DILATREND®

Carvedilol : β-blockade and beyond

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Contents

Beta Blockers

Classification of Beta-Blockers

1st generation

- nonselective for β_1 or β_2 blockade
- no ancillary properties

  ex) propranolol

2nd generation

- selective for β_1 or β_2 blockade
- no ancillary properties

  ex) bisoprolol, metoprolol, atenolol

3rd generation

- selective or nonselective blockade
- has potentially important ancillary properties

  ex) carvedilol, nebivolol

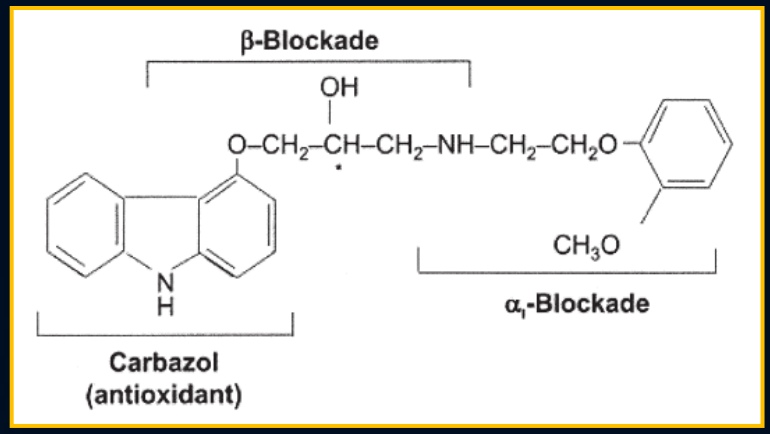
Ref. Am J Cardiol 1997;80(11A):26L–40L

Beta Blockers

- **β-blockers are not an homogeneous group of agents**
  - Potency and duration of action
  - Cardioselectivity (β_1 selectivity)
  - Intrinsic sympathomimetic activity (ISA)
  - Lipid solubility

Carvedilol : β blocker beyond β_1-blockade

3rd 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 : β blocker beyond β_1-blockade

Hemodynamic effect

Vasodilation

- α_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

- β_2-receptor blockade may prevent arrhythmias and, consequently, sudden cardiac death.[2)]
- α_1-receptor blockade by carvedilol reduces the potential for arrhythmias.[2)]

Ref. 1) Am J Cardiol, 1997;82(1A):41L-45L
2) Expert Rev Cardiovasc Ther. 2009;7(5):483-498
3) Expert Opin Drug Metab Toxicol. 2010:6(2):237-250.
4) Am J Hypertens 1998;11:15S–22S

Carvedilol : β blocker beyond β_1-blockade

Cardioprotective Effect

Anti-Adrenergic Activity

[Potentially deleterious effects of the different adrenergic receptors in the progression of HF & remodeling] [1)]

Effects	β 1	β 2	α 1	Effects	β 1	β 2	α 1
Positive inotropic	+++	++	+	Myocyte toxicity	+++	+	+
Positive chronotropic	+++	++	0	Tachyarrhythmias	++	++	+
Myocyte hypertrophy	+++	+	++	Vasoconstriction	0	-	++
Fibroblast hyperplasia	+++	+	NA	Sodium retention	0	0	++

- Not only the β_1 receptor, but also the β_2 and α_1 receptor are linked to downstream cellular signaling pathways in cardiac remodeling.[2)]
- Consequently, blocking only the β_1 receptor, leaves the heart unprotected to remodeling signals triggered by stimulation of the other adrenergic receptors.[2)]

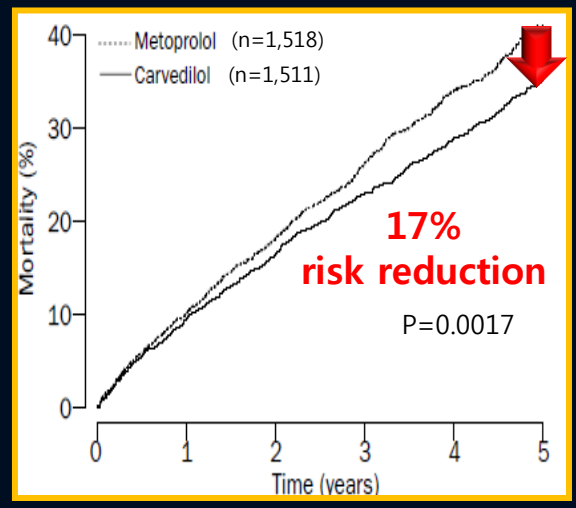
Ref. 1) Heart Fail Rev, 2004 ;9(2):123-130 *2) Cardiovasc Drugs Ther, 2010;24:351-358*

Carvedilol : β blocker beyond β_1-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, β_1 receptors are downregulated, whereas β_2 and α_1 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 β_1-selective β-blockers are used, β_2 and α_1 receptors become sensitized and upregulated. The selective overexpression of β_2 or α_1 receptors causes cardiac hypertrophy and congestive heart failure.

Ref. Expert Rev Cardiovasc Ther., 2012 ;10(1):13-25

Carvedilol : β blocker beyond β_1-blockade

Cardioprotective Effect

Anti-Adrenergic Activity

[Adrenergic & β-adrenergic receptor percentages in non-failing & failing human heart]

* p<0.05
vs non-failing

- Non-failing myocardium is dominated by the β_1 receptor subtype, whereas failing myocardium exhibits a mixture of receptor subtypes with β_2 and α_1 receptor subtype comprising approximately 50% of the total population.
- In the failing heart, the β_2 receptor represents 35%-40% of the total β receptor population.
- These data would suggest that β_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.

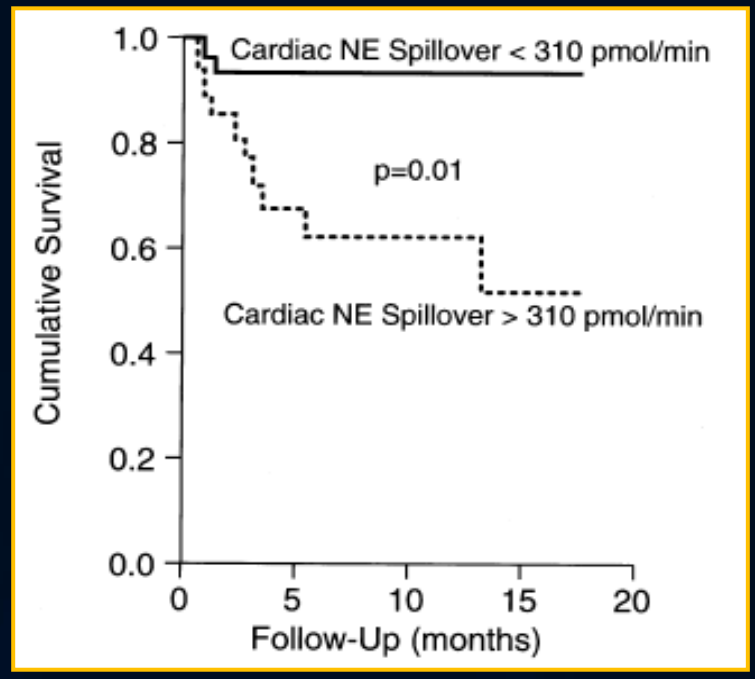
Ref. Eur Heart J, 1996;17 (Suppl B): 8-16

Carvedilol : β blocker beyond β_1-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.

