Pharmacotherapy Update: Cardiovascular & Renal Risk Reduction in Diabetes Mellitus

Michael Parker, PharmD, BS

Background
When uncontrolled, diabetes mellitus (DM) may lead to significant morbidity and mortality.1 Myocardial infarctions, cerebrovascular accidents, and kidney disease are just a few of the complications that patients with diabetes may experience throughout their lifetime. Due to the progressive nature of diabetes, preventing cardiovascular (CV) and renal manifestations in these patients is an important goal. As new clinical trial data emerge, it is increasingly difficult for the clinician to keep up-to-date with the appropriateness of initiating drugs for CV and renal protection for their patients with DM. Recently, as more quality evidence-based information has become available, it is apparent that a “one size fits all” approach to the management of DM is no longer a viable option. This is true not only for choosing glycated hemoglobin (A1c) goals, but also for selecting medications based on patient-specific factors. In this pharmacotherapy update, a guide for the customized utilization of aspirin, statins, and angiotensin converting enzyme inhibitors (ACE-I) or angiotensin-II receptor blockers (ARBs) is provided.

Do the CV benefits of low-dose aspirin outweigh the risks in the case of primary or secondary prevention of CV events?2-4 Aspirin confers a modest relative risk reduction in CV events of approximately 10%. The patients who will benefit the most from aspirin are those who have the highest baseline risk. When determining which patients with diabetes should take aspirin, the potential benefits of CV risk reduction must be weighed against the potential risk of a gastrointestinal bleed.

*For patients that qualify for low-dose aspirin therapy, a dose of 75 to 162 mg/day should be used.

- The use of low-dose aspirin in primary prevention of CV events (no prior history of vascular disease):
  - Use is warranted for diabetes patients with a high CV disease (CVD) risk (10-year risk of CVD events >10%), who do not have an increased risk for bleeding (risk factors: 1. History of GI bleed; 2. Peptic
ulcer disease; 3. Concomitant use of other agents that increase the risk of bleeding, such as warfarin or non-steroidal anti-inflammatory drugs [NSAIDs].

- The individuals in this high CVD risk category include the majority of men >50 and women >60 years of age with ≥1 of the following additional major CVD risk factors: smoking, hypertension (HTN), dyslipidemia, albuminuria, or family history of premature CVD (i.e., male first degree relative <55 years or female first degree relative <65 years of age).

- Use is not warranted for diabetes patients with low CVD risk (10-year risk of CVD events <5%).

- Clinical judgment is required for patients with intermediate CVD risk (10-year risk of CVD events 5 to 10%).

- The use of low-dose aspirin in secondary prevention of CV events (established CVD):
  - Low-dose aspirin should be used in secondary CVD prevention, unless the drug is contraindicated.
  - For patients with documented aspirin allergy, clopidogrel 75 mg/day should be initiated.
  - For up to 1 year after an acute coronary syndrome, dual antiplatelet therapy with clopidogrel and low-dose aspirin is warranted.

- CVD risk calculation tools for patients with diabetes may be found here to assist in CVD risk assessment (please review limitations/applicability of each tool prior to use):
  - For clinicians: UKPDS risk engine may be downloaded at: http://www.dtu.ox.ac.uk/RiskEngine/download.php; ARIC coronary heart disease (CHD) risk calculator (For patients 45 - 65 years of age without heart disease): http://www.aricnews.net/riskcalc/html/RC1.html

**Which patients with diabetes should be on a statin, and what cholesterol goals should be targeted?** 3,4

Generally, lifestyle modifications should be instituted for all patients with diabetes, including reduction of saturated fat, trans fat, and cholesterol intake. An increase in the intake of omega-3 fatty acids, viscous fiber, and plant sterols/stanols is also recommended for all patients. Additionally, if overweight/obese, weight loss is recommended. Increased physical activity has also been shown to improve the lipid parameters in patients with diabetes. It should be noted that combination lipid therapy is generally not recommended, since it has not been shown to provide additional CV benefit over statin monotherapy.

*Statins are contraindicated in pregnancy: Pregnancy Category X.*

- Statins should be taken by the following patients with diabetes, regardless of the baseline lipid levels:
  - Patients with overt CVD
  - Patients without CVD who are >40 years of age and have ≥1 of the following CVD risk factors:
    - Family history of CVD, HTN, smoking, dyslipidemia, or albuminuria

- Statins should be considered for lower risk patients (based on their UKPDS score) with diabetes (<40 years of age) if:
  - Low-density lipoprotein (LDL) cholesterol persists above 100 mg/dL or
  - >1 CVD risk factors are present

- Cholesterol goals for patients with diabetes:
  - LDL goal of <100 mg/dL for most patients
  - Optional LDL goal of <70 mg/dL for patients with overt CVD, utilizing a high-dose statin
If LDL goal is not reached on a maximally tolerated statin dose, a 30 to 40% reduction in LDL from baseline should alternatively be targeted.

