Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

February 20, 2007
The primary clinical decision that needs to be made is determining if the drugs within the therapeutic class of interest can be considered therapeutic alternatives.

A Therapeutic Alternative is defined by the AMA as: “drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses”\(^1\).

The Committee should not feel obligated to decide if every drug within the therapeutic class is exactly equal to all other drugs within the class, nor should they feel obligated to decide if every drug within the therapeutic class works equally well in every special patient population or in every disease.

In special situations (e.g., presence of comorbid conditions) and in special populations (e.g., pediatrics) use of a non-preferred drug might be the most appropriate therapy. These cases can be handled through prior authorization (PA). PA serves as a “safety valve” in that it facilitates use of the most appropriate agent regardless of PDL status.

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\(^1\) AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
RECOMMENDATION

The treatment of onychomycosis will not be allowed for cosmetic use and will be approved when health would be compromised without care. The two oral agents currently FDA labeled for the treatment of onychomycosis are terbinafine (Lamisil®) and itraconazole (Sporanox®). Terbinafine (Lamisil®) is considered a product whose safety and efficacy demonstrate that it is superior to itraconazole in the treatment of onychomycosis.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMISIL® (terbinafine) CC,QL</td>
<td>ITRACONAZOLE (compares to Sporanox®) CC,QL</td>
</tr>
<tr>
<td>SPORANOX® (itraconazole) CC,QL</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Criteria for Oral Antifungals used for Onychomycosis

Onychomycosis Class Criteria
Antifungals will be authorized for the diagnosis of nail fungal infections (onychomycosis) if the following are present:
- There is a positive lab culture
- If there is an underlying disease (i.e. diabetes, peripheral vascular disease, poor circulation, immunocompromised recipients, etc.)

Note:
For the diagnosis of onychomycosis – itraconazole (Sporanox®) should only be approved if the recipient has failed or has an intolerance or contra-indication to terbinafine (Lamisil®) AND if the clinical criteria for onychomycosis has been met. Approval will not be made for cosmetic reasons. For a non-onychomycosis diagnosis, Itraconazole (Sporanox®) is unrestricted.

Length of authorization: Up to 3 months. Max of 1 course per year for the diagnosis of onychomycosis.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION
RE-REVIEW: ANTI-INFECTIVE AGENTS: ORAL ANTIFUNGALS USED FOR SYSTEMIC INFECTIONS

RECOMMENDATION

Fluconazole (Diflucan®), ketoconazole (Nizoral®), itraconazole (Sporanox®), voriconazole (Vfend®), posiconazole (Noxafil®), fluvcytosine (Ancobon®), and griseofulvin (Gris-Peg® and others) are products whose safety and efficacy differ by virtue of their spectrum of activity, bioavailability, adverse effects, and potential for drug interactions.

- Voriconazole (Vfend®) and itraconazole (Sporanox®) share a spectrum of activity close to one another, although voriconazole (Vfend®) appears to be more active against Aspergillus spp. and some species of Candida. Careful use of voriconazole (Vfend®) is important if long-term value is to be preserved.
- Itraconazole (Sporanox®) will be subject to the onychomycosis criteria, but use will be unrestricted for systemic infections.
- Posiconazole (Noxafil®) is a new entry to the market having been approved on September 15, 2006. Posiconazole represents an important development in the triazole class as it has been shown to be a broad spectrum triazole, with fewer drug interactions and the only oral antifungal with significant activity against Zygomycetes. Posiconazole also is important, although cross resistance occurs, in that it may incur activity in fungal infections resistant to other azoles. Careful use of posiconazole (Noxafil®) is important if long-term value is to be preserved.
- Fluvcytosine (Ancobon®) has potential issues concerning both safety (potential for bone marrow depression) and efficacy (resistance emerges when used alone) such that it is considered an inferior product that should only be used in combination with other antifungal agents (typically IV amphotericin B).
- Griseofulvin (Gris-Peg® and others) is an antifungal agent particularly active against epidermophytin, microsporum, and trichophyton (tinea) organisms. It is used effectively for the systemic treatment of various tinea (ringworm) infections including tinea capitis (head), tinea corporis (body), tinea cruris (groin), tinea pedis (foot), and tinea unguium (nails). Griseofulvin is usually inactive against Candida albicans. Oral griseofulvin is the treatment of choice for tinea capitis infections in children and for that reason will be recommended as preferred.

Due to the relative safety and efficacy of fluconazole and ketoconazole in the treatment of fungal infections, these agents will be recommended as preferred, with fluvcytosine, itraconazole (brand and generic subject to onychomycosis criteria), posiconazole (Noxafil®), and voriconazole (Vfend®) subject to clinical criteria.
PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

**RE-REVIEW: ANTI-INFECTIVE AGENTS: Oral Antifungals Used for Systemic Infections**

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<tr>
<th>PREFERRED</th>
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<tbody>
<tr>
<td>GRISEOFULVIN</td>
<td>ANCOBON (flucytosine)</td>
</tr>
<tr>
<td>GRIS-PEG® (griseofulvin)</td>
<td>DIFLUCAN® (fluconazole)</td>
</tr>
<tr>
<td>GRifulvin V ® (griseofulvin)</td>
<td>ITRAConazole (compares to Sporanox®) CC</td>
</tr>
<tr>
<td>FLUCONAZOLE (compares to Diflucan®)</td>
<td>NIZORAL® (ketoconazole)</td>
</tr>
<tr>
<td>KETOConazole (compares to Nizoral®)</td>
<td>NOXAFIL® (posiconazole) CC</td>
</tr>
<tr>
<td>ANCOBON (flucytosine)</td>
<td>DIFLUCAN® (fluconazole)</td>
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<tr>
<td>ITRAConazole (compares to Sporanox®) CC</td>
<td>NIZORAL® (ketoconazole)</td>
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<tr>
<td>NIZORAL® (ketoconazole)</td>
<td>NOXAFIL® (posiconazole) CC</td>
</tr>
<tr>
<td>SPORANOX® (itraconazole) CC</td>
<td>VFEND® (voriconazole) CC</td>
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<tr>
<td>VFEND® (voriconazole) CC</td>
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**Criteria for Sporanox® (itraconazole)**

See onychomycosis criteria above.

**Criteria for Vfend® (voriconazole)**

Vfend® will be approved for the following diagnoses:

- Treatment of invasive aspergillosis
- Serious fungal infections caused by *S. apiospermum* and *Fusarium* species including *F. solani*
- As part of standard anti-fungal regimen in febrile neutropenic recipients
- Other fungal infections that are refractory (not responding) or resistant to other oral triazole agents [i.e. Diflucan® (Fluconazole), Nizoral® (Ketoconazole), Sporanox® (Itraconazole)]

**Note:**

If started as an inpatient hospital regimen and this is a continuation of therapy via home health or in a nursing home, then the drug is approvable

**Length of Authorization:** variable dependent upon disease state

**References**

Criteria for Noxafil® (Posiconazole)

Noxafil® (posiconazole) will be approved if **any** of the following are true

- As indicated for the prophylaxis of invasive *Aspergillus* and/or *Candida* in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoetic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD) or recipients with hematologic malignancies (leukemia, lymphoma, myelodysplastic syndromes) with prolonged neutropenia from chemotherapy
- Treatment of *Fusariosis* in patients with disease
- Treatment of *Zygomycetes* disease
- Treatment of other fungal infections or moulds that are refractory or resistant to Sporanox® (itraconazole) or Vfend® (voriconazole) or in patients who are intolerant to these medicinal products

**Note:**
If started as an inpatient hospital regimen and this is a continuation of therapy via home health or in a nursing home, then the drug is approvable

**Length of authorization:** for the length of therapy

**References**


**COMMITTEE VOTE:**

APPROVED DISAPPROVED APPROVED with MODIFICATION
NEW: ANTI-INFECTIVE AGENTS: PRESCRIPTION VAGINAL ANTIFUNGALS

RECOMMENDATION

All of the products in this category have been shown to be safe and effective for the local treatment of vulvovaginal candidiasis. The available clinical studies fail to show any significant differences in response rates or tolerability between the available vaginal antifungal products. Published reviews on these agents state that differences in formulation are not considered to be clinically relevant to therapeutic outcome and are more a function of patient preference. Miconazole is active against susceptible strains of *Trichophyton spp.*, *Epidermophyton spp.*, *Candida albicans*, and *Microsporum spp.*, whereas nystatin, terconazole, and butoconazole are active against *Candida albicans*. Nystatin is Pregnancy Category A and poorly absorbed; therefore this product should be available for pregnant or breast-feeding women. Based on this information, it is recommended that at least miconazole and nystatin be available within this category. The remaining vaginal antifungal products can be considered therapeutic alternatives to one another.

COMMITTEE VOTE

APPROVED    DISAPPROVED    APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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<thead>
<tr>
<th>PREFERRED</th>
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<tbody>
<tr>
<td>MICONAZOLE 3 vaginal supp., 200 mg</td>
<td>GYNAZOLE-1® (butoconazole, 2% cream)</td>
</tr>
<tr>
<td>(compares to Monistat® 3)</td>
<td>MONISTAT® 3 vaginal supp. (200 mg)</td>
</tr>
<tr>
<td>NYSTATIN vaginal tablets, 100,000 U</td>
<td>TERAZOL® 3, 7 (terconazole, 0.4%, 0.8% cream,</td>
</tr>
<tr>
<td>TERCONAZOLE 0.4%, 0.8% cream,</td>
<td>suppository)</td>
</tr>
<tr>
<td>suppository (compares to Terafol® 3, 7)</td>
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</tr>
<tr>
<td>ZAZOLE® (terconazole, 0.4%, 0.8% cream,</td>
<td></td>
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<tr>
<td>80 mg suppository)</td>
<td></td>
</tr>
</tbody>
</table>

References

Facts and Comparisons, www.factsandcomparison.com
Nyiřjesy P. Chronic vulvovaginal candidiasis. American Family Physician. 2001; 63(4):
USPDI, Micromedix, 2004
NEW: ANTI-INFECTIVE AGENTS: Antifungals for Oropharyngeal Candidiasis

RECOMMENDATION
All agents in this category are indicated for the treatment of oropharyngeal candidiasis. Clotrimazole troches are also indicated for prevention of oropharyngeal candidiasis. However, clotrimazole troches are not indicated for use in children less than 3 years of age, whereas nystatin oral suspension can be used even in infants. Based on this information, it is recommended that at least one oral clotrimazole product and at least one oral nystatin product be available.

COMMITTEE VOTE
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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<tbody>
<tr>
<td>CLOTRIMAZOLE troches (compares to Mycelex®)</td>
<td>MYCELEX® (clotrimazole)</td>
</tr>
<tr>
<td>NYSTATIN oral suspension, tablets, powder</td>
<td>MYCOSTATIN® oral tablets (nystatin)</td>
</tr>
</tbody>
</table>

References
Facts and Comparisions, www.factsandcomparison.com
USPD1, Micromedix, 2004
NEW: ANTI-INFECTIVE AGENTS: Vaginal Antiseptics

RECOMMENDATION
The products in this class all contain 0.9% acetic acid and 0.025% oxyquinoline sulfate, and are used to maintain a vaginal pH of around 4 in order to prevent growth of infectious bacteria or fungus. They are considered to have similar efficacy and tolerability, and can be considered therapeutic alternatives to one another.

COMMITTEE VOTE
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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<thead>
<tr>
<th>PREFERRED</th>
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<tbody>
<tr>
<td>ACID JELLY (oxyquinoline sulfate, ricinoleic acid, glacial acetic acid)</td>
<td></td>
</tr>
<tr>
<td>ACIDIC VAGINAL (oxyquinoline sulfate, ricinoleic acid, glacial acetic acid)</td>
<td></td>
</tr>
<tr>
<td>FEM PH (0.9% glacial acetic acid, 0.025% oxyquinoline sulfate)</td>
<td></td>
</tr>
<tr>
<td>RELAGARD (0.9% glacial acetic acid, 0.025% oxyquinoline sulfate) – priced as brand, but more utilization</td>
<td></td>
</tr>
</tbody>
</table>

References
Facts and Comparisons, www.factsandcomparison.com
USPDI, Micromedix, 2004
LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat. (Most medications in this class are used chronically, and thus would be approved for 1 year.)

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?
   Acceptable reasons include:
   - **Allergy** to medications not requiring prior approval
   - **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
   - **History** of unacceptable/toxic side effects to medications not requiring prior approval

2. The requested medication may be approved if both of the following are true:
   - If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
   - The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.
The information provided for each drug class within the Cardiovascular Agents is organized into the following sections when applicable:

BACKGROUND:
- General overview
- Pharmacology
- Therapeutic effect(s) (i.e., blood pressure lowering, lipid lowering, etc.)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

RECOMMENDATION
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)

RE-REVIEW: LIPOTROPICS – HIGH POTENCY STATINS

BACKGROUND

- The 3-hydroxy, 3-methyl-glutaryl-coenzyme A (HMG-CoA) Reductase Inhibitors, also known as the statins, have become standard treatment for hyperlipidemia. The high potency statins are the most effective class of drugs for lowering LDL cholesterol concentrations, and all agents in this class produce dose-dependent LDL lowering. There are numerous studies available which have found the use of statins to be associated with reduced morbidity and mortality, including reduced incidence of cardiovascular events.

- The statins competitively inhibit HMG-CoA reductase, the enzyme responsible for catalyzing the rate-limiting step in cholesterol biosynthesis, involving the conversion of HMG-CoA to mevalonate. Inhibition of cholesterol biosynthesis results in lower cholesterol levels in the liver, increases synthesis of LDL-receptors, and thus, increases uptake of LDL from the bloodstream. In addition, statins decrease production of VLDL particles, a precursor for LDL. Recent findings suggest that an effect on C-reactive protein (CRP) may also contribute to reduced cardiovascular events.

- The high potency statins have been found to produce the following effects on lipids:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin (Lipitor®)</td>
<td>-25% to -60%</td>
<td>-25% to -45%</td>
<td>+0.1% to +9%</td>
<td>-17% to -37%</td>
</tr>
<tr>
<td>rosuvastatin (Crestor®)</td>
<td>-35% to -60%</td>
<td>-30% to -45%</td>
<td>+8% to +14%</td>
<td>-10% to -35%</td>
</tr>
<tr>
<td>simvastatin (Zocor®)</td>
<td>-20% to -50%</td>
<td>-20% to -40%</td>
<td>+3% to +16%</td>
<td>-9% to -34%</td>
</tr>
<tr>
<td>simvastatin/ezetimibe (Vytorin®)</td>
<td>-35% to -60%</td>
<td>-30% to -45%</td>
<td>+6% to +12%</td>
<td>-23% to -35%</td>
</tr>
</tbody>
</table>
• All statins are relatively well-tolerated. The most common adverse reactions reported with the statins are headache, abdominal pain, constipation, diarrhea, nausea, and myalgia, but the incidence of these events is similar to placebo. All statins have been associated with rhabdomyolysis, but the problem occurs only in about 2 of every 100,000 people taking a statin. The risk of rhabdomyolysis is greater among individuals receiving statins in combination with cyclosporine, fibrates, macrolide antibiotics, certain anti-fungals, and niacin. In addition, elevated hepatic transaminases occur in 0.5 to 2% of individuals on statins; however, the incidence of clinically important transaminase elevations (>3 times the upper limit of normal) is the same as seen with placebo. With regard to safety during pregnancy, all statins are contraindicated in pregnancy (Category X).

• Numerous comparative trials have examined the impact of statins on cardiovascular outcomes. Both atorvastatin and simvastatin have been shown to significantly improve all-cause and cardiovascular mortality in large, double-blinded, placebo-controlled trials. No large outcomes trials are available for rosuvastatin and simvastatin/ezetimibe; however, similar lipid-lowering effects compared to atorvastatin would suggest that they would provide similar cardiovascular benefits.

• According to the ATP-III guidelines, statins should be considered first line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

**RECOMMENDATION**

Among the high potency statins, all agents in this class result in similar effects on lipids when dosed in equivalent doses. Simvastatin appears to produce lower maximum reductions in LDL and total cholesterol compared to atorvastatin, rosuvastatin and simvastatin/ezetimibe; however, it is a reasonable option for individuals requiring less than a 50% reduction in LDL. Atorvastatin, rosuvastatin, or simvastatin/ezetimibe should be available to individuals requiring more than a 45% reduction in LDL.