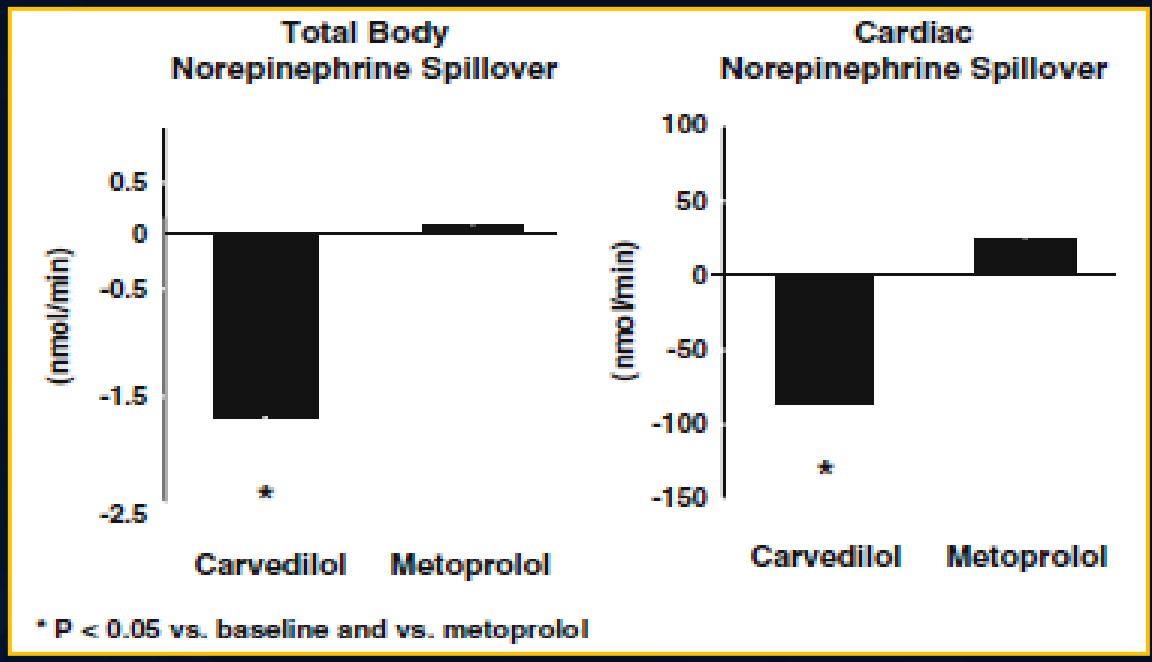
Ref. Am J Cardiol 1997;80(11A):7L–14L

Carvedilol : β blocker beyond β_1-blockade

Cardioprotective Effect

Anti-Adrenergic Activity

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



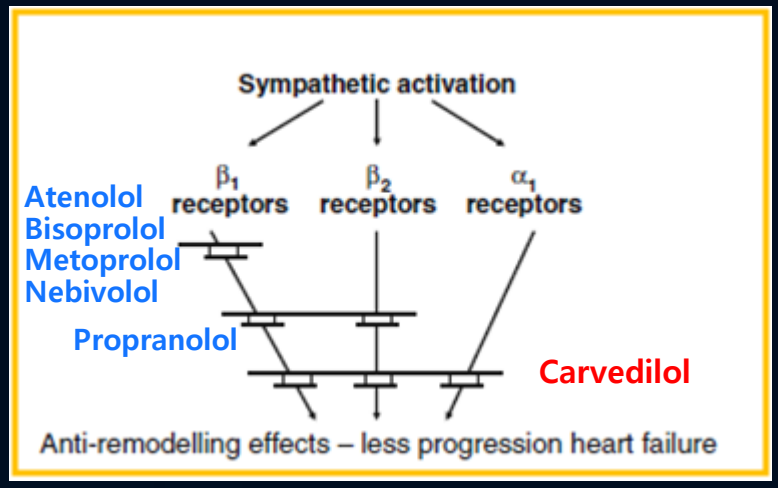
- In heart failure patients carvedilol exerts a more potent anti-adrenergic effect than metoprolol during stress.

Ref. Cardiovasc Drugs Ther, 2010;24:351–358

Carvedilol : β blocker beyond β_1-blockade

Cardioprotective Effect

Anti-Adrenergic Activity



	β_1 blockade	β_2 blockade	α_1 blockade	ISA	Ancillary effects
Carvedilol	+++	+++	+++	-	+++[a]
Metoprolol	+++	-	-	-	-
Bisoprolol	+++	-	-	-	-
Nebivolol	+++	-	-	-	++[b]

a : anti-oxidant, anti-apoptotic, anti-endothelin

b : NO generation

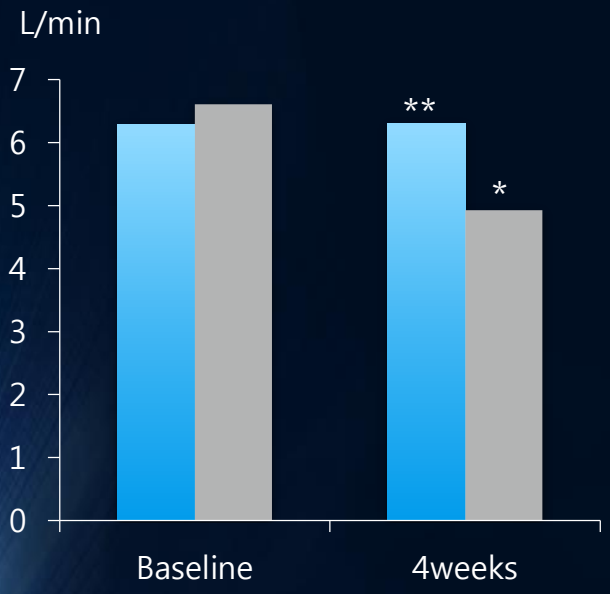
Ref. Cardiovasc Drugs Ther, 2010;24:351-358

Carvedilol : β blocker beyond β_1-blockade

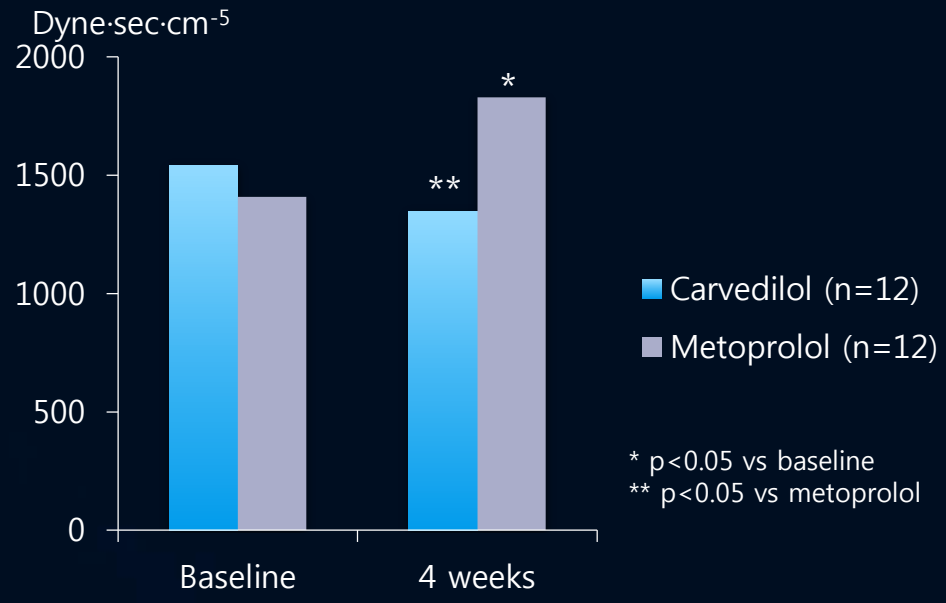
Cardioprotective Effect

Vasodilation

[Cardiac output] 1)



