1. **Beta-blocker comparison charts**
   a. **Mechanism of action comparison**
   b. **FDA-approved indications and maximal daily doses**
   c. **General BB comparison and misc. properties**
   d. **Metabolic effects of beta-blockers comparison table**

2. **Introduction**
3. **Background**
4. **Literature Review**
5. **Discussion**
6. **Conclusion**
7. **References**

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**Highlights: The Quick-Read Information**

1. True or False, non-vasodilating beta-blockers REDUCE the Cardiac Output (CO)?
   a. [True]; b. [False];

2. The GEMINI trial, published in 2004 with 35 weeks of follow up, demonstrated that which beta-blocker was beneficial to glycemic control in hypertensive diabetic patients?
   a. [nebivolol]; b. [atenolol]; c. [carvedilol]; d. [metoprolol tartrate]

3. True or False, insulin sensitizing antidiabetics such as metformin or TZDs do NOT impact the effect of a beta-blocker on insulin resistance?
   a. [True]; b. [False];

4. True or False, non-vasodilating beta-blockers are associated with significantly greater incidence of new onset diabetes compared with vasodilating beta-blockers?
   a. [True]; b. [False];

5. True or False, there are NO generically available vasodilating beta-blockers?
   a. [True]; b. [False];

6. Traditional beta-blockers (non-vasodilating), commonly cause which of the following?
   a. [decrease 1st phase insulin response]; b. [decrease clearance of plasma insulin]; c. [hyperinsulinemia]; d. [All of the above]

7. Which beta-blocker does NOT impact exercise tolerance?
   a. [metoprolol tartrate]; b. [atenolol]; c. [nebivolol]; d. [metoprolol succinate]

8. Which beta-blocker has demonstrated a clearly superior trough-to-peak ratio for its antihypertensive effect?
   a. [nebivolol]; b. [atenolol]

---
<table>
<thead>
<tr>
<th>NON-vasodilating</th>
<th>Vasodilating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-beta-selective antagonists</strong></td>
<td><strong>Mixed alpha1-beta antagonists</strong></td>
</tr>
<tr>
<td>Nadolol (Corgard®)</td>
<td>Carvedilol (Coreg®, Coreg CR®)</td>
</tr>
<tr>
<td>Penbutolol (Levatol®)</td>
<td>Labetalol (Trandate®, Normodyne®)</td>
</tr>
<tr>
<td>Pindolol (Visken®)</td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal®, Inderal LA®)</td>
<td></td>
</tr>
<tr>
<td>Sotalol (Betapace®, Sotalol AF®)</td>
<td></td>
</tr>
<tr>
<td>Timolol (Blocadren®)</td>
<td></td>
</tr>
<tr>
<td><strong>Beta1-selective antagonists</strong></td>
<td><strong>Beta1-selective antagonist with activation of Nitric Oxide (NO) pathway</strong></td>
</tr>
<tr>
<td>Acebutolol (Sectral®)</td>
<td>Nebivolol (Bystolic®)</td>
</tr>
<tr>
<td>Atenolol (Tenormin®)</td>
<td></td>
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<tr>
<td>Betaxolol (Kerlone®)</td>
<td></td>
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<tr>
<td>Bisoprolol (Zebeta®)</td>
<td></td>
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<tr>
<td>Esmolol (Brevibloc®)</td>
<td></td>
</tr>
<tr>
<td>Metoprolol (Lopressor®, Toprol®, Toprol XL®)</td>
<td></td>
</tr>
</tbody>
</table>

*Curren through June 2009; **Available generically; §ADRs = Adverse Drug Reactions; PAR = Prior Auth Req’d*
### Beta Blockers – FDA-Approved Adult Doses* and Maximum Daily Doses

