Metoprolol Succinate
SelokenZOC

Blood Pressure Control and Far Beyond...

Mohamed Abdel Ghany

Death Rates From Ischemic Heart Disease In Egypt is the Highest Compared to Other Countries In Africa And Middle East

Figure 1: Death rates from cardiovascular disease in selected countries in Africa and the Middle East. Drawn from data presented by the World Health Organization.

High Blood Pressure has Different causes

Patient 1

Patient 2

Patient 3

- Sympathetic Nervous System
- Renin-Angiotensin System
- Total Body Sodium
Excessive Sympathetic Stimulation is Harmful

- Cardiac Necrosis
- Cardiac Apoptosis
- Atheroma Formation
- Sympathetic Stimulation
- Atherosclerotic plaque Rupture
- LVH
- Vent Fibrillation

Beta-adrenergic Blockers have a central role in CV therapy

Adapted from, Luca Donazzan, Novel and Nonpharmacologic Approaches to Cardio Protection in Hypertension. Current Hypertension Reports. 16(5):430 · May 2014

Heart Rate

200 beats/min
Age: 200 days

40 beats/min
Age 60-70 Year
Heart Rate as a Predictor of All-Cause Mortality in Hypertension

Framingham study: 2,037 men; 36-year follow-up

HRs ≥ 88 b/m vs HRs < 65 b/m

IS CORRESPONDING TO 6 FOLDS SUDDEN CARDIAC DEATH

Blood Pressure Measurements: Should always be associated with Heart Rate Measurement

Heart rate values independently predicts with CV morbidity and fatal events in Hypertension

SelokenZOC
“Metoprolol Succinate”
Advanced Release Formulation

Advantages of Selective β1-Blockers

• No adverse effects on fasting plasma glucose.
• Do not affect lipid or triglyceride metabolism.
• Adverse effect profile comparable to placebo in clinical trials.
• Efficacy is better or comparable to other antihypertensive drugs.
• Favorable safety profile in COPD patients, PAD and ED.
BB Have a Different Pharmacological Profiles matching Different Needs and Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative $\beta_1$-Selectivity</th>
<th>VD</th>
<th>ISA</th>
<th>Lipid solubility</th>
<th>Average daily oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>0</td>
<td>+*</td>
<td>0</td>
<td>moderate</td>
<td>3.125–50 mg twice</td>
</tr>
<tr>
<td>Propranolol</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>high</td>
<td>40–180 mg twice</td>
</tr>
<tr>
<td>Atenolol</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>low</td>
<td>25–100 mg once</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>2.5–20 mg once</td>
</tr>
<tr>
<td><strong>Metoprolol Succinate</strong></td>
<td><strong>++</strong></td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td><strong>12.5–200 mg once</strong></td>
</tr>
<tr>
<td>Nebivelol</td>
<td>++</td>
<td>+(†NO)</td>
<td>0</td>
<td>high</td>
<td>1.25–10 mg once</td>
</tr>
</tbody>
</table>

*Intensive sympathetic activity  $\alpha$-blocker

Progress in Cardiovascular Diseases, 47(1) 2004: 11-33

SelokenZOC “Metoprolol Succinate”

- a lipophilic, selective $\beta_1$-receptor blocking agent
- In Advanced Extended Release formulation

- The tablets comprise a multiple unit system (pellets) containing metoprolol succinate.
- Each pellet acts as a separate drug delivery unit designed to deliver metoprolol continuously over the 24 hours.

**SelokenZOC vs Bisoprolol Plasma Profiles**

SelokenZOC have a less varying blood pressure-lowering effect over the 24-h day.

Plasma concentrations at steady state over the 24-h dose interval: Bisoprolol and metoprolol succinate

Metoprolol has 7 approved indications
Metoprolol in Hypertension and Heart Rate Control

Traditional Ranking of drugs to 1st, 2nd & 3rd ... line has now little scientific & practical justification & should be avoided.
JNC 8 2014 Guidelines for the management of high BP
Metoprolol is recommended By Name ...