[Systemic arterial resistance] 1)



- Traditional β-blockers, such as atenolol, metoprolol, bisoprolol and propranolol, lower BP primarily by reducing cardiac output.[2)]
- By contrast, vasodilatory β-blockers, such as carvedilol, lower BP partly by reducing systemic vascular resistance via α_1-inhibition.[2)]

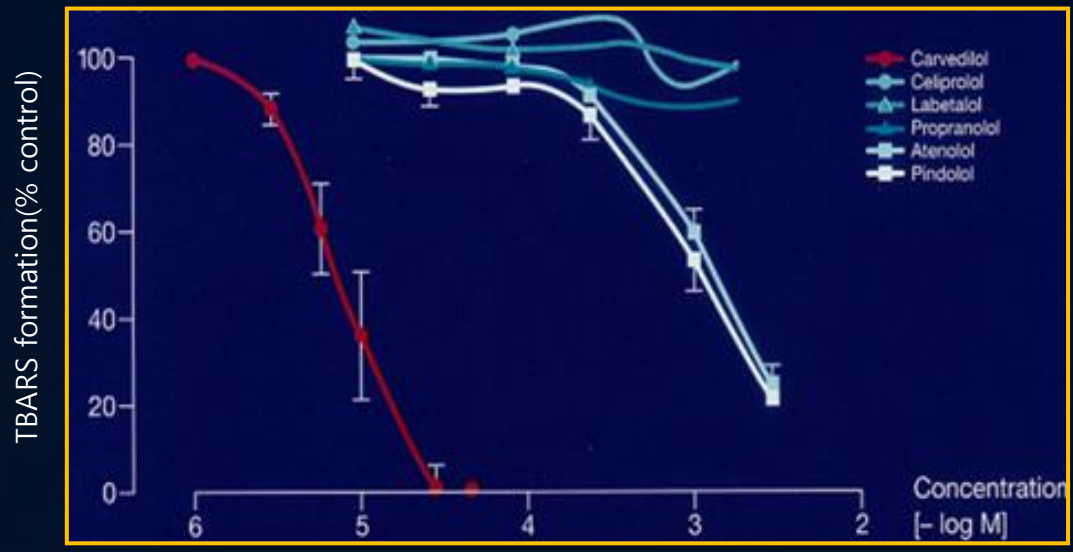
Ref. 1) Cardiovasc Drugs Ther, 1996;10(2):113-117 *2) Expert Rev Cardiovasc Ther. 2009;7(5):483-498.*

Carvedilol : β blocker beyond β_1-blockade

Cardioprotective Effect

Antioxidant Activity

[Effects on Fe^{++}-vitamin C-initiated lipid peroxidation in rat]



- Carvedilol rapidly inhibited Fe^{++}-vitamin C-initiated lipid peroxidation measured as TBARS in rat brain homogenate.

* TBARS : thiobarbituric acid reactive substances

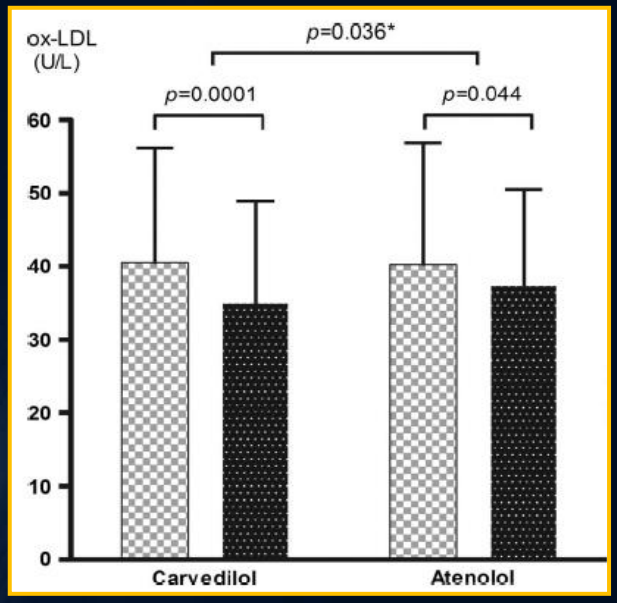
Ref. J Pharmacol Exp Ther., 1992;263(1):92-98

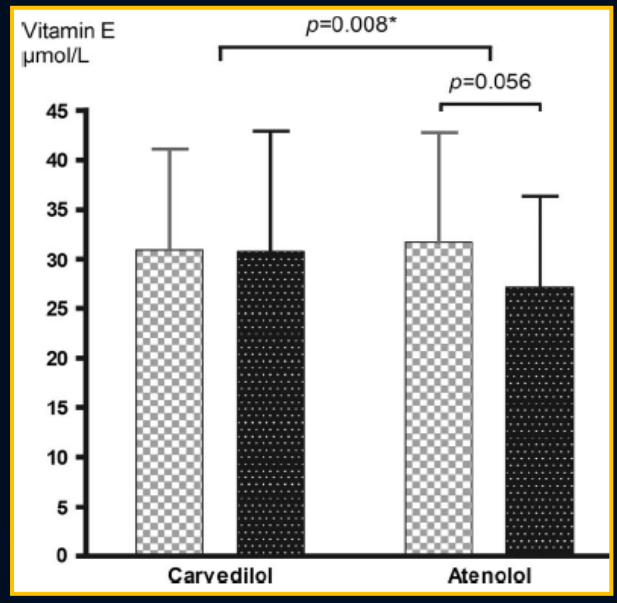
Carvedilol : β blocker beyond β_1-blockade

Cardioprotective Effect

Antioxidant Activity

[Antioxidative effects of carvedilol vs atenolol]