<table>
<thead>
<tr>
<th>Indication</th>
<th>Nadolol</th>
<th>Propranolol</th>
<th>Atenolol</th>
<th>Metoprolol</th>
<th>Carvedilol</th>
<th>Labetalol</th>
<th>Nebivolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angina</strong></td>
<td>40mg qd</td>
<td>IR: 10mg po bid-qid</td>
<td>50mg po qd</td>
<td>IR: 50mg po bid ER: 100mg po qd usual effective dose range 100 – 400mg qd</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>40mg qd</td>
<td>IR: 40mg po bid ER: 80mg po qd</td>
<td>25mg po qd</td>
<td>IR: 50mg po bid-tid ER: 25mg po qd</td>
<td>IR: 6.25mg po bid ER: 20mg po qd</td>
<td>100mg bid</td>
<td>5mg qd (titrate at 2-week intervals)</td>
</tr>
<tr>
<td><strong>Cardiomyopathy/Heart Failure</strong></td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>ER: Initially - 12.5mg qd (Class III); 25mg qd (Class II); double dose q 2 weeks until target dose of 200mg daily (if tolerated)</td>
<td>IR: 6.25mg po bid ER: 20mg po qd</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Post-MI/MI prophylaxis</strong></td>
<td>**</td>
<td>IR: 80mg po bid-tid ER: 120mg po qd</td>
<td>50mg po qd</td>
<td>IR: 100mg bid x at least 3 months; maintenance dose 50 – 100mg bid</td>
<td>IR: 6.25mg po bid ER: 20mg po qd</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Migraine Prophylaxis</strong></td>
<td>**</td>
<td>IR: 80mg/day div 2-3x ER: 80mg po qd</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Pheochromocytoma</strong></td>
<td>**</td>
<td>IR: 80mg po bid-tid ER: 80mg po qd</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Atrial fibrillation/flutter</strong></td>
<td>**</td>
<td>IR: 10mg po tid-qid</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>PSVT</strong></td>
<td>**</td>
<td>IR: 10mg po tid-qid</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>IHSS</strong></td>
<td>**</td>
<td>IR: 20mg po tid-qid ER: 80mg po qd</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Essential Tremor</strong></td>
<td>**</td>
<td>IR: 40mg po bid</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Thyrotoxicosis</strong></td>
<td>**</td>
<td>IR: 10mg po qd</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

<p>| <strong>Usual Maximum Daily Dose</strong>   | HTN: 320mg Angina: 240mg | IHSS: 160 | HTN: 100mg Angina: 200mg | IR: 450mg ER: 400mg | IR: 50/100mg ER: 80mg | 2400mg | 40mg |
| <strong>Non-vasodilating</strong>           | Non-selective β-adrenergic antagonists (class representatives) | selective β1-adrenergic antagonists (class representatives) | Mixed α1-β adrenergic antagonists (class representatives) | ‘3rd Gen’ selective |</p>
<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>FDA-Approved Indications</th>
<th>Available Strengths</th>
<th>Elimination</th>
<th>Lipophilicity</th>
<th>Misc. Properties</th>
<th>Insurance Info</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-selective B-adrenergic antagonists (class representatives)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol (Corgard®)</td>
<td>Angina, Hypertension</td>
<td>20, 40, 80, 120, 160mg Tablet</td>
<td>Renal</td>
<td>Low</td>
<td></td>
<td>Brand: 3rd Tier Generic: 1st Tier</td>
</tr>
<tr>
<td>Propranolol (Inderal®, Inderal LA)</td>
<td>Angina, Atrial Fibrillation/Flutter, Hypertension, IHSS, Migraine prophylaxis, Pheochromocytoma, PSVT, Thyrotoxicosis, Post-MI, Tremor</td>
<td>10, 20, 40, 60, 80mg Tablets 60, 120, 160mg ER Capsule 20mg-40mg/5ml oral soln 1mg/ml soln for inj</td>
<td>Hepatic</td>
<td>High</td>
<td>High ISA</td>
<td>Brand: 3rd Tier Generic: 1st Tier</td>
</tr>
<tr>
<td><strong>Selective B1-adrenergic antagonists (class representatives)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol (Tenormin®)</td>
<td>Acute MI, Angina, Hypertension, MI prophylaxis, Post-MI</td>
<td>25, 50, 100mg Tablets 0.5mg/ml soln inj</td>
<td>Renal</td>
<td>Low</td>
<td></td>
<td>Brand: 3rd Tier Generic: 1st Tier</td>
</tr>
<tr>
<td>Metoprolol (Lopressor®, Toprol®XL)</td>
<td>Acute MI, Angina, Cardiomyopathy, Heart Failure, Hypertension, MI prophylaxis, Post-MI</td>
<td>25, 50, 100mg Tablet (tart rate) 25, 50, 100, 200mg ER Tablet (succinate) 1mg/ml soln for inj</td>
<td>Renal</td>
<td>Moderate</td>
<td>MSA</td>
<td>Brand: 3rd Tier Generic: 1st Tier</td>
</tr>
<tr>
<td><strong>Mixed a1-b adrenergic antagonists (class representatives)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol (Coreg®, Coreg®CR)</td>
<td>Acute MI, Cardiomyopathy, Heart Failure, Hypertension, MI prophylaxis</td>
<td>3, 125, 6.25, 12.5, 25mg Tablet 10, 20, 40, 80mg ER Capsules</td>
<td>Hepatic</td>
<td>High</td>
<td>MSA</td>
<td>Brand: 3rd Tier Generic: 1st Tier</td>
</tr>
<tr>
<td>Labetalol (Normodyne®)</td>
<td>Hypertension</td>
<td>100, 200, 300mg Tablet 5mg/ml soln for inj</td>
<td>Hepatic</td>
<td>Moderate</td>
<td>MSA</td>
<td>Brand: 3rd Tier Generic: 1st Tier</td>
</tr>
<tr>
<td><strong>Highly Selective B1-adrenergic antagonists (3rd Gen)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nebivolol (Bystolic®)</td>
<td>Hypertension</td>
<td>2.5, 5, 10mg Tablet</td>
<td>Renal, Hepatic</td>
<td>High</td>
<td></td>
<td>Brand Only: 3rd Tier</td>
</tr>
</tbody>
</table>

**Lipid solubility** – Beta-blockers vary in their lipid solubility, the more lipid soluble the more likely CNS ADRs will occur.

