Dilatrend® SR

Carvedilol : a first-choice β-blocker

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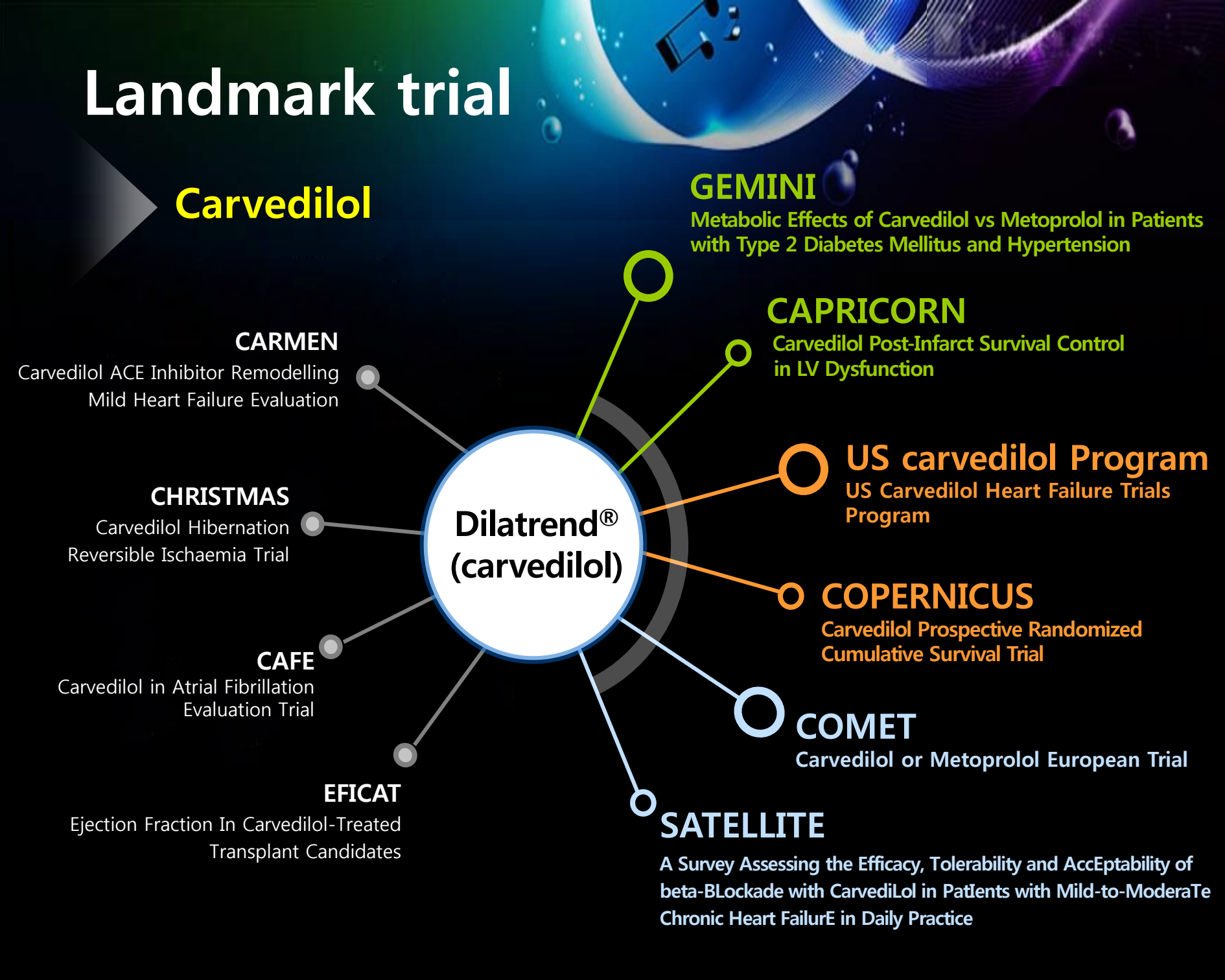
Landmark trial

Carvedilol



GEMINI
Metabolic Effects of Carvedilol vs Metoprolol in Patients with Type 2 Diabetes Mellitus and Hypertension