<table>
<thead>
<tr>
<th>Antihypertensive Medication</th>
<th>Initial Daily Dose, mg</th>
<th>Target Dose in RCs Reviewed, mg</th>
<th>No. of Doses per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>50</td>
<td>150-200</td>
<td>2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5</td>
<td>20</td>
<td>1-2</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eprosartan</td>
<td>400</td>
<td>600-800</td>
<td>1-2</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Losartan</td>
<td>50</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40-80</td>
<td>160-320</td>
<td>1-2</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>75</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>β-Blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50</td>
<td>100-200</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Blood pressures were recorded 24 hours after dosing. *P < 0.05
SBP & DBP were decreased after 4 weeks treatment with CR/ZOK (100 mg).

SelokenZOC: Has A Proved Efficacy in controlling H.R after 4 weeks of Treatment

- Reduction in supine BP (mmHg)

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>After Placebo</th>
<th>Metoprolol CR/ZOK mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>163 mmHg</td>
<td>143 mmHg</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>102 mmHg</td>
<td>93 mmHg</td>
<td></td>
</tr>
<tr>
<td>H.R</td>
<td>75 b/min</td>
<td>63 b/min</td>
<td></td>
</tr>
</tbody>
</table>

SelokenZOC providing greater efficacy than Bisoprolol toward the end of the 24-h day.

Metoprolol have a less varying blood pressure-lowering effect over the 24-h day.

There are differences between the two drugs in the diurnal pattern of their antihypertensive effects. This difference may be of clinical relevance, given the recognized diurnal pattern of CV events.


Is It Just Blood Pressure Control Or Is There Something Beyond?
MAPHY trial
(Metoprolol Atherosclerosis Prevention in Hypertensives)


MAPHY Study

**Study design:** randomized, open, parallel-group Study. Enrolling 3234 men Patients (1609 metoprolol, 1625 diuretics), aged 40-64 years. DBP at entry: 100-130 mm Hg

**Follow-up:** 842 days to 10.8 years (*mean 5 years*)

MAPHY Study Results

Metoprolol Reduced the risk of **Coronary events** by **24%**

Metoprolol Reduced the risk of **Stroke Events comparable to Diuretics**

![Graph showing comparison of coronary and stroke events between diuretics and metoprolol](image)


MAPHY Study

**Study Outcomes (Primary Prevention)**

**CV Mortality** is Reduced with Metoprolol by **58%**

![Bar chart showing mortality rates for cardiovascular and non-cardiovascular events](image)

MAPHY Study

Metoprolol Reduced the risk of **Sudden CV Death by 30%**

![Graph showing cumulative number of deaths over follow-up years, comparing Metoprolol and Diuretics, with p=0.017 and RRR=30%]

*Wikstrand et al, Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY study. Hypertension 1991;17;579-88*

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MAPHY Study

A significant reduction in the Heart Rate with Metoprolol

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entry (n=1639)</th>
<th>Last follow-up (n=1625)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>78.2 ± 11</td>
<td>77.3 ± 10</td>
</tr>
<tr>
<td></td>
<td>64.1 ± 10</td>
<td>74.1 ± 11†</td>
</tr>
</tbody>
</table>

*Wikstrand et al, Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY study. Hypertension 1991;17;579-88*
The MAPHY study demonstrated for the first time that metoprolol was superior to a thiazide diuretic in reducing total mortality, cardiovascular mortality, sudden cardiac death and was a lower risk for coronary events and comparable stroke prevention for similar reduction of BP.


Metoprolol in Chronic Stable Angina
Role of Metoprolol in Chronic Stable Angina

Effect of metoprolol and diltiazem on the total ischaemic burden in patients with chronic stable angina: a randomized controlled trial


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**Department of Cardiology, Sanjay Gandhi PGIMES, P.B. No. 375, Lucknow, India 226001
***Department of Cardiology, King George Medical College, Lucknow, India

(Received 3 March 1993; accepted 25 June 1993)

154 Patients, 68 received metoprolol (50-100 mg twice daily, and 66 received diltiazem (60-90 mg three times daily) and the drugs were given for 4 weeks.

Metoprolol significantly reduced the duration of total ischemic burden by 76% versus 43% for CCB “Diltiazem” & reduced frequency by 40.4% versus 24% for Diltiazem.