**COMMITTEE VOTE:**

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

**RE-REVIEW: LIPTROPICS - HIGH POTENCY STATINS**

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<tr>
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<tbody>
<tr>
<td>SIMVASTATIN (compares to Zocor®) QL</td>
<td>CRESTOR® (rosuvastatin) ST, QL</td>
</tr>
<tr>
<td></td>
<td>LIPITOR® (atorvastatin) ST, QL</td>
</tr>
<tr>
<td></td>
<td>VYTORIN® (simvastatin/ezetimibe) ST, QL</td>
</tr>
<tr>
<td></td>
<td>ZOCOR® (simvastatin) QL</td>
</tr>
</tbody>
</table>

**Quantity Limits**

- Crestor® (rosuvastatin): 1 /day
- Lipitor® (atorvastatin): 1 /day
- Simvastatin: 1/day
- Vytorin® (simvastatin/ezetimibe): 1 /day
- Zocor® (simvastatin): 1 /day

**Step Therapy Criteria for High Potency Statins**

Crestor, Vytorin, and Lipitor will be approved only for recipients who meet one of the following criteria:

- Have tried and failed to achieve goal lipid levels following an adequate trial of simvastatin
- Require greater than a 45% reduction in LDL
- Have a contraindication or intolerance to simvastatin
## RE-REVIEW: LIPOTROPICS – STATINS

### BACKGROUND

- The HMG-CoA Reductase Inhibitors, also known as the statins, have become standard treatment for hyperlipidemia. Statins are an effective class of drugs for lowering LDL cholesterol concentrations, and all agents in this class produce dose-dependent LDL lowering. There are numerous studies available which have found the use of statins to be associated with reduced morbidity and mortality, including reduced incidence of cardiovascular events.
- The statins competitively inhibit HMG-CoA reductase, the enzyme responsible for catalyzing the rate-limiting step in cholesterol biosynthesis, involving the conversion of HMG-CoA to mevalonate. Inhibition of cholesterol biosynthesis results in lower cholesterol levels in the liver, increases synthesis of LDL-receptors, and thus, increases uptake of LDL from the bloodstream. In addition, statins decrease production of VLDL particles, a precursor for LDL. Recent findings suggest that an effect on C-reactive protein (CRP) may also contribute to reduced cardiovascular events.
- The statins have been found to produce the following effects on lipids:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluvastatin (Lescol®)</td>
<td>-20% to -45%</td>
<td>-15% to -30%</td>
<td>+3% to +9%</td>
<td>-2.7% to -23%</td>
</tr>
<tr>
<td>fluvastatin XL (Lescol XL®)</td>
<td>-25% to -45%</td>
<td>-20% to -30%</td>
<td>+6% to +13%</td>
<td>-19% to -25%</td>
</tr>
<tr>
<td>Lovastatin (Mevacor®)</td>
<td>-20% to -45%</td>
<td>-15% to -30%</td>
<td>+3% to +10%</td>
<td>-6% to -27%</td>
</tr>
<tr>
<td>Lovastatin ER (Altoprev®)</td>
<td>-20% to -45%</td>
<td>-15% to -30%</td>
<td>+6% to +13%</td>
<td>-10% to -33%</td>
</tr>
<tr>
<td>Lovastatin/niacin ER (Advicor®)</td>
<td>-25% to -45%</td>
<td>Not available.</td>
<td>+17% to +32%</td>
<td>-29% to -49%</td>
</tr>
<tr>
<td>Pravastatin (Pravachol®)</td>
<td>-20% to -45%</td>
<td>-15% to -30%</td>
<td>+2% to +12%</td>
<td>-9% to -24%</td>
</tr>
</tbody>
</table>

- All statins are relatively well-tolerated. The most common adverse reactions reported with the statins are headache, abdominal pain, constipation, diarrhea, nausea, and myalgia, but the incidence of these events is similar to placebo. All statins have been associated with rhabdomyolysis, but the problem occurs only in about 2 of every 100,000 people taking a statin. The risk of rhabdomyolysis is greater among individuals receiving statins in combination with cyclosporine, fibrates, macrolide antibiotics, certain anti-fungals, and niacin. In addition, elevated hepatic transaminases occur in 0.5 to 2% of individuals on statins; however, the incidence of clinically important transaminase elevations (>3 times the upper
limit of normal) is the same as seen with placebo. With regard to safety during pregnancy, all statins are contraindicated in pregnancy (Category X).

- Several clinical trials have investigated the impact of statin use on cardiovascular morbidity and mortality. The LIPS trial concluded that fluvastatin significantly reduced cardiovascular events in patients with stable or unstable angina or ischemia following a successful percutaneous coronary intervention (PCI). The ALERT study showed that fluvastatin reduced the incidence of cardiac deaths and non-fatal MIs in renal transplant patients. The ALLHAT-LLT study compared pravastatin use to usual care, and found similar rates of all-cause mortality and CHD events between the two groups; however 26.1% of patients in the usual care group were using statins by the end of the study.

- According to the ATP-III guidelines, statins should be considered first line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

**RECOMMENDATION**

Among the statins, all agents in this class result in similar effects on LDL cholesterol and total cholesterol when dosed in equivalent doses. Advicor® (lovastatin/niacin ER) produces a greater reduction in triglycerides and a greater increase in HDL compared with the other agents in this class. For this reason, lovastatin/niacin ER should be available as a preferred agent on the PDL. In addition, pravastatin is not metabolized via the cytochrome P450 CYP enzyme system, and therefore, is less prone to drug interactions. For this reason, pravastatin should be made available to individuals receiving medications that inhibit Cytochrome P450 enzymes.

**COMMITTEE VOTE:**

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

**PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:**

**RE-REVIEW: LIPOTROPICS - STATINS**

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<tr>
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<tr>
<td>ADVICOR® (lovastatin/niacin) QL</td>
<td>MEVACOR® (lovastatin) QL</td>
</tr>
<tr>
<td>ALTOPREV® (lovastatin XL) QL</td>
<td>PRAVACHOL® (pravastatin) QL</td>
</tr>
<tr>
<td>LESCOL® (fluvastatin) QL</td>
<td>PRAVIGARD PAC® (buffered aspirin/pravastatin) QL</td>
</tr>
<tr>
<td>LESCOL XL® (fluvastatin XL) QL</td>
<td></td>
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<tr>
<td>LOVASTATIN (compares to Mevacor®) QL</td>
<td></td>
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<tr>
<td>PRAVASTATIN (compares to Pravachol) QL</td>
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</tbody>
</table>

**Quantity Limits**

ADVICOR®: 2/day
ALTOPREV®: 1/day
LESCOL®: 1/day
LESCOL XL®: 1/day
LOVASTATIN: 1/day
MEVACOR®: 1/day
PRAVACHOL®: 1/day
PRAVASTATIN: 1/day
PRAVIGARD PAC®: 1/day
BACKGROUND

- There is currently one statin/CCB combination product available, Caduet® (atorvastatin/amlodipine). This product is intended for use in patients for whom treatment with both amlodipine and atorvastatin is deemed appropriate. Amlodipine is indicated for the treatment of hypertension, treatment of chronic stable or vasospastic angina, and to reduce hospitalization in patients without heart failure who have recently angiographically documented CAD. Lipitor is indicated for the treatment of patients with hyperlipidemia.

- The statins competitively inhibit HMG-CoA reductase, the enzyme responsible for catalyzing the rate-limiting step in cholesterol biosynthesis, involving the conversion of HMG-CoA to mevalonate. Inhibition of cholesterol biosynthesis results in lower cholesterol levels in the liver, increases synthesis of LDL-receptors, and thus, increases uptake of LDL from the bloodstream. Amlodipine inhibits calcium ions from entering cells, resulting in decreased mechanical contration of cardiac and smooth muscle. This results in dilation of the arteries, a decrease in peripheral resistance, decreased blood pressure, and decreased afterload.

- Caduet® has been shown to result lipid changes comparable to those seen with Lipitor® (atorvastatin): 25 - 60% reduction in LDL, 0.1 - 9% increase in HDL, and 17-37% decrease in triglycerides. In addition, Caduet® has been shown to lower blood pressure comparable to Norvasc (amlodipine): reduction in systolic blood pressure ~17-25 mm Hg, reduction in diastolic blood pressure ~10-17 mm Hg.

- The side effect profile of Caduet® is similar to that seen with the individual agents. The most common adverse reactions experienced with Caduet® are headache, peripheral edema, and dizziness. As with Lipitor®, Caduet® would be expected to be associated with a small risk of myopathy, rhabdomyosis, and hepatic transaminase elevation. In addition, as with Lipitor®, Caduet® is pregnancy Category X.

- No long-term outcomes studies have been performed with Caduet® at this time.

- According to the ATP-III guidelines, statins should be considered first line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. According to the JNC-VII guidelines for hypertension, CCBs are first line therapy (in combination with ACE inhibitors or beta-blockers) for high-risk CHD patients and diabetic patients. For patients who do not have high risk CHD or diabetes, CCBs are appropriate add-on therapy if blood pressure is not controlled on a thiazide diuretic or other recommended first line agent.
RECOMMENDATION
Caduet® produces lipid lowering effects similar to those seen with the other high potency statins. In addition, Caduet® produces blood pressure lowering effects comparable to those seen with amlodipine. However, given the availability of high potency statins and amlodipine on the PDL and the challenges associated with titrating individuals to the proper dose of atorvastatin and amlodipine on the fixed dose combination product, it is recommended that Caduet be non-preferred on the PDL and subject to clinical criteria.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>RE-REVIEW: LIPOTOPICS – STATIN / CCB COMBINATION PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
<tr>
<td>CADUET® (atorvastatin/amlodipine)</td>
</tr>
</tbody>
</table>

Quantity Limits
Caduet® (atorvastatin/amlodipine) : 1/day

Clinical Criteria for Caduet® (atorvastatin/amlodipine)
Caduet® will only be authorized for recipients who:
1) Are receiving amlodipine therapy, AND
2) Have tried and failed, or have a contraindication or intolerance to, simvastatin plus one other high potency statin

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References
Facts and Comparisons. 4.0. http://online.factsandcomparisons.com
RE-REVIEW: LIPOTROPICS – CHOLESTEROL ABSORPTION INHIBITORS

BACKGROUND

- There is currently one cholesterol absorption product available, Zetia® (ezetimibe). This product inhibits absorption of both dietary cholesterol and cholesterol in the bile. As a result, this product results in reductions in LDL, total cholesterol, and triglycerides, and elevates HDL. It can be used alone or in combination with other lipid lowering medications. When used with statins or other cholesterol lowering agents, Zetia® has been found to exhibit a synergistic effect.
- Zetia® inhibits cholesterol absorption along the brush border of the small intestine, reducing delivery of intestinal cholesterol to the liver. This results in decreased cholesterol stores, increased cholesterol uptake from the blood, and ultimately, reductions in LDL, total cholesterol, triglycerides, and apolipoprotein B, as well as slight increases in HDL.
- Use of Zetia® has been found to result in the following lipid changes:

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zetia® monotherapy</td>
<td>-18%</td>
<td>-12% to -13%</td>
<td>+1%</td>
<td>-8%</td>
</tr>
<tr>
<td>Addition of Zetia® to ongoing statin therapy</td>
<td>-25%</td>
<td>-17%</td>
<td>+3%</td>
<td>-14%</td>
</tr>
<tr>
<td>Addition of Zetia® to ongoing bile acid sequestrant therapy</td>
<td>-19%</td>
<td>-18%</td>
<td>0%</td>
<td>-14%</td>
</tr>
</tbody>
</table>

- Zetia® is generally well-tolerated. Common adverse reactions include abdominal pain, diarrhea, arthralgia, sinusitis, and fatigue, but incidence is low (<4%) and similar to that seen with placebo. With regard to pregnancy, Zetia® is considered Category C.
- No long-term outcomes studies on the impact of Zetia® (ezetimibe) on cardiovascular morbidity and/or mortality are available at this time.
- Zetia® (ezetimibe) was not available at the time the ATP-III guidelines were published. However, the 2004 NCEP update to the ATP-III guidelines lists ezetimibe as reasonable add-on therapy for those not achieving lipid goals on statin therapy alone, or for those who wish to achieve their lipid goals with a lower dose of statin.

RECOMMENDATION

Zetia® (ezetimibe) is less effective than the available statins, producing only a small reduction in LDL (<20%) and triglycerides (<10%). For this reason, the majority of Zetia® use is in combination with other lipid lowering drugs, namely statins, bile acid sequestrants, fibrates, and niacin. Zetia® should be available for individuals requiring it in combination with other lipid lowering therapies. However, the use of Zetia® as monotherapy should be reserved for individuals who cannot tolerate or have a contraindication to a statin. In addition, use of Zetia® in combination with a statin should be reserved for those individuals who have tried and failed, are intolerant to, or have a contraindication to a combination high potency statin/ezetimibe product, provided a combination product is preferred on the PDL.

[Note: For individuals stabilized on a statin that produces equivalent LDL lowering to the combination statin/ezetimibe product, the requirement to try the combination product prior to approving Zetia® for use with the statin should be waived.]
COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>RE-REVIEW: LIPOTROPICS - CHOLESTEROL ABSORPTION INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>ZETIA® (ezetimibe) ST, QL</td>
</tr>
</tbody>
</table>

Quantity Limits

ZETIA® (ezetimibe): 1/day

Step Therapy Criteria for Zetia® (ezetimibe)

For requests for Zetia® use as monotherapy (without any other lipid lowering medications), recipients must have tried and failed, been intolerant to, or have a contraindication to a statin.

For requests for Zetia® in combination with a statin, an adequate trial of Vytorin® is required, unless one of the following is met:
1) The recipient has a contraindication or history of intolerance to simvastatin, OR
2) The recipient is stabilized on Lipitor® 80mg, Crestor® 20mg, or Crestor® 40mg

Use of Zetia® in combination with bile acid sequestrants, fibrates, or niacin will be approved.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References

Facts and Comparisons. 4.0. http://online.factsandcomparisons.com
BACKGROUND

- There are currently two distinct fibric acid derivatives available in the United States: fenofibrate and gemfibrozil. While there are four fenofibrate products on the market today, available in different strengths, all products achieve similar plasma concentrations at the highest available dose. Furthermore, the micronized and non-micronized products are considered therapeutically equivalent. Fibrates are used predominantly in patients with high triglycerides, but can also be useful for raising HDL. They may be used in combination with other lipid lowering medications; however concomitant use with statins may increase the risk of myopathy and rhabdomyolysis.

- The fibrates serve as agonists for the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha). As a result of activation of this receptor, fibrates cause increased lipolysis and elimination of triglycerides from the bloodstream, increased HDL production, and greater conversion of small, dense LDL particles to larger, more buoyant particles.

- Fibrates have been associated with the following lipid changes:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibric acids (fenofibrate, gemfibrozil)</td>
<td>-27% to +9%</td>
<td>-4% to -26%</td>
<td>+6% to +18%</td>
<td>-29% to -54%</td>
</tr>
</tbody>
</table>

- Fibrates are generally well-tolerated, with the most common adverse reactions including abnormal LFTs, dyspepsia, abdominal pain, headache, backpain, and constipation. In addition, fibric acids may cause cholelithiasis (gall stones). Myopathy/rhabdomyolysis have also been reported, although this risk is increased with concomitant statin use. Fenofibrate appears to be less likely to cause myopathy/rhabdomyolysis than gemfibrozil. With regards to pregnancy, both gemfibrozil and fenofibrate are Category C.

- In addition to the interaction between the fibrates (mainly gemfibrozil) and the statins, there are some other drug interactions worth noting. Gemfibrozil has been shown to inhibit the metabolism of repaglinide, sulfonylureas, and TZDs, resulting in an increased risk of hypoglycemia. Gemfibrozil may also decrease cyclosporine levels, resulting in a decrease in its immunosuppressive effects.

- Several large, randomized, placebo-controlled outcomes studies have investigated the impact of fibrate use on cardiovascular morbidity and mortality. The FIELD study examined fenofibrate use over 2 years in Type 2 diabetics with no previous history of CV disease. This study failed to show a statistically significant reduction in coronary events, but this was thought to be due to high statin use among individuals in the placebo group. Once the data was adjusted for statin use, the study showed that fenofibrate therapy was associated with a 19% reduction in CHD events, and a 15% reduction in total CV disease. The Helsinki Heart Study examined the impact of gemfibrozil on cardiovascular events over a five-year period, and found that gemfibrozil use resulted in a 34% reduction in the incidence of MI and cardiac death compared to placebo. The Veterans’ Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) also looked at the impact of gemfibrozil use, and found that it resulted in a 22% relative risk reduction in MI and cardiovascular death.
According to the ATP-III guidelines, fibrates should be recommended as first line treatment for individuals who have very high triglycerides, or who have elevated beta-VLDL. In addition, fibrate therapy may be considered an option for individuals with CHD who have low LDL levels and atherogenic dyslipidemia. Combination therapy with a statin should be considered for those who have atherogenic dyslipidemia and elevated LDL levels; however, this does impart an increased risk for myopathy.

RECOMMENDATION

The available fibric acid derivatives exhibit similar effects on LDL, total cholesterol, triglycerides, and HDL. Given the similar efficacy and tolerability of the agents in this class, they can be considered therapeutic alternatives to one another. However, fenofibrate has been associated with a lower risk of myopathy/rhabdomyolysis when used in combination with a statin, and gemfibrozil has more potential drug-drug interactions than fenofibrate. Thus, a fenofibrate product should be available to individuals requiring dual therapy with a statin, or who are currently receiving repaglinide, a TZD, a sulfonylurea, or cyclosporine.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: LIPOTOPICS – FIBRIC ACID DERIVATIVES

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMFIBROZIL (Compares to Lopid®)</td>
<td>ANTARA® (fenofibrate)CC</td>
</tr>
<tr>
<td>TRICOR® (fenofibrate)CC</td>
<td>LOFIBRA® (fenofibrate)CC</td>
</tr>
<tr>
<td>LOPID® (gemfibrozil)</td>
<td>TRIGLIDE® (fenofibrate)CC</td>
</tr>
</tbody>
</table>

Criteria for Fenofibrate Products

Fenofibrates will be approved for individuals who are receiving current therapy with at least one of the following:
1) HMG-CoA Reductase inhibitor (statin)
2) Repaglinide
3) Sulfonylurea
4) Thiazolidinedione
5) Cyclosporine

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


Facts and Comparisons. 4.0. http://online.factsandcomparisons.com

RE-REVIEW: LIPOTROPICS – BILE ACID SEQUESTRANTS

BACKGROUND

- Bile acid sequestrants are used to lower LDL cholesterol. They have no systemic absorption and a different mechanism of action from the other lipid lowering drugs. Therefore, the bile acid sequestrants can be administered in combination with other lipid lowering therapies in order to provide additional LDL reduction.

