosterone therapy use as a time-varying covariate was associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% CI, 1.04 to 1.58).

- JAMA. 2013;310:1829-1836
FDA Drug Safety Communication - Testosterone Products

• A cohort study of the risk of acute non-fatal myocardial infarction (MI) following an initial topical testosterone (TT) prescription (N = 55,593) in a large US health-care database.
  – Compared the incidence rate of MI in the 90 days following the initial prescription (post-prescription interval) with the rate in the one year prior to the initial prescription (pre-prescription interval) (post/pre).
  – Also compared post/pre rates in a cohort of men prescribed phosphodiesterase type 5 inhibitors (PDE5I; sildenafil or tadalafil, N = 167,279), and compared TT prescription post/pre rates with the PDE5I post/pre rates, adjusting for potential confounders.

• PLOS ONE www.plosone.org January 2014 Volume 9 Issue 1 85805
FDA Drug Safety Communication- Testosterone Products

Results:

• In all subjects, the post/pre-prescription rate ratio (RR) for TT prescription was 1.36 (1.03, 1.81). In men aged 65 years and older, the RR was 2.19 (1.27, 3.77) for TT prescription and 1.15 (0.83, 1.59) for PDE5I, and the ratio of the rate ratios (RRR) for TT prescription relative to PDE5I was 1.90 (1.04, 3.49).

• The RR for TT prescription increased with age from 0.95 (0.54, 1.67) for men under age 55 years to 3.43 (1.54, 7.56) for those aged >75 years (ptrend = 0.03), while no trend was seen for PDE5I (ptrend = 0.18). In men under age 65 years, excess risk was confined to those with a prior history of heart disease, with RRs of 2.90 (1.49, 5.62) for TT prescription and 1.40 (0.91, 2.14) for PDE5I, and a RRR of 2.07 (1.05, 4.11).
“At this time, FDA has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death. Patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals. Health care professionals should consider whether the benefits of FDA-approved testosterone treatment is likely to exceed the potential risks of treatment. The prescribing information in the drug labels of FDA-approved testosterone products should be followed.”
FDA Approves Testosterone Undecanoate Injection

• March 6, 2014 the FDA approved Aveed (testosterone undecanoate) injection for the treatment of adult men with hypogonadism (commonly known as Low-T) that is associated with a deficiency or absence of the male hormone testosterone. Aveed is a new prescription medicine indicated to produce serum testosterone levels in the normal range by administration of a single 3-mL (750 mg) intramuscular injection given once at initiation of therapy, at 4 weeks, and then every 10 weeks thereafter.
Approval of Aveed is based on data from an 84-week Phase 3 trial of hypogonadal men in the U.S. Men enrolled in the study had an average age of 54 years and a serum total testosterone level of less than 300 ng/dL. In the Phase 3 study, Aveed increased mean serum testosterone levels, maintaining them for up to 10 weeks at steady state (between weeks 14-24). Aveed is approved with a Risk Evaluation and Mitigation System (REMS) requiring prescriber education and certification as well as restricted product distribution.
Testosterone Undecanoate Injection - Aveed

• Indicated for replacement therapy in adult males for conditions associated with a **deficiency or absence of endogenous testosterone**, including primary hypogonadism (congenital or acquired) and hypogonadotrophic hypogonadism (congenital or acquired).

• Aveed has a Boxed Warning for serious pulmonary oil microembolism (POME) reactions and anaphylaxis. It should be used in patients who require therapy and in whom the benefits of the product outweigh the serious risks of POME and severe allergic reaction (anaphylaxis). **It must be prescribed and administered by trained healthcare providers in a doctor's office, clinic, or hospital.**
  
  – Patients must remain in the administering physician's office or clinic for at least 30 minutes after injection so that short-term reactions may be observed and treated.
Testosterone Undecanoate Injection - Aveed

• Other potential adverse effects include worsened *prostate enlargement*, liver toxicity, peripheral edema, sleep apnea, and venous thrombosis.

• Shortly after Endo announced the approval, the consumer group Public Citizen called on the FDA to reverse it, citing recent studies that suggest increased cardiovascular risk with testosterone products.
What’s New 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals

• The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD.
  – The Expert Panel was unable to find randomized clinical trial (RCT) evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.

• Circulation. published online November 12, 2013
  http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation
What’s New 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

• The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.

• Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.
High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)

<table>
<thead>
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<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
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<tr>
<td>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

Specific statins and doses are noted in bold that were evaluated in RCTs. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.
What’s New 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

Global Risk Assessment for Primary Prevention

• This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women. (Controversial?)
  – By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
  – It also indicates, based on RCT data, those high-risk groups that may not benefit.
  – Before initiating statin therapy, this guideline recommends a discussion by clinician and patients.
Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Risk Factors for ASCVD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
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<tr>
<td>Age</td>
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<tr>
<td>Race</td>
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<tr>
<td>Total Cholesterol</td>
<td>210</td>
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<tr>
<td>HDL Cholesterol</td>
<td>28</td>
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<tr>
<td>Systolic BP</td>
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<tr>
<td>Diabetes</td>
<td>No Yes</td>
</tr>
<tr>
<td>Smoker</td>
<td>No Yes</td>
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</table>
Pooled Cohort Risk Assessment Equations Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Results

ASCVD Risk Evaluation

10-year risk of atherosclerotic cardiovascular disease: 42.4%
10-year risk in a similar patient with optimal risk factors: 9.6%
### AHA/ACC Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

#### NNT for Statins for 5 Years:

<table>
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<th>10-year risk of CVD events</th>
<th>5-year NNT for CVD events</th>
<th>5-year NNT for myocardial infarction</th>
<th>5-year NNT for stroke</th>
<th>5-year NNT for mortality</th>
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<tr>
<td>5%</td>
<td>160</td>
<td>278</td>
<td>910</td>
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<td>108</td>
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<td>80</td>
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<tr>
<td>20%</td>
<td>40</td>
<td>70</td>
<td>228</td>
<td>250</td>
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</table>

Abbreviations: CVD, cardiovascular disease; NNT, number needed to treat (to prevent 1 outcome)

* no apparent mortality reduction in lowest-risk patients ([BMJ 2013 Oct 22;347:f6123](https://www.bmj.com/content/347/bmj.f6123))

Courtesy: DynaMed
AHA/ACC Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

• The new guidelines have also drawn considerable criticism especially when it comes to primary prevention and the new recommendation for a 10 year CV risk level of 7.5% with the new risk calculator.