**Beta receptor selectivity** – B Bs have differing affinity for beta receptors, beta1 blocking effects provide protection from ischemic metabolic changes & contribute to BP reduction, more beta1 selective, LESS likely to adversely affect lung function or cause hypokalemia.

**Intrinsic sympathomimetic activity (ISA)** – Agents with ISA capable of exerting low level agonist activity at beta-receptors while simultaneously acting as receptor antagonist. B Bs w/ISA may be LESS likely to impair myocardial function or adversely affect lung function. They reduce resting HR LESS than other B Bs, disadvantage for treating angina.

**Membrane stabilizing effects (MSAs)** – MSAs involve the inhibition of action potential propagation across the membrane, producing a nerve block.

Current through July 2009; **MSA**: Membrane Stability Activity, **ISA**: Intrinsic Sympathomimetic Activity, **FFA**: Free fatty acid.
**INTRODUCTION**

Hypertension and type II diabetes are conditions that commonly occur simultaneously. For example, Type II diabetic patients have a 40-60% greater risk of developing hypertension when compared with the general population. Uncontrolled hypertension in diabetic patients increases the risk of cardiovascular complications such as stroke and coronary artery disease (CAD). Cardiovascular risk can be reduced by attaining and maintaining established therapeutic goals utilizing antihypertensive drug regimens including combinations of, but not limited to, thiazide diuretics, ACE inhibitors, calcium channel blockers, and beta-blockers. Beta-blockers have been shown to reduce cardiovascular risk in patients with both of these chronic conditions. However, beta-blocker therapy may worsen glycemic and/or lipemic control and may lead to microalbuminuria. Several recent clinical studies have demonstrated that cardioselective (vasodilating) beta-blockers have less deleterious effects on insulin sensitivity/insulin resistance, HbA1c, and lipid levels of hypertensive patients with type II diabetes.

**BACKGROUND**

Vasodilating beta-blockers tend to have a more favorable hemodynamic profile when compared with non-vasodilating beta-blockers. Vasodilating beta-blockers reduce peripheral vascular resistance (PVR) while maintaining or improving cardiac output (CO), stroke volume, and left ventricular function. In contrast, non-vasodilating beta-blockers tend to raise the PVR and reduce the CO and left ventricular function. Therefore, vasodilating beta-blockers appear to be more effective in reducing cardiovascular events than non-vasodilating beta-blockers.

One recent clinical study, the Glycemic Effect in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, found that carvedilol appeared to benefit glycemic control, whereas metoprolol tartrate was detrimental. The GEMINI trial was published in 2004 and had up to 35 weeks of follow-up. Since then another vasodilating beta-blocker (nebivolol) was approved in 2007. Therefore, a literature search was performed to compare vasodilating and non-vasodilating beta-blockers in regard to glycemic or metabolic control and durability of the type of benefit seen with vasodilating beta-blockers (carvedilol and nebivolol) since the GEMINI trial was published. Unfortunately, there were no other studies published after the GEMINI trial to compare vasodilating beta-blockers and non-vasodilating beta-blockers in specific regard to glycemic or metabolic control.

**LITERATURE REVIEW**

**Links:** Trials and articles relevant to subject at hand...

- [GEMINI trial]
- [Journal of Clinical Hypertension 2008 article]
- [YES TONO trial]
- [Journal of Clinical Pharmacy and Therapeutics 2006 article]
- [SENIORS trial]
- [ASCOT-BPLA trial]
- [ALPINE study]
- [COMET trial substudy]

**GEMINI**

**Design:**
The GEMINI trial was a randomized, double-blind, parallel-group trial comparing the effects of carvedilol and metoprolol tartrate on glycemic control in hypertensive patients with type II diabetes.

**Intervention/Method:**

- The study consisted of 1,235 patients that were on standard antidiabetic therapies, along with either an ACE inhibitor or an angiotensin II receptor blocker.
- The patients were randomized to receive a 6.25mg to 25mg dose of carvedilol twice daily or a 50 to 200mg dose of metoprolol tartrate twice daily.
- The patients were then followed for 35 weeks.
- Insulin resistance was measured by the Homeostasis Model Assessment - Insulin Resistance (HOMA-IR).
- Urinary albumin/creatinine ratio (ACR) was used as a measure of microalbuminuria.