- Bile acid sequestrants bind to bile acids in the intestine to form an insoluble complex, which is secreted in the feces. By binding bile acids in the gut, the bile acid sequestrants cause increased hepatic uptake of cholesterol, resulting in reduced serum cholesterol levels.

- Bile acid sequestrants product the following effects on lipids:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Acid Sequestrants</td>
<td>-12% to -30%</td>
<td>-9% to -13%</td>
<td>+3% to +9%</td>
<td>0% to +25%</td>
</tr>
<tr>
<td>(cholestyramine, colestipol, colesevelam)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Bile acid sequestrants are usually well-tolerated at low doses, but at higher doses GI side effects are very common. The most frequent adverse reactions include flatulence, constipation, dyspepsia, and abdominal pain. Colesevelam has been reported to cause less GI side effects (flatulence, constipation, etc.) than cholestyramine and colestipol, but head-to-head studies are not available. With regards to use in pregnancy, bile acid sequestrants are thought not to pose fetal harm since they are not systemically absorbed. Currently, colesevelam and colestipol are Category B drugs, and cholestyramine is Category C due to lack of well-controlled studies.

- The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) examined the impact of cholestyramine on the risk of CHD, and found that after 7.4 years of use, cholestyramine reduced the risk of CHD death by 24% and non-fatal MI by 19%. Other studies have found similar beneficial outcomes when bile acid sequestrants are combined with other lipid lowering treatments.

- The ATP-III guidelines recommend bile acid sequestrants for individuals with moderate elevations in LDL, individuals with very high LDL levels on concomitant statin therapy, and for use in pregnant women with elevated LDL cholesterol. The guidelines recognize the utility of these agents to be used in combination with other lipid lowering drugs.

RECOMMENDATION

The various bile acid sequestrants produce similar lipid changes (LDL lowering, as well as impact on TC, TG, and HDL), and can thus be viewed as therapeutic alternatives to one another. However, colesevelam has been associated with lower rates of GI-related side effects as well as fewer drug-drug interactions (i.e., does not decrease absorption of co-administered drugs) compared to cholestyramine and colestipol. Given these benefits of colesevelam over the other bile acid sequestrants, it is recommended that this agent be preferred on the PDL.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION
PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

### RE-REVIEW: LIPOTROPICS – BILE ACID SEQUESTRANTS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOLESTYRAMINE (compares to Questran®)</td>
<td>COLESTID® (colestipol)</td>
</tr>
<tr>
<td>CHOLESTYRAMINE LIGHT (compares to Questran Light®)</td>
<td>PREVALITE (cholestyramine)</td>
</tr>
<tr>
<td>WELCHOL® (colselevelam)</td>
<td>QUESTRAN® (cholestyramine)</td>
</tr>
<tr>
<td></td>
<td>QUESTRAN LIGHT® (cholestyramine)</td>
</tr>
</tbody>
</table>

**References**


Facts and Comparisons. 4.0. [http://online.factsandcomparisons.com](http://online.factsandcomparisons.com)


### RE-REVIEW: LIPOTROPICS – NIACIN DERIVATIVES

**BACKGROUND**

- Niacin (nicotinic acid) is the most effective agent available for modifying all of the lipoprotein abnormalities associated with atherogenic dysplasia. It is associated with a modest reduction in LDL, total cholesterol, and triglycerides, and is the most effective drug for raising HDL levels. Long-term outcomes studies are available which show that niacin use results in reductions in cardiovascular morbidity and mortality; however, side effects tend to limit the use of this drug.
- Nicotinic acid inhibits lipolysis in adipocytes, decreases production of VLDL particles by the liver, and increases HDL cholesterol by reducing its hepatic uptake. In addition, it promotes a shift from the small dense LDL particles to the larger, more buoyant LDL particles, which are less atherogenic.
- The lipid lowering effects of niacin are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>-5% to -25%</td>
<td>-5% to -25%</td>
<td>+15% to +35%</td>
<td>-20% to -50%</td>
</tr>
</tbody>
</table>

- Niacin is often associated with flushing; however, this reaction is more common with the immediate-release formulation. Other side effects experienced with niacin include gastrointestinal symptoms, such as nausea, vomiting, dyspepsia, flatulence, and diarrhea. Serious, but less common, adverse events include hepatotoxicity, hyperuricemia (and gout), and hyperglycemia. The incidence of hepatotoxicity is greater among the sustained-release niacin formulation (although not with Niaspan®). Rare cases of fulminant hepatitis have been reported with the sustained-release preparations. With regards to use in pregnancy, it is not known whether nicotinic acid at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women.
• Nicotinic acid has been shown to reduce the risk of recurrent myocardial infarction as well as total mortality in a large, long-term, double-blinded outcomes study. In addition, several trials have shown niacin to decrease rates of atherosclerotic progression when used in combination with statins.
• According to the ATP-III guidelines, niacin should be considered as monotherapy for individuals with atherogenic dyslipidemia who require only a moderate reduction in LDL. In addition, niacin should be considered for combination therapy with other lipid lowering drugs in individuals who have significantly elevated LDL levels along with atherogenic dyslipidemia.

RECOMMENDATION

The immediate-release, sustained-release, and extended-release formulations of niacin are equally effective in reducing LDL, total cholesterol, and triglycerides, and in increasing HDL. Therefore, these agents can be considered therapeutic alternatives. However, the extended-release formulation is better tolerated than the other available formulations (less flushing compared to the immediate release formulations, less hepatotoxic compared to sustained-release formulations). Therefore, the extended-release niacin formulation (Niaspan®) should be preferred on the PDL.

COMMITTEE VOTE:

APPROVED    DISAPPROVED    APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>RE-REVIEW: LIPOTROPICS – NIAcin DERIVATIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
<tr>
<td>NIACOR® (niacin, immediate-release)</td>
</tr>
<tr>
<td>NIASPAN® (niacin, extended-release)</td>
</tr>
</tbody>
</table>

References

Facts and Comparisons. 4.0. http://online.factsandcomparisons.com
NEW: LIPOTROPICS - OMEGA-3 FATTY ACIDS

BACKGROUND

- There is currently one prescription omega-3 fatty acid product available - Omacor® is a combination of two ethyl esters found in fish oil (eicosapentanoic acid (EPA) and docosahexanoic acid (DHA)). It is indicated as an adjunct to diet for the treatment of individuals with very high triglyceride levels (TG>500 mg/dL).
- Although the mechanism of action is not completely understood, Omacor® is thought to reduce hepatic synthesis/secretion of triglycerides, leading to reduced levels of triglycerides in the serum.
- The effect of Omacor® on lipid levels is as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in LDL</th>
<th>Change in Total Cholesterol</th>
<th>Change in HDL</th>
<th>Change in Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omacor®</td>
<td>+45%</td>
<td>-10%</td>
<td>+9%</td>
<td>-45%</td>
</tr>
</tbody>
</table>

- The most common adverse events associated with the use of Omacor® are dyspepsia, abnormal LFTs, constipation, flatulence, and back pain.
- Currently, there are no long-term outcomes studies examining the effect of Omacor® on cardiovascular outcomes.
- According to the ATP-III guidelines, omega-3 fatty acids represent alternatives to fibrates or nicotinic acid for the treatment of hypertriglyceridemia; however, more definitive clinical trials are required before these agents can be strongly recommended.

RECOMMENDATION

Omega-3 fatty acids are a reasonable treatment option for individuals with hypertriglyceridemia; however similar reductions in triglycerides can be obtained with niacin and fibrates, with more favorable effects on LDL and HDL cholesterol. For this reason, Omacor® is recommended to be non-preferred on the PDL and subject to step therapy criteria.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>NEW: LIPOTROPICS – OMEGA-3 FATTY ACIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
</tbody>
</table>

Criteria for Omacor® (omega-3-acid ethyl esters)

Omacor will be approved for individuals with hypertriglyceridemia who have tried and failed an adequate trial of both of the following:
1) A niacin product (Niacor®, Niaspan®, etc.)
2) A fibrate (gemfibrozil, fenofibrate, etc.)
COMMITTEE VOTE:

APPROVED  
DISAPPROVED  
APPROVED with MODIFICATION

References


Facts and Comparisons. 4.0. http://online.factsandcomparisons.com


RE-REVIEW: DIURETICS – CARBONIC ANHYDRASE INHIBITORS

BACKGROUND

- Carbonic anhydrase inhibitors (CAIs) are used as adjunctive treatment for edema due to congestive heart failure, drug-induced edema, certain epilepsies (petit mal, unlocalized seizures), glaucoma, and acute mountain sickness.
- The agents reversibly inhibit carbonic anhydrase, interfering with the reabsorption of bicarbonate at the proximal renal tubule, causing an increased excretion of sodium, potassium, bicarbonate and water, thus producing an alkaline diuresis. Evidence seems to indicate that acetazolamide also has utility as an adjuvant in the treatment of certain dysfunctions of the CNS (e.g., epilepsy). Inhibition of carbonic anhydrase in this area appears to retard abnormal, paroxysmal, excessive discharge from CNS neurons. Furthermore, carbonic anhydrase reduces the rate of aqueous humor formation in the eye, resulting in decreased intra-ocular pressure (IOP).
- Acetazolamide tablets have a duration of action lasting 8 to 12 hours, compared to the sustained-release capsules (Diamox® Sequels) which can last 18 to 24 hours after each dose. The prolonged continuous effect of acetazolamide sustained-release capsules permits a reduction in dosage frequency (twice daily instead of every 4 hours).
- CAIs are generally well tolerated. The most common adverse reactions reported are malaise, drowsiness or dizziness, anorexia, weight loss, D/N/V, metallic taste, polyuria, numbness/tingling in extremities. Metabolic acidosis and bone marrow depression, although less common, can also occur. Methazolamide is a sulfonamide derivative, therefore, should be avoided in patients with sulfa allergies. CAIs are rated as pregnancy category C and should only be used in pregnancy if the potential benefit justifies the potential risk to the fetus.
- Currently, carbonic anhydrase inhibitors are used for adjunctive treatment for glaucoma, edema due to congestive heart failure, drug-induced edema, epilepsies, and acute mountain sickness.

RECOMMENDATION

Among the CAIs, all agents in this class exhibit similar effects with regards to safety and efficacy and are considered to be therapeutically alternatives to one another. The efficacy of acetazolamide sustained-release capsules is comparable to the immediate release acetazolamide. In order to ensure patient and prescriber choice, it is recommended that at least two CAI products be available on the preferred drug list.
COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: DIURETICS – CARBONIC ANHYDRASE INHIBITORS

<table>
<thead>
<tr>
<th>PREFERRED</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ACETAZOLAMIDE*</td>
<td>DIAMOX® SEQUELS (acetazolamide)</td>
</tr>
<tr>
<td>METHAZOLAMIDE (compare to Neptazane®)</td>
<td></td>
</tr>
</tbody>
</table>

* Brand name Diamox® is no longer available

References


RE-REVIEW: DIURETICS – THIAZIDE AND RELATED DIURETICS

BACKGROUND

- Thiazide diuretics are used as adjunctive therapy in edema associated with mild congestive heart failure (CHF), hepatic cirrhosis, and corticosteroid and estrogen therapy. They can also be used as the sole therapeutic agent or to enhance other antihypertensive drugs in more severe forms of hypertension.
- Thiazide diuretics increase the urinary excretion of sodium and chloride by inhibiting reabsorption of sodium and chloride in the ascending Loop of Henle and the early distal tubules. Other common actions include increased potassium and bicarbonate excretion, decreased calcium excretion, and uric acid retention.
- The most common adverse effects reported with thiazide and thiazide-like diuretics are electrolyte imbalances (hypokalemia, hyponatremia/hypochloremia, hypomagnesemia, hypercalcemia, hyperuricemia), photosensitivity, and glucose intolerance. These agents may also decrease renal function in renally impaired patients (except metolazone), and may increase serum cholesterol (expect indapamide).
- Thiazide and related diuretics should only be used in patients with a CrCL \( \geq 30 \text{ ml/min} \). During initial therapy with thiazide diuretics, plasma volume decreases which contributes to the hypotensive effect. With chronic therapy, cardiac output normalizes, peripheral vascular resistance falls, and there is a persistent small reduction in extracellular volume. At maximal therapeutic dosages all thiazides are approximately equal in diuretic efficacy, but metolazone may be more effective in patients with impaired renal function.
- According to the JNC-VII Guidelines, thiazide and related diuretics are recommended as first line therapy for drug treatment of uncomplicated hypertension either as monotherapy or in combination with other agents. They are also effective in treating mild heart failure in patients with normal kidney function.
RECOMMENDATION

Among the thiazide and related diuretics, all agents in this class result in similar effects on blood pressure when dosed in equivalent doses and can be considered therapeutic alternatives to one another. Indapamide is the only thiazide-type diuretic which does not appear to increase serum cholesterol. In addition, metolazone is the only diuretic in this class which is more effective in patients with renal function. For this reason, indapamide and metolazone should be preferred on the PDL in addition to at least two other agents to ensure patient and prescriber choice.

COMMITTEE VOTE:

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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RE-REVIEW: DIURETICS – LOOP DIURETICS

BACKGROUND

- Loop diuretics provide the most pronounced diuresis, but do not have the added benefit of arterial vasodilation seen with thiazides. They are used in the treatment of hypertension (alone or in combination with other antihypertensives), as well as in the management of edema associated with congestive heart failure and hepatic or renal disease.
- Loop diuretics inhibit reabsorption of sodium and chloride in the ascending loop of Henle and the distal renal tubule, interfering with the chloride-binding co-transport system, thus causing an increased excretion of water, sodium, chloride, magnesium, and calcium.
- These agents are effective in reducing volume overload in heart failure patients with a CrCl < 30 ml/min.
- The most common adverse effects reported with loop diuretics are electrolyte imbalances (hyponatremia, hypokalemia, hypochloremia, hypomagnesemia, hypocalcemia), orthostatic hypotension, photosensitivity, hyperglycemia, and hyperuricemia. These agents may also increase LDL and total cholesterol. Ototoxicity and gastric hemorrhage is seen with ethacrynic acid.

References


Loop diuretics provide the most pronounced diuresis, but do not have the added property of arterial vasodilation seen with thiazides. Loop diuretics are reserved for patients with significant renal insufficiency (CrCL < 30ml/min) or when a vigorous diuresis is desired as in congestive heart failure, ascites, or pulmonary edema. Edecrin® is the only loop diuretic that can be used in patients with a sulfa allergy.

**RECOMMENDATION**

Among the loop diuretics, all agents in this class result in similar effects on hypertension, edema associated with congestive heart failure, renal disease, or hepatic disease when dosed in equivalent doses. In addition, ethacrynic acid can also be used for short-term management of ascites due to malignancy and idiopathic edema, and is the only loop diuretic available for patients with a sulfa allergy. Based on this information, it is recommended that ethacrynic acid be available on the PDL in addition to at least two other loop diuretic agents to ensure patient and prescriber choice.

**COMMITTEE VOTE:**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

**PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:**

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**References**


RE-REVIEW: DIURETICS – POTASSIUM SPARING DIURETICS

BACKGROUND

- Potassium-sparing diuretics can be used alone or in combination with other diuretics in the treatment of edema and hypertension. In addition to the treatment of edema and hypertension, aldosterone antagonists can be used to treat primary aldosteronism.

- The potassium-sparing diuretics (triamterene and amiloride) interfere with sodium reabsorption at the distal tubule, thus decreasing potassium secretion. They exert a weak diuretic and antihypertensive effect when used alone. Spironolactone is an aldosterone antagonist acting primarily through competitive binding of receptors at the aldosterone-dependent-sodium-potassium exchange site in the distal convoluted tubule. Eplerenone (Inspra®) is a selective blocker of aldosterone at the mineralcortocoid receptor. It is a 9-a, 11-a epoxy derivative of spironolactone designed to minimize the adverse effects seen with spironolactone due to androgen and progesterone receptor binding.

- The most common adverse effect reported with potassium-sparing diuretics is hyperkalemia. Patients with diabetes and proteinuria and/or patients with renal dysfunction are at higher risk of hyperkalemia. In addition, triamterene may elevate liver enzymes and cause thrombocytopenia. Amiloride is generally well tolerated, but may cause orthostatic hypotension. The nonselective binding of spironolactone to androgen and progesterone receptors is associated with a loss of libido, menstrual irregularities, gynecomastia, and impotence. Spironolactone also carries a black box warning for tumorgenicity based on chronic toxicity studies in rats. Eplerenone may cause hypertriglyeridemia and increased liver enzymes. It is contraindicated in patients with type 2 diabetes and microalbuminuria, SCr > 2 mg/dL in males or > 1.8 mg/dL in females, and CrCL < 50 mL/min. It also carries drug interactions with CYP450 3A4 inhibitors (ketoconazole, erythromycin, verapamil) resulting in a 1.4 to 1.7-fold increase of Cmax.