• Ridker and Cook in a Lancet Editorial commend the new guideline for its emphasis on improving and simplifying use of statins. However, they calculate that the risk prediction algorithm used in the guideline has “systematically overestimated” cardiovascular risks, and could therefore lead to overtreatment.

  – Lancet November 23. 2013 pp 1680
How many of the 33 million expected to have risk >7.5% actually have risk that is much lower?

The Lancet, Volume 382, Issue 9907, Pages 1762 - 1765
AHA/ACC Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

• Treating to LDL cholesterol targets is no longer recommended; rather, clinicians should determine whether a patient falls into one of four mutually exclusive high-risk groups and should initiate statin therapy as follows:

  1. Patients with clinical atherosclerotic cardiovascular disease (ASCVD) should receive high-intensity (age, <75) or moderate-intensity (age, ≥75) statin therapy

  2. Patients with LDL cholesterol levels ≥190 mg/dL should receive high-intensity statin therapy.

J Am Coll Cardiol 2013 Nov 12; [e-pub ahead of print]
AHA/ACC Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

3. Patients with diabetes aged 40–75 with LDL cholesterol levels of 70–189 mg/dL and without clinical ASCVD should receive at least moderate-intensity statin therapy (and possibly high-intensity statin therapy when estimated 10-year ASCVD risk is ≥7.5%)

4. Patients without clinical ASCVD or diabetes but with LDL cholesterol levels of 70–189 mg/dL and estimated 10-year ASCVD risk ≥7.5% should receive moderate- or high-intensity statin therapy

J Am Coll Cardiol 2013 Nov 12; [e-pub ahead of print]
AHA/ACC Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

• High-intensity statin therapies are atorvastatin (40–80 mg) or rosuvastatin (Crestor; 20–40 mg). Moderate-intensity statin therapies include atorvastatin (10–20 mg), rosuvastatin (5–10 mg), simvastatin (20–40 mg), pravastatin (40–80 mg), and several others

• With few exceptions, use of lipid-modifying drugs other than statins is discouraged.

• Lifestyle modification is recommended for all patients, regardless of cholesterol-lowering drug therapy
  – J Am Coll Cardiol 2013 Nov 12; [e-pub ahead of print]
High Potency Statins vs. Simvastatin vs. Simvastatin plus Ezetimibe?

• The UK General Practice Research Database reviewed 9597 patients (57% male, mean age of 65 ±13 years) matched study criteria (had survived 30 days after their first acute myocardial infarct (AMI), had not received prior statin or ezetimibe therapy and were started on a statin within 30 days of AMI were included).
• Primary outcome was all cause mortality
• Simvastatin (n=6990 (72.8%)); high-potency statin (n=1883, (19.6%)); and ezetimibe/statin combination (n=724 (7.5%)). During a mean follow-up of 3.2 years, there were 1134 (12%) deaths.
  – the study lacked statistical power to determine any mortality effect with ezetimibe.

Heart 2014; DOI: 10.1136/heartjnl.2013.304678
Proportional Hazards Ratio for Risk of Death
Heart 2014; DOI: 10.1136/heartjnl.2013.304678

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<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
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<tr>
<td>High-potency statin monotherapy</td>
<td>0.72</td>
<td>0.59 to 0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ezetimibe/statin combination</td>
<td>0.96</td>
<td>0.64 to 1.43</td>
<td>0.847</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>0.84</td>
<td>0.74 to 0.95</td>
<td>0.009</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.08</td>
<td>1.08 to 1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker (yes vs no)</td>
<td>1.44</td>
<td>1.25 to 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic (yes vs no)</td>
<td>1.44</td>
<td>1.13 to 1.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Further MI during follow-up</td>
<td>1.45</td>
<td>1.32 to 1.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular drugs (yes vs no)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.57</td>
<td>0.48 to 0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>0.68</td>
<td>0.59 to 0.79</td>
<td>&lt;0.001</td>
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<tr>
<td>ACE-I</td>
<td>0.72</td>
<td>0.62 to 0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DHP CCB</td>
<td>0.57</td>
<td>0.47 to 0.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
AHA/ACC Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

• This guideline represents a paradigm shift for most clinicians and patients. The rationale for abandoning LDL cholesterol targets is that randomized trials showing benefits of statins generally have examined fixed-dose statin therapy, rather than titrated therapy, to achieve prespecified LDL cholesterol goals. Additionally, some drugs that “improve” the lipid profile (a surrogate endpoint) do not improve clinical outcomes, and statins are thought to exert benefit through pleiotropic effects apart from LDL cholesterol–lowering.

— J Am Coll Cardiol 2013 Nov 12; [e-pub ahead of print]
Am Acad Neurology Evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation

• These guidelines have been endorsed by the World Stroke Organization

• For patients with NVAF, which therapies that include antithrombotic medication, as compared with no therapy or with another therapy, reduce stroke risk and severity with the least risk of hemorrhage?
  