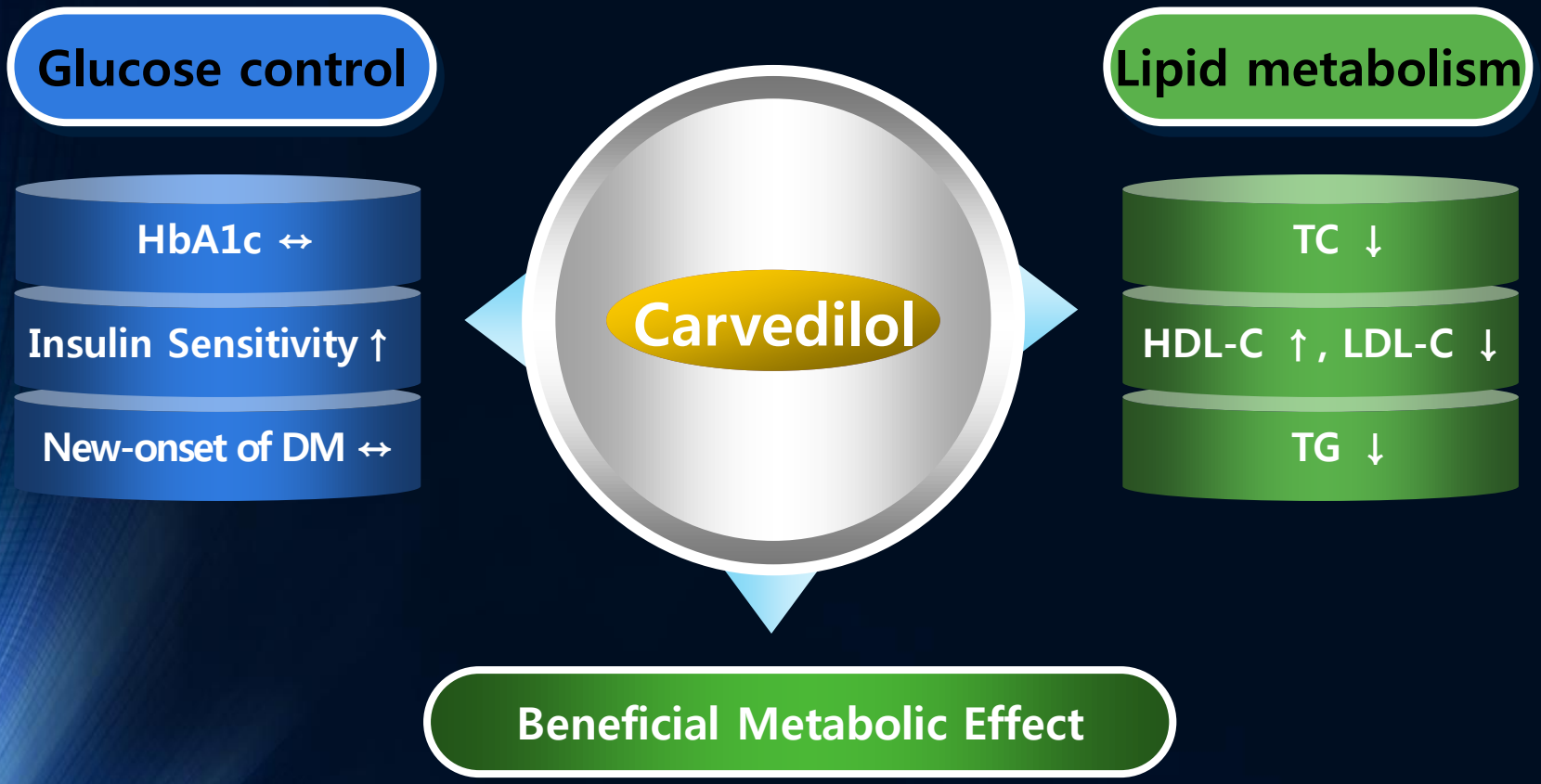


- This is the first long-term randomized parallel-group study comparing markers of oxidative stress of 2 beta blockers in patients after an AMI. (n=204)
- The results indicate that carvedilol exerts a stronger antioxidant effect than atenolol, as assessed by the ox-LDL and vitamin E levels.

Ref. J Cardiovasc Pharmacol., 2007 Jan;49(1):27-32.

Carvedilol : β blocker beyond β_1-blockade

- Metabolic Effect

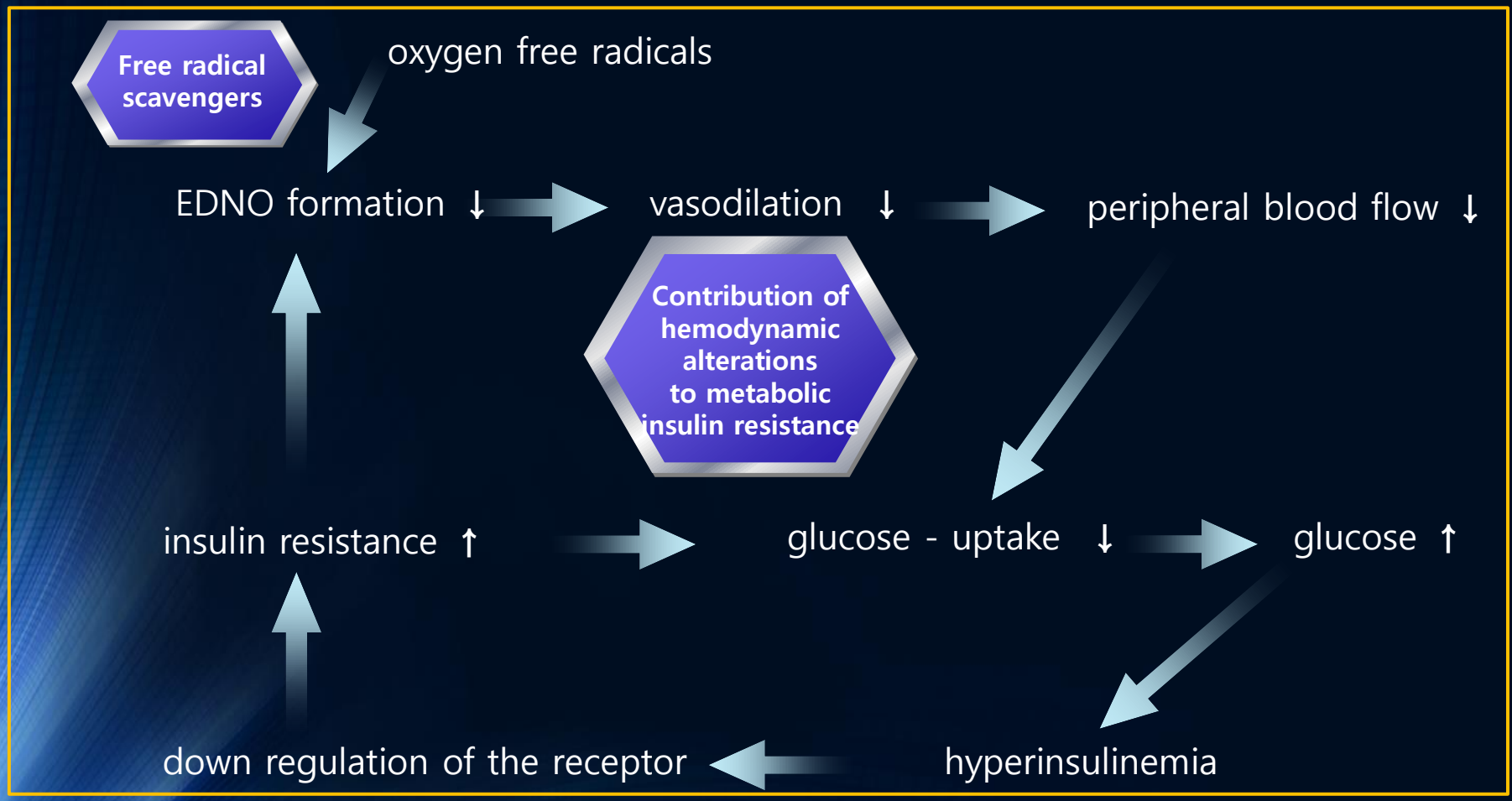


Ref. 1) Vascular Health and Risk Management 2008:4(1) 23–30 2) JAMA. 2004;292:2227-2236