**Primary Outcome:**

- Difference in HbA1c change from baseline between the two groups after 5 months of maintenance therapy.
Secondary Outcomes:

- HbA1c changes from baseline in the individual treatment groups, changes in systolic and diastolic blood pressure, fasting glucose and insulin resistance, lipid panel (total cholesterol, LDL, HDL, and triglycerides), ACR, and withdrawal rates. At study completion, the difference in HbA1c from baseline between carvedilol and metoprolol tartrate treated groups was a small but statistically significant 0.13% (p = 0.004) for the modified intention-to-treat analysis.
- Blood pressure reduction was similar in both groups.
- In carvedilol treated patients, HOMA-IR was significantly REDUCED (-9.1%, p = 0.004).
- In metoprolol tartrate treated patients, there was only a 2.0% reduction (p = 0.48) in HOMA-IR, which was NOT statistically significant.

Definition – Homeostasis Model Assessment – Insulin Resistance (HOMA-IR):
The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function. It was first described under the name HOMA by Matthews et al. in 1985.

- This method has been validated in numerous studies, including the following [Link]
  - HOMA IR = FIRI x FP G / 22.5
    - [FIRI is fasting plasma insulin level (μU/ml) and FP G is fasting plasma glucose level (mmol/l)]

Definition – Albumin to Creatinine Ratio (ACR): NKDEP Quick Reference [Link]
- Estimates the 24-hr urine albumin excretion.
- Urine albumin (mg/dL) / Urine Creatinine (g/dL) = UACR in mg/dL

Results:

- The differences in total cholesterol and triglyceride level reductions between the two groups were 2.9% (p = 0.001) and 9.8% (p<0.001), respectively.
  - This showed that carvedilol treated patients had GREATER improvements in total cholesterol and triglyceride levels compared with metoprolol tartrate treated patients.
  - NO difference in LDL or HDL level was reported between the two groups.
- In addition, the difference in ACR ratio reduction was 16.2% (p = 0.003) between carvedilol and metoprolol tartrate treated patients.
- Only 6.4% of patients progressed to microalbuminuria in the carvedilol treated group, compared to 10.3% in the metoprolol tartrate treated group.
  - Frequency of progression to microalbuminuria was LOWER in carvedilol treated patients compared with metoprolol tartrate treated patients.

Comments:

In the GEMINI trial, many participating patients were also taking insulin sensitizers [thiazolidinediones (TZDs) and metformin] to help control their diabetes. Insulin sensitizers may help compensate for the insulin resistance caused by
beta-blockers. Therefore, a retrospective analysis of GEMINI data was performed to determine whether the beneficial glycemic control with carvedilol would be affected when insulin sensitizers were administered together.\(^4\)

**Note:**
- **This retrospective analysis showed NO significant effect on HOMA-IR in either the carvedilol or metoprolol tartrate treated groups taking TZDs or metformin concomitantly.**
- In contrast, when the patients were NOT taking TZDs or metformin, a 13.2% increase (p< 0.01) on HOMA-IR was seen in metoprolol tartrate treated group and a 4.8% decrease (p = 0.37) on HOMA-IR was seen in carvedilol treated group.
  - However, the decrease on HOMA-IR in the carvedilol treated group was NOT statistically significant.
- Study investigators concluded that the concomitant administration of insulin sensitizers appeared to offset the insulin resistance effect of metoprolol tartrate.

In another analysis of the GEMINI trial, Messerli F et al\(^10\) showed that there was a statistically significant difference in weight gain between carvedilol and metoprolol treated patients. This is important for many reasons including, not the least of which is a reduction in insulin sensitivity being associated with weight gain.

- Compared with baseline, patients taking metoprolol experienced a significant mean weight gain (1.2±0.16 kg; P <0.001), whereas
- Patients taking carvedilol did NOT (0.17±0.19 kg; P=0.36)
- Compared with metoprolol-treated patients, carvedilol-treated patients were MORE likely to experience NO weight change (44 vs. 35%; P=0.005)
- Those treated with carvedilol were LESS likely to experience a weight gain of >7% (1.1 vs. 4.5%; P=0.006)

**Falkner et al – Journal of Clinical Hypertension**

Another recent study published in January 2008 showed that treatment with extended-release (ER) metoprolol succinate lowered blood pressure WITHOUT altering insulin sensitivity in hypertensive patients with type II diabetes.\(^9\)

**Study Aim:**
- The goal of the study was to evaluate the metabolic effects (insulin sensitivity, lipid levels, and HgA\(_1c\)) of ER metoprolol.