  – In patients who have NVAF but no risk factors, the absolute risk of major bleeding (3%/year) is larger than the absolute reduction in stroke from anticoagulation (1.3%/year).
Selection of a Specific Oral Anticoagulant

To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose one of the following options:

- **Warfarin**, target international normalized ratio (INR) 2.0–3.0
- **Dabigatran** 150 mg twice daily (if creatinine clearance [CrCl] > 30 mL/min)
- **Rivaroxaban** 15 mg/day (if CrCl 30–49 mL/min) or 20 mg/day
- **Apixaban** 5 mg twice daily (if serum creatinine < 1.5 mg/dL) or 2.5 mg twice daily (if serum creatinine > 1.5 and < 2.5 mg/dL, and body weight < 60 kg or age at least 80 years [or both])

Level B

Neurology® 2014;82:716–724
Relative risk reductions of various outcomes in patients with nonvalvular atrial fibrillation receiving various antithrombotic regimens as compared with warfarin or its derivatives

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug</th>
<th>Relative risk reduction and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>Trifuslal &amp; acenocoum</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Trifuslal &amp; acenocoum</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Trifuslal &amp; acenocoum</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>Trifuslal &amp; acenocoum</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel &amp; ASA</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Trifuslal &amp; acenocoum</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

Acenocoum = acenocoumarol; ASA = acetylsalicylic acid; CI = confidence interval.
Am Acad Neurology Evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation

GI bleeding risk

• Clinicians might offer apixaban to patients with NVAF and GI bleeding risk who require anticoagulant medication. Level C

INR monitoring

• Clinicians should offer dabigatran, rivaroxaban, or apixaban to patients unwilling or unable to submit to frequent periodic testing of INR levels.

Neurology® 2014;82:716–724
Patients unsuitable for warfarin

• Clinicians should offer apixaban to patients unsuitable for being treated, or unwilling to be treated, with warfarin. Level B

• Where apixaban is unavailable, clinicians might offer dabigatran or rivaroxaban. Level C

• Where oral anticoagulants are unavailable, clinicians might offer a combination of aspirin and clopidogrel. Level C
**Am Acad Neurology Evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation**

Special populations

- Clinicians should routinely offer oral anticoagulants to elderly patients (aged > 75 years) with NVAF if there is no history of recent unprovoked bleeding or intracranial hemorrhage.

- Clinicians might offer oral anticoagulation to patients with NVAF who have dementia or occasional falls. However, clinicians should counsel patients or their families that the risk–benefit ratio of oral anticoagulants is uncertain in patients with NVAF who have moderate to severe dementia or very frequent falls.

*Neurology® 2014;82:716–724*
New Indication: Apixaban - Eliquis

• FDA approved 3-13-2014 for the prophylaxis of hip and knee replacement surgery based upon clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery.
  – A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight (≤60 kg), 2528 patients with Body Mass Index ≥33 kg/m², and 625 patients with severe or moderate renal impairment.
Apixaban - Eliquis

- Apixaban was started 12-24 hours post surgery while enoxaparin was started in ADVANCE 1 - 12-24 hours post surgery and continued for 10-14 days; in ADVANCE 2 - 9-15 hours prior to surgery and continued for 10-14 days and in ADVANCE 3 – 9-15 hours prior to surgery and continued for 32-38 days.
Apixaban - Eliquis

• ADVANCE 1 Trial (knee) apixaban 2.5 mg BID vs. enoxaparin 30 mg BID
  – Combined total DVT and all cause death 8.99% vs. 8.55%
    RR 1.02, p - NS

• ADVANCE 2 Trial (knee) apixaban 2.5 mg BID vs. enoxaparin 40 mg QD
  – Combined total DVT and all cause death 15.06% vs. 24.37%
    RR 0.62, p < 0.0001, NNT 11

• ADVANCE 3 Trial (hip) apixaban 2.5 mg BID vs. enoxaparin 40 mg QD
  – Combined total DVT and all cause death 1.39% vs. 3.86%
    RR 0.36, p < 0.0001, NNT 41
Apixaban - Eliquis

- The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily.
- The initial dose should be taken 12 to 24 hours after surgery.
  - In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
  - In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.
Rivaroxaban - Xarelto

- July 5, 2011 The FDA approved rivaroxaban a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement.

- The recommended dose of is **10 mg taken orally once daily with or without food**. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.
  - For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
  - For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.
Dosage of Enoxaparin?

• Most of the trials (RECORD 1, 2 and 3) used the European approved dose of enoxaparin 40 mg/d. Enoxaparin was usually started the evening before surgery and continued 6 to 8 h postoperatively.

• RECORD 4 used the US FDA approved dose of enoxaparin: 30 mg bid dosing rather than 40 mg once daily and started 12 h postoperation.
Rivaroxaban - Xarelto

- RECORD 1 (Hip) R=1.1% vs. E=3.9%, RRR 71%, ARR 2.8%, NNT=36
- RECORD 2 (Hip) R=2.0% vs. E=8.4%, RRR 76%, ARR 6.4%, NNT=16
- RECORD 3 (Knee) R=9.7% vs. E=18.8%, RRR 48%, ARR 9.1%, NNT=11
- RECORD 4 (Knee) US approved dosing R=6.9% vs. E=10.1%, RRR 31%, ARR 3.19%, NNT=32
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

• May 10, 2013 The Food and Drug Administration today approved Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.
  – Developed by GlaxoSmithKline, in collaboration with Theravance.
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta

• Maintenance treatment of COPD: 1 inhalation of Breo Ellipta 100 mcg/25 mcg (fluticasone furoate /vilanterol inhalation powder) once daily. Cost $256.81 WAC

• The plasma half-life of the components is ~ 24 hours and 21 hours respectively

• FDA Box Warning as with all other LABA containing medications Asthma Related Deaths but NOT indicated for patients with asthma
Fluticasone furoate /Vilanterol inhalation powder – Breo Ellipta
Fluticasone furoate / Vilanterol inhalation powder – Breo Ellipta

Be careful, every time you move the cover you move to the next dose!
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler by GSK

• A combination of umeclidinium, an anticholinergic (LAMA), and vilanterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

• Not indicated for the relief of acute bronchospasm or for the treatment of asthma
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

• Inhalation Powder. Inhaler containing 2 double-foil blister strips of powder formulation for oral inhalation. One strip contains umeclidinium 62.5 mcg per blister and the other contains vilanterol 25 mcg per blister.
  – The half-life of both components is about 11 hours
  – Dose is one inhalation once a day.

