DILATREND®

Carvedilol: β-blockade and beyond

Donghoon Choi, M.D., Ph.D.

Division of Cardiology
Severance Cardiovascular Hospital
Yonsei University Health System
Chapter I  Beta Blockers

Chapter II  Carvedilol: β blocker beyond β1-blockade

1  Cardioprotective Effect

2  Metabolic Effect

3  Renal Effect

4  Tolerability

Chapter III  Conclusion
Beta Blockers

- Classification of Beta-Blockers

- 1st generation
  - nonselective for $\beta_1$ or $\beta_2$ blockade
  - no ancillary properties
    ex) propranolol

- 2nd generation
  - selective for $\beta_1$ or $\beta_2$ blockade
  - no ancillary properties
    ex) bisoprolol, metoprolol, atenolol

- 3rd generation
  - selective or nonselective blockade
  - has potentially important ancillary properties
    ex) carvedilol, nebivolol

Ref. Am J Cardiol 1997;80(11A):26L–40L
Beta Blockers

- β-blockers are not an homogeneous group of agents
  - Potency and duration of action
  - Cardioselectivity ($\beta_1$ selectivity)
  - Intrinsic sympathomimetic activity (ISA)
  - Lipid solubility
Carvedilol: β-blocker beyond β$_1$-blockade

3$^{rd}$ generation vasodilating β-blocker

- Carvedilol is a third-generation, combination β$_1$-, β$_2$-, α$_1$-adrenergic receptor antagonist.
- Carvedilol has been marketed worldwide for the treatment of hypertension, chronic heart failure and coronary artery disease.
- History
  - In 1990, a first approval of carvedilol was obtained in Germany.
  - In 1994, carvedilol was marketed in Korea.
  - In 1995, carvedilol was marketed in USA.

Ref. Am J Cardiol, 2006;98(7A):1L-4L. R&D focus‘carvedilol’
Carvedilol: $\beta$ blocker beyond $\beta_1$-blockade

### Hemodynamic effect

**Vasodilation**
- $\alpha_1$-receptor blockade by carvedilol decreases peripheral vascular resistance. 2)

### Anti-oxidant activity

**Potent antioxidant effect more than vitamin E**
- Carvedilol is a potent anti-oxidant, 10-fold more than vitamin E. 1)
- Cavedilol's metabolites are 30 – 80 times more potent than carvedilol and up to 1000-fold more potent than vitamin E. 1), 3)

### Anti-proliferative & Anti-apoptotic activity

- Carvedilol in vitro and in vivo has been shown to have antiproliferative effects on smooth muscle cells 4)

### Anti-arrhythmic effect

- $\beta_2$-receptor blockade may prevent arrhythmias and, consequently, sudden cardiac death. 2)
- $\alpha_1$-receptor blockade by carvedilol reduces the potential for arrhythmias. 2)

---

Ref. 1) Am J Cardiol, 1997;82(1A):41L-45L  
Carvedilol: \( \beta \) blocker beyond \( \beta_1 \)-blockade

- **Cardioprotective Effect**

- **Anti-Adrenergic Activity**

<table>
<thead>
<tr>
<th>Effects</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
<th>( \alpha_1 )</th>
<th>Effects</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
<th>( \alpha_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive inotropic</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>Myocyte toxicity</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Positive chronotropic</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>Tachyarrhythmias</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Myocyte hypertrophy</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>Vasoconstriction</td>
<td>0</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Fibroblast hyperplasia</td>
<td>+++</td>
<td>+</td>
<td>NA</td>
<td>Sodium retention</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

- Not only the \( \beta_1 \) receptor, but also the \( \beta_2 \) and \( \alpha_1 \) receptor are linked to downstream cellular signaling pathways in cardiac remodeling.\(^2\)

- Consequently, blocking only the \( \beta_1 \) receptor, leaves the heart unprotected to remodeling signals triggered by stimulation of the other adrenergic receptors.\(^2\)

Ref. 1) Heart Fail Rev, 2004;9(2):123-130  
2) Cardiovasc Drugs Ther, 2010;24:351-358
Carvedilol: β blocker beyond β₁-blockade

- **Cardioprotective Effect**

- **Anti-Adrenergic Activity**
  - In the Carvedilol Or Metoprolol European Trial (COMET), patients with heart failure treated with carvedilol had a 17% lower risk of death than those treated with metoprolol (P=0.0017).

  - In heart failure patients, β₁ receptors are downregulated, whereas β₂ and α₁ receptors are upregulated. In the normal heart, β1 and β2 receptors are in a ratio of approximately 70:30, which becomes approximately 60:40 in heart failure patients.

  - When β₁-selective β-blockers are used, β₂ and α₁ receptors become sensitized and upregulated. The selective overexpression of β₂ or α₁ receptors causes cardiac hypertrophy and congestive heart failure.