**Design:**
- The study consisted of 41 patients that were on antidiabetic therapy, along with an ACE inhibitor or an angiotensin II receptor blocker, and a diuretic as part of their ongoing treatment.

**Note:**
- Which particular other medications used by the patients, such as antidiabetic agents (i.e., were patients on TZDs or Metformin, known to significantly reduce insulin resistance caused by beta blockers??), were NOT provided.

**Exclusion Criteria:**
- patients with asthma, heart failure, or reduced renal function (serum creatinine > 1.4mg/dL)
- patients taking three or more antihypertensive agents

**Intervention/Method:**
- All patients received ER metoprolol succinate with a starting dose of 50 mg/day, which was titrated upward every 2 weeks to a dosage that achieved the target blood pressure (<130/85 mmHg); the maximum daily dose of ER metoprolol succinate was set at 200 mg.
- Insulin sensitivity was measured by the insulin clamp procedure prior to and 12 weeks after the addition of metoprolol succinate to usual therapy.

**Results:**
- This study showed that ER metoprolol succinate had NO significant effect on insulin sensitivity, lipid profile, and HgA\(_1c\) in hypertensive patients with type II diabetes (whereas shorter-acting metoprolol tartrate was associated with increased HgA\(_1c\) and insulin resistance in the GEMINI trial). Tables II and III for detailed results.

**Investigator Conclusion:**
- ER metoprolol succinate had NO effect on insulin sensitivity, which could possibly be attributed to pharmacokinetic differences (t\(_{\text{max}}\), peak-trough plasma level fluctuation index, mean relative bioavailability, and plasma concentration profile) between the two different preparations of metoprolol.
Limitations:

✓ Include its short duration, small number of subjects (n=41), potential masking of insulin resistance by certain antidiabetic drugs, and its funding by AstraZeneca Pharmaceuticals, the manufacturer of ER metoprolol succinate (Toprol® XL).

Comments:

This study was much smaller than GEMINI, used XL metoprolol succinate instead of immediate release metoprolol tartrate and primarily used the insulin clamp procedure to measure insulin resistance instead of just the HOMA-IR method.

<table>
<thead>
<tr>
<th>Table II. Insulin Sensitivity Determined by Insulin Clamp Before and During ER Metoprolol Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual Treatment</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Glucose (basal), mg/dL</td>
</tr>
<tr>
<td>Glucose (clamp), mg/dL</td>
</tr>
<tr>
<td>Insulin (basal), μU/mL</td>
</tr>
<tr>
<td>Insulin (clamp) ([I]), μU/mL</td>
</tr>
<tr>
<td>M, mg/kg/min</td>
</tr>
<tr>
<td>M/I</td>
</tr>
<tr>
<td>M', mg/kg FFM/min</td>
</tr>
<tr>
<td>M'/I</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *No significant difference by paired analysis. Abbreviations: ER metoprolol, extended-release metoprolol succinate; FFM, fat-free mass; Ic, plasma insulin concentration during steady-state hyperinsulinemia; M, insulin-mediated glucose uptake; M/I, glucose uptake adjusted for level of steady state hyperinsulinemia; M', glucose uptake adjusted for adiposity; M'/I, glucose uptake adjusted for adiposity and steady state hyperinsulinemia.

Table III. Metabolic Measures Before and During ER Metoprolol Treatment

<table>
<thead>
<tr>
<th><strong>Usual Treatment</strong></th>
<th><strong>Usual Treatment + ER Metoprolol</strong></th>
<th><strong>P Value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA</td>
<td>2.96±2.16</td>
<td>2.89±2.44</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.15±0.02</td>
<td>0.15±0.03</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>7.5±2.2</td>
<td>7.1±1.4</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>177±50</td>
<td>180±40</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>44±12</td>
<td>43±12</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>106±35</td>
<td>112±24</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>153±126</td>
<td>1250±98</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Abbreviation: ER metoprolol, extended-release metoprolol succinate; HUL, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL, low-density lipoprotein cholesterol; QUICKI, quantitative insulin sensitivity check index.

YES TO NO Study

As far as the newest vasodilating beta-blocker (nebivolol), there were a few recent studies conducted in hypertensive patients with type II diabetes.

**Design:**

✓ The largest prospective, OPEN-label, multicenter, post-marketing surveillance study conducted in Germany to evaluate the effects of nebivolol on hypertensive patients with type II diabetes.6

**Intervention/Method:**

✓ Nebivolol was administered either as monotherapy or as an add-on therapy to other antihypertensive agents in 2,838 patients for a minimum period of 3 months.

**Primary Outcome:**

✓ The change in blood pressure from baseline.