• FDA Box WARNING: ASTHMA-RELATED DEATH
  – Available as both a 30 dose and 7 dose institutional inhaler
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

• Drug Interactions:
  – Vilanterol is a CYP 3A4 substrate so use caution when patients are taking strong 3A4 inhibitors (i.e. clarithromycin, protease inhibitors, azole antifungals)
  – Umeclidinium is a CYP 2D6 substrate (no significant interactions seen?)
  – MAO inhibitors and Tricyclics may increase QTc
  – Anticholinergics are likely additive to umeclidinium, caution in males with BPH
  – Beta blockers?
Umeclidinium and Vilanterol – Anoro Ellipta Inhaler

• Both components may increase CV risk?
  – A dose-dependent increase in heart rate was observed (~9-20 Beats per minute increase with higher than recommended doses)

• Adverse Effects:
  – include pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain.

• Cost: $269.65/ 30 doses WAC
CAUTION: If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled.
Comparison Of Long Acting Bronchodilators

POET-COPD Trial (Prevention Of Exacerbations with Tiotropium in COPD)

• R, DB trial of tiotropium (18 mcg QD) vs salmeterol (50 mcg BID) in 7376 patients with moderate-to-very-severe COPD X 1 year
• 50% receiving inhaled steroids, using PRN beta-agonists PRN
• Results: Tiotropium was superior:
  • Increased time to first exacerbation - 187 days vs 145 days (p< 0.001)
  • Reduced number of moderate or severe exacerbations – 0.64 vs 0.72 (p=0.002) Requiring oral steroids or antibiotics
  • Reduced number of severe exacerbations – 0.09 vs 0.13 (p< 0.001) Requiring hospitalization
• No difference in serious adverse events

### Therapeutic Options: COPD Medications

<table>
<thead>
<tr>
<th><strong>Beta_2-agonists</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting beta_2-agonists (SABA)</td>
<td></td>
</tr>
<tr>
<td>Long-acting beta_2-agonists (LABA)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Anticholinergics</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting anticholinergics (SAMA)</td>
<td></td>
</tr>
<tr>
<td>Long-acting anticholinergics (LAMA) tiotropium or aclindinium bromide</td>
<td></td>
</tr>
</tbody>
</table>

Combination short-acting beta_2-agonists + anticholinergic in one inhaler (SABA/SAMA) CombiVent Respirmat

Combination long-acting beta_2-agonists + anticholinergic in one inhaler (LABA/LAMA)

<table>
<thead>
<tr>
<th><strong>Methylxanthines (theophylline)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroids (ICS)</td>
<td></td>
</tr>
</tbody>
</table>

Combination long-acting beta_2-agonists + corticosteroids in one inhaler (ICS/LABA)

<table>
<thead>
<tr>
<th><strong>Systemic corticosteroids</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphodiesterase-4 inhibitors (roflumilast)</td>
<td></td>
</tr>
</tbody>
</table>

© 2014 Global Initiative for Chronic Obstructive Lung Disease
Long-acting inhaled bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.

Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.

Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
Regular treatment with inhaled corticosteroids improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV$_1$ < 60% predicted.

Inhaled corticosteroid therapy is associated with an increased risk of pneumonia.

Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients.
An inhaled corticosteroid combined with a long-acting beta_2_-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.

Combination therapy is associated with an increased risk of pneumonia.

Addition of a long-acting beta_2_-agonist/inhaled glucocorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

*(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommended First choice</th>
<th>Alternative choice</th>
<th>Other Possible Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SAMA prn or SABA prn</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA or LAMA</td>
<td>LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA and/or LAMA</td>
<td>ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE

Exacerbations per year

- 2 or more
- or
- ≥ 1 leading to hospital admission
- 1 (not leading to hospital admission)
- 0

<table>
<thead>
<tr>
<th>GOLD 4</th>
<th>GOLD 3</th>
<th>GOLD 2</th>
<th>GOLD 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>0</td>
<td>1 (not leading to hospital admission)</td>
<td>2 or more</td>
<td>or ≥ 1 leading to hospital admission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMA prn or SABA prn</td>
<td>ICS + LABA or LAMA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABA or LAMA</td>
<td>ICS + LABA and/or LAMA</td>
</tr>
</tbody>
</table>

CAT < 10 mMRC 0-1  ~~  CAT ≥ 10 mMRC ≥ 2

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COPD Treatment and CV Events?

• A nested case-control analysis of a retrospective cohort study in Ontario compared the risk of events between older COPD patients newly prescribed inhaled long acting beta-agonists (LABA) and long acting anticholinergics (LAMA), after matching and adjusting for prognostic factors

• Main Outcome and Measures: An emergency department visit or a hospitalization for a cardiovascular event.

  — JAMA Intern Med. Published online May 20, 2013
COPD Treatment and CV Events?

- Results: Of 191,005 eligible patients, 53,532 (28.0%) had a hospitalization or an emergency department visit for a cardiovascular event.