- Many clinical studies have compared the effects of potassium sparing diuretics. The RALES trial examined the effects of spironolactone in Class III/IV heart failure and found that aldosterone antagonism had a very important role in heart failure management. The study found that spironolactone reduced risk of death or hospitalization in CHF patients already on standard medications, such as ACE inhibitors and loop diuretics. In available studies involving mild to moderate hypertensive patients, eplerenone appeared as effective as spironolactone for reducing blood pressure; however, the comparative ability of these agents to reduce target-organ damage has not been investigated (Epstein et al, 1998). The largest trial of eplerenone (EPHESUS), involving patients with heart failure following an MI, does not include a spironolactone comparator group. However, eplerenone plus standard care resulted in a significantly lower mortality from any cause or any cardiac cause vs. standard therapy alone (87% ACEIs; 75% beta adrenergic antagonists) in the symptomatic post-AMI patient with left systolic CHF (ejection fraction 33%). The primary advantage of eplerenone over spironolactone is a potentially lower incidence of endocrine-related adverse effects, such as gynecomastia or sexual dysfunction related to greater selectivity for aldosterone receptors versus other steroid receptors.

- Potassium-sparing diuretics should ideally be reserved for patients who have been treated with a diuretic and then develop hypokalemia to help restore normal serum potassium levels. They also help prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop (e.g., cardiac arrhythmias). The ACC/AHA recommends aldosterone antagonism consideration in patients with heart failure.
RECOMMENDATION

The potassium-sparing diuretics are an essential class of medications for the treatment of hypertension, edema, and/or hyperaldosteronism. There are differences among the available potassium-sparing diuretics with regards to indications, receptor selectivity, and side-effect profiles. To meet these needs, it is recommended at least two agents be available on the PDL. Since the effect on hypertension and edema in heart failure patients is similar between spironolactone and eplerenone, it is recommended that eplerenone be reserved for patients who are unable to tolerate spironolactone due to documented endocrine adverse effects, or in patients who develop ADR's on spironolactone.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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<td>INSPIRA® (eplerenone) ST</td>
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* Brand name is no longer available † No CMS Rebate on brand name product

Step Therapy for Inspra® (eplerenone)

Inspra® will be approved for recipients meeting one of the following criteria:

- History of an adequate trial and failure on spironolactone
- Inability to tolerate spironolactone due to documented endocrine adverse effects or other adverse drug reactions.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

References


Anon: Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (The Randomized Aldactone Evaluation Study (RALES)). Am J Cardiol 1996a; 78:902-907


RE-REVIEW: DIURETICS – COMBINATION DIURETICS

BACKGROUND

- Different types of diuretics work in different areas of the nephron. Diuretics can be used alone, but since they are not always effective alone, they are often combined into a single tablet or capsule with another diuretic. Currently available diuretic combination products include: amiloride/hctz, spironolactone/hctz, and triamterene/hctz.

- Potassium-sparing diuretics interfere with sodium reabsorption in the distal convoluted tubule, thereby promoting excretion of sodium and water, and retention of potassium. Amiloride and triamterene have a direct inhibitory effect on the entry of sodium into the cells, while spironolactone competitively inhibits the action of aldosterone. The antidiuretic effect of hydrochlorothiazide is a result of mild sodium and water depletion leading to increased reabsorption of glomerular filtrate in the proximal renal tubule and reduced delivery of tubular fluid available for excretion. Diuretics lower blood pressure initially by reducing plasma and extracellular fluid volume; cardiac output also decreases. Eventually, the extracellular fluid volume and the cardiac output return to normal with an accompanying decrease in peripheral vascular resistance. Spironolactone is a competitive inhibitor of aldosterone; neither amiloride nor triamterene has this effect.

- Diuretics are generally well tolerated, however, the electrolyte imbalances may occur, especially, hyperkalemia, hypokalemia, or hyponatremia (confusion; dryness of mouth; increased thirst; irregular heartbeat; mood or mental changes; muscle cramps or pain; numbness or tingling in hands, feet, or lips; shortness of breath or difficulty breathing; unusual tiredness or weakness; weak pulse; weakness or heaviness of legs).

- All combination diuretics exhibit similar safety and efficacy. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that most patients be treated with a diuretic-based regimen. A combination of a thiazide and a loop diuretic is thought to be beneficial in patients with heart failure unresponsive to either drug alone.

RECOMMENDATION

Since many patients require multiple antihypertensive medications to meet their blood pressure goals, the combination diuretic products offer a valuable treatment option for patients. Current data suggest that combination diuretics can be considered therapeutic alternatives to one another regarding safety and efficacy. In order to ensure patient and prescriber choice, it is recommended that at least two combination diuretic products be available as preferred agents on the PDL.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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RE-REVIEW: ANTI-HYPERTENSIVES: BETA-BLOCKERS

BACKGROUND

- Beta-blockers remain a valuable class of medications for the treatment of a variety of medical conditions, including hypertension, heart failure, angina, myocardial infarction (MI), arrhythmias, and migraine.
- Beta-blockers bind to beta-adrenergic receptors, competitively inhibiting the response to sympathetic stimulation. As a result, beta-blockers decrease heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Beta-blockers are classified by their effect on various adrenergic receptors, either mixed $\alpha/\beta$, mixed $\beta_1/\beta_2$ (non-selective), and selective $\beta_1$ (cardioselective). In addition, some beta-blockers have intrinsic sympathomimetic activity (ISA), resulting in a smaller reduction in heart rate than beta-blockers without ISA.
  - $\alpha$-/\$\beta$-blockers: carvedilol, labetalol
  - Non-selective $\beta$-blockers: nadolol, penbutolol, pindolol, propranolol, sotalol, timolol
  - Cardioselective $\beta$-blockers: acebutolol, atenolol, betaxolol, bisoprolol, metoprolol
  - $\beta$-blockers with ISA: acebutolol, pindolol, penbutolol
- The most common adverse reactions associated with beta-blockers are hypotension, dizziness, and bradycardia. Mixed $\alpha$-/\$\beta$-blockers tend to cause more orthostatic hypotension than other beta-blockers. Beta-blockers can also cause bronchoconstriction and exacerbation of bronchospasm in asthma or other lung diseases, although this is more common in non-selective agents. With regards to use in pregnancy, atenolol is a Category D, while the rest are Bs or Cs.
- There are numerous outcomes studies available that have looked at cardiovascular outcomes associated with the use of beta-blockers. The Cardiac Insufficiency Bisoprolol Study (CIBIS-II) found bisoprolol use significantly reduced all-cause mortality in patients with NYHA Class III and IV heart failure. The US Carvedilol Heart Failure Study, COPERNICUS, CAPRICORN, and COMET trials showed carvedilol significantly reduced all-cause mortality among heart failure, as well. And the MERIT-HF trial found metoprolol succinate ER reduced all-cause mortality in NYHF Class II-IV patients.
- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) recommends thiazide diuretics as first line treatment for hypertension for most patients; however, beta-blockers are listed as a reasonable option for add-on therapy in situations where blood pressure remains uncontrolled on a diuretic. In addition, the JNC-VII guidelines do list several compelling indications, for which beta-blockers should be first-line therapy. These indications include:
  - Ischemic heart disease or angina pectoris
  - Heart failure (along with ACE inhibitors)
  - Diabetes (along with ACE inhibitors or ARBs, esp, for diabetic patients with CAD)
  - Acute coronary syndrome/unstable angina and acute MI
  - Post-MI (along with ACE inhibitors)
RECOMMENDATIONS

The non-selective beta-blockers exert their effect on beta-adrenergic receptors in both the heart and smooth muscle, whereas the cardio-selective beta-blockers have greater affinity for the beta_{1}-receptors in the heart. The alpha- / beta-blockers exert an additional vasodilatory effect due to blockade of alpha_{1}-receptors. It is recommended that the PDL include options among all three of these categories.

NON-SELECTIVE BETA-BLOCKERS
- The various non-selective beta-blockers differ in their indications and the presence/absence of ISA. In order to ensure sufficient therapeutic choice in this category, it is recommended that the PDL include non-selective beta-blockers encompassing all of the following indications: hypertension, angina pectoris, MI, ventricular arrhythmias, hypertrophic subaortic stenosis, migraine prophylaxis, and pheochromocytoma. In addition, it is recommended that at least one non-selective beta-blocker with ISA be preferred on the PDL. Furthermore, in order to ensure patient and prescriber choice within this category, it is recommended that at least 3 non-selective beta-blockers be included on the PDL.

CARDIOSELECTIVE BETA-BLOCKERS
- The various cardioselective beta-blockers display similar efficacy and safety, and thus, can be considered therapeutic alternatives to one another. However, only metoprolol is FDA-approved for CHF. Since the American College of Cardiology and the American Heart Association specifically recommend metoprolol, bisoprolol, or carvedilol for CHF, it is recommended that at least metoprolol and bisoprolol be preferred among the cardioselective beta-blockers on the PDL. In order to ensure patient and prescriber choice within this category, it is recommended that a minimum of 3 cardioselective beta-blockers be available as preferred on the PDL.

ALPHA-/BETA-BLOCKERS
- The available alpha-/beta-blockers exhibit similar efficacy and safety, and thus can be considered therapeutic alternatives to one another. However, carvedilol has additional indications for CHF and post-MI in patients with left ventricular dysfunction. In addition, the American College of Cardiology and the American Heart Association specifically recommend metoprolol, bisoprolol, or carvedilol for CHF. For this reason, it is recommended that carvedilol be preferred on the PDL. However, in order to ensure patient and prescriber choice within this category, it is recommended that at least 2 alpha-/beta-blockers be preferred on the PDL.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION
### RE-REVIEW: ANTI-HYPERTENSIVES – BETA-BLOCKERS

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**Quantity Limits**

- Coreg®: 2 /day
- Coreg CR®: 1/day
- Innopran XL®: 80 mg - 2/day, 120 mg – 1/day
- Levatol®: 2/day
- Toprol XL®: 1/day

**Clinical Criteria for Coreg®, Coreg CR® (carvedilol)**

Coreg® and Coreg CR® will be approved for recipients with any of the following diagnoses:

- Heart failure
- History of acute MI
- Left ventricular dysfunction, with LVEF ≤ 40%.

In order to be approved, the patient must not be on concurrent treatment with another Beta-Blocker or Alpha-Adrenergic Blocker (i.e. Hytrin®, Prazosin®, Cardura® etc.)

### COMMITTEE VOTE:

- APPROVED
- DISAPPROVED
- APPROVED with MODIFICATION
Clinical Criteria for Toprol XL® (metoprolol succinate ER)

Toprol XL should be approved for recipients with a diagnosis of heart failure or cardiomyopathy.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


Facts and Comparisons. 4.0. http://online.factsandcomparisons.com


RE-REVIEW: ANTI-HYPERTENSIVES – BETA-BLOCKER / DIURETIC COMBINATIONS

BACKGROUND

- Beta-blockers and thiazide diuretics are key treatment options in the management of hypertension. Currently available beta-blocker/thiazide combination products include: atenolol/chlorthalidone, bisoprolol/HCTZ, metoprolol/HCTZ, nadolol/bendroflumethiazide, propranolol/HCTZ, and timolol/HCTZ.
- The JNC-VII guidelines for hypertension recommend thiazide diuretics as first line treatment for hypertension for most patients; however, beta-blockers are a reasonable option for add-on therapy in situations where blood pressure remains uncontrolled on a diuretic. In addition, the JNC-VII guidelines do list several compelling indications for which beta-blockers should be first-line therapy, including ischemic heart disease or angina pectoris, heart failure, diabetes, acute coronary syndrome/unstable angina and acute MI, and post-MI.
- See the background information sections for Beta-Blockers and Thiazide Diuretics for further information.
RECOMMENDATION

Diuretics and/or beta-blockers are first line therapy for hypertension for many different patient populations. Since most patients require multiple anti-hypertensive medications to meet their blood pressure goals, the combination beta-blocker/diuretic products offer a valuable treatment option for many patients. Current data suggests that the thiazide diuretics can be considered therapeutic alternatives to one another with regards to safety and efficacy. The available beta-blockers differ in their receptor selectivity (non-selective β-blockers, cardioselective β-blockers, and mixed α-/β-blockers) and the presence or absence of intrinsic sympathomimetic activity (ISA). There are not any mixed α-/β-blocker/diuretic combination products available, and the currently available beta-blocker/diuretic combination products all lack ISA. Based on this information, it is recommended that at least one cardioselective beta-blocker/diuretic combination product and at least one non-selective beta-blocker/diuretic combination be available as preferred agents on the PDL.

COMMITTEE VOTE

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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References


Facts and Comparisons. 4.0. http://online.factsandcomparisons.com

RE-REVIEW: ANTI-HYPERTENSIVES – CALCIUM CHANNEL BLOCKERS

BACKGROUND

- Calcium channel blockers (CCBs) are widely used in the treatment of hypertension and angina pectoris. There are two main categories of calcium channel blockers: dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine) which are potent vasodilators, and non-dihydropyridines (verapamil, diltiazem) which are less potent vasodilators and have more of a depressive effect on cardiac conduction and contractility.

- CCBs inhibit calcium ions from entering the cell, causing a decrease in mechanical contraction of myocardial and smooth muscle. This results in dilation of the systemic arteries, decreased peripheral resistance, decreased blood pressure, and decreased afterload.
  - Nimodipine has a greater effect on cerebral arteries than on arteries elsewhere in the body, perhaps because it is highly lipophilic, allowing it to cross the blood-brain barrier. For this reason, it is indicated only for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage (SAH).

- CCBs are usually well-tolerated. The most common adverse events reported for the non-dihydropyridines are dizziness, edema, fatigue, flushing, headache, and nausea. For the dihydropyridines, AV block has been reported, along with headache, dizziness, and edema. In addition, verapamil is often associated with constipation.

- Many clinical studies have compared the various CCBs. In general, all of the CCBs produce similar blood pressure lowering effects. As expected, the non-dihydropyridines result in decreased heart rate compared to the dihydropyridines. Of note, short-acting nifedipine has been associated with increased coronary mortality in patients with a history of MI, and thus, should not be used for the treatment of hypertension.

- With regards to cardiovascular morbidity/mortality, a few studies have looked at these outcomes with the use of CCBs.
  - The ALLHAT study showed that the calcium channel blocker amlodipine produced similar outcomes of combined fatal CHD and nonfatal MI as chlorthalidone and lisinopril. However, in this study, amlodipine demonstrated a higher risk of heart failure and related hospitalization than chlorthalidone.
  - The ACTION trial compared the use of nifedipine gastrointestinal therapeutic system (GITS) to placebo in 7,665 angina patients, and found nifedipine GITS use resulted in a significantly lower combined endpoint of death and any cardiovascular event/procedure compared to placebo.
  - And last but certainly not least, the NICOLE study examined the effects of nisoldipine on coronary atherosclerosis and cardiovascular outcomes in 826 patients who had undergone coronary angioplasty. This study found that the incidence of revascularizations, as well as overall clinical cardiovascular events, were less frequent with nisoldipine compared to placebo.

- The JNC-VII guidelines for hypertension recommend CCBs as first line therapy (in combination with ACE inhibitors or beta-blockers) for high-risk CHD patients and diabetic patients. For patients who do not have high risk CHD or diabetes, however, these agents would be an appropriate add-on therapy if blood pressure was not controlled on a thiazide diuretic or other recommended first line agent.
Due to safety concerns, CCBs are usually not used in congestive heart failure. However, two long-acting dihydropyridines, felodipine and amlodipine, have been shown to be relatively safe in patients with chronic heart failure. In the V-HEFT III trial, Felodipine did not worsen HF or show a difference in mortality when compared to placebo in patients with primarily New York Heart Association (NYHA) class II HF. In the PRAISE-I trial, amlodipine was found to be safe, showing no difference in mortality compared to placebo in patients with advanced (NYHA class III-IV) HF. Based on this data, the VA guidelines on the pharmacologic management of chronic heart failure, state that patients with systolic HF and concomitant HTN should be maximized on therapy with agents such as diuretics, ACEIs, and beta-adrenergic blockers, or beta-adrenergic blockers and nitrates in patients with concomitant angina, before adding other agents. However, in patients who are not adequately controlled on these agents, treatment with a long-acting dihydropyridine (felodipine or amlodipine) may be considered.

RECOMMENDATION

Calcium channel blockers are a useful class of drugs for the treatment of hypertension and angina. Significant differences exist between the dihydropyridines and non-dihydropyridines, with regards to physiologic effects on vasodilation and heart rate, such that agents from both classes must be available on the PDL.