**Secondary Outcome:**

✓ Changes in metabolic parameters.

**Results:**

✓ Changes in metabolic parameters are summarized in Table V below
✓ After 3 months of nebivolol therapy, the mean decrease in SBP from baseline was 21.1 mmHg (p<0.001) and the mean decrease in DBP from baseline was 10.9 mmHg (p< 0.001)
✓ This study also showed an IMPROVEMENT in almost all metabolic parameters, including lipid levels, HgA1c, and microalbuminuria.
In addition, the percentage of patients with microalbuminuria DECREASED from 10.1% to 6.8% at the end of the nebivolol treatment period (p<0.001).
NO severe adverse events (ADRs) were reported and a LOW rate of reported ADRs seen at the end of the study.

Investigator Conclusion:

Study investigators concluded that a large reduction of blood pressure was seen with nebivolol, either as monotherapy or as add-on therapy to other antihypertensive agents in hypertensive patients with type II diabetes.

NOTE: NO negative effects on glycemic control or metabolic parameters were seen.

Table V. Changes in metabolic parameters

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline mean</th>
<th>SD</th>
<th>Change from baseline after 3 months mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>2797</td>
<td>96.6</td>
<td>14.7</td>
<td>-1.0</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>1644</td>
<td>135.1</td>
<td>34.2</td>
<td>-13.1</td>
<td>27.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycosylated haemoglobin %</td>
<td>1465</td>
<td>6.93</td>
<td>0.6</td>
<td>-0.25</td>
<td>0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>1327</td>
<td>225.7</td>
<td>43.8</td>
<td>-16.3</td>
<td>31.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>1368</td>
<td>156.7</td>
<td>39.8</td>
<td>-13.3</td>
<td>27.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>1337</td>
<td>49.8</td>
<td>17.0</td>
<td>2.4</td>
<td>16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>1161</td>
<td>205.4</td>
<td>108.5</td>
<td>-24.1</td>
<td>75.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1332</td>
<td>1.04</td>
<td>0.56</td>
<td>0.0</td>
<td>0.43</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria present</td>
<td>1190</td>
<td>48</td>
<td>4.0</td>
<td>39</td>
<td>3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Microalbuminuria present (&lt;300mg/L/24h)</td>
<td>1173</td>
<td>132</td>
<td>11.3</td>
<td>100</td>
<td>8.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Statistical test applied: Student’s t-test.
b Statistical test applied: McNemar test.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; SD = standard deviation.


One other small study also suggested that nebivolol has NO negative effects on glycemic and metabolic control in hypertensive patients with type II diabetes.³

Intervention/Method:

This small study was conducted in 26 patients in Birmingham, England.
The patients were NOT taking any antihypertensive agents before enrollment and they were treated with nebivolol 5mg daily over the 6-month study period.
Lipid profile, LDL subfractions, lipid hydroperoxides (LHPs), and total antioxidant capacity (TAC) were taken before and after 6 months of treatment.

Primary Outcome:
The primary endpoint of this study was the change in blood pressure from baseline.

Secondary Outcome:
Secondary endpoints included the effect on glycemic control, lipid profile, and markers of oxidative stress after 6 months of treatment with nebivolol.

Results:
Mean ambulatory daytime SBP decreased from 149.1 ± 9.3 to 140.1 ± 13.9 mmHg (p = 0.02) and the mean daytime DBP decreased from 84 ± 7.09 to 77.8 ± 9.52 mmHg (p< 0.001).
Glycemic control did NOT appear to be affected by nebivolol, and there was NO significant change in HbA₁c (from 7.6 ± 1.3 to 7.7 ± 1.4) (no p-value reported).
In terms of lipid profile, there were NO significant differences in total cholesterol and triglyceride levels after 6 months of treatment (no p-value reported).
However, HDL improved significantly from 1.12 ± 0.19 to 1.25 ± 0.36 mmol/L (p = 0.009)
Whereas the LDL subfractions worsened (increased from 1.7 ± 0.7 to 2.3 ± 0.7 (p = 0.0002))
TAC was significantly reduced from 501 ± 57 to 422 ± 29 trolox equivalent (p< 0.001)
No change in LHPs was reported after treatment with nebivolol

Investigator Conclusion:
Study investigators concluded that SBP and DBP were improved by a mean of 5 mmHg WITHOUT negative effects on glycemic control and metabolic parameters (NO changes in total cholesterol and triglycerides; with improved HDL).
However, a statistically significant INCREASE in LDL subfractions and a statistically significant DECREASE in TAC were reported in this study.