- Patients newly prescribed a LABA and/or a LAMA were found to have a greater risk of an event compared with nonuse of those medications (respective adjusted odds ratios, 1.31 [95% CI, 1.12-1.52; P<.001] and 1.14 [1.01-1.28; P=.03]).
  - No significant difference in events between the 2 medications (adjusted odds ratio of long-acting inhaled beta-agonists compared with anticholinergics, 1.15 [95% CI, 0.95-1.38; P=.16]).

- JAMA Intern Med. Published online May 20, 2013
Vortioxetine - Brintellix by Takeda

• A Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant approved for treatment of major depressive disorder (MDD).
  – a 5-hydroxytryptamine 1A (5-HT1A) agonist, 5-HT1B partial agonist, 5-HT3 antagonist, 5-HT7 antagonist, and 5-HT transporter protein inhibitor
  – net effect of these activities is an increase in the levels of 5-HT, noradrenaline, dopamine, and acetylcholine, and histamine in the ventral hippocampus and medial prefrontal cortex
Vortioxetine - Brintellix

- The **half-life of vortioxetine is approximately 66 hours** because of the large apparent volume of distribution.
- About 98% bound to plasma proteins.
- Metabolized mainly by cytochrome P450 (CYP 2D6) with 6 total metabolites with little to no antidepressant activity
  - Vortioxetine and its primary metabolite have been shown to be substrates and weak inhibitors of CYP2C19, but coadministration studies have not shown clinical significance in humans.
- Vortioxetine has minimal renal clearance, and negligible amounts of the drug found in urine.
Vortioxetine - Brintellix

• The labeling for vortioxetine contains the **boxed warning regarding suicidal thoughts and behaviors that is required for all antidepressants.** Use of antidepressants in the treatment of children, adolescents, and young adults was associated with increases in the risk of suicidal thoughts and behaviors and a trend towards reduced risk in patients 65 years and older.

• All patients will need to be monitored for changes in mental function, behavior, and suicidal ideation.

• Use of antidepressants may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Activation of mania/hypomania may occur in patients with major affective disorder.
### Table 2. Adverse Events (≥ 2%) Reported in Patients in the Placebo-Controlled Studies, Listed in Order of Magnitude of Incidence

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Vortioxetine 5 mg/day (n = 1,013)</th>
<th>Vortioxetine 10 mg/day (n = 699)</th>
<th>Vortioxetine 15 mg/day (n = 449)</th>
<th>Vortioxetine 20 mg/day (n = 455)</th>
<th>Placebo (n = 1,621)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>21%</td>
<td>26%</td>
<td>32%</td>
<td>32%</td>
<td>9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>7%</td>
<td>10%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7%</td>
<td>7%</td>
<td>6%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>6%</td>
<td>8%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Table 5. ASEX Incidence of Treatment Emergent Sexual Dysfunction in Patients with No Sexual Dysfunction at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Vortioxetine 5 mg/day (n = 65:67)</th>
<th>Vortioxetine 10 mg/day (n = 94:86)</th>
<th>Vortioxetine 15 mg/day (n = 57:67)</th>
<th>Vortioxetine 20 mg/day (n = 67:59)</th>
<th>Placebo (n = 135:162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>22%</td>
<td>23%</td>
<td>33%</td>
<td>34%</td>
<td>20%</td>
</tr>
<tr>
<td>Males</td>
<td>16%</td>
<td>20%</td>
<td>19%</td>
<td>29%</td>
<td>14%</td>
</tr>
</tbody>
</table>

*Sample size for each group is the number of patients (females:males) without sexual dysfunction at baseline. ASEX – Arizona Sexual Experience Scale*
Drug Interactions:

• The risk of serotonin syndrome is increased when vortioxetine is used with other drugs that affect the serotonergic neurotransmitter system (eg, SSRIs, SNRIs, triptans, buspirone, tramadol, tryptophan)
  – Serotonin syndrome symptoms may include changes in mental status (eg, agitation, hallucinations, delirium, coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or GI symptoms (eg, nausea, vomiting, diarrhea).
Drug Interactions:

- **Bupropion:** The active metabolites of bupropion inhibit CYP2D6, the primary metabolizing agent of vortioxetine. Multiple doses of bupropion 150 mg twice daily coadministered with vortioxetine 10 mg once daily increased the steady-state plasma exposure of vortioxetine 2-fold. Reduction in vortioxetine dose by 50% or avoidance of bupropion therapy may be necessary.

- **NSAIDs:** vortioxetine and NSAID,s may both inhibit platelets and increase the risk of bleeding.

- **Warfarin:** vortioxetine is a weak inhibitor of CYP2C9 in vitro, which is known to metabolize warfarin. However, multiple daily doses of vortioxetine 10 mg had no effect on the steady-state pharmacokinetics or pharmacodynamics of warfarin.
Dosage:

- The recommended starting dose is 10 mg administered orally once daily without regard to meals.
- Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States.
- The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials.
- A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses.
- The maximum recommended dosage for known CYP2D6 poor metabolizers is 10 mg/day.
- Vortioxetine is available as 5, 10, 15, and 20 mg immediate-release tablets. Cost: $209.25 for 30 tabs WAC.
Vortioxetine - Brintellix

• Abrupt discontinuation of antidepressant therapy can produce discontinuation symptoms (e.g., headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, runny nose) during the next week. Some patients experienced these types of symptoms after abrupt discontinuation of vortioxetine 15 and 20 mg/day.
CONCLUSION: Vortioxetine has a mechanism of action that is different from other antidepressant medications. The results from the evaluated clinical studies are mixed. Some studies show no benefit compared with placebo, while others did show a benefit. Several of the studies have used duloxetine as an active comparator, but were not designed to compare the efficacy of vortioxetine with duloxetine. Vortioxetine appears to be well tolerated. Its place in the treatment of patients with MDD, who are treatment-naive and non–treatment naive, remains to be documented.
Levomilnacipran -Fetzima by Forest

• A Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) both levomilncaipran and milnacipran bind to both serotonin and norepinephrine transporters with high affinity, but milnacipran preferentially blocks norepinephrine reuptake compared with serotonin reuptake by an approximately 3 to 1 ratio, while levomilnacipran has a 2-fold greater potency for norepinephrine.
Levomilnacipran - Fetzima

• Levomilnacipran is indicated for the treatment of major depressive disorder (MDD).
  – Milnacipran is indicated for the management of fibromyalgia. Levomilnacipran is not approved for the management of fibromyalgia.