Carvedilol : β blocker beyond β_1-blockade

□ Metabolic Effect

[Interplay between hemodynamic and metabolic alterations]



* EDNO : Endothelium-derived nitric oxide

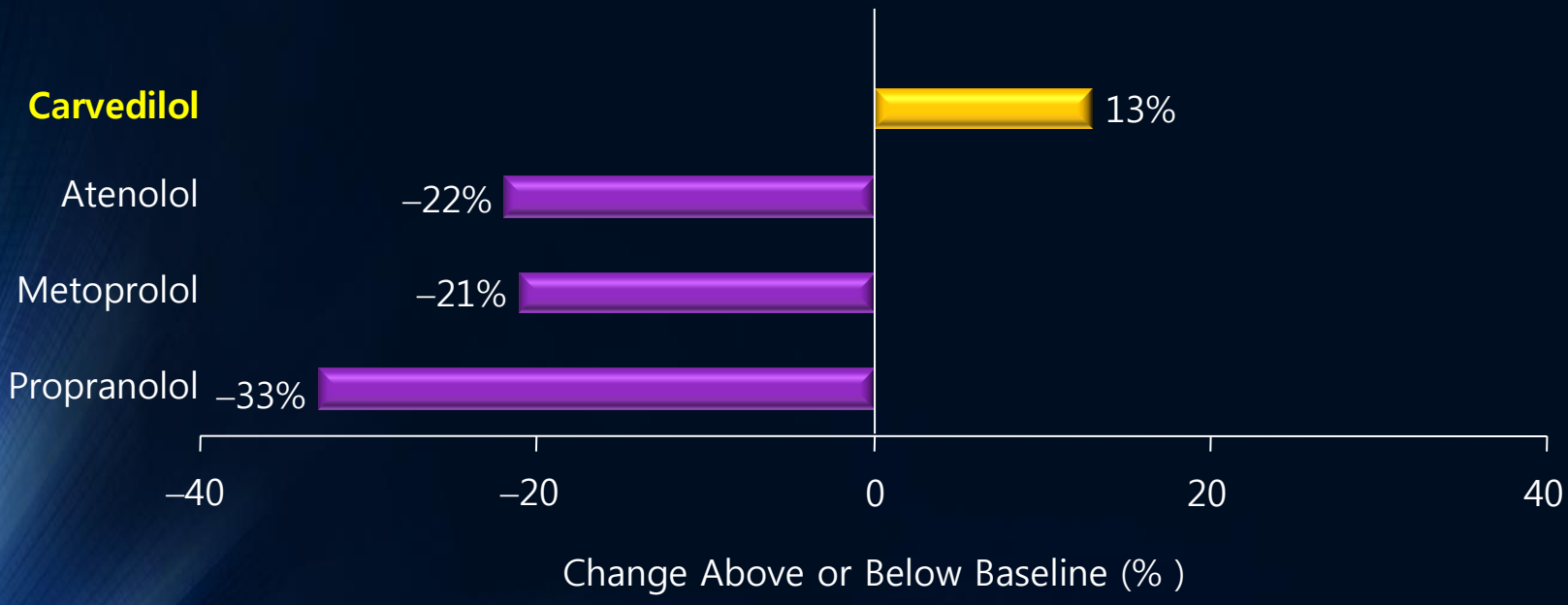
Ref. Am J Hypertens 1998;11:1258–1265

Carvedilol : β blocker beyond β_1-blockade

Metabolic Effect

Effect on insulin sensitivity

[Effect on insulin sensitivity in patients with HTN]



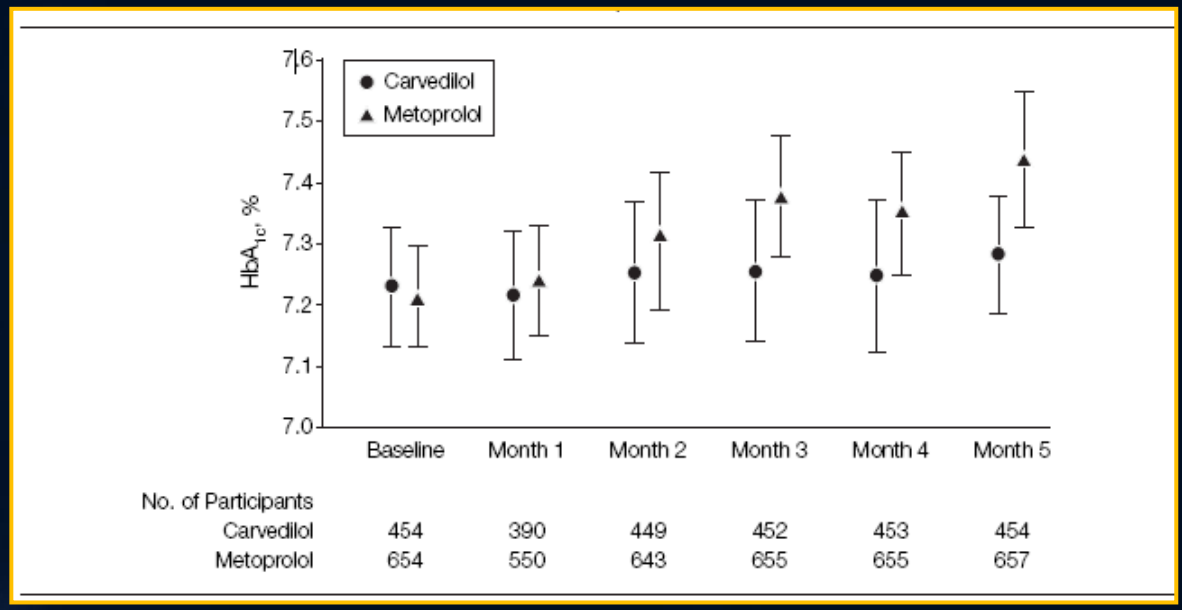
Ref. Am J Hypertens 1998;11:1258–1265

Carvedilol : β blocker beyond β_1-blockade

Metabolic Effect

- GEMINI study : Hypertension with T2DM

[Change in HbA_{1C}]



- 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).