CAPRICORN
Carvedilol Post-Infarct Survival Control in LV Dysfunction

US carvedilol Program
US Carvedilol Heart Failure Trials Program

COPERNICUS
Carvedilol Prospective Randomized Cumulative Survival Trial

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SATELLITE
A Survey Assessing the Efficacy, Tolerability and AccEptability of beta-BLockade with CarvediLol in PatIents with Mild-to-ModeraTe Chronic Heart FailurE in Daily Practice

CARMEN
Carvedilol ACE Inhibitor Remodelling Mild Heart Failure Evaluation

CHRISTMAS
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EFICAT
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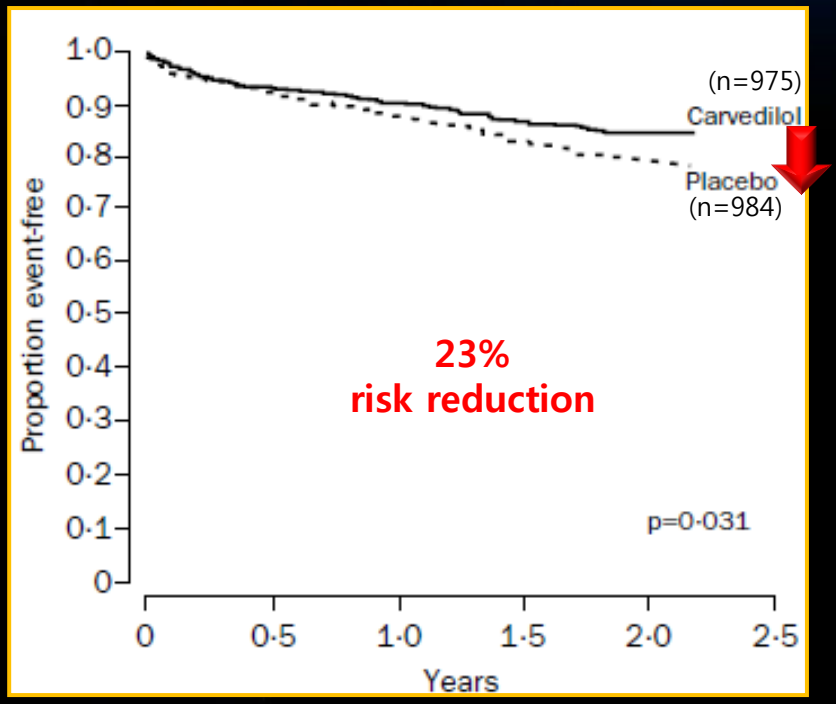
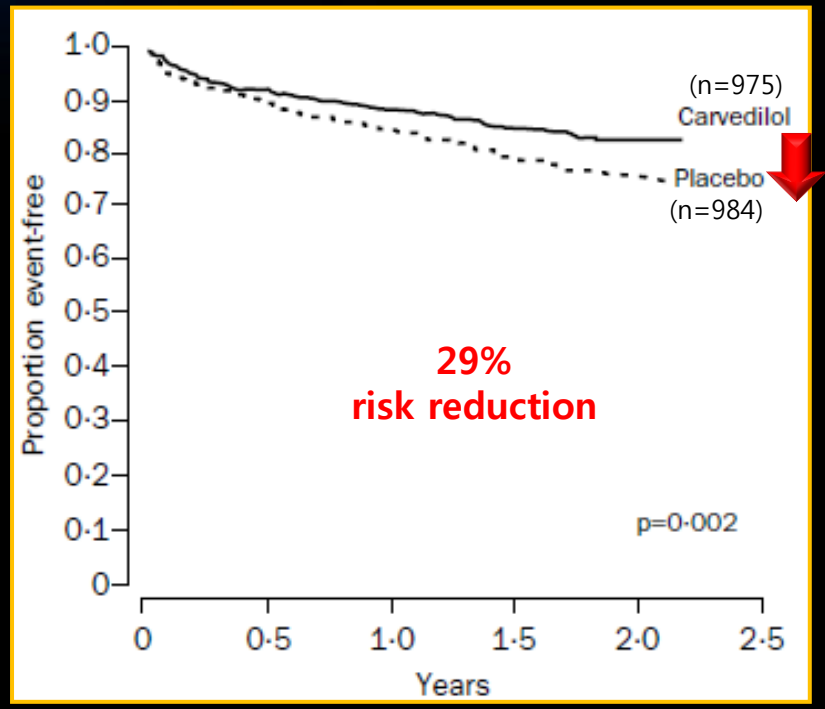
Landmark trial

