AN APPLICATION TO RECOMMEND THAT BETA-BLOCKERS BE ADDED TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR HEART FAILURE (12.4) AND THAT THE REPRESENTATIVE OF THE BETA-BLOCKER CLASS BE SWITCHED TO BISOPROLOL FROM ATENOLOL

Authors:
Sandeep P. Kishore, M.Sc.
Weill Cornell Medical College/ The Rockefeller University/Sloan-Kettering Institute, New York, NY

Maryam N. Shafaee, M.D.
Department of Medicine, NewYork-Presbyterian Hospital; Weill Cornell Medical Center, New York, NY

Matthew R. Price, B.S.

Rajesh Vedanthan, M.D., M.P.H.
Cardiovascular Institute, Mount Sinai Medical Center, New York, NY

Faculty Advisor:
Marcus M. Reidenberg, M.D., Professor of Pharmacology, Medicine and Public Health, New York, NY
1. Executive Summary

In light of the most recent guidelines from the National Institute of Clinical Excellence (NICE) of the United Kingdom and the Heart Failure Society of America (HFSA) indicating beta-blockers for the treatment of heart failure (Class I, Level of Evidence: A) we propose that the Expert Panel kindly consider:

1) Adding beta-blockers as a therapeutic class for medicines for treatment of patients with heart failure (Section 12.4 of the current List); and

2) Changing the named member of the beta-blocker class from atenolol to a cost-effective agent that can address all indications for beta-blockade (Section 12.1-12.4 of the current List; angina, arrhythmia, hypertension and heart failure).

Of the three beta-blockers that are appropriate for all indications (carvedilol, metoprolol succinate and bisoprolol), bisoprolol would be a better representative of the class because of its cost-effectiveness, demonstrated efficacy for heart failure, simplified once daily dosing, and relative safety in patients with co-morbid chronic obstructive pulmonary disease (COPD). In this application, we review data for all three beta-blockers indicated for heart failure.

Noting that the Expert Panel currently indicates use of any beta-blocker, we seek to modify the named representative of this class of drugs on the Model List to maintain the square box rather than add a new product.

2. N/A

3. Name of the organizations consulted and/or supporting the application

*Individuals on behalf of organizations supporting the application are listed below:*

Sanjay Basu, MD, PhD
Department of Medicine, University of California-San Francisco;
Division of General Internal Medicine, San Francisco General Hospital;
Board of Directors, Nyaya Health (Nepal)

Asaf Bitton, MD, MPH
Associate Physician, Division of General Internal Medicine, Brigham & Women’s Hospital;
Instructor, Department of Health Care Policy, Harvard Medical School

Gene Bukhman, MD, PhD
Senior Technical Advisor on Non-communicable Disease, Ministry of Health, Rwanda
Associate Clinical Director, Partners In Health, Rwanda
Director, Program in Global Noncommunicable Disease and Social Change, Harvard Medical School
Associate Physician Brigham and Women's Hospital
Jill Kalman, MD  
Director of the Cardiomyopathy Program, Mount Sinai Medical Center; Associate Professor of Cardiology, Mount Sinai School of Medicine  

Patrick T. Lee, MD, DTM&H  
Director, Global Primary Care Program, Massachusetts General Hospital  
Instructor in Medicine, Harvard Medical School  
Medical Director, Tiyatien Health (Liberia)  

Rajesh Panjabi, MD, MPH  
Co-Founder & Executive Director, Tiyatien Health (Liberia)  
Clinical Fellow in Medicine, Harvard Medical School  

4. International Proprietary Name (INN)  
Bisoprolol fumarate  

5. Formulation proposed for inclusion  
Bisoprolol fumarate tablets (1.25, 2.5 mg, 5 mg and 10mg)  

6. International availability  
Bisoprolol fumarate is already registered for use in a variety of low and middle income countries, including Tanzania, Uganda, South Africa, Kenya, Sudan, India, Jordan, Oman, Namibia, and Lebanon. It has also been approved for use in the United States, Canada, United Kingdom, and Australia.  