Carvedilol: $\beta$ blocker beyond $\beta_1$-blockade

- **Cardioprotective Effect**

- **Anti-Adrenergic Activity**

[ Adrenergic & $\beta$-adrenergic receptor percentages in non-failing & failing human heart ]

- Non-failing myocardium is dominated by the $\beta_1$ receptor subtype, whereas failing myocardium exhibits a mixture of receptor subtypes with $\beta_2$ and $\alpha_1$ receptor subtype comprising approximately 50% of the total population.

- In the failing heart, the $\beta_2$ receptor represents 35%-40% of the total $\beta$ receptor population.

- These data would suggest that $\beta_1$ selective blocker may have inherent limitations in their ability to inhibit the adverse biological effects of elevated cardiac adrenergic drive in the failing human heart.

Ref. *Eur Heart J*, 1996;17 (Suppl B): 8-16
Carvedilol: β blocker beyond β₁-blockade

- Cardioprotective Effect
  - Anti-Adrenergic Activity

[Detrimental effects of sympathetic activation]

- Activation of the sympathetic nervous system specifically of cardiac sympathetic nerves, contributes to progression of heart failure and sudden death.

Ref. Am J Cardiol 1997;80(11A):7L–14L
Carvedilol: $\beta$ blocker beyond $\beta_1$-blockade

- Cardioprotective Effect

  - Anti-Adrenergic Activity

  [ Comparison of the effect on total body & cardiac norepinephrine spillover ]

- In heart failure patients carvedilol exerts a more potent anti-adrenergic effect than metoprolol during stress.

Ref. Cardiovasc Drugs Ther, 2010;24:351–358
Carvedilol: β blocker beyond β₁-blockade

- Cardioprotective Effect

- Anti-Adrenergic Activity

![Diagram of sympathoadrenal system and effects of various drugs]

<table>
<thead>
<tr>
<th></th>
<th>β₁ blockade</th>
<th>β₂ blockade</th>
<th>α₁ blockade</th>
<th>ISA</th>
<th>Ancillary effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+++a</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++b</td>
</tr>
</tbody>
</table>

*a*: anti-oxidant, anti-apoptotic, anti-endothelin  
*b*: NO generation

Ref. *Cardiovasc Drugs Ther, 2010;24:351-358*
Carvedilol: $\beta$ blocker beyond $\beta_1$-blockade

- **Cardioprotective Effect**

- **Vasodilation**

  

  ![Cardiac output](chart1)

  ![Systemic arterial resistance](chart2)

  - Traditional $\beta$-blockers, such as atenolol, metoprolol, bisoprolol and propranolol, lower BP primarily by reducing cardiac output.\(^2\)

  - By contrast, vasodilatory $\beta$-blockers, such as carvedilol, lower BP partly by reducing systemic vascular resistance via $\alpha_1$-inhibition.\(^2\)

Ref. 1) Cardiovasc Drugs Ther. 1996;10(2):113-117

Carvedilol: β-blocker beyond β₁-blockade

- Cardioprotective Effect

- Antioxidant Activity

[Effects on Fe²⁺-vitamin C-initiated lipid peroxidation in rat]

Carvedilol rapidly inhibited Fe²⁺-vitamin C-initiated lipid peroxidation measured as TBARS in rat brain homogenate.

*TBARS: thiobarbituric acid reactive substances

Carvedilol: β blocker beyond β₁-blockade

- Cardioprotective Effect
- Antioxidant Activity

This is the first long-term randomized parallel-group study comparing markers of oxidative stress of 2 beta blockers in patients after an AMI. (n=204)

The results indicate that carvedilol exerts a stronger antioxidant effect than atenolol, as assessed by the ox-LDL and vitamin E levels.

Carvedilol: β blocker beyond β₁-blockade

- Metabolic Effect

Glucose control
- HbA1c ↔
- Insulin Sensitivity ↑
- New-onset of DM ↔

Lipid metabolism
- TC ↓
- HDL-C ↑, LDL-C ↓
- TG ↓

Beneficial Metabolic Effect

Carvedilol: \(\beta\) blocker beyond \(\beta_1\)-blockade

- **Metabolic Effect**

  [Interplay between hemodynamic and metabolic alterations]

  - Free radical scavengers
  - Oxygen free radicals
  - EDNO formation \(\downarrow\)
  - Vasodilation \(\downarrow\)
  - Peripheral blood flow \(\downarrow\)
  - Insulin resistance \(\uparrow\)
  - Glucose uptake \(\downarrow\)
  - Glucose \(\uparrow\)
  - Down regulation of the receptor
  - Hyperinsulinemia