- **CAPRICORN** (multicentre, randomised, placebo-controlled trial)
  (Effect of carvedilol on outcome after MI in patients with LV dysfunction, N=1959)

[All-cause mortality]



[All-cause mortality or Non-fatal MI]



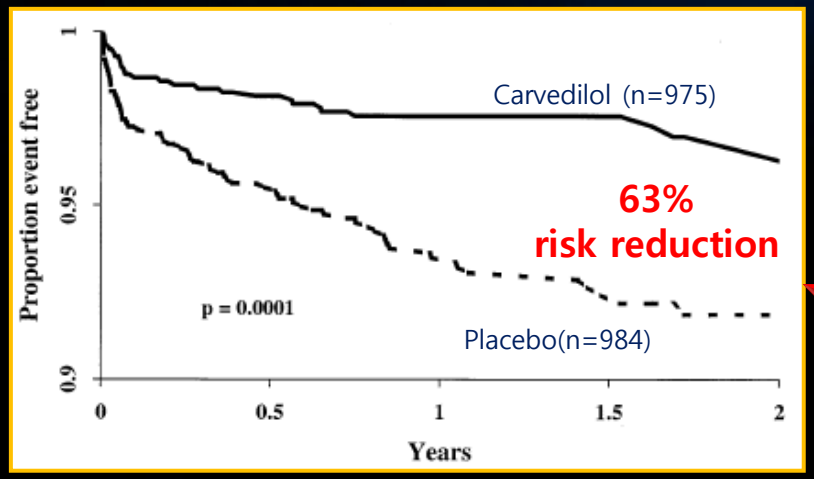
- Carvedilol reduced the frequency of all-cause and cardiovascular mortality, and recurrent, non-fatal myocardial infarctions.
- These beneficial effects are additional to those of evidence-based treatments for acute myocardial infarction including ACE inhibitors.