Bisprolol is manufactured by companies in a variety of countries (partial listing below):  

<table>
<thead>
<tr>
<th>Country</th>
<th>Manufacturers</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Unichem Laboratories, Cipla, Aurobindo, Matrix</td>
</tr>
<tr>
<td>Germany</td>
<td>Evonik Degussa, Merck KgA</td>
</tr>
<tr>
<td>Ireland</td>
<td>Corden Pharmaceuticals</td>
</tr>
<tr>
<td>South Africa</td>
<td>Adcock-Ingram Ltd., Pharma Dynamics, and Sandoz-Hexal</td>
</tr>
<tr>
<td>Egypt</td>
<td>Hikma</td>
</tr>
<tr>
<td>Canada</td>
<td>Apotex Pharmaceuticals</td>
</tr>
<tr>
<td>Spain</td>
<td>Norman SA</td>
</tr>
</tbody>
</table>

7. Listing as individual medicine or representative of therapeutic group  
Representative of therapeutic group (beta-blockers)
8. Information Supporting the Public Health Relevance

Few studies accurately document the global burden of heart failure, but available data indicate that heart failure is prevalent and increasing globally. This is driven by both communicable and non-communicable causes, including rheumatic heart disease (in Asia and Africa); Chagas disease (in South America); coronary artery disease in Europe, North America and most developed middle-income countries; hypertension in sub-Saharan Africa and elsewhere (Mendez G et al, 2001); and viral and immunologically mediated etiologies to an uncertain extent worldwide.

According to the Disease Control Priorities Project (DCPP), the risk of heart failure is increased two- and three-fold in hypertensive men and women, respectively (DCCP, 2006). Heart failure is five times more common in survivors of acute myocardial infarction (MI) than in patients without MI. The prevalence of heart failure in high-income countries is 2 to 3% with an incidence of 0.1 to 2%; prevalence increases with age (0.7 per 1,000 for those younger than 50 years of age versus 27 per 1,000 for those >65 (McKelvie, 2003).

HIV is also associated with heart failure. The median prevalence of HIV-associated cardiomyopathy in low and middle income countries is 32% and on the rise (Nzuobontante D, 2002; Twagirumukiza M, 2007). The prognosis for patients with AIDS and heart failure is particularly poor with one-year mortality rates as high as 40 percent and five-year mortality rates ranging from 26 to 75 percent (McMurray, 2000). AIDS patients on highly active antiretroviral therapy (HAART) show a 26% relative risk increase in the rate of myocardial infarction per every year of HAART exposure (DAD Study Group, 2007), which can contribute to the development of ischemic heart disease-related heart failure.

9. Treatment Details

The most recent guidelines from NICE in the U.K. and the HFSA, both published in 2010, recommend administration of beta-blocker drugs as part of the treatment of patients with heart failure (NICE, 2010; HFSA, 2010) and specifically cite metoprolol succinate, bisoprolol and carvedilol. A lack of evidence supporting the use of atenolol for heart failure undermines listing it as a representative of the class. Beta-blockers are indicated as an essential component of heart failure therapy, given the clear reduction in mortality compared with ACE inhibitors and diuretics alone. They are to be used lifelong; the dosing details for the three beta-blockers indicated for heart failure are presented in Section 10 and Section 15 of this application.

10. Summary of comparative effectiveness in a variety of clinical settings

The CIBIS II trial (1999) was the first to show significant beneficial effects of beta-blockers in patients with chronic heart failure. The study compared bisoprolol (target dose 10 mg daily) with placebo in 2647 patients with ischemic and non-ischemic chronic heart failure (left ventricular ejection fraction (LVEF) below 35%) in New York Heart Association grade III or IV. The trial found a 34% reduction in all-cause mortality (p<0.0001), a 44% reduction in sudden death (p<0.0011) and a 20% reduction in all-cause hospital admissions (p<0.0006). The treatment
effects were independent of the severity or cause of heart failure. This trial was followed by trials with metoprolol succinate (MERIT-HF, 1999) and the carvedilol (COPERNICUS, 2001); data for study populations, dosing, follow-up time and primary endpoints (all-cause mortality) are summarized below:

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Bisoprolol</td>
<td>Metoprolol succinate</td>
<td>Carvedilol</td>
</tr>
<tr>
<td>2647 patients in NYHA class III or IV with LVEF &lt;35% on diuretics and ACE inhibitors</td>
<td>3991 patients in NYHA class II-IV with LVEF &lt;40% on diuretics and ACE-inhibitors</td>
<td>2289 patients in NYHA class IV with LVEF&lt;25% on diuretics and ACE-inhibitors</td>
<td></td>
</tr>
<tr>
<td>Dosing for treatment arm</td>
<td>1.2mg titrated to 2.5, 3.75, 5, 7.5 and 10 mg according to patient tolerance.</td>
<td>12.5 mg (NYHA III/IV) and or 25 mg (NYHA II), titrated to 200 mg over 8 weeks</td>
<td>3.125 mg titrated to 6.25 mg, 12.5 mg and 25 mg over 2-week intervals per patient tolerance</td>
</tr>
<tr>
<td>Mean Follow-Up</td>
<td>1.3 years</td>
<td>1 year</td>
<td>10.4 months</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Change in all-cause mortality versus placebo*</td>
<td>-34% (p&lt;0.0001)</td>
<td>-34% (p&lt;0.00015)</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Change in sudden deaths</td>
<td>-44% (p&lt;0.0011)</td>
<td>-41% (p&lt;0.0002)</td>
</tr>
<tr>
<td>Change in hospitalizations to heart failure</td>
<td>-20% (p&lt;0.0006)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Change in deaths to heart failure</td>
<td>-36% (p&lt;0.0001)</td>
<td>-</td>
<td>-24% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-49% (p&lt;0.0023)</td>
<td>-24% (p&lt;0.001)</td>
</tr>
</tbody>
</table>

*Placebo = treatment with diuretics and ACE-inhibitors alone

Only one placebo-controlled study, the beta-blocker evaluation of survival (BEST, 2001) with bucindolol failed to show survival benefit. It remains unclear why this is the case, though the drug has strong beta-2 blockade properties, weak alpha-1 vasodilatory properties and intrinsic sympathomimetic activity (unlike the other beta-blockers) that might mitigate beneficial effects.

A meta-analysis of 14 trials completed by Shibata et al found a reduction of 34% in the composite endpoint of mortality or hospital admission with beta-blocker therapy in patients with heart failure. Inclusion of two other trials (COPERNICUS and BEST) by Funck-Brentano yielded a composite endpoint of 29% reduction (as shown below). A more recent meta-analysis by Bangalore et al confirmed this reduction (~30% reduction) (Bangalore S, 2007).
Further analyses show overall mortality benefits (Brophy JM, 2001; Lechat P et al, 1998), in the elderly and the young (Dubin, BR, 2005), in men and women (Shekelle, PG 2003), in patients with (Bell DS, 2006) and without diabetes (Hass SJ, 2003), in patients with ejection fraction above or below 25% (Bouzamondo A, 2003), and in patients receiving and not receiving inhibitors of the renin-angiotensin system (RAS) (Krum, H 2005).

In addition, the COPERNICUS study found consistent reductions in mortality independent of age, sex and ethnicity. Studies were performed across countries in North and South America, Europe, Asia and Africa (United States, Canada, Mexico, Argentina, United Kingdom, Hungary, Lithuania, Poland, the Netherlands, Portugal, Ukraine, Switzerland, Russia, Israel and South Africa). Newer data also indicate that heart failure treatments are also effective in non-Caucasian patients (The Cardiac Insufficiency Bisoprolol Study: Safety and Tolerant Dose-range in Chinese Patients, 2010). These data suggests the medicines are efficacious for the proposed use and are efficacious in diverse settings and populations.