For all patients, targeting LDL goals remains the preferred strategy, however the following goals also apply:

- Triglyceride levels <150 mg/dL
- High-density lipoprotein (HDL) >40 mg/dL and >50 mg/dL in men and women, respectively

**Should all patients with DM be placed on an ACE-I or ARB regardless of the presence of HTN or micro-/macroalbuminuria?**

Diabetes, HTN, and nephropathy are intertwined. To reduce the risk of nephropathy, or the progression of micro- to macroalbuminuria, control of both hyperglycemia and HTN are paramount. Albuminuria is characterized by the presence of albumin in urine, with microalbuminuria defined as albumin levels of 30 to 300 mg/L and macroalbuminuria as >300mg/L in a spot sample. As of January 2013, the American Diabetes Association set new standards for blood pressure (BP) control in patients with diabetes. The new systolic BP (SBP) goal for patients with DM is <140 mmHg. A more stringent SBP goal of <130 mmHg may be considered for younger patients when this goal can be achieved in the absence of undue treatment burden. The diastolic BP (DBP) goal for patients with diabetes remains at < 80 mmHg.

*ACE-Is & ARBs should generally be avoided in pregnancy: Pregnancy Category: ACE-I = D; ARBs = C/D.

- In DM patients with HTN (defined as BP ≥140/80 mmHg on more than 1 occasion):
  - The use of an ACE-I or ARB should be included in the antihypertensive regimen with or without the presence of micro- or macroalbuminuria
    - If 1 class is not tolerated, the other may be substituted
- In DM patients without hypertension, select from the appropriate subcategory below:
  - With microalbuminuria alone, the use of an ACE-I or ARB is not supported by randomized controlled trials, since the progression to kidney disease is not slowed.
  - With macroalbuminuria, the evidence does support the use of an ACE-I or ARB to slow the progression of kidney disease.

**Disclaimer:** This article is for informational purposes only. Each clinician should use his/her own professional judgment per individual patient.

**References:**


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**Apixaban: A New Direct Factor Xa Inhibitor**

*Chris Diehl, PharmD*

**Background**

For over 50 years, warfarin has been the only oral anticoagulant available for primary and secondary prevention of thromboembolic events. It has been shown to be effective and is prescribed to millions of patients every year. However, the Food and Drug Administration (FDA) has labeled warfarin as a narrow therapeutic index (NTI) drug which requires constant monitoring of the international normalized ratio (INR). This monitoring has created a need for safe oral anticoagulants that are not considered NTI. In the past 3 years, the FDA has approved dabigatran (Pradaxa®), a direct thrombin inhibitor, and rivaroxaban (Xarelto®), a direct Factor Xa Inhibitor. On December 28th, 2012, the FDA approved apixaban (Eliquis®), another direct Factor Xa inhibitor.
There are many benefits to these new drugs. Unlike warfarin, they do not require constant INR monitoring. Additionally, the dosing is consistent and does not have to be adjusted (except in cases of declining kidney function). However, dabigatran, rivaroxaban, and apixaban do not have an antidote, and because of this, irreversible bleeding is a major concern. Additionally, these drugs are considerably more expensive than warfarin (approximately $200 - $250 versus $84 [with monitoring], respectively, per 30 days).³

Apixaban is currently approved for stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation.⁴ It is important to note that apixaban, along with rivaroxaban and dabigatran, are not to be used in patients with mechanical heart valves. The drug is available in 2.5 and 5 mg oral tablets. Patients should take 5 mg twice daily with or without food and dosing should be adjusted down to 2.5 mg twice daily in patients over the age of 80 years, weighing less than 60 kg, or with serum creatinine level >1.5 mg/dL. Additionally, patients taking strong inhibitors of cytochrome P450 (CYP) 3A4 and P-glycoprotein, including verapamil, amiodarone, protease inhibitors, erythromycin, and ketoconazole, should use 2.5 mg twice daily. Apixaban is contraindicated in patients with active bleeding. Side effects include risk of major bleeding, rare cases of syncope, and hypersensitivity reactions including rash.⁴

Guidelines for antithrombotic therapy were issued by the American College of Chest Physicians (ACCP) in February, 2012, in which the ACCP addresses the management of patients with atrial fibrillation. The ACCP recommends usage of an oral anticoagulant in patients with a CHADS2 score >1.⁵ Among the oral anticoagulants, the ACCP recommends dabigatran as a preferred agent to dose-adjusted warfarin. Of note, apixaban was not available at the time of publication.