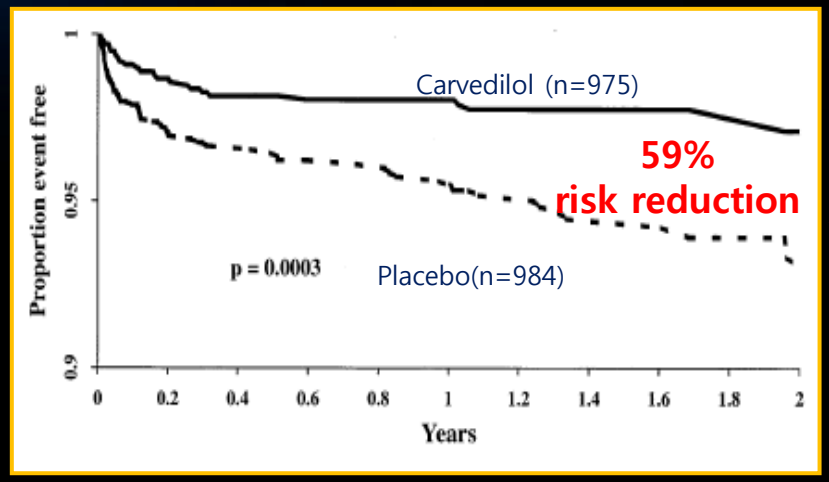
Ref. Lancet 2001; 357: 1385–1390

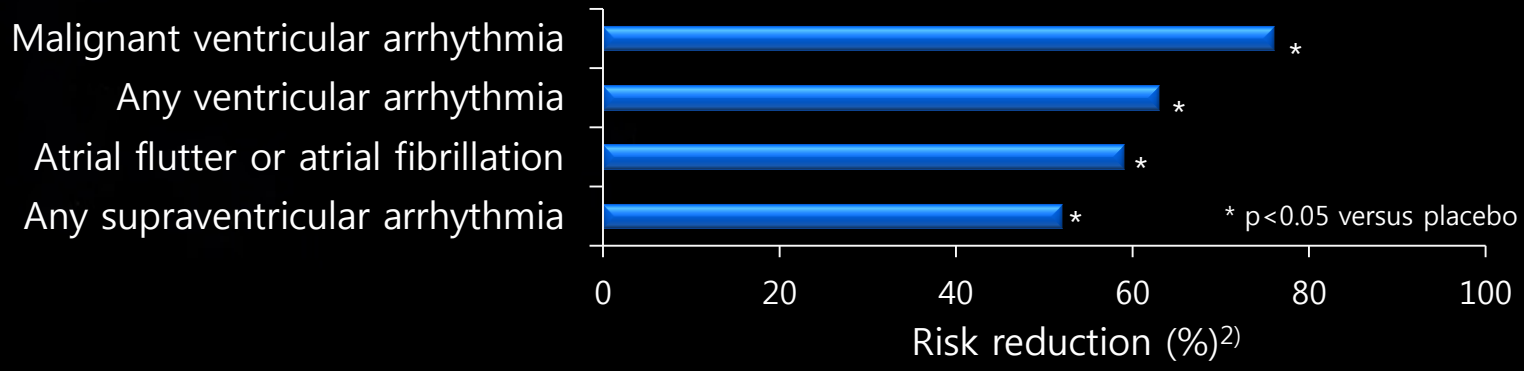
Landmark trial

□ CAPRICORN : Antiarrhythmic effect after AMI

[Survival free of any ventricular arrhythmia]1) **[Survival free of atrial fibrillation or atrial flutter]2)**







Carvedilol has a powerful antiarrhythmic effect after AMI, even in patients already treated with an ACEI.

Ref. 1)J Am Coll Cardiol 2005;45:525–S30 *2)J Cardiovasc Pharmacol Ther., 2005;10 Suppl 1:S59-S68*

Landmark trial

SATELLITE (prospective observational survey, 6 M, 531 physicians from 10 countries)

[Efficacy of the carvedilol treatment in ambulatory daily practice]

		Baseline (n=3,721)	3 months (n=3,542)	6 months (n=3,409)	P value
NYHA class	I	199 (5%)	674 (19%)	1,076 (32%)	<0.001
	II	1,807 (49%)	2,247 (63%)	1,981 (58%)	<0.001*
	III	1,689 (45%)	537 (15%)	279 (8%)	<0.001
	IV	8 (0.2%)	12 (0.3%)	8 (0.2%)	ns
Fatigue	Absent	308 (8%)	844 (24%)	1,251 (37%)	<0.001
	Mild	1,633 (44%)	2,036 (57%)	1,787 (52%)	<0.001*
	Moderate	1,503 (40%)	570 (16%)	291 (9%)	<0.001
	Severe	241 (6%)	36 (1%)	25 (1%)	<0.001*
Shortness of breath	Absent	239 (6%)	898 (25%)	1,405 (41%)	<0.001
	Mild	1,588 (43%)	2,017 (57%)	1,677 (49%)	<0.001*
	Moderate	1,600 (43%)	525 (15%)	243 (7%)	<0.001
	Severe	248 (7%)	37 (1%)	26 (1%)	<0.001*

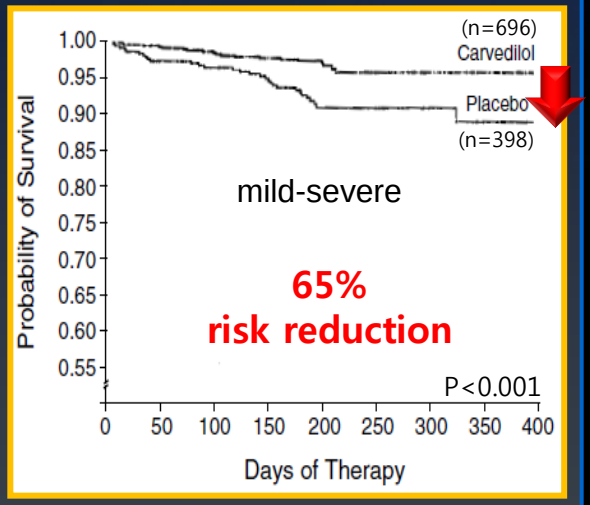
* Baseline vs 3 & 6 months

- The mean NYHA class improved throughout the survey from baseline 2.4±0.6 to 2.0±0.6 at 3 months and 1.8±0.6 at 6 months, respectively ($p<0.001$ for both).
- During the follow-up, patients experienced significantly less fatigue and shortness of breath than at baseline.