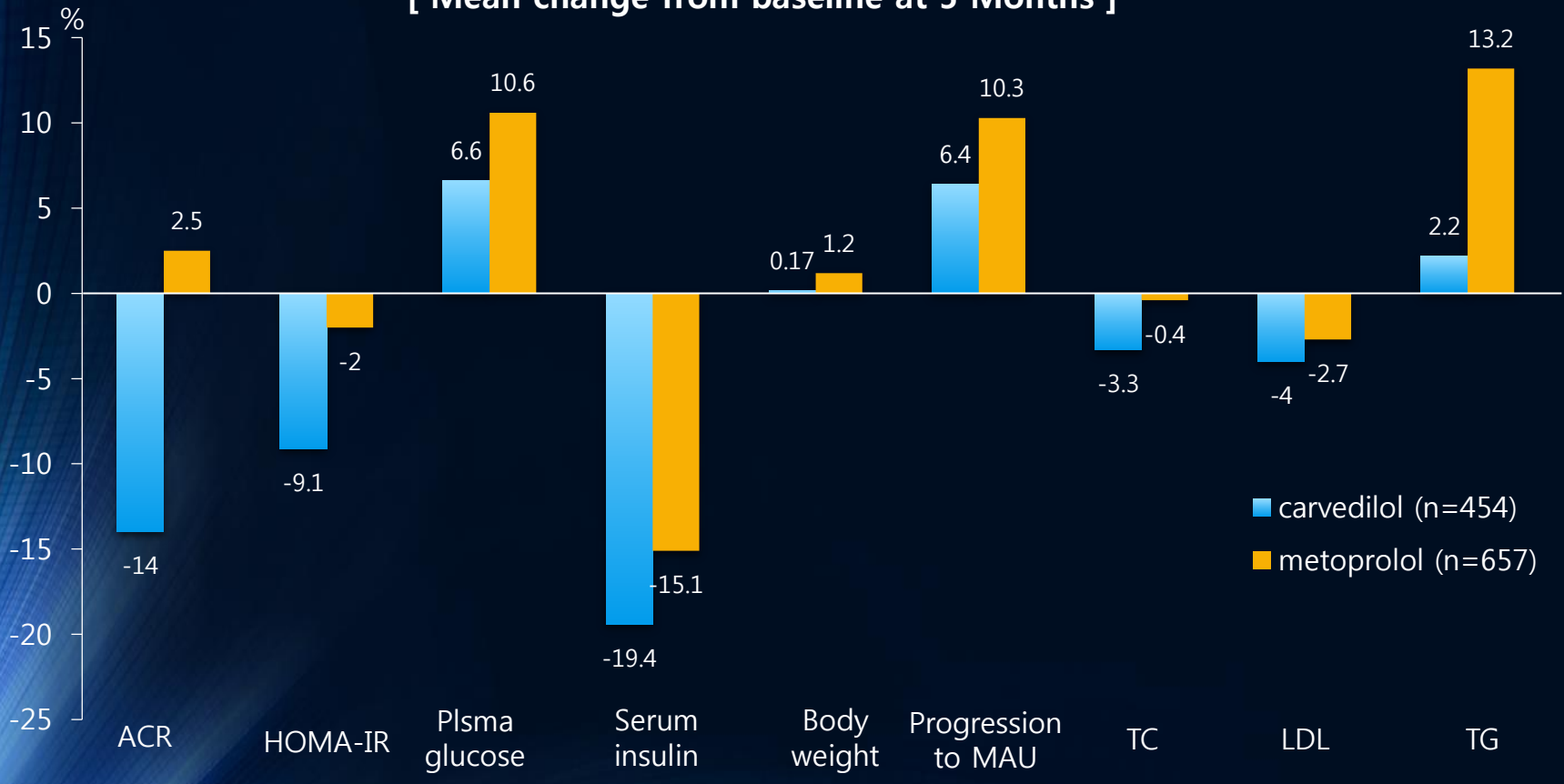
Ref. JAMA. 2004;292:2227-2236

Carvedilol : β blocker beyond β_1-blockade

Metabolic Effect

GEMINI study : Hypertension with T2DM

[Mean change from baseline at 5 Months]



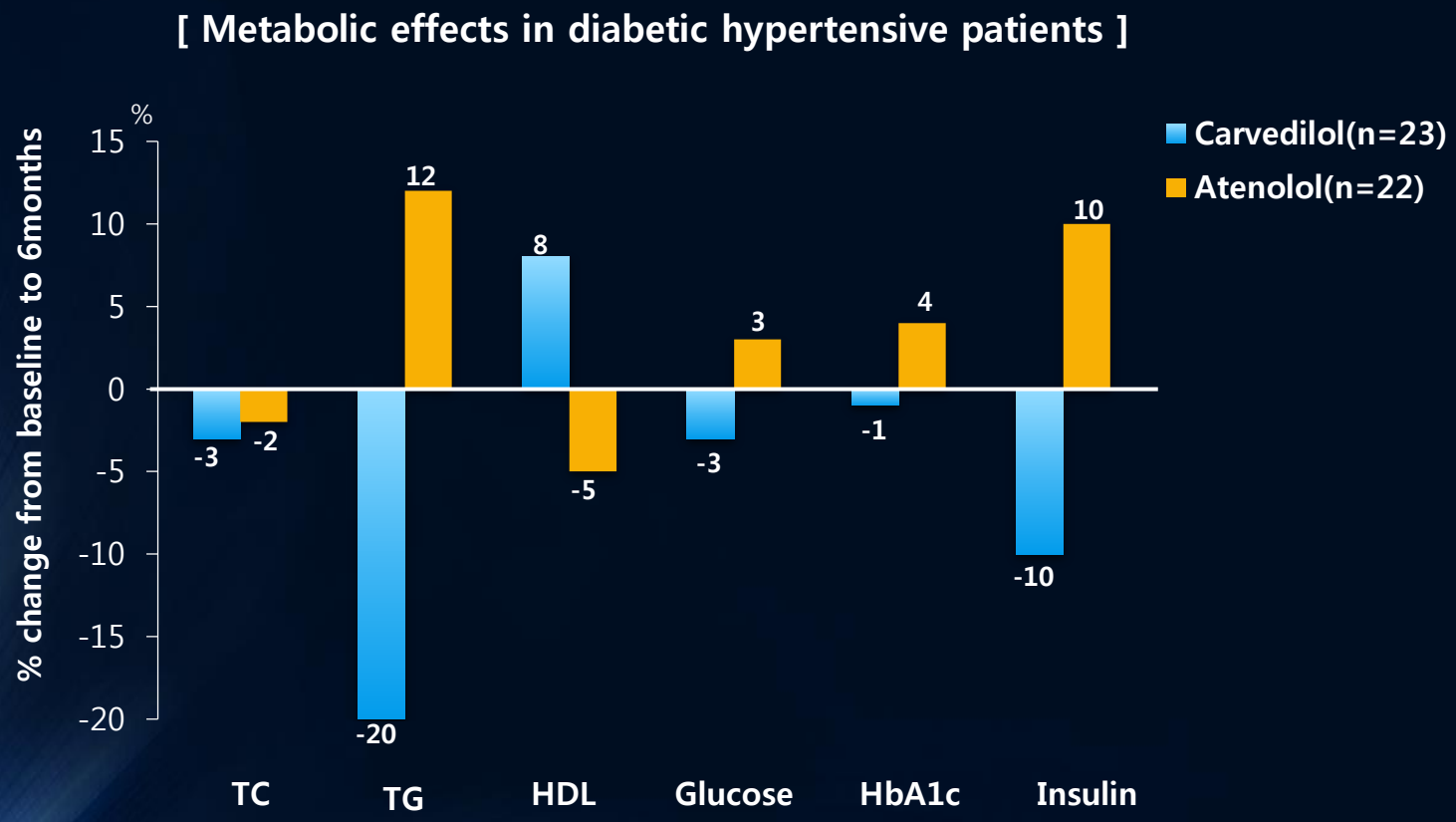
* ACR : urinay albumin/creatinine ratio, HOMA-IR : homeostatic model assessment-insulin resistance, MAU : microalbuminuria