- Within the dihydropyridine class, the agents have been shown to exhibit similar reductions in blood pressure when used in equipotent doses, except for immediate-release nifedipine which is not recommended for the treatment of hypertension due to increased coronary mortality in patients with a history of MI. Since amlodipine and felodipine have data showing that they can be used safely in CHF patients, it is recommended that they be among the preferred dihydropyridine agents on the PDL. In addition, given the unique indication of nimodipine, it should be available as a preferred agent. Given the safety concerns associated with immediate-release nifedipine IR, it is recommended that it be non-preferred on the PDL.

- Within the non-dihydropyridine class, verapamil and diltiazem produce similar effects on blood pressure and heart rate. However, given some differences in side effects between these two agents, and allow for prescriber/patient choice within this category, it is recommended that both verapamil and diltiazem be preferred on the PDL.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

## RE-REVIEW: ANTI-HYPERTENSIVES - CALCIUM CHANNEL BLOCKERS, DIHYDROPYRIDINE

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<td>Sular® (nisoldipine) QL</td>
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### Quantity Limits

- **Cardene®**: 20 mg 3/day, 30 mg 3/day
- **Cardene SR®**: 2/day
- **DynaCirc®**: 2.5 mg = 2/day, 5 mg = 4/day
- **DynaCirc CR®**: 5 mg = 1/day, 10 mg = 2/day
- **Isradipine**: 2.5 mg = 2/day, 5 mg = 4/day
- **Sular®**: 10, 20, 40 mg = 1/day, 30 mg = 2/day

## NEW: ANTI-HYPERTENSIVES - CALCIUM CHANNEL BLOCKERS, NON-DIHYDROPYRIDINE

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<td>Verelan PM® (verapamil, extended-release)</td>
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### Quantity Limits

- **Covera-HS®**: 180 mg - 2 per day, 240 mg - 1 per day
- **Cardizem LA®**: 1 per day
RE-REVIEW: ANTI-HYPERTENSIVE AGENTS - ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

BACKGROUND

- ACE Inhibitors have become a cornerstone in the treatment of both hypertension and CHF. They have been shown to reduce mortality in CHF, delay progression of diabetic nephropathy, and reduce the risk of cardiovascular outcomes in high-risk patients. The renoprotective effect of ACE inhibitors has been found to exceed the effect resulting from blood pressure reduction alone.

- ACE inhibitors target the renin-angiotensin-aldosterone system, preventing the conversion of angiotensin I to angiotensin II by the enzyme ACE. Reduction in angiotensin II results in decreased vasoconstriction, decreased aldosterone secretion, and increased plasma renin. The end result is a reduction in blood pressure and total peripheral resistance, as well as decreased sodium and water retention.

- The incidence of adverse events appears to be similar across all ACE inhibitors. Cough, dizziness, fatigue, and headache are the most common. In addition, although rare (incidence < 1%), all ACE inhibitors can cause angioedema. With regards to use in pregnancy, ACE inhibitors are contraindicated (Category X), as they have been associated with fetal toxicity and death.

- There are numerous comparative clinical trials available evaluating the antihypertensive effects of ACE inhibitors. These trials suggest very similar efficacy and tolerability among all of the ACE inhibitors when given in equipotent doses. With regards to cardiovascular morbidity and mortality, multiple outcomes studies have demonstrated a beneficial effect associated with the ACE inhibitors. Some of the key outcomes studies are described below.

  - SOLVD – This trial demonstrated that enalapril significantly reduced all-cause mortality and heart failure-related mortality compared with placebo among patients with NYHA Class II-III (ejection fraction ≤35%).
  - CONSENSUS – This trial demonstrated that enalapril significantly reduced all-cause mortality, as well as symptoms, among NYHA Class IV patients.
  - HOPE – The HOPE trial demonstrated that ramipril significantly reduced the incidence of death, MI, and stroke in patients with vascular disease or diabetes with other cardiovascular risk factors. In addition, the HOPE trial showed ramipril reduced the rate of new onset heart failure, as well as new onset diabetes, MI, and revascularization.
EUROPA – This trial showed that perindopril significantly reduced the composite endpoint of cardiovascular mortality, MI, or cardiac arrest in patients with a history of MI, CAD, coronary revascularization, or a positive stress test.

THE SAVE – This trial showed captopril significantly reduced cardiovascular morbidity and mortality vs. placebo among patients with asymptomatic LV dysfunction after MI.

According to the JNC-VII Guidelines for hypertension, thiazide diuretics are recommended as first line treatment for hypertension for most patients; however, ACE inhibitors are listed as a reasonable option for add-on therapy in situations where blood pressure remains uncontrolled on a diuretic. In addition, ACE inhibitors are recommended as first line therapy in patients with the following compelling indications:

- CHF (along with beta-blockers)
- Post-MI (along with beta-blockers)
- High-risk cardiovascular disease
- Diabetes (along with beta-blockers)
- Chronic kidney disease
- Recurrent stroke prevention (in combination with a diuretic)

**RECOMMENDATION**

The ACE inhibitors are an essential class of drugs for the treatment of hypertension and CHF. The available data suggest that all ACE inhibitors provide similar efficacy and tolerability when used in equipotent doses, and thus can be considered therapeutic alternatives to one another. Given that enalapril, ramipril, and captopril currently have the most data linking their use to reduced mortality, it is recommended that these agents be available either as preferred agents on the PDL, or via clinical criteria.

**COMMITTEE VOTE:**

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

**PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:**

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<td>Univase®</td>
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Clinical Criteria for Altace® (ramipril)

Altace® will be authorized only if the Recipient has met all the criteria for the HOPE/MICRO-HOPE Trial. If a history of any of the following are present, then a prior authorization will be given:

- Coronary Artery Disease (CAD)
- History of Stroke
- Peripheral Vascular Disease
- Diabetes
- Chronic renal disease (CrCl defined as < 40ml/min)

COMMITTEE VOTE:

APPROVED           DISAPPROVED           APPROVED with MODIFICATION

References

- Facts and Comparisons. 4.0. http://online.factsandcomparisons.com
RE-REVIEW: ANTI-HYPERTENSIVES – ACE INHIBITOR / DIURETIC
COMBINATIONS

BACKGROUND

- ACE inhibitors and thiazide diuretics are both key classes of drugs for the treatment of hypertension and CHF.
- According to the JNC-VII Guidelines for hypertension, thiazide diuretics are recommended as first line treatment for hypertension for most patients; however, ACE inhibitors are listed as a reasonable option for add-on therapy in situations where blood pressure remains uncontrolled on a diuretic. In addition, ACE inhibitors are recommended as first line therapy in patients with CHF, post-MI, high-risk cardiovascular disease, diabetes, chronic kidney disease, and recurrent stroke prevention (in combination with a diuretic).
- See the background information sections for ACE Inhibitors and Diuretics for further information.

RECOMMENDATION

Diuretics and ACE inhibitors are first line therapy for hypertension for many different patient populations. Since many patients require multiple anti-hypertensive medications to meet their blood pressure goals, the combination ACE inhibitor/diuretic products offer a valuable treatment option for many patients. Current data suggests that the available ACE inhibitors can be considered therapeutic alternatives to one another with regards to safety and efficacy. The available thiazide diuretics can be considered therapeutic alternatives to one another, as well, although all available ACE inhibitor/diuretic combinations contain hydrochlorothiazide. Based on this information, all agents in the agents in this class can be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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RE-REVIEW: ANTI-HYPERTENSIVES – ACE INHIBITORS / CALCIUM CHANNEL BLOCKER COMBINATIONS

BACKGROUND

- ACE inhibitors and calcium channel blockers are key treatment options in the management of hypertension.
- The JNC-VII treatment algorithm for hypertension includes low-dose combination therapy as a therapeutic option. Low-dose combinations may lower the incidence of adverse events compared to high-dose monotherapy, thus increasing patient tolerability and achievement of desired blood pressure outcomes.
- Currently, there are no head-to-head trials comparing the various ACE inhibitor/CCB combination products. Clinical trials involving the individual combination products suggest that all reduce blood pressure about 10-25 mm Hg systolic and about 6-13 mm Hg diastolic. In addition, available studies confirm that combination ACE inhibitor/CCB therapy reduces blood pressure to a greater extent than an ACE inhibitor or CCB alone.
- See the background information sections for ACE Inhibitors and Calcium Channel Blockers for further information.

RECOMMENDATION

The combination ACE inhibitor/CCB combination products provide a reasonable treatment option for patients not managed on monotherapy with an ACE inhibitor or CCB. It is thought that combination products may increase compliance over separate therapy with an ACE inhibitor and CCB. While there are no head-to-head trials comparing the ACE inhibitor/CCB combination products, available data from clinical trials for the individual products suggest that they provide similar blood pressure reduction and thus can be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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Quantity Limits

Lexxel® : 1 per day
Lotrel® : 1 per day
Tarka® : 1 per day

References


Facts and Comparisons. 4.0. http://online.factsandcomparisons.com


RE-REVIEW: ANTI-HYPERTENSIVES – ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

BACKGROUND

- Angiotensin-II receptor blockers are indicated for the treatment of hypertension and CHF. According to package insert information, all ARBs lower blood pressure to a similar degree and are equally well-tolerated. ARBs offer an alternative to ACE inhibitors when side effects, such as cough, become a limiting factor in treatment.
- ARBs selectively block the binding of angiotensin II to the AT1-receptor in the vascular smooth muscle and adrenal glands. Angiotensin II is a potent vasoconstrictor and also causes release of aldosterone and antidiuretic hormone, as well as sympathetic activation. By blocking the binding of angiotensin II to its receptor, ARBs produce a reduction in blood pressure and peripheral resistance.
- The available ARBs produce similar reductions in both systolic blood pressure (SBP) and diastolic blood pressure (DBP), typically ~ 8-12 mm Hg reduction in SBP, and ~4-8 mm Hg reduction in DBP. Similarly to the ACE inhibitors, the ARBs have also been shown to have a renoprotective effect, which appears not to be due to blood pressure reduction alone.
- All of the ARBs are fairly well-tolerated, and they do not produce cough and hyperkalemia as is commonly seen with ACE inhibitors. However, all of the ARBs have been associated with angioedema.
- There are currently numerous comparative, randomized, controlled clinical trials that have evaluated the ARBs.
  - Hypertension: Among the studies comparing the antihypertensive effects of the ARBs, irbesartan, olmesartan, and telmisartan appear to produce greater BP reductions than losartan at their higher doses. Advantages in BP lowering with telmisartan versus losartan or valsartan appear to be present only 18 to 24 hours after dosing, most likely due to the longer elimination half-life of telmisartan. In addition, candesartan has been shown to be more effective at reducing blood pressure than losartan.
  - Diabetic nephropathy: There are currently 3 large placebo-controlled trials evaluating the impact of ARBs on diabetic nephropathy.
    - IDNT – This study looked at the use of irbesartan vs. amlodipine in 1,715 diabetic hypertensive patients over 2.6 years and found that irbesartan produced significantly greater reductions in the development of end-stage renal disease (ESRD) and CHF compared to amlodipine. No significant difference was found in the incidence of cardiovascular death.
IRMA-2 – This study looked at the use of irbesartan 150 mg and 300 mg among patients with type 2 diabetes and microalbuminuria over a 2-year period. Irbesartan was found to be associated with greater reductions in diabetic nephropathy versus placebo, with the greatest reductions occurring in patients receiving the 300 mg dose. A sub-study of IRMA-2 further showed that the renoprotective effects associated with irbesartan 300 mg use were persistent one month after discontinuation of the ARB.

RENAAL – This study looked at the use of losartan in 1,513 type 2 diabetic patients and found that losartan resulted in lower rates of proteinuria, less doubling of serum creatinine (25% risk reduction), and less progression to ESRD (28% risk reduction) versus placebo.

Congestive Heart Failure: Two large placebo-controlled trials have examined the impact of ARBs on CHF.

CHARM trial – This study looked at the use of candesartan in 7,600 patients with CHF and found that candesartan use resulted in lower overall mortality, lower rates of cardiovascular death, fewer CHF-related hospitalizations, and improved NYHA classifications compared to placebo. In addition, discontinuation rates due to adverse effects were similar between the candesartan and placebo groups.

Val-HeFT – This trial looked at the use of valsartan in 5,010 patients with CHF who were on an existing regimen of diuretics, digoxin, beta-blockers, and/or ACE inhibitors. The study found that valsartan was associated with a lower incidence of all-cause mortality, a lower hospitalization rate, an increased ejection fraction, and an improved NYHA Classification compared to placebo.

According to the JNC-VII Guidelines for hypertension, thiazide diuretics are recommended as first line treatment for hypertension for most patients; however, ARBs are listed as a reasonable option for add-on therapy in situations where blood pressure remains uncontrolled on a diuretic. In addition, ARBS are recommended as an alternative to ACE inhibitors in patients with the following compelling indications:

- CHF (along with beta-blockers)
- Diabetes (along with beta-blockers)
- Chronic kidney disease

**RECOMMENDATION**

All ARBs exhibit similar blood pressure lowering and renoprotective effects when used in equipotent doses. Therefore, the agents in this class can be considered therapeutic alternatives to one another. However, the JNC-VII guidelines recommend ACE inhibitors as first line therapy for patients with compelling indications, such as CHF, diabetes, and chronic kidney disease, with ARBs reserved for patients who are intolerant of ACE inhibitors. For this reason, ARBs should be subject to step therapy criteria, requiring trial and failure, intolerance, or contraindication to an ACE inhibitor prior to approval of an ARB.

**COMMITTEE VOTE**

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

RE-REVIEW: ANTI-HYPERTENSIVE AGENTS - ANGIOTENSIN II RECEPTOR BLOCKERS Class ST

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Step Therapy Criteria for ARBs:

- ARBs used for hypertension will be reserved for those patients who have a contraindication to an ACE inhibitor (history of ACE-induced angioedema or hypersensitivity to ACE inhibitors), or who are unable to tolerate an ACE-inhibitor due to cough.
- ARBs will be approved for patients with diabetic nephropathy, heart failure, left ventricular hypertrophy, hyperkalemia, or renal insufficiency.

COMMITTEE VOTE

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


Facts and Comparisons. 4.0. http://online.factsandcomparisons.com


RE-REVIEW: ANTI-HYPERTENSIVES – ARB / DIURETIC COMBINATIONS

BACKGROUND

- ARBs and thiazide diuretics are both important classes of drugs for the treatment of hypertension and CHF.
- According to the JNC-VII Guidelines for hypertension, thiazide diuretics are recommended as first line treatment for hypertension for most patients; however, ARBs are listed as a reasonable option for add-on therapy in situations where blood pressure remains uncontrolled on a diuretic. In addition, ARBs are recommended as an alternative to ACE inhibitors in patients with the following compelling indications: CHF, diabetes, and chronic kidney disease.
- See the background information sections for ARBs and Diuretics for further information.

RECOMMENDATION

Since many patients require multiple anti-hypertensive medications to meet their blood pressure goals, the combination ARB/diuretic products offer a valuable treatment option for many patients. Current data suggests that the available ARBs can be considered therapeutic alternatives to one another with regards to safety and efficacy. The available thiazide diuretics can be considered therapeutic alternatives to one another, as well, although all available ARB/diuretic combinations contain hydrochlorothiazide. Based on this information, all agents in the agents in this class can be considered therapeutic alternatives to one another. Since the JNC-VII guidelines recommend that ARBs be reserved for patients who are intolerant to ACE inhibitors, the ARB/diuretic combination products should be subject to step therapy criteria, requiring trial and failure, intolerance, or contraindication to an ACE inhibitor prior to approval.

COMMITTEE VOTE

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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References

Facts and Comparisons. 4.0. http://online.factsandcomparisons.com
NEW: ANTI-HYPERTENSIVES – CENTRALLY-ACTING ANTI-ADRENERGICS

BACKGROUND

- The agents in this class stimulate alpha-adrenergic receptors in the brain, resulting in a reduction in sympathetic outflow. This produces a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure.
- Agents in this class are rarely used as first-line treatment for hypertension. They are most often used as add-on therapy in individuals who have tried and failed at least one (usually more) anti-hypertensive medications.
- Common adverse events associated with the centrally-acting anti-adrenergics include dry mouth, somnolence, dizziness, nausea/vomiting, constipation, and headache. All of the products also have some serious side effects, although rare (such as AV-block with clonidine, agranulocytosis and thrombocytopenia with clonidine/chlorthalidone, cardiac arrhythmias and increased liver enzymes with guanabenz, and CHF, toxic epidermal necrosis, and bone marrow depression with methyldopa). The clonidine patches are also associated with contact dermatitis (erythema, pruritis, etc.). With regards to use in pregnancy, guanfacine and methyldopa are Pregnancy Category B, while the rest are Category C. Methyldopa is recommended as the agent of choice in pregnancy due to several long-term follow-up studies supporting its safe use.
- Large comparative trials are lacking in this class of medications.
- According to the JNC-7 guidelines for hypertension, the centrally-acting anti-adrenergics are not recommended as first-line or compelling therapy; however, they represent a class of medications that do have utility as add-on therapy in individuals not meeting their goals on first line agents. In pregnancy, however, JNC-7 guidelines do recommend methyldopa as a first-line agent for the treatment of hypertension due to several studies showing stable utero-placental blood flow and an absence of long-term adverse effects in children exposed to methyldopa in utero.