**Literature Review**

There have been 2 major trials investigating the efficacy and safety of apixaban for the treatment of patients with nonvalvular atrial fibrillation. The first study, entitled “Apixaban versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation who have Failed or are unsuitable for Vitamin K Antagonist Treatment” (AVERROES), was a randomized double-blind trial.⁶ Participants were randomized to receive apixaban 5 mg twice daily or aspirin 81 – 324 mg daily. The primary outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism. Other outcomes measured were occurrence of major bleeding, death from vascular causes, and death from any cause.

A total of 5599 patients were enrolled in the study for a mean duration of 1.1 years.⁶ The study was terminated early because of the overwhelming benefit in favor of apixaban. The average age of patients was 70 years, with approximately 59% male and CHADS2 score of 2.

The endpoints of the AVERROES trial are summarized below:⁶

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban</th>
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<tbody>
<tr>
<td></td>
<td>(N = 2808)</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>(N=2791)</td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.6</td>
</tr>
<tr>
<td>Stroke, systemic embolism, or death</td>
<td>4.6</td>
</tr>
<tr>
<td>Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event</td>
<td>5.3</td>
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</tbody>
</table>
As shown above, apixaban was associated with significantly greater reduction in all primary outcomes compared to aspirin.\(^6\) Additionally, the incidence of bleeding events was similar for apixaban and aspirin. Therefore, patients with atrial fibrillation who are unable to tolerate warfarin therapy should consider the use of apixaban over aspirin for prevention of stroke and systemic embolism due to its increased benefits with minimal additional risk.

The second major study, entitled “Apixaban versus Warfarin in Patients with Atrial Fibrillation” (ARISTOTLE), was also a randomized double-blind trial, involving over 18,000 patients.\(^7\) Patients with atrial fibrillation plus 1 other risk factor for stroke were randomized to receive apixaban 5 mg twice daily, or warfarin with a target INR of 2.0 – 3.0. The primary outcome measured noninferiority in ischemic or hemorrhagic stroke or systemic embolism. Secondary outcomes tested the superiority of apixaban to warfarin in prevention of ischemic or hemorrhagic stroke or systemic embolism, and rate of major bleeding and death from any cause.

At baseline, patients had a median age of 70 years, approximately 35% were female with a weight of 82 kg, and the median CHADS2 score was 2.1.\(^6\) The mean follow-up period was 1.8 years.

Further results of the ARISTOTLE trial are summarized below:\(^7\)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (%/year; N = 9120)</th>
<th>Warfarin (%/year; N = 9081)</th>
<th>Hazard Ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>3.52</td>
<td>3.94</td>
<td>0.89 (0.80 – 0.998)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke, systemic embolism, myocardial infarction, or death from any cause</td>
<td>4.85</td>
<td>5.49</td>
<td>0.88 (0.80 – 0.97)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

As shown, apixaban satisfied noninferiority when compared to warfarin in the primary outcome, and was found to be superior in the secondary outcome (p=0.01). Apixaban was significantly safer in regard to major bleeding in all categories except for gastrointestinal bleeding, which showed a non-significant reduction compared to warfarin.

**Conclusion**

Despite the recent approval of dabigatran and rivaroxaban, apixaban is the first oral anticoagulant that has shown to be superior in the outcomes described above, in concert with a lower risk of major bleeding. With an improved safety profile, less monitoring, as well as effective prevention against stroke and embolism, apixaban may change anticoagulation standards.

However, there are other issues that require consideration. The mean follow-up in the previously described trials was less than 2 years; long-term safety and efficacy of apixaban in patients with atrial fibrillation have yet to be determined. Additionally, apixaban is administered twice daily which may present a barrier to adherence. Warfarin, as a generic drug, is significantly less expensive than apixaban; cost is another significant barrier to consider. Finally, apixaban is only indicated for nonvalvular atrial fibrillation and it may not be financially viable for patients already stable on warfarin.

Apixaban is a new anticoagulant that holds promise for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The clinician should note that there are risks and benefits associated with usage of any of the oral anticoagulants, and treatment must be individualized for each patient.

**References**

Overview of the Treatment of Irritable Bowel Syndrome
Kerri O’Connor, PharmD

Background
Irritable bowel syndrome (IBS) is a common bowel disorder affecting an estimated 5-20% of the US population.\(^1\) Importantly, IBS is associated with a significant decrease in health-related quality of life and an increased financial burden attributable to missed work days and hospitalizations.\(^2\) Common symptoms include abdominal pain and disturbed bowel habits, characterized by the patient’s predominant symptoms: constipation, diarrhea, or a mix of both.\(^1,2\) Often these symptoms are nonspecific, making it difficult to accurately diagnose. Abnormalities in intestinal and colonic transit time, as well as increased motility after meals leading to abdominal pain, have been noted in patients with IBS.