Ref. Int J Cardiol., 2007;122(2):149-155

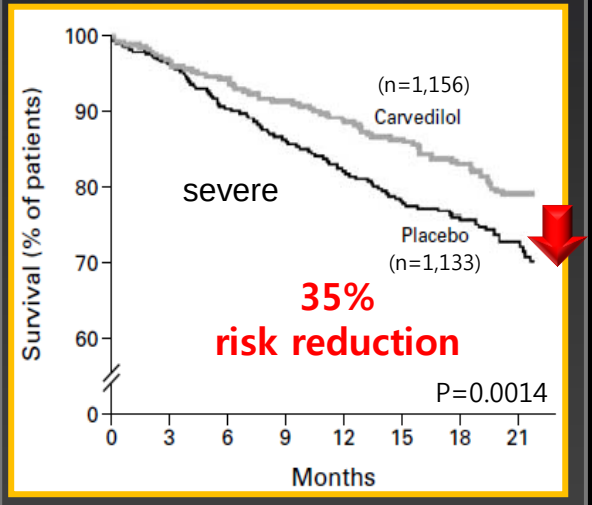
Landmark trial

US carvedilol HF trials program [1)]



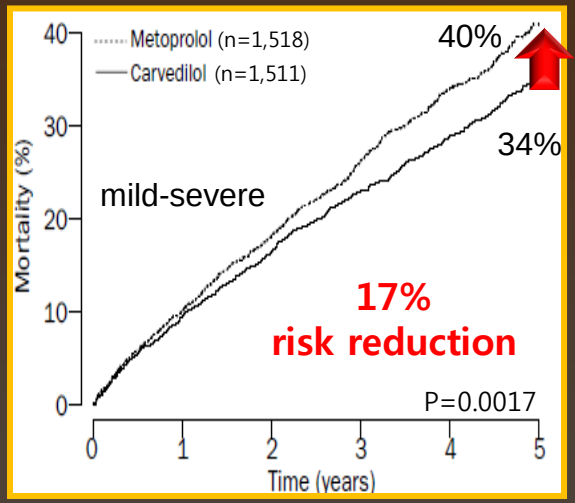
Early termination by DSMB due to significant beneficial effect of carvedilol on survival

COPERNICUS [2)]



Early termination by DSMB due to significant beneficial effect of carvedilol on survival

COMET [3)]



* DSMB : data and safety monitoring board

Ref. 1) N Engl J Med 1996;334:1349-1355 2) N Engl J Med 2001;344:1651-1658 3) Lancet 2003; 362: 7–13

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Comparison with β_1 selective BBs

[Clinical trials of β-blockers in patients with CHF][1), 2)]

	Carvedilol			Bisoprolol	Nebivolol
	US Carvedilol HF trials program	COPERNICUS severe	COMET mild-severe	CIBIS-II	SENIORs
Patients	1,094 *	2,289 *	3,029	2,647	2,128
Control	placebo	placebo	metoprolol	placebo	placebo
LVEF (%)	≤ 35%	**≤ 25%**	≤ 35%	≤ 35%	≤ 35%
Reduction in all-cause mortality	65%	**35%**	17%	34%	12%(ns)

*** Early termination due to significant effect of carvedilol on survival**

Ref. 1)Trends Pharmacol Sci., 2011;32(4):206-212 2)Eur Heart J., 2005;26(3):215-225.