  *EDNO: Endothelium-derived nitric oxide*

Carvedilol: \( \beta \) blocker beyond \( \beta_1 \)-blockade

- Metabolic Effect

- Effect on insulin sensitivity

[ Effect on insulin sensitivity in patients with HTN ]

- Carvedilol: 13%
- Atenolol: -22%
- Metoprolol: -21%
- Propranolol: -33%

Carvedilol: \(\beta\) blocker beyond \(\beta_1\)-blockade

- **Metabolic Effect**

- GEMINI study: Hypertension with T2DM

- Carvedilol treatment did not increase HbA1c levels (0.02%; \(p = 0.65\)), whereas metoprolol treatment significantly increased HbA1c levels from baseline (0.15%; \(p < 0.001\)).

Ref. *JAMA.* 2004;292:2227-2236
Carvedilol: β-blocker beyond β₁-blockade

Metabolic Effect

GEMINI study: Hypertension with T2DM

[Mean change from baseline at 5 Months]

- ACR
- HOMA-IR
- Plasma glucose
- Serum insulin
- Body weight
- Progression to MAU
- TC
- LDL
- TG

Carvedilol (n=454)
Metoprolol (n=657)

* ACR: urinary albumin/creatinine ratio,  HOMA-IR: homeostatic model assessment-insulin resistance,  MAU: microalbuminuria

Ref. JAMA. 2004;292:2227-2236
Carvedilol: $\beta$ blocker beyond $\beta_1$-blockade

- Metabolic Effect

- Effect on metabolic risk factors

[ Metabolic effects in diabetic hypertensive patients ]

Carvedilol: \( \beta \) blocker beyond \( \beta_1 \)-blockade

- **Metabolic Effect**

  - Effect on new-onset of DM in COMET

  ![Graph showing Development of new-onset diabetes](image)

  - New-onset diabetes was diagnosed in 119/1,151 (10.3%) vs 145/1,147 (12.6%) in the carvedilol and metoprolol treatment groups (HR 0.78, \( p = 0.048 \)).
  - Diabetic events occurred in 122/1,151 (10.6%) patients in the carvedilol group and 149/1,147 (13.0%) patients in the metoprolol group (HR 0.78, \( p = 0.039 \)).

* Diabetic events: diabetic coma, peripheral gangrene, diabetic foot, decreased glucose tolerance, hyperglycaemia

Ref. *Heart* 2007;93:968–973
# Carvedilol: β blocker beyond β\textsubscript{1} blockade

## Renal Effect

- Effect on chronic kidney disease

[ Renal effects in chronic kidney disease (CKD) ]

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol</th>
<th>Atenolol</th>
<th>Propranolol</th>
<th>Metoprolol</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Vascular Resistance</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Renal Blood Flow</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>GFR</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

Carvedilol: β blocker beyond β₁-blockade

- Renal Effect

- Effect on microalbuminuria

[Regression of microalbuminuria]

<table>
<thead>
<tr>
<th></th>
<th>Patients with microalbuminuria (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol (n=4,014)</td>
<td>38</td>
</tr>
<tr>
<td>β-blocker (n=586)</td>
<td>24</td>
</tr>
<tr>
<td>ACEI (n=592)</td>
<td>37</td>
</tr>
<tr>
<td>CCB (n=470)</td>
<td>34</td>
</tr>
<tr>
<td>Diuretics (n=165)</td>
<td>32</td>
</tr>
</tbody>
</table>

Carvedilol: $\beta$ blocker beyond $\beta_1$-blockade

- Tolerability
- COLA study

[ Tolerability of carvedilol among patients with “traditional” precautions ]

- In COLA, 88% of all patients (n=808) with heart failure tolerated treatment with carvedilol, determined from the percentage of patients able to be maintained on a stable dose of therapy for 3 months after initiation.

Ref. Am J Cardiol 2004;93(suppl):58B–63B
**Carvedilol: β blocker beyond β₁-blockade**

- **Tolerability**

- **COLA II study**

![Bar chart showing tolerability to carvedilol according to age in COLA II](chart)

- Tolerability was defined as being on 6.25 mg bid of carvedilol at 6 months having received a total of 3 months therapy.

- Tolerability overall was 80% with age 70–75 years 84.3%, 76–80 years 76.8% and >80 years 76.8%.

Several pathophysiologic/pharmacologic studies have documented that not all β-blockers are created equal.

In particular, the new vasodilating compounds, such as carvedilol, have been shown to differ in their cardiovascular effects from traditional β-blockers.

Carvedilol, in contrast to the classic β-blockers, maintains cardiac output, has little effect on heart rate, and decreases blood pressure by decreasing systemic vascular resistance.

Ref. Am J Cardiol 2004;93(suppl):7B–12B
Thank you