• Levomilnacipran undergoes desethylation to form desethyl levomilnacipran by CYP 3A4, approximately 58% of the dose is excreted in urine as unchanged levomilnacipran. N-desethyl levomilnacipran is the major metabolite excreted in the urine and accounted for approximately 18% of the dose.

• The elimination T1/2 is ~12 hours vs. 6-8 hours for milnacipran
# Levomilnacipran - Fetzima

Table 1. FDA-Approved Indications for SNRIs

<table>
<thead>
<tr>
<th>Indications</th>
<th>Levomilnacipran</th>
<th>Duloxetine</th>
<th>Desvenlafaxine</th>
<th>Milnacipran</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic musculoskeletal pain</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic peripheral neuropathic pain</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDD</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Panic disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Social anxiety disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Extended-release formulations only.
## Levomilnacipran - Fetzima

### Table 5: Summary of Results for the Primary Efficacy Endpoint MADRS

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo Subtracted Diff (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1 (fixed dose)</strong></td>
<td>Levomilnacipran (ER 40 mg/day)*</td>
<td>36.0 (4.1)</td>
<td>-14.8 (1.0)</td>
<td>-3.2 (-5.9, -0.5)</td>
</tr>
<tr>
<td></td>
<td>Levomilnacipran (ER 80 mg/day)*</td>
<td>36.1 (3.9)</td>
<td>-15.6 (1.0)</td>
<td>-4.0 (-6.7, -1.3)</td>
</tr>
<tr>
<td></td>
<td>Levomilnacipran (ER 120 mg/day)*</td>
<td>36.0 (3.9)</td>
<td>-16.5 (1.0)</td>
<td>-4.9 (-7.6, -2.1)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>35.6 (4.5)</td>
<td>-11.6 (1.0)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Study 2 (fixed-dose)</strong></td>
<td>Levomilnacipran (ER 40 mg/day)*</td>
<td>30.8 (3.4)</td>
<td>-14.6 (0.8)</td>
<td>-3.3 (-5.5, -1.1)</td>
</tr>
<tr>
<td></td>
<td>Levomilnacipran(ER 80 mg/day)*</td>
<td>31.2 (3.5)</td>
<td>-14.4 (0.8)</td>
<td>-3.1 (-5.3, -1.0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>31.0 (3.8)</td>
<td>-11.3 (0.8)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Study 3 (flexible-dose)</strong></td>
<td>Levomilnacipran (ER 40 - 120 mg/day)*</td>
<td>35.0 (3.6)</td>
<td>-15.3 (0.8)</td>
<td>-3.1 (-5.3, -0.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>35.2 (3.8)</td>
<td>-12.2 (0.8)</td>
<td>--</td>
</tr>
</tbody>
</table>
Adverse Reactions Occurring in > 2% of Levomilnacipran-Treated Patients and ≥ 2 Times the Rate of Placebo-Treated Patients Reported in the Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo (N = 1,040)</th>
<th>Levomilnacipran 40 to 120 mg/day (N = 1,583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>2%</td>
<td>9%</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Heart rate increased</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Ejaculation disorder</td>
<td>&lt; 1%</td>
<td>5%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Testicular pain</td>
<td>&lt; 1%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary hesitation</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Levomilnacipran - Fetzima

Increased Heart Rate and Blood Pressure:

- In short-term clinical studies, levomilnacipran treatment was associated with a mean increase in heart rate of 7.4 beats per minute (bpm) compared to a mean decrease of 0.3 bpm in placebo-treated patients.
  - Heart rate increase in levomilnacipran-treated patients receiving doses of 40 mg, 80 mg and 120 mg was 7.2, 7.2, and 9.1 bpm.

- In the short-term, placebo-controlled MDD studies, the mean increase from initiation of treatment in systolic BP was 3 mm Hg and diastolic BP was 3.2 mm Hg, as compared to no change in the placebo group. There were no dose-related changes in systolic and diastolic blood pressure observed.

- In patients exposed to one-year, open-label treatment of levomilnacipran (doses range from 40-120 mg once daily), the mean change from initiation of treatment in systolic BP was 3.9 mm Hg and diastolic BP was 3.1 mm Hg.
Levomilnacipran - Fetzima

• FDA BOX WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
  – Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants.
  – Monitor for worsening and emergence of suicidal thoughts and behaviors. (this includes daily monitoring by families and caregivers for any changes in behaviors, emergence of agitation or irritability).
  – Not approved for use in pediatric patients
Drug Interactions:

• **Monoamine Oxidase Inhibitor (MAOI), Linezolid or Methylene Blue** - At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with levomilnacipran. Conversely, at least 7 days should be allowed after stopping levomilnacipran before starting an MAOI antidepressant. With linezolid or intravenous methylene blue there is an increased risk of serotonin syndrome.