Comparison with β_1 selective BBs

[Key tolerability parameters in large-scale CHF trials of β-blocker]

	β-blocker	Control	Study Drug Discontinuation (RR)	% Reaching Target Dose
US carvedilol HF program	Carvedilol	placebo	0.73	80
COPERNICUS	Carvedilol	Placebo	0.84	74
MERIT-HF	Metoprolol CR/XL	Placebo	0.9	64
CIBIS II	Bisoprolol	placebo	1	57.5

* RR : relative risk

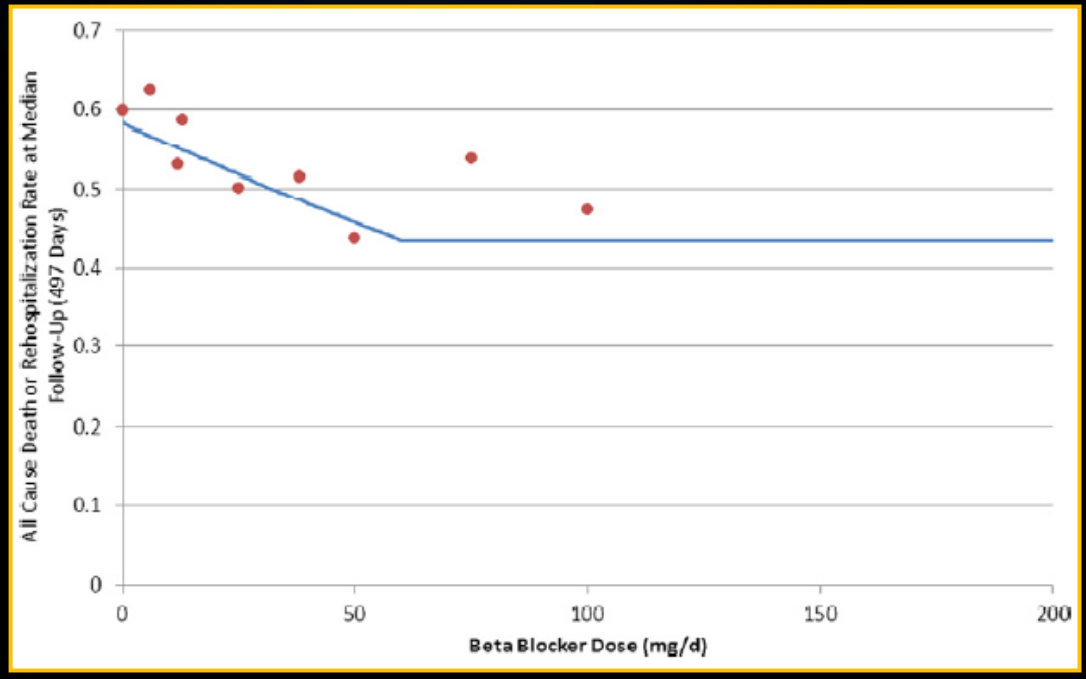
- In clinical studies, discontinuation rates (because of adverse events), serious adverse event rates, mean achieved dose, and percentage reaching target dose strongly suggest good tolerability.
- In contrast to widely held perceptions about tolerability of β–blockade in heart failure, carvedilol appears to be an extremely well-tolerated agent, even during initiation and in the most advanced patients.

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

Relationship of Beta-Blocker Dose With Outcomes in Ambulatory Heart Failure Patients With Systolic Dysfunction (HF-ACTION)

Relationship of β-blocker dose with outcomes in HF

[All-cause death or hospitalization rate by β-blocker dose at baseline]



- Dots : event rate at most common doses on the basis of distribution of doses
- Beta-blocker dose : standardized with carvedilol equivalents and analyzed by discrete dose groups (0, 1-13, 14-25, 26-50, 51-200 mg daily)