Ref. JAMA. 2004;292:2227-2236

Carvedilol : β blocker beyond β_1-blockade

Metabolic Effect

Effect on metabolic risk factors



Ref. Rev Cardiovasc Med, 2004;5 Suppl 1:S18-S27

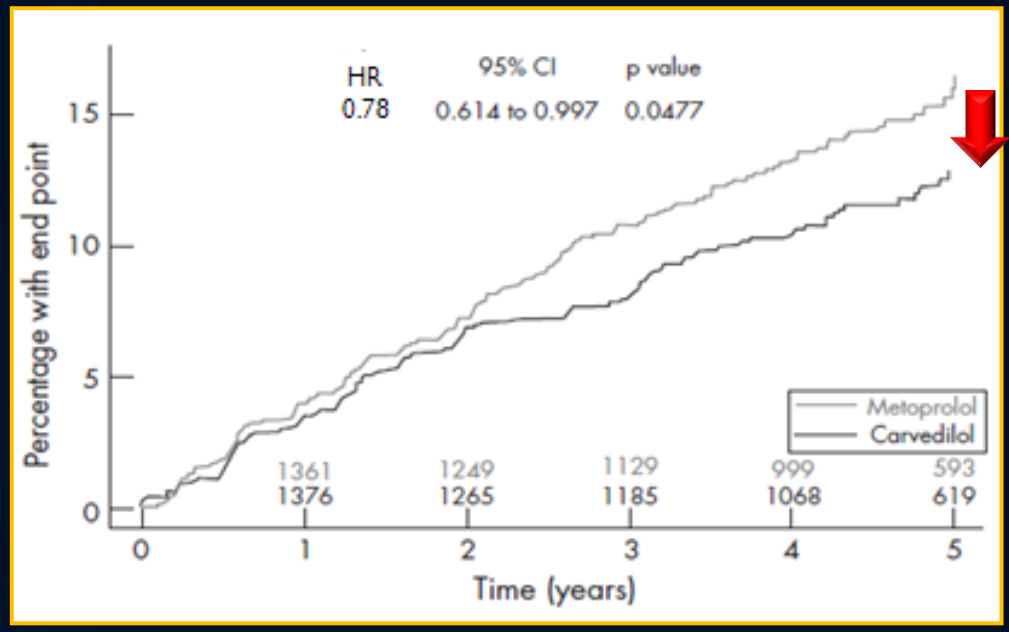
Ann Intern Med., 1997 ;15;126(12):955-959.

Carvedilol : β blocker beyond β_1-blockade

Metabolic Effect

Effect on new-onset of DM in COMET

[Development of new-onset diabetes]



22%
Risk Reduction

(n=1,147)
(n=1,151)

- 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_1-blockade

Renal Effect

- Effect on chronic kidney disease

[Renal effects in chronic kidney disease (CKD)]

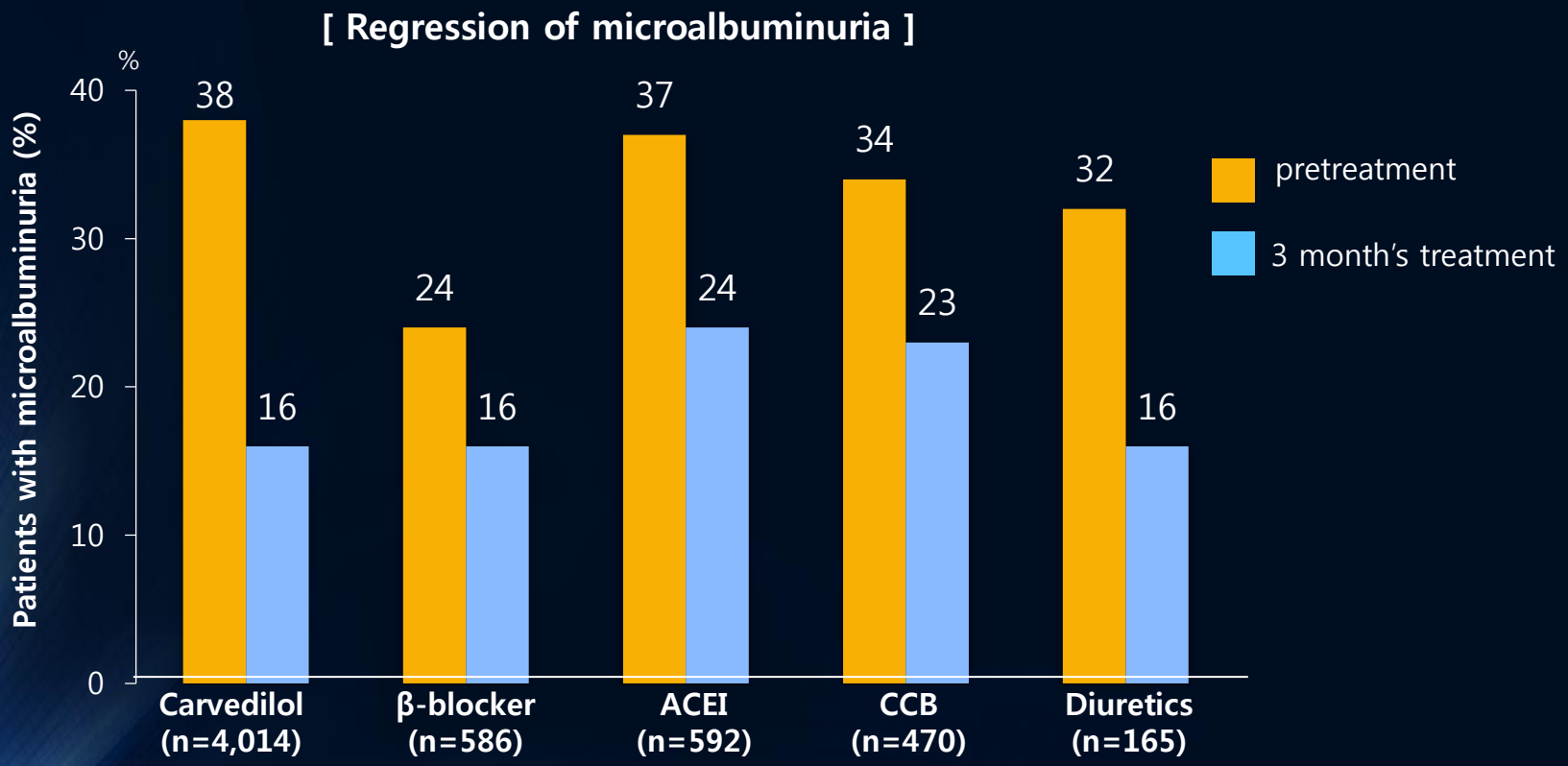
	Carvedilol	Atenolol	Propranolol	Metoprolol	Labetalol
Renal Vascular Resistance	↓	↔	↑	↓	↔
Renal Blood Flow	↑	↔	↓	↔	↔
GFR	↑	↔	↓	↔	↔