• **Strong Inhibitors of Cytochrome P450 (CYP3A4)** including (ketoconazole, clarithromycin, ritonavir) – limit the dose of levomilnacipran to no more than 80 mg/day
Serotonin Syndrome:

- Serotonin syndrome has been reported with SSRIs and SNRIs, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclics, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John’s Wort).
  - Symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).
Levomilnacipran - Fetzima

Dosage:
• **Recommended dose**: 40 mg to 120 mg once daily with or without food.
• Initiate dose at 20 mg once daily for 2 days and then increase to 40 mg once daily.
• Based on efficacy and tolerability, increase dose in increments of 40 mg at intervals of 2 or more days.
• **The maximum recommended dose is 120 mg once daily.**
• Take capsules whole; do not open, chew or crush.
• **Renal Impairment**: Do not exceed 80 mg once daily for moderate impairment (creatinine clearance of 30-59 ml/min). Do not exceed 40 mg once daily for severe renal impairment (creatinine clearance of 15-29 ml/min).
• **Discontinuation**: Reduce dose gradually whenever possible.

Cost: 20, 40, 80 and 120 mg caps - **$194.28/30 caps all sizes WAC**
CONCLUSION: Levomilnacipran is approved only for the treatment of MDD, while the racemic mixture, milnacipran, is approved only for the treatment of fibromyalgia. There are no head-to-head clinical trials of either of these drugs or against other SNRIs in the treatment of MDD or fibromyalgia. Both drugs are SNRIs and have similar contraindications, warnings, and precautions. Without head-to-head comparisons in studies lasting longer than 11 weeks, the value of this drug is unknown.
Conjugated Estrogens + Bazedoxifene – Duavee by Pfizer

- Duavee is conjugated estrogens 0.45 mg plus bazedoxifene 20 mg/tab for treating moderate to severe hot flashes and preventing osteoporosis.
  - Think of it as an alternative to Prempro.
- Bazedoxifene is added just to inhibit estrogen's endometrial effects...as an alternative to a progestin.
- Bazedoxifene is a selective estrogen receptor modulator (SERM)like raloxifene (Evista). But combining bazedoxifene and estrogen doesn't work better than estrogen alone to prevent bone loss.
- Save Duavee for women who want to use estrogen for menopausal symptoms...but need an alternative to a progestin.
- Adverse Effects: >5%-≥ 5%) were muscle spasms, nausea, diarrhea, dyspepsia, abdominal pain upper, oropharyngeal pain, dizziness, and neck pain
- Cost: $105.84/30 tabs WAC
  - Prescriber’s Letter March 2014
New Pen Device for Bydureon (once weekly exenatide)

• March 3, 2014: U.S. FDA Approves Bydureon® Pen (exenatide extended-release for injectable suspension) for Once-Weekly Treatment of Adults with Type 2 Diabetes.

• Each pen contains the recommended weekly dose of 2 mg and replaces the weekly trays which required patients to mix and draw up the dose (the trays will continue to be available as well as the pens)

  — Now from Astra Zeneca
Canagliflozin - Invokana

- Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- The FDA has asked for five postmarketing studies for the drug including a cardiovascular outcomes trial, an enhanced pharmacovigilance program, a bone safety study and two pediatric studies.
- Available as 100 mg and 300 mg tablets
  - Cost: $277.41/30 tabs WAC both sizes
Canagliflozin - Invokana

Mechanism of Action

• Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion.

• Maximal suppression of mean RTG over the 24-hour period was seen with the 300 mg daily dose to approximately 70 to 90 mg/dL in patients with type 2 diabetes in Phase 1 studies.
Canagliflozin - Invokana

Warnings and Precautions

• **Hypotension** - canagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating canagliflozin particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating canagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected.

• Monitor for signs and symptoms after initiating therapy. Keep up with fluids/hydration.
Canagliflozin - Invokana

Patients with Renal Impairment

- **Canagliflozin** increases serum creatinine and decreases eGFR.
  - Patients with hypovolemia may be more susceptible to these changes.
  - No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m² or greater).
  - **The dose of canagliflozin is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m².**
  - Canagliflozin should be discontinued or not be initiated in patients with an eGFR less than 45 mL/min/1.73 m².
  - Assessment of renal function is recommended prior to initiation of canagliflozin therapy and periodically thereafter.
Canagliflozin - Invokana

Genital Mycotic Infections:
• Canagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. (10-12% in women and 3-4% in men).

Urinary Tract Infections:
• 4-6% of patients

Increased Urination/Polyuria:
• 4-6% of patients
Canagliflozin Efficacy

**MONOTHERAPY**
- Placebo: 8.0% (N=584)
- DUAL +MET: 7.9% (N=1284)
- DUAL +SU*: 8.4% (N=127)
- TRIPLE +MET+SU: 8.1% (N=469)
- TRIPLE +MET +PIO: 7.9% (N=342)
- TRIPLE +INSULIN (±AHAs)*: 8.3% (N=1718)

**ADD-ON**
- Older Subjects² AHA: 7.7% (N=714)

**Change from Baseline in A1C (%)**
- Placebo-Subtracted Difference
  - MONOTHERAPY: -0.91%†, -1.16%†
  - DUAL +MET: -0.62%†, -0.77%†
  - DUAL +SU*: -0.74%†, -0.83%†
  - TRIPLE +MET+SU: -0.71%†
  - TRIPLE +MET +PIO: -0.62%†
  - TRIPLE +INSULIN (±AHAs)*: -0.65%†, -0.73%†
  - Older Subjects² AHA: -0.57%†, -0.70%†

**Dosages**
- Cana 100 mg
- Cana 300 mg
Canagliflozin - Invokana

Recommended Dosage

• The recommended starting dose of canagliflozin is 100 mg once daily, taken before the first meal of the day.

• In patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily.

• The dose is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m2.

• Canagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m2.
Dapagliflozin-Farxiga (far-SEE-guh) by Astra Zeneca

• December 13, 2013 The FDA Advisory panel voted 10 to 1 in favor of approval for AstraZeneca and Bristol-Myers Squibb's diabetes drug dapagliflozin.
  – follows the FDA's previous rejection of dapagliflozin in January 2012, primarily due to concerns about bladder cancer and liver toxicity.
  – all the panelists strongly advised that the sponsors move forward with a planned large postmarketing trial designed to provide enough statistical power to answer outstanding questions about cardiovascular safety as well as malignancy and liver toxicity. DECLARE-TIMI 58 trial has already begun recruiting the first of an anticipated 17,150 patients.
Dapagliflozin-Farxiga

• It is an inhibitor of the sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, responsible for the majority of the reabsorption of filtered glucose from the tubular lumen.

• Dapagliflozin 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day.
Dapagliflozin-Farxiga

Pharmacokinetics:

• Absorption – Cmax and AUC are dose proportional and peak levels occur at 2 hours after oral dosing, oral bioavailability is ~78% (91% protein bound)

• Metabolism - metabolism of dapagliflozin to inactive metabolites is primarily mediated by UGT1A9;
  – UDP-glucuronosyltransferase, an enzyme of the glucuronidation pathway that transforms small lipophilic molecules, into water-soluble, excretable metabolites

• Elimination – primarily renal with a mean elimination T1/2 of ~12.9 hours
# Dapagliflozin-Farxiga

## Efficacy in 24 week studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dapagliflozin</th>
<th>N</th>
<th>A1C (%)*</th>
<th>FPG (mg/dl)*</th>
<th>Weight (Kg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>10mg</td>
<td>70</td>
<td>-0.7</td>
<td>-24.7</td>
<td></td>
</tr>
<tr>
<td>Add to metformin</td>
<td>10mg</td>
<td>211</td>
<td>-0.5</td>
<td>-25.5</td>
<td>-2.0</td>
</tr>
<tr>
<td>Initial combo with metformin</td>
<td>10mg</td>
<td>135</td>
<td>-0.5</td>
<td>-17.5</td>
<td>-1.4</td>
</tr>
<tr>
<td>Add to glimepiride</td>
<td>10mg</td>
<td>151</td>
<td>-0.7</td>
<td>-26.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>Add to pioglitazone</td>
<td>10mg</td>
<td>140</td>
<td>-0.6</td>
<td>-24.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Add to sitagliptin</td>
<td>10mg</td>
<td>223</td>
<td>-0.48</td>
<td>-27.9</td>
<td>-1.89</td>
</tr>
<tr>
<td>Add to insulin +/- orals</td>
<td>10mg</td>
<td>194</td>
<td>-0.6</td>
<td>-25.0</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

* Values are placebo/active control adjusted to reflect the effect of the addition of dapagliflozin
Dapagliflozin-Farxiga

- Female genital mycotic infections 6.9% and 25% in women with a history of genital mycotic infections
- Urinary tract infections 4.3 – 5.7%
- Increased urination 2.9 - 3.8%
- Male genital mycotic infections 2.8%
- Discomfort with urination 2.1%
- Mean % change in lipids: increase TC 2.5% and LDL 2.9%
- Hypotension: especially in the elderly, those with renal dysfunction and patientss on diuretics
Dapagliflozin-Farxiga

• Renal-related adverse reactions, including renal failure and blood creatinine increase, were more frequent in patients treated with dapagliflozin

  – Overall population Patients (%) with at least one event: 6.7% (n=2026 up to 104 wks)
  – 65 years of age and older: 14.0% (n=620)
  – eGFR ≥30 and <60 mL/min/1.73 m2: 28.3% (n=251)
  – 65 years of age and older and eGFR ≥30 and <60 mL/min/1.73 m2: 35.1% (n=134)
Dapagliflozin-Farxiga

• Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors and hematuria were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin.
Dapagliflozin-Farxiga

Dosage:

• The recommended starting dose of dapagliflozin is 5 mg once daily, taken in the morning, with or without food. In patients tolerating 5 mg once daily, the dose can be increased to 10 mg once daily.

Cost - $277.46/30 tabs 5 or 10 mg WAC

– Correct volume depletion prior to starting
– Monitor renal function prior to initiation of therapy and periodically thereafter
– Should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m²
– Should be discontinued when eGFR is persistently less than 60 mL/min/1.73 m²
• 1 (True or False) While the current (2013) American Heart Association and American College of Cardiology guideline's for heart failure still include the potential use of digitalis on the basis of reduced hospitalization, newer data from suggests that when digoxin is added to an ACE inhibitor and a beta blocker that the risk of hospitalization is NOT reduced and the risk of mortality is increased.
2. (True or False) On Jan 31, 2014 the FDA announced that they are investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products based upon two recent observational trials which did suggest an increase in these events in men who are considered candidates for testosterone replacement therapy.
Post Test

• 3. Which of the following statements is/are true concerning the new Lipid Guidelines as of November 2013?
  – A. LDL cholesterol levels are no longer listed as a goal of therapy
  – B. Patients with heart disease should only be treated with atorvastatin 40-80 mg or rosuvastatin 20-40mg
  – C. Patients who have an LDL cholesterol level of less than 40 mg/dl on a statin should be considered for reducing the dose by 50%
  – D. All of the above
4. When treating patients with COPD (chronic obstructive pulmonary disease) which of the following statements is incorrect?

- A. The most important thing a patient can do is to stop smoking.
- B. The regular use of a long acting antimuscarinic (LAMA) like tiotropium or aclidinium bromide is preferred over the use of a long acting beta agonist (LABA) based upon the POET-COPD Trial
- C. Both the LAMA’s and the LABA’s have been reported to increase the risk of cardiovascular events
- D. None of the above, all are correct