SENIORS Trial
[Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure]
✓ Nebivolol found to be an effective and well tolerated drug in elderly (>70 yrs) patients with heart failure, regardless of ejection fraction. Advanced age population unique to such trials.
✓ A subanalysis of this trial presented at the World Congress of Cardiology meeting in 2006, was in agreement with other trials finding NO negative impact on lipid or carbohydrate metabolism by nebivolol.

ASCOT-BPLA Trial
[Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm]
✓ Found amloidipine 10 mg +/- perindopril to be better than atenolol 100 mg +/- bendroflumethiazide for those with hypertension and additional risk factors.
  o Amlodipine arm BP 164.1/94.8→136.1/77.4 mmHg
  o Atenolol arm BP 163.9/94.5→137.7/79.2 mmHg
✓ Atenolol arm: INCREASE of 0.2 mmol/l glucose & DECREASE of HDL by 0.1 mmol/l more than amloidipine arm (baseline glucose was 6.2 mmol/l)
✓ As a tertiary outcome, new onset diabetes was 5.9% for amloidipine arm vs. 8.3% for atenolol arm (p<0.0001)

ALPINE Study
[Antihypertensive Treatment and Lipid Profile in a North Sweden Efficacy Evaluation]
✓ Antihypertensive treatment with a diuretic, if needed combined with a beta-adrenoreceptor blocker (atenolol), was associated with an aggravated metabolic profile.
✓ The ARB candasartan alone or in combination with calcium antagonist felodipine did NOT aggravate the metabolic profile.

COMET Trial – substudy
[Carvedilol or Metoprolol European Trial]
✓ Primary finding was a statistically significant risk reduction in overall mortality in the carvedilol group compared with the metoprolol group.
✓ Secondary finding – new onset diabetes was REDUCED in the carvedilol arm compared w/metoprolol arm
  o Risk reduction of 23% (p = 0.0334)

DISCUSSION
Here are some miscellaneous points to consider and further information on the newest beta-blocker, nebivolol.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Insulin Sensitivity (%)</th>
<th>TGs (%)</th>
<th>HDL-C (%)</th>
<th>Total Cholesterol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>-33</td>
<td>+25</td>
<td>-10</td>
<td>+9</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>-21</td>
<td>+30</td>
<td>-7</td>
<td>-1</td>
</tr>
<tr>
<td>Atenolol</td>
<td>-22</td>
<td>+18</td>
<td>-9</td>
<td>NC</td>
</tr>
<tr>
<td>Pindolol</td>
<td>-17</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Dilevalol</td>
<td>+10</td>
<td>-22</td>
<td>N/A</td>
<td>-6</td>
</tr>
<tr>
<td>Carvedirol</td>
<td>+13</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>+35</td>
<td>-15</td>
<td>+5</td>
<td>NC</td>
</tr>
</tbody>
</table>

a Mean values of various studies
b Not specified which formulation was used for the average values provided
N/A = Not available, NC = No change

Adapted from Kveiborg B et al, Am J Cardiovasc Drugs 2006;6(4):211 (Table II)

✓ It has been demonstrated that the decrease in insulin sensitivity correlates with a reduced blood flow in peripheral tissue such as skeletal muscles.
Traditional beta-blockers reduce first phase insulin secretion, which is important in the development of type II DM. BBs also appear to reduce insulin clearance and thereby increase plasma insulin; hyperinsulinemia then leads to a worsening of insulin sensitivity.

Glucose clamp studies have shown a decrease in insulin sensitivity in patients who did NOT gain weight and it is therefore possible that decreased insulin sensitivity does NOT play an important role as a direct mechanism for weight gain.
- On the other hand, decreased insulin sensitivity causes an increased insulin level and can increase appetite and lipolysis, changes which could explain weight gain seen after treatment with BBs.

Nebivolol is as effective as atenolol in reducing blood pressure, but has a more homogeneous effect over 24 hours, as documented by a clearly superior trough-to-peak ratio for its antihypertensive effect.

In contrast to other beta-blockers, nebivolol does NOT reduce exercise tolerance.

In contrast to other 3rd generation beta-blockers such as labetalol and carvedilol, that mediate a vasodilatory effect through alpha1-adrenoreceptor antagonism, nebivolol mediates endothelium-dependent arterial and venous dilatation via the L-arginine-nitric oxide-dependent pathway.
- These effects are thought to be due to the l-enantiomer, whereas the blood pressure lowering properties of nebivolol appear to be provided by the d-enantiomer.