Total Ischemic Burden (TIB): Composite of silent and symptomatic myocardial ischemia measured on 48 h of Halter monitoring.

Metoprolol in Myocardial Infarction
Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: signs of HF, evidence of a low output state, increased risk for cardiogenic shock,* or other contraindications to use of oral beta blockers (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease).

Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use.

*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age >70 years, systolic BP <120 mm Hg, sinus tachycardia >110 bpm or heart rate <60 bpm, and increased time since onset of symptoms of STEMI.
Pre-specified subgroup of Patients with history of Myocardial Infarction

Methods: This was a prespecified subgroup analysis of a double-blind, randomized trial: the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). Patients with CHF in New York Heart Association class II to IV with an ejection fraction (EF) ≤ 0.40 and a history of being hospitalized for an acute MI (n = 1926) were randomized to metoprolol succinate controlled release/extended release (CR/XL) versus placebo. Mean EF was 0.28, and the mean follow-up was 1 year.

Am Heart J 2003;146:721–8.)

In MERIT-HF Post MI patients, SelokenZOC Significantly reduced the Total mortality by 40%

In MERIT-HF Post MI patients, SelokenZOC significantly reduced the Sudden Cardiac Death by 50%

SelokenZOC
Metoprolol Succinate in CHF Patients


Recommendations for the Pharmacological Treatment for patients with symptomatic HFrEF (NYHA Class II-IV)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A beta-blocker is recommended; in addition to an ACE-İ, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
<td>1, 163-165</td>
</tr>
<tr>
<td>An ACE-İ is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.</td>
<td>I</td>
<td>A</td>
<td>167-173</td>
</tr>
</tbody>
</table>

Table 7.2 Evidence-based doses of disease-modifying drugs in key randomized trials in heart failure with reduced ejection fraction (or after myocardial infarction)

<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>Dose</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25-5 őd</td>
<td>10 őd.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>2.5-5 őd.</td>
<td>25-50 őd.</td>
</tr>
<tr>
<td>Metoprolol succinate (CR/XL)</td>
<td>25-100 őd.</td>
<td>200 őd.</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>1.25 őd.</td>
<td>10 őd.</td>
</tr>
</tbody>
</table>

Gerasimos Filippatos, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, doi:10.1093/eurheartj/ehw128

A Double-Blind, Placebo Controlled Survival Study with Metoprolol CR/XL in Patients with Decreased Ejection Fraction (£0.40) and Symptoms of Heart Failure (NYHA II-IV)

The recommended starting dose is **12.5 mg** in patients with **NYHA functional class III–IV** heart failure and **25 mg** in **class II** heart failure.

**Study design**

The trial was terminated early after 1 year due to the significant reduction in all-cause mortality achieved with SelokenZOC

**SelokenZOC “Metoprolol Succinate” Significantly Reduced Mortality due to worsening of heart failure by 49%**

**Primary Endpoints**
- Death plus hospitalization from any cause (time to first event)
- Death from any cause

**Secondary Endpoints**
- Sudden Death
- Death from Worsening heart failure


Take Home Message:

• SelokenZOC: in an advanced Extended Release formulation offers a continuous and even $\beta_1$-Blockade with once daily dosing.¹

• SelokenZOC: Has A Proved Efficacy in controlling H.R after 4 weeks of Treatment ²

• Metoprolol is the only Beta Blocker studied in primary prevention Trial Proved To Reduce mortality & morbidity vs diuretics in hypertensive patients.³

Take Home Message:

• Metoprolol has a superior Efficacy in Reducing Frequency and duration of total ischemic burden compared to Calcium Chanel Blocker diltiazem in patients with stable angina.⁴

• Metoprolol is the only selective BB mentioned in the ACCF/AHA guidelines for the STEMI management.⁵

• In Post-MI patients, SelokenZOC reduced the total death by 40% and sudden cardiac death by 50% compared to placebo.⁶

• In MERIT-HF Study, SelokenZOC reduced the Total Mortality by 34%, Sudden Cardiac death by 41% and the CHF worsening by 49% risk reduction.⁷
THANK YOU