Non-pharmacologic Treatment
Patients should keep a diary of their symptoms in order to identify and avoid triggers such as specific food or stress.\(^1\) Increasing fiber intake to 25 grams per day has also shown to help reduce symptoms. Soluble fiber including psyllium and polycarbophil should be recommended over insoluble fiber (wheat or corn bran).\(^1,2\) Psychological treatment should also be considered, as many patients with this disorder also have mental health problems including anxiety and depression.

Pharmacologic Treatment
Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) help decrease abdominal pain in addition to overall IBS symptoms and have been shown to be more effective than placebo. Typically, TCAs should be used for diarrhea-predominant IBS and SSRIs for constipation-predominant IBS. However, it is important to note that there are limited data available on the use of these agents in IBS.\(^2\) Antispasmodics are used for the acute relief of abdominal pain, especially when symptoms are exacerbated by food. They are typically dosed as needed, 30 minutes prior to meals.\(^1,2\) There are few medications indicated specifically for constipation- or diarrhea-predominant IBS. Unfortunately, serious side effects also limit treatment options. The medications indicated for IBS are summarized in the chart below.

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Common Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antispasmodics:</strong></td>
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<tr>
<td>Dicyclomine (Bentyl®)</td>
<td>Anticholinergic</td>
<td>20 mg QID for 1 week, then 40 mg QID</td>
<td>Dizziness, nausea, dry mouth, blurred vision</td>
</tr>
<tr>
<td>Hyoscymine (Levsin®)</td>
<td>Anticholinergic</td>
<td>Varies depending on dosage form; given every 4 hours (IR) or every 12 hours (ER)</td>
<td>Dry mouth, constipation, blurred vision, drowsiness</td>
</tr>
<tr>
<td><strong>Constipation-Predominant:</strong></td>
<td></td>
<td></td>
<td></td>
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\(^1\) References: 1, 2.
<table>
<thead>
<tr>
<th>Tegaserod (Zelnorm®)</th>
<th>Serotonin (SHT-4) agonist; leads to increased peristalsis</th>
<th>6 mg BID 30 minutes before meals for 4-6 weeks</th>
<th>Headache, abdominal pain</th>
<th>Only available for emergency treatment for women &lt;55 years old through the FDA (due to potentially serious cardiovascular side effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubiprostone (Amitiza®)</td>
<td>Increases intestinal fluid secretion by activating chloride channels</td>
<td>8 mcg BID with food and water</td>
<td>Headache, nausea, diarrhea</td>
<td>Safety and efficacy not evaluated in men</td>
</tr>
<tr>
<td>Linacotide (Linzess™)</td>
<td>Guanylate cyclase C agonist; leads to increased intestinal fluid and GI transit</td>
<td>290 mcg QD on empty stomach</td>
<td>Diarrhea</td>
<td>Approved for men and women</td>
</tr>
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</table>

**Diarrhea-Predominant:**

<table>
<thead>
<tr>
<th>Loperamide (Imodium®)</th>
<th>Inhibits peristalsis, increases viscosity and transit time</th>
<th>4 mg for 1 dose then 2 mg after each loose stool MDD=16mg</th>
<th>Constipation, nausea, abdominal pain</th>
<th>If no improvement after 10 days, it is unlikely to be effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alosetron (Lotronex®)</td>
<td>Serotonin (5-HT3) antagonist; leads to decreased pain, transit time and GI secretions</td>
<td>0.5 mg BID for 4 weeks, if inadequate, increase to 1 mg BID for 4 weeks</td>
<td>Constipation (also a boxed warning)</td>
<td>Prescribers must enroll in the Prometheus Prescribing Program under REMS to prescribe</td>
</tr>
</tbody>
</table>

IR = immediate release; ER = extended release; 5-HT = 5-Hydroxytryptophan; BID = twice daily; QD = daily; MDD = maximum daily dose; REMS = risk evaluation and mitigation strategy

**Conclusion**

IBS is a common medical condition with limited, but expanding, pharmacological treatment options. Nonpharmacologic measures, such as increasing fiber, avoiding trigger foods, and treating possible underlying conditions, such as depression and anxiety, should be recommended for all patients. More safe and efficacious treatment options are necessary, and many potential medications are currently under investigation.

**References:**

Author Biographies

**Michael Parker** graduated with his BS in biology from George Mason University in 1998 and his PharmD from Wingate University in 2012. He is currently a PGY1 Ambulatory Pharmacy resident at Lifetime Health in Buffalo, NY. His current research involves disparities in standards of care among patients with type 2 diabetes.

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