11. Summary of comparative effectiveness on safety

a. Adverse Events
A study of cause-specific adverse effects is provided below for metoprolol succinate from the MERIT-HF trial examining key reasons for drug withdrawal; rates of these events were similar with bisoprolol and carvedilol, and do not appear to occur more frequently than with placebo. On
balance, data stemming from the continued use of beta blockers in diverse population settings suggests the adverse effects are not significant.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Metoprolol succinate(%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>3.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>All patients with adverse events</td>
<td>9.8</td>
<td>11.7</td>
</tr>
</tbody>
</table>

(Summarized from Hjalmarson et al, 2000 and Funck-Brentano 2006)

b. Early Withdrawal
Mortality is greater in patients withdrawn from therapy. In CIBIS-II, 42% of participants achieved the target bisoprolol dose of 10 mg daily. At a mean follow-up of 1.3 years, withdrawal from the study drug was reported in 192 patients (15%) in the bisoprolol group and 194 patients (15%) in the placebo group. In COPERNICUS (mean follow-up 130.4 months), the mean dose of carvedilol achieved was 37 mg daily. Withdrawal rates at 1 year were 18.5% in the placebo group and 14.8% in the carvedilol group. Analysis of the individual component trials of the United States Carvedilol Program found overall discontinuation rates of 18.3% in the placebo group and 10.8% in the carvedilol group.

c. Individual tolerance of beta blockade in heart failure
Factors associated by univariate analysis with reduced tolerance were age, low diastolic blood pressure, raised plasma urea concentration, and NYHA class (3% intolerance among those in NYHA Class I and 22% intolerance among those in NYHA Class IV). Both carvedilol and bisoprolol are safe and tolerated by the elderly (BETANIC study, Yebra-Yebra M, 2010).

12. Summary of available data on Cost and Cost-Effectiveness
a. International Costs
The cost of all doses of bisoprolol averages $0.11/day in the United States, compared to $0.14/day for carvedilol and $0.87/day for metoprolol succinate, according to the 114th edition of the Red Book: Pharmacy’s Fundamental Reference 2010 Edition by Thomson Reuters. Carvedilol is listed on the Management Sciences for Health International Drug Price Indicator Guide with average price per tablet of $0.20 or $144 per year for twice daily treatment (neither metoprolol succinate nor bisoprolol was listed).
A survey of the costs per defined daily dose (DDD) of carvedilol and metoprolol succinate in relation to the cost of bisoprolol is provided below for 2010 (and 2005-2010 where data was available):

*The cost of beta blockers for heart failure per DDD (Relative to Bisoprolol) by Country*

**USA (2010)**
- Bisoprolol: 1.0
- Carvedilol: 1.3
- Metoprolol succinate: 7.9

**Sweden (2005-2010)**
- Bisoprolol: 1.0
- Carvedilol: 2.3
- Metoprolol succinate: 5.6

**South Africa (2010)**
- Bisoprolol: 1.0
- Carvedilol: 3.6
- Metoprolol succinate: n/a

In all cases, the cost of carvedilol and metoprolol succinate exceeds the cost of bisoprolol.

*b. Number Needed To Treat (NNT)*

The number of patients needed to treat (NNT) with a beta-blocker as opposed to no beta-blocker (normalized to 1-year) to avoid one death ranges from 15 to 43. The study durations were from 6 months to 1.3 years.

<table>
<thead>
<tr>
<th>Study</th>
<th>NNT (1-year)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS II (Bisprolol)</td>
<td>23</td>
<td>1.3 years</td>
</tr>
<tr>
<td>MERIT-HF (Metoprol succinate)</td>
<td>27</td>
<td>1 year</td>
</tr>
<tr>
<td>COPERNICUS (Carvedilol)</td>
<td>15</td>
<td>10.4 months</td>
</tr>
<tr>
<td>US CARVEDILOL</td>
<td>15</td>
<td>6-12 months</td>
</tr>
<tr>
<td>CAPRICORN (Carvedilol)*</td>
<td>43</td>
<td>1.3 years</td>
</tr>
</tbody>
</table>

* post-MI patients

c. *Cost-effectiveness in developing countries*

One projection examined whether beta-blockers (in addition to enalapril and diuretics) are cost-effective treatments for patients with heart failure. Gaziano et al modeled the addition of an ACE inhibitor with metoprolol to a baseline of diuretic treatment across the six World Bank Regions. The authors find that the ACE inhibitor + metoprolol regimen for heart failure is cost-effective across the six World Bank regions with incremental cost-effective ratios (ICER) ranging from $124 to $275 depending on the general the availability of hospital facilities (Gaziano, TA 2005).
13. Summary of regulatory status
Generic bisoprolol is registered in the United States and United Kingdom. Numerous countries including India, China, and South Africa have registered and are producing generic bisoprolol, and generics are available in US and EU markets. Five generic firms supply generic bisoprolol in the United States. The US regulatory body (Food & Drug Administration, FDA) dates of approval are for the three beta-blockers approved for heart heart failure is provided below:

**US FDA Approval Date**
- bisoprolol fumarate: July 31, 1992
- metoprolol succinate (tablet): January 10, 1992
- carvedilol: September 14, 1995

14. Availability of pharmacopoeial standards
Bisoprolol fumarate:
- British National Pharmacopoeia (yes)
- USP (yes)
- International Pharmacopeia (no)

15. Proposed (new/adapted) text for the WHO Model Formulary
As an example, bisoprolol will be quoted as a representative of a generic beta blocker available. Bisoprolol is cardioselective beta blocker useful for the treatment of heart failure.

*From MICROMEDEX®:*
*How supplied:* 1.25, 2.5, 3.75, 5, 7.5 or 10 mg of bisoprolol fumarate as the active ingredient
*Dosing:* 1 week of therapy with 1.25 mg once-daily. If tolerated, then 1 week of therapy at 2.5 mg once-daily, followed by 1 week of therapy at 3.75mg once-daily. If tolerated, then increase to 5mg of therapy once-daily for 4 weeks followed by 7.5 mg therapy once-daily for 4 weeks, followed 10mg once-daily as maintenance therapy.
*Contraindications:* cardiogenic shock, hypersensitivity to bisoprolol, overt cardiac failure, second and third degree AV block and severe sinus bradycardia
*Precautions:* anesthesia/surgery (myocardial depression), avoid abrupt withdrawal, bronchospastic disease, congestive heart failure, diabetes mellitus hyperthyroidism/thyrotoxicosis, liver disease, peripheral vascular disease and renal impairment
*Drug interactions:* Major drug interaction of concern (Amiodarone)
*Pediatric Use:* Safety and efficacy not established in children.
*Pregnancy use:* Bisoprolol use is not recommended during pregnancy.
*Adverse effects:* The most common are diarrhea, headache, rhinitis, upper respiratory infection and fatigue.
Special section requesting that:
THE REPRESENTATIVE OF THE BETA-BLOCKER CLASS BE SWITCHED TO
BISOPROLOL FROM ATENOLOL

a. Can atenolol be used for heart failure?
While atenolol is a commonly prescribed beta-blocker, its effect in patients with heart failure has not been well studied. At present, there is no high quality evidence to support the use of atenolol for treatment of patients with heart failure. In light of the evidence-base and the availability of newer, off-patent beta-blockers, we recommend against using atenolol for this condition, despite its relatively low cost ($0.01 to $0.05/day according to the Red Book and the International Drug Price Indicator Guide).

A step-down procedure for transition from atenolol to a recommended first-line beta-blocker for the treatment of heart failure is provided here (Abraham WT, 2003).

b. Which beta-blocker (metoprolol succinate, carvedilol or bisoprolol) to recommend?

1. As described above, there is little evidence to suggest atenolol is a suitable candidate for heart failure treatment.

2. The next generation beta-blockers indicated for heart failure, all presently off-patent, include: carvedilol, a non-selective beta-adrenergic receptor blocker that also induces alpha-1-adrenergic receptor blockade; and bisoprolol and metoprolol succinate, both highly selective beta-1-adrenergic receptor (cardioselective) blockers.

3. One study comparing bisoprolol with carvedilol found equivalent improvement in patients with of severe HF. Here, bisoprolol showed favorable effects in patients with atrial fibrillation. The percent changes in heart rate and plasma brain natriuretic peptide levels were also significantly better in the bisoprolol group than in the carvedilol group (Konishi, 2010).


5. Bisoprolol and metoprolol succinate are generally administered once-daily while carvedilol is used twice-daily. The NICE guidelines report that patients on a once-daily regimen have higher adherence rates than with twice daily dosing (91% vs 83%).