AACE Evidence-based recommendations for management of hypertension and concomitant type 2 diabetes
- Beta-blockers (preferably drugs that block both the alpha AND beta receptors) as 2nd or 3rd line agent – Evidence Level 1 (highest)

Other trials of nebivolol measuring metabolic impact:

<table>
<thead>
<tr>
<th>Study</th>
<th>Type and number of patients</th>
<th>Type and duration of drug treatment</th>
<th>Impact on metabolic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dadov et al.[8]</td>
<td>35 hypertensive and diabetic</td>
<td>Nebivolol vs placebo; 8 weeks</td>
<td>Significant reduction in triglycerides with nebivolol</td>
</tr>
<tr>
<td>Peciel et al.[9]</td>
<td>18 hypertensive</td>
<td>Nebivolol; 6 weeks</td>
<td>No change in lipid or carbohydrate metabolism</td>
</tr>
<tr>
<td>Flather et al.[11]</td>
<td>2128 with congestive heart failure</td>
<td>Nebivolol vs placebo; mean follow-up 21 months</td>
<td>Incidence of new-onset diabetes mellitus similar with nebivolol and placebo</td>
</tr>
<tr>
<td>Poirier et al.[30]</td>
<td>25 hypertensive with glucose intolerance</td>
<td>Nebivolol vs atenolol; 16 weeks (crossover design)</td>
<td>No change in insulin sensitivity with nebivolol, significant reduction (20%) with atenolol</td>
</tr>
<tr>
<td>Fogari et al.[31]</td>
<td>30 hypertensive and diabetic</td>
<td>Nebivolol vs atenoloid; 6 months</td>
<td>Both drugs neutral on lipid profile and insulin sensitivity</td>
</tr>
<tr>
<td>Makotkin et al.[32]</td>
<td>36 hypertensive and diabetic with ischaemic heart disease</td>
<td>Nebivolol vs metoprolol; 9 weeks</td>
<td>Reduction in serum triglycerides with nebivolol; no change with metoprolol</td>
</tr>
<tr>
<td>Fitzos et al.[25]</td>
<td>30 hypertensive and dyslipidaemic</td>
<td>Nebivolol + pravastatin vs atenoloid + pravastatin; 24 weeks</td>
<td>No change in triglycerides and reduction of HOMA index (20%) with nebivolol; no change in HOMA index and increase in triglycerides (19%) with atenoloid</td>
</tr>
<tr>
<td>Celik et al.[13]</td>
<td>80 hypertensive</td>
<td>Nebivolol vs metoprol; 6 months</td>
<td>Reduction in HOMA index and insulin levels with nebivolol</td>
</tr>
<tr>
<td>Agabiti Rosell et al.[34]</td>
<td>68 hypertensive</td>
<td>Nebivolol vs lisinopril; 3 months</td>
<td>No adverse effect on carbohydrate and lipid metabolism with either drug</td>
</tr>
<tr>
<td>Lacourciere et al.[36]</td>
<td>51 hypertensive</td>
<td>Nebivolol vs nifedipine sustained-release; 12 weeks</td>
<td>Reduction in total and LDL cholesterol with both drugs</td>
</tr>
<tr>
<td>Lacourciere and Amcet[45]</td>
<td>240 hypertensive</td>
<td>Nebivolol vs HCTZ vs nebivolol + HCTZ (lactical design); 12 weeks</td>
<td>No change in serum lipids, lipoproteins or apolipoproteins with any treatment. Small increase in triglycerides with HCTZ</td>
</tr>
</tbody>
</table>

HCTZ = hydrochlorothiazide; HOMA = Homeostasis Model Assessment; LDL = low-density lipoprotein.

CONCLUSION

There were no head-to-head comparisons between vasodilating and non-vasodilating beta-blockers in regard to glycemic or metabolic control in patients with type II diabetes and hypertension after the GEMINI trial. The GEMINI trial was the first randomized trial that compared two beta-blockers’ effects (vasodilating vs. non-vasodilating) on glycemic control and other cardiovascular risk factors.
However, there were some studies conducted on the newest vasodilating beta-blocker (nebivolol) in regard to glycemic and metabolic control after the GEMINI trial as mentioned above. It appears that vasodilating beta-blockers do NOT have negative effects on metabolic parameters in terms of insulin sensitivity, HbA$_{1c}$, and lipid profiles. Notably, the addition of a vasodilating or non-vasodilating beta-blocker does NOT seem to affect insulin resistance in patients already taking an insulin sensitizer (TZDs or metformin). On the contrary, non-vasodilating beta-blockers have demonstrated worsened metabolic parameters following their initiation in the absence of insulin sensitizing agents.

Therefore, vasodilating beta-blockers could be considered for diabetic patients when beta-blockers are warranted. In contrast, more pharmacokinetic and pharmacodynamic studies need to be conducted on non-vasodilating beta-blockers since the different preparations of non-vasodilating beta-blockers may result in different glycemic and/or metabolic control.
Some Key references:


Individual product information sheets for each drug were also utilized. Links to each provided in first chart.


Quiz Answer Key:
1. a
2. c
3. b
4. a
5. b
6. d
7. c
8. a