RECOMMENDATION

The centrally-acting anti-adrenergic agents represent a useful group of medications, mainly for use as add-on therapy in individuals not responding adequately to other anti-hypertensive medications. Among the centrally-acting anti-adrenergics, all agents produce similar reductions in blood pressure; however, some key differences exist between these agents. Clonidine has been studied for numerous uses other than hypertension, and can be a useful agent in attention deficit hyperactivity disorder, Tourette’s syndrome, reduction of hot flashes, spasticity, systemic lupus erythematosus, and other diagnoses. Methyldopa is considered the agent of choice in the treatment of hypertension in pregnancy. Guanabenz and guanfacine tend to be associated with more somnolence than the other agents (up to 50% incidence), and guanabenz can cause anxiety (12-17% incidence) and gynecomastia (3% incidence), which are not seen with the other agents. Based on this information, it is recommended that at least clonidine and methyldopa be available as preferred agents on the PDL.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION
CARDIOVASCULAR AGENTS

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

NEW: ANTI-HYPERTENSIVE AGENTS - CENTRALLY-ACTIVE ANTI-ADRENERGICS

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<tr>
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<td>CATAPRES-TTS ® (clonidine transdermal patches)</td>
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<td>GUANFACINE (compares to Tenex®)</td>
<td>GUANABENZ (compares to Wytensin®)</td>
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<td>METHYLDOPA</td>
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<td>METHYLDOPA / HYDROCHLOROTHIAZIDE</td>
<td>TENEX® (guanfacine)</td>
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References

NEW: ANTI-HYPERTENSIVE AGENTS - PERIPHERALLY-ACTING ANTI-ADRENERGICS

BACKGROUND
There are two main categories of products within the peripherally-acting anti-adrenergic class: alpha-adrenergic receptor blockers (doxazosin, prazosin, and terazosin) and post-ganglionic adrenergic blockers (reserpine). While the agents in this class are effective at reducing blood pressure, they are usually reserved for second- or third-line therapy due to the relatively high incidence of side effects, including orthostatic hypotension. Alpha-blockers may be reasonable first line therapy in select patients with concurrent benign prostatic hyperplasia (BPH). Reserpine may also be used in the treatment of certain psychiatric disorders (mainly agitated psychotic states in patients unable to tolerate phenothiazines or those who also require concomitant antihypertensive treatment), as well as in the treatment of thyrotoxicosis (off-label) in patients who are resistant to propranolol.

- Doxazosin, prazosin, and terazosin selectively block the alpha1-adrenergic receptors, resulting in decreased smooth muscle tone and systemic vascular resistance, and therefore, a reduction in blood pressure. Reserpine depletes catecholamine stores in the vesicles of sympathetic neurons, resulting in depression of sympathetic nerve function, and thus, a reduction in blood pressure and heart rate.

- Alpha-adrenergic blockers are commonly associated with orthostatic hypotension – this most often occurs with the first dose, dosage increases, or following an interruption in therapy. Other common adverse events observed with alpha-blockers are edema, palpitations, dizziness, N/V, headache, and somnolence. Common adverse events seen with reserpine include orthostatic hypotension, dizziness, nasal congestion, lethargy, and psychiatric depression. In addition, reserpine has been linked to the following rare but serious side effects: cardiac dysrhythmia, gastrointestinal hemorrhage, and thrombocytopenia.

- There are not many large scale outcomes trials for the alpha-blocker class. A report from the ALLHAT study examined differences in cardiovascular outcomes in adults >55 years old with hypertension and glucose disorders between treatment with chlorthalidone versus doxazosin. This analysis found no differences in all-cause mortality or incidence of MI among the two treatment groups. However, there was a difference in cardiovascular disease (MI, revascularization procedures, angina, stroke, HF, and peripheral arterial disease) favoring use of chlorthalidone. In addition, a meta-analysis examining outcomes among the various anti-
hypertensive medications found that low-dose diuretics reduced risks of CHF (RR 0.51) and cardiovascular events (RR 0.84) significantly more than alpha-blockers.

- There are no large scale outcomes trials available for reserpine.
- According to the JNC-7 guidelines for hypertension, the peripherally-acting anti-adrenergics are not recommended as first-line or compelling therapy; however, they represent a class of medications that do have utility as add-on therapy in individuals not meeting their goals on first-line agents. Alpha-blockers may be useful in individuals with BPH or other urinary outflow obstruction.

RECOMMENDATION
The peripherally-acting anti-adrenergics represent a group of medications mainly used as add-on therapy in individuals not responding adequately to other anti-hypertensive medications. The alpha-blockers represent a reasonable first-line treatment option in individuals with BPH or urinary outflow obstruction who do not have a “compelling indication” for another first line treatment (compelling indications set forth in the JNC-7 guidelines for hypertension). All alpha-blockers produce similar reductions in blood pressure and have similar tolerability; therefore, they can be considered therapeutic alternatives to one another. In order to ensure patient and prescriber choice, it is recommended that at least 2 alpha-blockers be available as preferred agents on the PDL.

Reserpine should be reserved for patients not responding to other anti-hypertensive treatments, as it has the potential risk for serious side effects. However, given reserpine’s additional uses in psychiatric disorders and thyrotoxicosis, it is recommended that it be available as a preferred agent on the PDL.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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<td>TERAZOSIN (compares to Hytrin®)</td>
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<td>RESERPINE</td>
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References
NEW: ANTI-HYPERTENSIVE AGENTS – GANGLIONIC BLOCKERS

BACKGROUND

• There is currently only one ganglionic blocker available in the U.S.: Inversine® (mecamylamine). This agent is indicated for treatment of moderately severe to severe essential hypertension and/or treatment of uncomplicated cases of malignant hypertension.

• Mecamylamine inhibits acetylcholine at the autonomic ganglia, resulting in a reduction in blood pressure in both hypertensive and normotensive individuals.

• Mecamylamine is contraindicated in patients with mild to moderate, or labile hypertension, as well as in individuals with coronary insufficiency or recent MI. Mecamylamine is also contraindicated in patients with uremia or renal insufficiency manifested by an elevated BUN, patient receiving antibiotics and sulfonamides, patients with glaucoma, and patients with organic pyloric stenosis. Concomitant use with other antihypertensives requires a reduction in the dose of mecamylamine and/or the other agents in order to avoid excessive hypotension. Common adverse events associated with the use of mecamylamine include: orthostatic hypotension, dizziness, constipation, nausea, vomiting, xerostomia, sedation, and fatigue. Rare but serious adverse events associated with mecamylamine use include tremor, choreiform movements, mental aberrations, and convulsions (usually associated with large doses).

• There are no large scale outcomes studies available for mecamylamine.

• The JNC-7 guidelines for hypertension do not recommend mecamylamine as either first or second-line therapy for essential hypertension. According to JNC-7, most patients with blood pressures > 160/100 mm Hg (Stage 2 hypertension) should be started on dual therapy, usually involving a thiazide diuretic, ACE inhibitor or ARB, beta-blocker, or calcium channel blocker.

RECOMMENDATION

Inversine (mecamylamide) should be reserved only for patients with severe essential hypertension or malignant hypertension who fail to respond to alternative antihypertensive therapies, such as thiazide diuretics, beta-blockers, ACE inhibitors/ARBs, and calcium channel blockers. Due to the numerous contraindications, drug interactions, and serious adverse events associated with the use of mecamylamide, this agent should be non-preferred on the PDL and subject to clinical criteria ensuring that alternative therapies have been tried first.

COMMITTEE VOTE:

APPROVED    DISAPPROVED    APPROVED with MODIFICATION

NEW: ANTI-HYPERTENSIVE AGENTS – GANGLIONIC BLOCKERS

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Clinical Criteria for Inversine® (mecamylamine):

Inversine® (mecamylamine) may be approved for individuals with moderately severe to severe essential hypertension and/or malignant hypertension who have tried and failed agents in at least two of the following antihypertensive medication categories:

• Thiazide diuretics
• ACE inhibitors or ARBs
• Beta-blockers
• Calcium channel blockers
NEW: ANTI-HYPERTENSIVE AGENTS – AGENTS FOR PHEOCHROMOCYTOMA

BACKGROUND

- Pheochromocytoma is a rare catecholamine-secreting tumor that arises from chromaffin cells, usually in the adrenal medulla. Due to their excessive catecholamine secretion, pheochromocytomas are associated with hypertension, tachycardia, palpitations, headache, sweating, flushing, and anxiety. If left untreated, pheochromocytomas can be fatal. The treatment of choice for pheochromocytomas is surgical resection of the tumor, which usually results in a cure of the hypertension. Careful treatment with alpha- and beta-blockers is required preoperatively to control blood pressure and prevent intraoperative hypertensive crises. In those for whom surgery is contraindicated, alpha-blockers or tyrosine-kinase inhibitors can be used to reduce catecholamine levels long-term.

- Phenoxybenzamine (Dibenzyline®) is the preferred alpha-blocker in preparation for surgery in patients with pheochromocytoma. It is a long-acting alpha-adrenergic receptor blocker that irreversibly binds to alpha receptors reducing peripheral resistance and increasing cardiac output. Phenoxybenzamine is also believed to inhibit the uptake of catecholamines into both adrenergic nerve terminals and extraneural tissues. As a result of these actions, phenoxybenzamine lowers both supine and upright BPs.

- Metyrosine (Demser®) inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. In patients with pheochromocytoma, administration of metyrosine reduces catecholamine biosynthesis by 35-80% as measured by urinary catecholamine levels. Metyrosine is indicated for preoperative preparation of patients for surgery, management of patients when surgery is contraindicated, and chronic treatment of patients with malignant pheochromocytoma. It is usually reserved for patients who are refractory to phenoxybenzamine therapy, or as an adjunct to phenoxybenzamine therapy.

- Phenoxybenzamine has been associated with postural hypotension, tachycardia, nasal congestion, miosis, GI irritation, drowsiness, and fatigue. The incidence of hypotension and tachycardia is greater when administered with another alpha- or beta-blocker. Metyrosine is associated with sedation in almost all patients, although this tends to wane after 2-3 days. Metyrosine is also associated with extrapyramidal symptoms (EPS) in ~10% of patients, diarrhea in ~10% of patients, anxiety and psychic disturbances, galactorrhea, nasal congestion, N/V, and dry mouth.

- There are no large outcomes studies available for the pheochromocytoma agents.

- According to the American Association of Clinical Endocrinologists 2006 Hypertension Guidelines definitive treatment by surgical excision of the tumor cures hypertension in about 75% of pheochromocytoma cases. Preoperative control as well as management of any residual disease (particularly with malignant involvement) is best accomplished with a-adrenergic blocking agents and addition, as needed, of BBs or CCBs (or both).
RECOMMENDATION
While surgery is usually the treatment of choice for pheochromocytoma, phenoxybenzamine and metyrosine have a role in the preoperative preparation of patients for surgery, management of patients for whom surgery is contraindicated, and chronic treatment of patients with malignant pheochromocytoma. Based on current hypertension guidelines from the AACE, phenoxybenzamine is considered an agent of choice for preoperative management of pheochromocytoma or control of residual disease. Metyrosine is not mentioned in the AACE hypertension guidelines. In addition, it is associated with serious side effects (EPS, sedation, anxiety/psychiatric disturbances. Therefore, phenoxybenzamine should be available as a preferred agent on the PDL, while metyrosine should be reserved for patients not responding to phenoxybenzamine or for use as an adjunct to phenoxybenzamine therapy.

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References
NEW: ANTI-HYPERTENSIVE AGENTS – PERIPHERAL VASODILATORS AND COMBINATIONS

BACKGROUND

- The peripheral vasodilator class consists of two agents: hydralazine and minoxidil. Hydralazine is indicated for the treatment of essential hypertension (either alone or as adjunct therapy); whereas minoxidil is indicated only for treatment of severe hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of diuretic plus 2 other antihypertensives. It is only in severe cases of hypertension such as this that the benefits of using minoxidil outweigh the risks.

- Hydralazine and minoxidil produce a direct vasodilating effect on the peripheral blood vessels, resulting in a reduction in blood pressure. In addition, these drugs are associated with an increase in cardiac rate and output secondary to the drop in blood pressure.

- The most common adverse events associated with hydralazine are headache, anorexia, nausea, vomiting, diarrhea, palpitations, tachycardia, hypotension, edema, and nasal congestion. In addition to these, hydralazine use has also been linked to blood dyscrasias, lymphadenopathy, splenomegaly, SLE-like symptoms, peripheral neuritis, angina attacks, and MI. For minoxidil, the most common adverse events include elongation/thickening/enhanced pigmentation of hair (80% incidence), changes in the direction and magnitude of T waves (60% incidence), tachycardia, angina attacks, nausea/vomiting, edema, and pericardial effusion, occasionally with tamponade (3% incidence). Other rare side effects associated with minoxidil use include thrombocytopenia, leukopenia, rashes including bullous eruptions and Stevens-Johnson syndrome, and breast tenderness.

- There are limited large-scale outcomes trials for the peripheral vasodilators. The Vasodilator Heart Failure Trial (V-HeFT) II showed that patients with mild to moderate HF who received enalapril for an average of 2.5 years experienced a significant decrease of 28% (P=0.016) in the risk of death at 2 years compared to patients on the combination hydralazine and isosorbide dinitrate (HYD/ISDN) (ARR 5.41%; NNT=18.5).

- The ACC/AHA guidelines for CHF recommend the addition of a combination of hydralazine and a nitrate for patients with reduced LVEF who are already taking an ACE inhibitor and beta-blocker for symptomatic HF and who have persistent symptoms.

RECOMMENDATION

The peripheral vasodilators should be reserved for patients not achieving optimal blood pressure control on first- and second-line antihypertensive agents (ACE inhibitors, beta-blockers, etc.). Based on the ACC/AHA guidelines for CHF, hydralazine (in combination with a nitrate) is recommended as add-on therapy in patients with reduced LVEF who are already taking an ACE inhibitor and beta-blocker and continue to have persistent HF symptoms. For this reason, at least one hydralazine formulation should be preferred on the PDL. Minoxidil, however, is associated with more severe side effects than hydralazine and must be administered under close physician supervision, usually with concomitant beta-blocker and diuretic use to prevent tachycardia, increased myocardial workload, and fluid accumulation. Minoxidil is usually only recommended in situations of severe symptomatic hypertension that is not manageable with maximum therapeutic doses of a diuretic plus 2 other antihypertensives. For this reason, minoxidil is recommended to be non-preferred on the PDL and subject to clinical criteria.

COMMITTEE VOTE:

APPROVED
DISAPPROVED
APPROVED with MODIFICATION
### NEW: ANTI-HYPERTENSIVE AGENTS – PERIPHERAL VASODILATORS AND COMBINATIONS

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<td>Minoxidil tablets *</td>
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* Loniten® is no longer manufactured.

#### Clinical Criteria for Minoxidil Tablets:

Minoxidil tablets will be approved only for patients meeting all of the following:

- Diagnosis of severe hypertension (symptomatic or associated with target organ damage)
- Have tried and failed to achieve adequate blood pressure control on a diuretic PLUS at least 2 of the following (unless contraindication or intolerance to):
  - ACE inhibitor / ARB
  - Beta-blocker
  - Calcium channel blocker
- Does NOT have a diagnosis of pheochromocytoma (as minoxidil may stimulate secretions of catecholamines from the tumor)

#### COMMITTEE VOTE:

| APPROVED | DISAPPROVED | APPROVED with MODIFICATION |

#### References


NEW: ANTI-ANGINAL AGENTS - NITRATES

BACKGROUND

- All agents in this class are indicated for the treatment and/or prevention of angina pectoris.
  - Sublingual isosorbide dinitrate, sublingual nitroglycerin, nitroglycerin lingual spray, and amyl nitrite can be used to relieve acute symptoms of angina pectoris. The sublingual and spray formulations of nitroglycerin have an onset of action of 1-3 minutes, while sublingual isosorbide dinitrate takes up to 10 minutes for effect.
  - Sustained-release nitroglycerin, transdermal nitroglycerin, topical nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate can be used to prevent angina symptoms in patients with coronary artery disease. These products all require up to 45-60 minutes for onset of action. The extended-release formulations of isosorbide dinitrate and isosorbide mononitrate have longer durations of action and thus reduce the number of doses required per day compared to the immediate-release formulations.
- The nitrates form free radical nitric oxide (NO) in the body, which produces smooth muscle vasodilation in the veins and arteries, thereby decreasing both preload and afterload.
- The most common adverse events associated with the nitrates are hypotension, headache, tachycardia, and dizziness. The topical formulations (transdermal patches and ointment) can also cause contact dermatitis/rash.
- The ACC/AHA Guidelines for Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease recommend that sublingual nitroglycerin or nitroglycerin spray be used for the immediate relief of symptoms of angina. To help prevent MI or death in patients with chronic stable angina, combination therapy with a beta-blocker, aspirin (or clopidogrel), a statin, and an ACE inhibitor (in pts with CAD, diabetes, and/or LV systolic dysfuncton) should be used; however long-acting nitrates (or calcium channel blockers) are recommended when beta-blockers are contraindicated or unsuccessful.
- The ACC/AHA Guidelines for CHF recommend the addition of a combination of hydralazine and a nitrate for patients with reduced LVEF who are already taking an ACE inhibitor and beta-blocker for symptomatic HF and who have persistent symptoms.