7. As stated above, the cost of bisoprolol averages $0.11/day in the United States, compared to $0.14/day for carvedilol and $0.87/day for metoprolol succinate. Globally, the cost of bisoprolol is less than carvedilol and metoprolol succinate; bisoprolol is registered and manufactured in several high, middle and low income countries.

8. On balance, based on cost, availability, once-daily dosing, adherence, and the consensus view that cardioselective beta-blockers are safer to use in patients with COPD (4th leading cause of mortality according to WHO Global Burden of Disease) we recommend **bisoprolol** as the representative beta-blocker.

c. Efficacy of bisoprolol as an anti-anginal, anti-arrhythmic and anti-hypertensive

a. **Anti-anginal**

The data are largely collective (referring to beta-blockers as a class, rather than to individual agents). All beta-blockers are effective in patients with angina pain because they reduce myocardial oxygen demand and because of the negative chronotropic effect, raising myocardial perfusion. As such, guidelines recommend these as first-line therapy in patients with (class I, LOE: A) and without (class I, LOE: B) prior MI unless contraindications exist (Gibbons R, 2003). Most anti-anginal effects of beta-blockers result from beta-1-receptor inhibition (favoring bisoprolol over less selective agents) (Pepine CJ, 1994). The Total Ischemic Burden Bisoprolol Study (TIBBS), found greater heart rate variability (considered prognostically favorable) with bisoprolol than nifedipine (Weber F, 1999).

b. **Anti-arrhythmic**

Compared to the carvedilol, more bisoprolol-treated patients were converted from atrial fibrillation to sinus rhythm compared to carvedilol (48% vs 16%, P=0.03) (Konishi, 2010). Bisoprolol has also shown efficacy for suppression of paroxysmal atrial fibrillation (Ishiguro H, 2008). In addition, bisoprolol has equivalent effect at maintaining sinus rhythm as sotalol following electrical cardioversion for acute atrial fibrillation (Plewan A, 2001). The finding of lower rate of admission to hospital for ventricular tachycardia or fibrillation in the CIBIS-II bisoprolol group also supports the drug’s antiarrhythmic effect (CIBIS-II, 1999).

c. **Antihypertensive**

The role of beta-blockade versus other anti-hypertensive agents has been contested. The NICE guidelines recommend beta-blockers as 4th-line therapy for patients with uncomplicated hypertension, citing the scant mortality benefit seen with atenolol, which was the agent used in over 75% of trials investigating the effect of beta-blockade for hypertension. The evidence on whether newer beta-blockers, including vasodilators, would have greater effect remains unclear. In the specific instance of bisoprolol, efficacy compared favorably with hydrochlorothiazide, amlodipine and losartan monotherapy in the GENRES study using a crossover design (Hiltunen TP, 2007). This trend also holds with younger patients: bisoprolol lowers blood pressure more effectively than atenolol (Neutel JM, 1993), lisinopril, amlodipine and thiazides (Deary, 2002).
Based on these findings, we believe bisoprolol is equivalent or superior to atenolol for indications 12.1-12.4 on the WHO Model List of Essential Medicines.

**Conclusion:**

Robust evidence supports the use of beta-blockade to treat heart failure, resulting in the incorporation of beta-blockers as first-line therapies to supplement ACE-inhibitors and diuretics in major national treatment guidelines. Consistent with recent evidence, we urge the WHO Expert Panel to favorably consider addition of the beta-blocker class of cardiovascular medications to Section 12.4 of the Model List of Essential Medicines.

In addition, the representative choice of beta-blocker should cover all indications listed in Section 12.1 – 12.4. Accordingly, we recommend bisoprolol for this purpose, on the basis of cost, availability, once-daily dosing, adherence, and ability to use in patients with COPD. The availability of newer beta-blockers with different pharmacologic properties (i.e. alpha-1 blocking vasodilatory properties) should prompt a thorough review of this class, and we believe the Expert Panel should add notes to this effect on the formulary.
REFERENCES


Data on efficacy in non-Caucasian populations is from The Cardiac Insufficiency Bisoprolol Study: Safety and Tolerant Dose-range in Chinese Patients. J Cardiac Fail 2006; 12: Suppl 1, S155. P


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