Ref. Kidney Int, 2006;70(11):1905-1913

Carvedilol : β blocker beyond β_1-blockade

Renal Effect

Effect on microalbuminuria



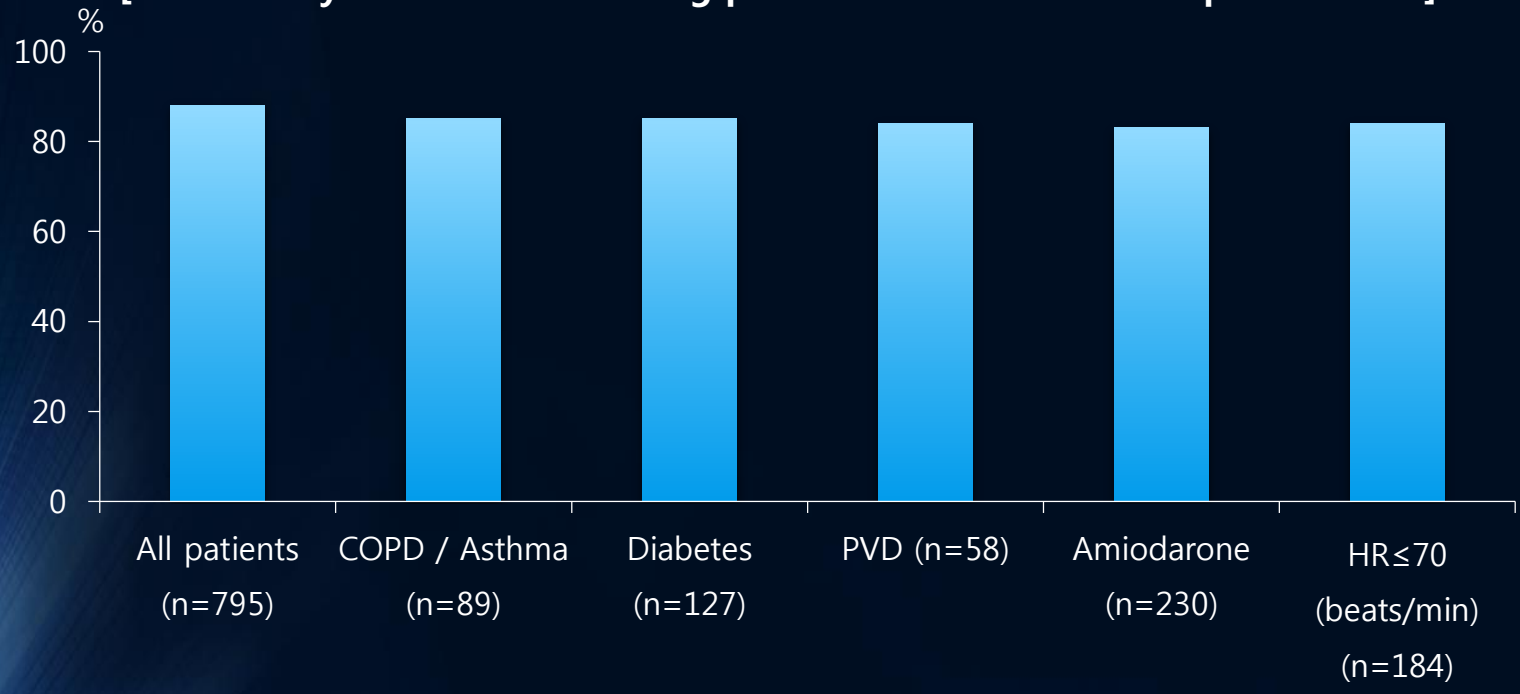
Ref. Am J Hypertens 1998;11:15S–22S

Carvedilol : β blocker beyond β_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.

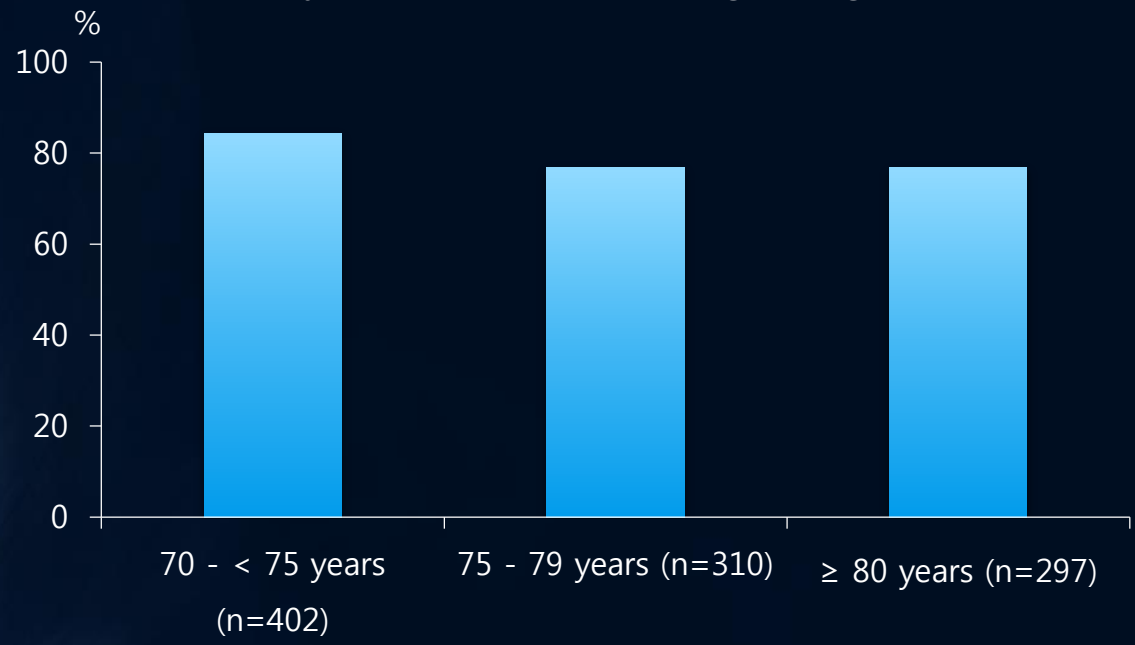
Ref. Am J Cardiol 2004;93(suppl):58B–63B

Carvedilol : β blocker beyond β_1-blockade

Tolerability

COLA II study

[Tolerability to carvedilol according to age in COLA II]



- 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%.

Ref. Eur J Heart Fail. 2006;8(3):302-307

Conclusions

3rd generation vasodilating β-blocker

	Ideal Drug	Traditional β-Blockers	Carvedilol	α_1-Adrenoceptor Blocker	ACE Inhibitor or ARB	DHP–Calcium Antagonist	Thiazide Diuretic
Mean arterial blood pressure	↓	↓	↓	↓	↓	↓	↓
Total peripheral resistance	↓	(↑)	(↓)	↓	↓	↓	↓
Cardiac output	0	(↓)	0	0	0	0	0
Heart rate	0/↓	↓	0/↓	(↑)	0	(↑)	0
Activation of sympathetic nervous system	↓	↓	↓	(↑)	↓	↑	↑
Renin-angiotensin-aldosterone system	↓	↓	↓	0	↓	↑	↑
Lipid metabolism	0/+	–	0	0/+	0	0	–
Glucose metabolism	0/+	–	0	0	0/+	0	–

↑ increase (activation); ↓ decrease (inhibition); 0 no effect; + positive effect; - negative effect; ( ) predominantly after acute administration.

- 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