RECOMMENDATION

Nitrates are an important class of medications for the treatment and prevention of angina pectoris, as well as for the management of CHF patients.

- For the treatment of acute angina: The nitroglycerin sublingual tablets and lingual spray formulations exhibit similar onset of action and similar efficacy at relieving acute angina symptoms; therefore, they can be considered therapeutic alternatives to one another. The sublingual isosorbide dinitrate formulation has a longer onset of action than the sublingual or lingual nitroglycerin formulations, and amyl nitrate has a shorter duration of action than nitroglycerin and is flammable; therefore, these products can be considered inferior for the treatment of acute angina.
- For the prevention of angina symptoms: Sustained-release nitroglycerin tablets, transdermal nitroglycerin, topical nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate appear to exhibit similar efficacy and safety; therefore, they can be considered therapeutic alternatives to one another. However, in order to ensure adequate patient and prescriber choice, it is recommended that at least one isosorbide dinitrate product, at least one isosorbide mononitrate product, and at least one non-oral nitroglycerin formulation (either transdermal or topical) be available.
COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

NEW: ANTI-ANGINAL AGENTS – NITRATES

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ISOSORBIDE MONONITRATE (Compares to ISMO®, Monoket®, and Imdur®)  
NITROGLYCERIN sublingual tablets, extended-release capsules, ointment, and transdermal patches | Amyl nitrite  
Dilatrate-SR® (isosorbide dinitrate, sustained-release capsules)  
Imdur® (isosorbide mononitrate, extended-release tablets)  
ISMO® (isosorbide mononitrate, tablets)  
Isordil® (isosorbide dinitrate, tablets)  
Isochron® (isosorbide dinitrate, extended-release tablets)  
Minitran® (nitroglycerin, transdermal patches)  
Monoket® (isosorbide mononitrate, tablets)  
Nitrek® (nitroglycerin, transdermal patches)  
Nitro-Dur® (nitroglycerin, transdermal patches)  
Nitrolingual® (nitroglycerin, aerosol lingual spray)  
NitroMist® (nitroglycerin, aerosol lingual spray)  
NitroQuick® (nitroglycerin, sublingual tablets)  
Nitrostat® (nitroglycerin, sublingual tablets)  
Nitro-Time® (nitroglycerin, extended-release capsules) |

References


BACKGROUND

- There is currently one combination vasodilator / nitrate combination available - BiDil® (hydralazine / isosorbide dinitrate). BiDil® is indicated for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status.
- Please refer to the background information sections above for Peripheral Vasodilators and Nitrates for information in the mechanism of action, therapeutic effects, and adverse events of hydralazine and isosorbide dinitrate.
- The approval of BiDil® was based in part on the results of the African-American Heart Failure Trial (A-HeFT). The study involved 1,050 self-identified black patients with severe heart failure who had already been treated with a loop diuretic, an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, and a beta blocker. Patients on BiDil® experienced a 43% reduction in death and a 39% decrease in hospitalization for heart failure compared to placebo, and a decrease of their symptoms of heart failure.
- The current ACC/AHA guidelines for CHF recommend the addition of a combination of hydralazine and a nitrate for patients with reduced LVEF who are already taking an ACE inhibitor and beta-blocker for symptomatic HF and who have persistent symptoms.
  - No reference to BiDil® is made in the guidelines; however, it is stated that “the addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACE inhibitors and beta-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF.”
- Currently, the benefit of BiDil® in non-African-American populations has not been studied.

RECOMMENDATION

Based on the current ACC/AHA guidelines for CHF, the combination of hydralazine and isosorbide dinitrate represents a reasonable choice for individuals with reduced LVEF who are already taking an ACE inhibitor and beta-blocker for symptomatic HF and who have persistent symptoms. However, there is no data to suggest that the benefit of hydralazine and isosorbide dinitrate is greater with BiDil® than with the two agents individually. Since the individual agents are available on the PDL and provide easier titration/dose adjustment than the combination product, it is recommended that BiDil® be non-preferred on the PDL.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

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Clinical Criteria for BiDil (hydralazine / isosorbide dinitrate):

BiDil® will be approved for patients who meet all of the following criteria:

1. Diagnosis of heart failure
2. Currently on standard therapy for heart failure (loop diuretic, ACE inhibitor/ARB, and beta-blocker)
3. Has documented non-compliance with a four times daily regimen
4. Cannot take the two products individually
NEW: ANTI-ANGINAL AGENTS – MISCELLANEOUS

BACKGROUND

- Ranexa® (ranolazine) is indicated for the treatment of chronic angina; however, because ranolazine prolongs the QT interval, its use should be reserved for individuals who have not achieved an adequate response on other anti-anginal drugs. Ranolazine should be used in conjunction with amlodipine, beta-blockers, or nitrates.
- The mechanism of action of ranolazine is unknown, but it has been found to produce anti-anginal and anti-ischemic effects that are not dependent on heart rate or blood pressure.
- Common adverse events associated with ranolazine include dizziness, headache, constipation, and nausea. Ranolazine is contraindicated in patients with pre-existing QT prolongation, hepatic function impairment, receiving QT-prolonging drugs, or on potent or moderately potent CYP3A inhibitors, including diltiazem.
- A few large trials have investigated the use of ranolazine in chronic angina.
  - The Efficacy of Ranolazine In Chronic Angina (ERICA) trial enrolled 565 adults with stable coronary disease and \( \geq 3 \) angina attacks per week and randomized them to receive either ranolazine (n=281) or placebo (n=284). Compared with placebo, ranolazine significantly reduced angina frequency and nitroglycerin consumption.
  - The Combination Assessment of Ranolazine In Stable Angina (CARISA) trial assessed the impact of ranolazine vs. placebo on exercise toleration and angina frequency in 823 adults with severe chronic angina who were already taking standard doses of atenolol, amlodipine, or diltiazem. This study found that twice-daily doses of ranolazine increased exercise capacity and reduced angina frequency compared to placebo.
- The ACC/AHA Guidelines for Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease recommend combination therapy with a beta-blocker, aspirin (or clopidogrel), a statin, and an ACE inhibitor (in pts with CAD, diabetes, and/or LV systolic dysfunction); long-acting nitrates or calcium channel blockers are recommended when beta-blockers are contraindicated or unsuccessful. Ranexa® is not included in the ACC/AHA guidelines for angina.

RECOMMENDATION

Given the limited clinical trials available and the risk of QT interval prolongation, it is recommended that Ranexa® be reserved for patients with chronic angina who have not achieved an adequate response on beta-blockers, long-acting nitrates, and/or calcium channel blockers. To ensure appropriate use, it is recommended that Ranexa® be non-preferred on the PDL and subject to clinical criteria.
NEW: ANTI-ANGINAL AGENTS – MISCELLANEOUS

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Clinical Criteria for Ranexa® (ranolazine):
Ranexa® (ranolazine) should be approved only for individuals with chronic angina who have failed to achieve an adequate response on at least two of the following agents:
- Beta-blocker
- Long-acting nitrate
- Calcium channel blocker (dihydropyridine only)

Ranexa® (ranolazine) should NOT be approved for individuals with any of the following contraindications:
- Pre-existing QT prolongation
- Hepatic function impairment (Child-Pugh classes A, B, or C)
- Receiving QT-prolonging drugs (including Class Ia and Class III antiarrhythmics, ziprasidone)
- On potent or moderately potent CYP3A inhibitors (including diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, ketoconazole and other azole antifungals)

References
Ranexa™ (ranolazine extended-release tablets) prescribing information, CV Therapeutics, Inc. 2006.
NEW: ANTI-HYPERTENSIVES – PULMONARY ARTERIAL HYPERTENSION AGENTS

BACKGROUND

- There are two oral agents approved for the treatment of pulmonary arterial hypertension (PAH): Revatio® (sildenafil citrate) and Tracleer® (bosentan).
- Revatio® inhibits the phosphodiesterase type-5 (PDE5) enzyme in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. By inhibiting PDE5, sildenafil increases cGMP within the pulmonary vascular smooth muscle cells, resulting in relaxation (vasodilation).
- Tracleer® is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Endothelin-1 (ET-1) is a neurohormone which binds to ET_A and ET_B receptors in the endothelium and vascular smooth muscle and causes vasoconstriction. ET-1 concentrations are elevated in the plasma and lung tissue of patients with PAH, suggesting a pathogenic role for ET-1 in this disease.
- Common adverse events associated with Revatio® include headache, flushing, rash, diarrhea, indigestion, dizziness, abnormal vision, and nasal congestion. In rare circumstances, use of Revatio® can result in myocardial infarction, non-arteritic ischemic optic neuropathy, and priapism. Tracleer® is commonly associated with headache, edema, hypotension, palpitations, flushing, indigestion, N/V, decreased hemoglobin, and elevated liver enzymes. In rare circumstances, Tracleer® can cause hepatic cirrhosis and angioedema.
- A few trials have evaluated the impact of these agents on patients with PAH:
  - The Sildenafil Use in Pulmonary Arterial Hypertension (SUPER-1) study randomized 278 patients to placebo (n = 70) or sildenafil 3 times daily: 20 mg (n = 69), 40 mg (n = 68), or 80 mg (n = 71). The 80 mg tid dose was found to significantly improve 6-minute walk test results compared to placebo. In addition, 35% of patients in the pooled sildenafil groups improved by 1 functional class compared with 7% of patients in the placebo group.
  - In the Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Hypertension (BREATHE-1), 213 patients with NYHA class III PAH were randomly assigned to receive placebo or 62.5 mg bosentan twice daily for 4 weeks followed by either of 2 doses of bosentan (125 or 250 mg twice daily) for a minimum of 12 weeks. At Week 16, patients treated with bosentan showed significant improvements in the 6-minute walking distance (difference of 44 m compared to placebo). The Borg dyspnea index and WHO functional class were also improved in the bosentan group.
- According to the 2004 Guidelines on Diagnosis and Treatment of Pulmonary Arterial Hypertension from the European Society of Cardiology, both sildenafil and bosentan are recommended for treatment of idiopathic PAH (supported by Level A evidence). The 2005 ACCP Evidence-Based Clinical Practice Guidelines on Pulmonary Arterial Hypertension recommend bosentan for PAH patients who have failed or are not candidates for CCB therapy (based on Level A evidence), and suggests using sildenafil in patients who have failed or are not candidates for other available therapy (Category C evidence).
RECOMMENDATION
Both Revatio® and Tracleer® represent reasonable options for the treatment of PAH. While there seems to be somewhat stronger evidence in support of Tracleer® at this time, it is recommended that both agents be available for patients with a diagnosis of PAH since they offer different side effect profiles and mechanisms of action. Given the numerous off-label uses of Revatio® and its potential to cause serious adverse events (myocardial infarction, non-arteritic ischemic optic neuropathy, etc.), it is recommended that Revatio® be subject to clinical criteria in order to ensure it is being used for PAH.

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

NEW: ANTI-HYPERTENSIVES – PULMONARY ARTERIAL HYPERTENSION AGENTS

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<td>REVATIO® (sildenafil citrate) C5, QL</td>
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Clinical Criteria for Revatio® (sildenafil)
Revatio® (sildenafil) will be approved only for the treatment of Pulmonary Arterial Hypertension (PAH) / Primary Pulmonary Hypertension (PPH).

Quantity Limits
Revatio®: 3/day

COMMITTEE VOTE:

APPROVED       DISAPPROVED       APPROVED with MODIFICATION

References
NEW: VASOPRESSORS

BACKGROUND
- There is currently one oral vasopressor agent available—ProAmatine® (midodrine). This product is indicated for the treatment of orthostatic hypotension in patients whose lives are considerably impaired despite standard clinical care, fluid expansion, and lifestyle alterations.
- Midodrine forms an active metabolite, desglymidodrine, that serves as an alpha-1 agonist, producing an increase in vascular tone and blood pressure.
- Midodrine can cause marked elevations in both supine and sitting blood pressure. Midodrine should not be used in patients with pretreatment systolic BP > 180 mm Hg, as these patients are thought to be at an increased risk for supine hypertension.
- The most common side effects associated with midodrine are hypertension, piloerection, pruritus, shivering, paresthesia, and dysuria. In addition, midodrine has a 13.4% incidence of increased supine systolic arterial pressure of 200 mmHg or above.
- There are currently no large scale outcomes trials or national guidelines pertaining to midodrine use.

RECOMMENDATION
Midodrine can be a useful agent in the treatment of orthostatic hypotension in individuals who continue to be symptomatic (experiencing dizziness, syncope, etc.) despite standard clinical care, fluid expansion, and lifestyle alterations. While there is a significant risk of supine systolic hypertension, it is difficult to identify the recipients who are most at risk for this adverse event. Risk assessment is usually based on pre-treatment blood pressure readings, and this information is not always available in situations where patients switch physicians. Therefore, it is recommended that midodrine be available as a preferred agent on the PDL.

COMMITTEE VOTE:
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NEW: VASOPRESSORS

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References
NEW: CARDIAC GLYCOSIDES

BACKGROUND

- Cardiac glycosides are used for the treatment of mild to moderate heart failure and to control ventricular response rate in patients with chronic atrial fibrillation.
- Digoxin inhibits sodium-potassium ATPase, leading to an increase in the intracellular concentration of sodium and thus (by stimulation of sodium-calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system, mediated by effects on the autonomic nervous system. This results in an increase in the force and velocity of myocardial systolic contraction, a decrease in the degree of activation of the sympathetic nervous system and renin-angiotensin system, and slowing of the heart rate and decreased conduction velocity through the AV node.
- In general, the adverse reactions of cardiac glycosides are dose dependent and occur at doses higher than those needed to achieve a therapeutic effect. High doses of digoxin may produce a variety of rhythm disturbances, such as first, second, or third-degree heart block, AV dissociation, ventricular tachycardia, and ventricular fibrillation. Digoxin may also produce blurred or yellow vision and N/V/D.
- There are several studies have examined the impact of digoxin:
  - Two 12-week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and 88 (PROVED trial) patients with New York Heart Association (NYHA) class II or III heart failure previously treated with digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with digoxin tablets. Both trials demonstrated better preservation of exercise capacity in patients randomized to digoxin. Continued treatment with digoxin reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy. The larger study also showed treatment-related benefits in NYHA class and patients' global assessment. In the smaller trial, these trended in favor of a treatment benefit.
  - The Digitalis Investigation Group (DIG) main trial was a multicenter, randomized, double-blind, placebo-controlled mortality study of 6,801 patients with heart failure and left ventricular ejection fraction less than or equal to 0.45. At randomization, 67% were NYHA class I or II, 71% had heart failure of ischemic etiology, 44% had been receiving digoxin, and most were receiving concomitant ACE inhibitor (94%) and diuretic (82%). Patients were randomized to placebo or digoxin tablets, the dose of which was adjusted for the patient's age, sex, lean body weight, and serum creatinine, and followed for up to 58 months (median 37 months). The median daily dose prescribed was 0.25 mg. Overall all-cause mortality was 35%, with no difference between groups (95% confidence limits for relative risk of 0.91 to 1.07). Digoxin was associated with a 25% reduction in the number of hospitalizations for heart failure, 28% reduction in the risk of a patient having at least 1 hospitalization for heart failure, and 6.5% reduction in total hospitalizations (for any cause).
The benefits of digoxin are seen at all levels of left ventricular ejection fraction, but the greatest benefit of digoxin is seen among patients at high risk, those with ejection fractions of 25% or less, those with cardiomegaly, and those in New York Heart Association functional class III or IV. Other clinical trials suggest that characteristics such as a low cardiac index, a high pulmonary capillary wedge pressure, or the presence of a third heart sound (S3 gallop) are also strong predictors of digoxin benefit in patients with CHF in normal sinus rhythm. The beneficial hemodynamic effects of digoxin are additive to those of angiotensin-converting-enzyme inhibitors.

RECOMMENDATION

Digoxin represents a useful drug in the treatment of heart failure. Based on available studies, digoxin use has been associated with improved exercise capacity, reduced progression of heart failure, and reduced hospitalizations for CHF patients. For this reason, it is recommended that digoxin be preferred on the PDL.

COMMITTEE VOTE:

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NEW: CARDIAC GLYCOSIDES

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References


NEW: ANTI-ARRHYTHMICS, ORAL

BACKGROUND

- There are several different classes of oral anti-arrhythmic drugs:
  - Class I anti-arrhythmics inhibit the transmembrane influx of sodium
    - Class Ia (quinidine, procainamide, and disopyramide) is effective at treating both supraventricular and ventricular arrhythmias.
    - Class Ib (mexiletine) is more effective at treating ventricular arrhythmias than supraventricular arrhythmias.
    - Class Ic (flecainide, propafenone, moricizine) is mainly used for treating supraventricular arrhythmias
  - Class II anti-arrhythmics are beta-adrenergic blockers, used mainly used to treat SA and AV nodal arrhythmias (these products were reviewed previously in the packet).
  - Class III anti-arrhythmics prolong refractoriness in atrial and ventricular fibers by blocking potassium channels. Class III anti-arrhythmics are mainly used for supraventricular tachyarrhythmias. The oral Class III drug include amiodarone and dofetilide.
  - Class IV anti-arrhythmics are calcium-channel blockers, used mainly used to treat SA and AV nodal arrhythmias (these products were reviewed previously in the packet).
- The various classes of anti-arrhythmics differ in their actions on the heart and thus, the types of arrhythmias they are used to treat.
- All anti-arrhythmics are associated with adverse events. Some of the most common adverse events encountered with all of the anti-arrhythmics are hypotension, dizziness, syncope, nausea, and vomiting. Serious side effects associated with these products include cardiac dysrhythmia, chest pain, torsade de pointes, hepatotoxicity, hematologic disorders, and SLE.
- Current guidelines from the American College of Physicians and the American Academy of Family Physicians (2003) recommend the following drugs for patients whose lives are compromised by atrial fibrillation (and could benefit from rhythm maintenance): amiodarone, disopyramide, propafenone, and sotalol. The ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation support the use of pharmacologic agents for cardioversion to sinus rhythm in patients with persistent atrial fibrillation. In addition, they recommend the use of sotalol or amiodarone for patients at increased risk of developing post-operative atrial fibrillation.
- No guidelines are available for the treatment of ventricular arrhythmias.

RECOMMENDATION

Given the differences in mechanism of action and effect between the different classes of anti-arrhythmic, these agents cannot be deemed therapeutic alternatives. Even within a class of anti-arrhythmics, there are distinct differences in effect and adverse event profiles. For this reason, it is recommended that the various unique chemical entities included in the Anti-Arrhythmic class all be preferred on the PDL. It will be left up to the prescriber’s discretion which agent best suits his/her patient.

COMMITTEE VOTE:

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**NEW: ANTI-ARRHYTHMICS, ORAL**

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**References**


**NEW: HEMOSTATICS, ORAL**

**BACKGROUND**

- There is currently one oral hemostatic agent available—Amicar® (aminocaproic acid). This product is indicated for the treatment of hemorrhage (when fibrinolysis contributes to bleeding), as well as hematuria (both surgical and non-surgical).
- The fibrinolysis-inhibitory effects of aminocaproic acid appear to be exerted principally via inhibition of plasminogen activators and to a lesser degree through antiplasmin activity.
- When there is uncertainty as to whether the cause of bleeding is primary fibrinolysis or disseminated intravascular coagulation (DIC), this distinction must be made before administering aminocaproic acid because aminocaproic acid administered to a patient with DIC may produce potentially fatal thrombus formation.
- The most common side effects associated with aminocaproic acid are nausea, vomiting, asthenia, dizziness, and headache. Its use has also been associated with bradyarrhythmia, hypotension, rash, thrombotic disorder, drug-induced myopathy, rhabdomyolysis, and renal failure.
- According to the 2006 Institute for Clinical Systems Improvement (ICSI) Anticoagulation Therapy Supplement, aminocaproic acid may be a useful treatment option for patients on anticoagulant therapy who are undergoing low bleeding-risk procedures, such as dental procedures, skin biopsies, and cataract surgery. Aminocaproic acid, along with pressure, topical thrombin, and gelatin sponges, was presented as a reasonable option to help control local bleeding, without having to alter the patient’s dose of warfarin.

**RECOMMENDATION**

As the only oral hemostatic agent, aminocaproic acid represents a useful drug for the treatment of individuals experiencing hemorrhage due to fibrinolysis, as well as hematuria (both surgical and non-surgical). For this reason, it is recommended that aminocaproic acid be available as a preferred agent on the PDL.
COMMITTEE VOTE:

**APPROVED**  **DISAPPROVED**  **APPROVED with MODIFICATION**

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**References**


**RE-REVIEW: PLATELET AGGREGATION INHIBITORS**

**BACKGROUND**

- Inhibitory effects on the aggregation of platelets have lead to a significant decrease in the rate of vascular events for both primary and secondary cardiovascular prevention trials. They are useful in the treatment and prevention of cardiovascular and cerebrovascular thrombotic events.
- The platelet aggregation inhibitors discussed in this review are distinctively different in their mechanisms of action.
  - Aspirin is the oldest antiplatelet agent and works via irreversible inhibition of cyclooxygenase.
  - Dipyridamole (Persantine®) inhibits the uptake of adenosine into platelets, resulting in increased levels of platelet cyclic-3',5'-adenosine monophosphate (cAMP), and ultimately inhibition of platelet aggregation in response to stimuli such as platelet activating factor (PAF), collagen, and adenosine diphosphate (ADP).
  - Aggrenox®, the combination of aspirin and extended-release dipyridamole, utilizes the two different mechanisms of action of its components to inhibit platelet aggregation.
  - Clopidogrel and ticlopidine inhibit the binding of adenosine diphosphate (ADP) to their platelet receptors and subsequently inhibit platelet aggregation. The indications for clopidogrel and ticlopidine include secondary prevention of stroke, myocardial infarction, acute coronary syndrome or other vascular death.
- Hematologic adverse reactions are the major concern for this group of drugs. Serious side effects associated with this class include thrombocytopenia and agranulocytosis, both of which occur more frequently with ticlopidine. A significant drug-drug interaction between clopidogrel and two widely used statins has recently been published; atorvastatin and simvastatin substantially decrease the antiplatelet activity of clopidogrel.
- There are several studies that have examined the antiplatelet agents:
  - The CAPRIE study is a large study that concluded that clopidogrel is more effective than aspirin in the prevention of secondary stroke, MI or other cardiovascular death in high-risk patients.
  - The CURE study found that the combination of aspirin and clopidogrel produced a favorable effect in the prevention of vascular death compared to aspirin alone.
o ESPS compared aspirin, dipyridamole ER, the combination of both, and placebo. The results showed that the combination of aspirin and dipyridamole ER significantly reduced the rate of stroke or death in high risk patients with history of stroke or transient ischemic attack.

o The CLASSICS trial compared clopidogrel to ticlopidine and found that ticlopidine had a higher incidence of neutropenia, thrombocytopenia and major bleeding, although efficacy was equivalent.

- According to the most recent guidelines from both the American Heart Association and the American Academy of Neurology, the use of aspirin or clopidogrel is recommended as first line therapy for the majority of patients with vascular disease. The American College of Cardiology has recommended acute and long-term antiplatelet treatment with aspirin, clopidogrel or the combination of the two agents for patients with acute coronary syndromes or myocardial infarction. In stroke prevention, the combination of aspirin and dipyridamole (Aggrenox®) as well as ADP antagonists have demonstrated favorable outcomes in clinical trials. However, dipyridamole monotherapy has not been proven efficacious in stroke prevention.

**RECOMMENDATION**

Platelet aggregation inhibitors are used to prevent and treat a variety of thrombotic events including MI, stroke and TIA, and peripheral artery disease. Clinical data suggests similar efficacy in aspirin, dipyridamole, ticlopidine, clopidogrel, and aspirin combined with dipyridamole ER in preventing recurrent vascular events among patients with vascular disease. According to the most recent guidelines from both the American Heart Association and the American Academy of Neurology, the use of aspirin or clopidogrel is recommended as first line therapy for the majority of patients with vascular disease. For this reason, it is recommended that clopidogrel be available as a preferred agent on the PDL (as aspirin is available OTC). In addition, given the studies showing greater efficacy for the combination aspirin/dipiridamole product, it is recommended that this combination be preferred on the PDL, as well.

**COMMITTEE VOTE:**

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**References**

NEW: INTERMITTENT CLAUDICATION

BACKGROUND

- Intermittent claudication due to lower extremity peripheral arterial disease (PAD) is characterized by temporary pain brought on by muscle exertion usually in the calf muscles. Agents in this class are used to reduce symptoms of intermittent claudication.
- The agents in this class have different mechanisms of action.
  - Cilostazol and its active metabolites inhibit phosphodiesterase activity and suppress degradation of cyclic adenosine monophosphate (cAMP) resulting in an increase in cAMP in platelets and blood vessels. It reversibly inhibits platelet aggregation induced by various stimuli, including thrombin, adenosine diphosphate (ADP), collagen, arachidonic acid, epinephrine, and shear stress. Cilostazol produces non-homogenous vasodilation, with greater dilation in femoral beds than in vertebral, carotic, or superior mesenteric arteries, but without effect in renal arteries. Modest effects on circulating plasma lipids have been examined in patients taking cilostazol.
  - Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity, thereby increasing blood flow to the affected microcirculation and enhance tissue oxygenation.
- These agents are generally well tolerated. Cilostazol is associated with headache, diarrhea, and palpitations. Common adverse drug reactions with pentoxifylline include dyspepsia, dizziness, GI disturbances, and nausea. Cilostazol is contraindicated in patients with congestive heart failure of any severity due to the inhibition of phosphodiesterase. It is also contraindicated in patients with active bleeding such as bleeding peptic ulcers, intracranial disorders, and patients with hemostatic disorders. Pentoxifylline is contraindicated in patients with recent cerebral or retinal hemorrhage.
There are several studies that have examined the intermittent claudication agents:

- The ability of cilostazol to improve walking distance in patients with stable intermittent claudication was studied in 8 large, randomized, placebo-controlled, double-blind trials of 12- to 24-week duration using dosages of 50 mg twice daily (n = 303), 100 mg twice daily (n = 998), and placebo (n = 973). Efficacy was determined primarily by the change in maximal walking distance from baseline (compared with change on placebo) on one of several standardized exercise treadmill tests. Compared with patients treated with placebo, patients treated with cilostazol 50 or 100 mg twice daily experienced statistically significant improvements in walking distances both for the distance before the onset of claudication pain and the distance before exercise-limiting symptoms supervened (maximal walking distance). The effect of cilostazol on walking distance was seen as early as the first on-therapy observation point of 2 or 4 weeks.

- Good quality double-blind trails evaluating the effectiveness of pentoxifylline for intermittent claudication are limited. In a meta-analysis of six randomized trials, authors concluded that pentoxifylline had small effects on pain-free and total walking distance.

Walking distance in intermittent claudication can be improved by both exercise rehabilitation and by pharmacological treatments. Cilostazol has been shown to increase walking distance in patients treated with intermittent claudication. In the 2005 AHA/ACC Practice Guidelines on the management of PAD, cilostazol is recommended for patients with PAD without heart failure. The use of pentoxifylline is not well supported by the 2004 ACCP Conference on Antithrombotic and Thrombolytic Therapy Evidence Based Guidelines. It should be considered as second-line therapy to cilostazol.

**RECOMMENDATION**

Current data suggests cilostazol is more efficacious than pentoxifylline in treating intermittent claudication. It is recommended that at least cilostazol be available as a preferred agent on the PDL.

**COMMITTEE VOTE:**

**APPROVED**

**DISAPPROVED**

**APPROVED with MODIFICATION**

### NEW: INTERMITTENT CLAUDICATION

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**References**

NEW: ORAL ANTICOAGULANTS

BACKGROUND

- Anticoagulants are used to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or embolization after MI. They are also used for the prophylaxis or treatment of venous thrombosis, pulmonary embolism, atrial fibrillation, or cardiac valve replacement.
- Warfarin sodium is an anticoagulant that exerts its effect by blocking the regeneration of vitamin K(1) epoxide, thus inhibiting synthesis of vitamin K-dependent clotting factors which include factors 2, 7, 9 and 10, and the anticoagulant proteins C and S.
- Hematologic adverse reactions are the major concern for anticoagulants, where fatal or nonfatal hemorrhage from any issue or organ may occur. Necrosis of skin and other tissues can appear with in a few days at the start of therapy. Hepatitis, jaundice and an elevation of liver enzymes may also occur.
- There are several studies that have examined the antigoagulant agents:
  - In 5 prospective randomized controlled clinical trials (AFASAK, SPAF, BAATAF, CAFA, and SPINAF) involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke. The risk reduction ranged from 60% to 86%. The incidence of major bleeding in these trials ranged from 0.6% to 2.7%. Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2 to 4.5) or low INR (1.4 to 3). There was a significant reduction in minor bleeds at the low INR.
  - WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. (But note that a lower INR was achieved and increased bleeding was associated with INRs above 4.) The primary endpoint was a combination of total mortality and recurrent infarction. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. All study endpoints favored the warfarin study group decreased mortality, recurrent MI, and cerebrovascular events.
- Warfarin is often the oral anticoagulant used for outpatient treatment and prophylaxis of venous thrombosis and pulmonary embolism, treatment of patients with heart disease and embolization, prophylaxis of thrombosis in patients following myocardial infarction and prophylaxis of thrombosis in patients with congenital deficiency of antithrombin III, protein C or protein S.
RECOMMENDATION
Oral anticoagulants are used to prevent thrombotic events including MI, stroke and TIA. Warfarin is effective in preventing recurrent vascular events among patients with vascular disease. It is recommended that warfarin sodium products be available as preferred agents on the PDL.

COMMITTEE VOTE:
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NEW: ORAL ANTICOAGULANTS

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References

NEW: INJECTABLE ANTICOAGULANTS

BACKGROUND

- There are two main types of injectable anticoagulants that are commonly used on an outpatient basis: low molecular weight heparins (LMWHs) and Selective Factor-Xa Inhibitors.
  - There are currently 3 LMWHs available: dalteparin, enoxaparin, and tinzaparin. Dalteparin (Fragmin®) is FDA-approved for DVT prophylaxis in hip replacement, abdominal surgery, and immobile patients at risk for thromboembolic complications, as well as for prophylaxis of ischemic complications in acute coronary syndrome (ACS). Enoxaparin (Lovenox®) is FDA-approved for DVT prophylaxis in hip replacement, knee replacement, abdominal surgery, and immobile patients at risk for thromboembolic complications, as well as DVT treatment, pulmonary embolism (PE) treatment given with warfarin, and prophylaxis of ischemic complications in patients with unstable angina or non-Q-wave MI (when given with aspirin). Tinzaparin (Innohep®) is FDA-approved for DVT treatment.
  - There is currently one Selective Factor-Xa Inhibitor available – fondaparinux (Arixtra®). Fondaparinux is indicated for DVT prophylaxis in hip replacement, knee replacement, hip fracture surgery, and abdominal surgery, as well as DVT treatment and treatment of acute PE (when initial therapy is administered in the hospital).

- LMWHs work by binding to and potentiating the action of antithrombin III (AT-III), and thus inhibiting the action of Factor Xa. Fondaparinux works by selectively binding to and inhibiting ATIII, resulting in the neutralization of factor Xa. Because the LMWHs and fondaparinux target Factor Xa rather than thrombin, they do not require monitoring of partial thromboplastin time (PTT) as unfractionated heparin does.
Hematological adverse reactions are the major concern for this group of drugs. Serious side effects associated with these agents include major bleeding, thrombocytopenia, elevations of AST/ALT, and injection site reactions. All agents in this class have a black box warning for the risk of spinal/epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed in patients who are anticoagulated with LMWHs, heparinoids, or fondaparinux for prevention of antithrombotic complications. All four agents in this class are pregnancy category B. Fondaparinux is contraindicated in patients with renal insufficiency and in patients with a body weight less than 50kg.

Several trials have examined the impact of LMWHs in both prophylaxis use and outpatient use. Below is a summary of the clinical trials.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Development of post-operative DVT (%)</th>
<th>Treatment: Recurrent VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Hip Replacement</td>
<td>Total Knee Replacement</td>
</tr>
<tr>
<td>dalteparin</td>
<td>4 - 30</td>
<td>--</td>
</tr>
<tr>
<td>enoxaparin</td>
<td>6 - 38</td>
<td>19 - 37</td>
</tr>
<tr>
<td>fondaparinux</td>
<td>1.7 - 5.6</td>
<td>12.5</td>
</tr>
<tr>
<td>tinzaparin</td>
<td>21 - 31</td>
<td>45</td>
</tr>
</tbody>
</table>

A meta-analysis of LMWH versus unfractionated heparins found that all agents were able to reduce mortality rates after acute DVT with similar safety and efficacy.

Studies in orthopedic surgery (hip fracture, hip replacement, and knee replacement) have found fondaparinux to be more effective than LMWHs at reducing the incidence of post-operative venous thromboembolism (VTE), although this benefit was accompanied by an increased risk of bleeding. For DVT prophylaxis, similar rates of thrombotic events and similar bleeding rates were seen between fondaparinux and the LMWHs.

The American College of Chest Physicians (ACCP) recommends the use of LMWHs or fondaparinux in prophylaxis and treatment of VTE. Although the various products differ in their FDA-approved indications, the ACCP makes no distinction between products for orthopedic surgery prophylaxis or treatment of VTE.

**RECOMMENDATION**

Low molecular weight heparins (LMWHs) and selective factor-Xa inhibitors are effective agents at reducing the risk of venous thromboembolism. Based on the available clinical literature and treatment guidelines, these injectable anticoagulants all produce similar anticoagulant effects, display similar safety/tolerability, and have similar clinical utility; therefore, all agents in this class can be considered therapeutic alternatives to one another.
COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

NEW: LOW MOLECULAR WEIGHT HEPARINS (LMWH)

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
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<tbody>
<tr>
<td>LOVENOX® (enoxaparin)</td>
<td>ARIXTRA® (fondaparinux)</td>
</tr>
<tr>
<td></td>
<td>FRAGMIN® (dalteparin)</td>
</tr>
<tr>
<td></td>
<td>INNOHEP® (tinzaparin)</td>
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</tbody>
</table>

References