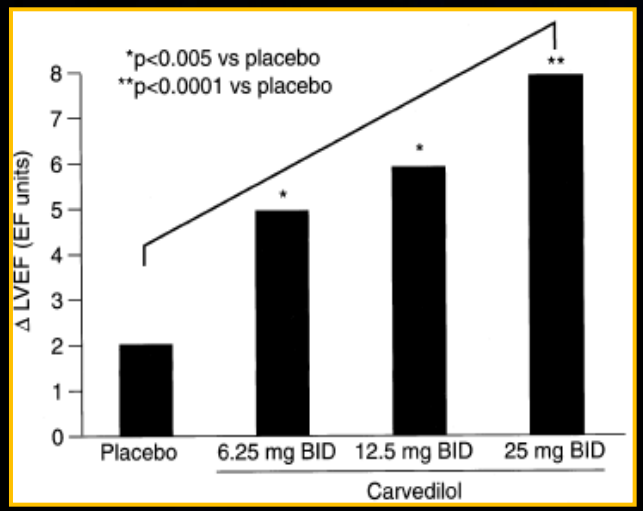
- There was a significant inverse relationship between β-blocker dose and the endpoint of all-cause death or hospitalization in HF, supporting recommendations that titrating doses up to 50 mg/day might confer a benefit in such patients(n=2,325).

Ref. J Am Coll Cardiol, 2012;60:208-215

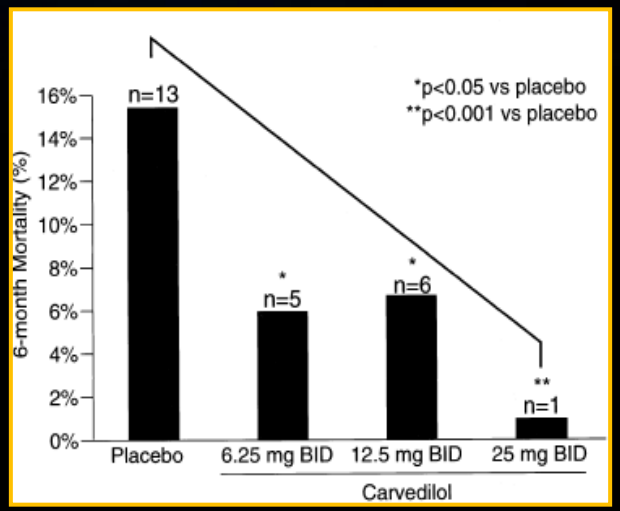
Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure (MOCHA)

Relationship of β-blocker dose with outcomes in HF

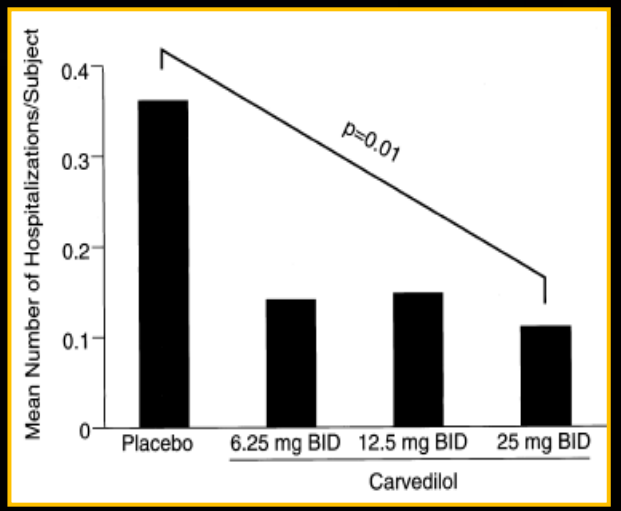
[LV function]



[Mortality]



[Hospitalization]



- Carvedilol produced dose-related improvements in LV function and dose-related reductions in mortality and hospitalization rate.

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

Comparison with β_1 selective BBs

□ Systematic review & Meta-analysis I

[Meta-analysis of β-blockers in survivors of an AMI & in patients with CHF]

	Placebo	Active treatment	Odds ratio (95% CI)
Survivors of Acute Myocardial Infarction (32 trials, N=26,580)			
β-blockers with β_2-and/or α_1-blockade	715/5579	549/5851	0.69 (0.61, 0.79)
β_1-selective β-blockers	289/2887	248/2968	0.79 (0.66, 0.95)
β-blockers with intrinsic sympathomimetic activity	467/4598	416/4687	0.85 (0.74, 0.99)
Patients With Chronic Heart Failure (28 trials, N=15,905)			
β-blockers with β_2-and/or α_1-blockade	293/1854	207/2206	0.58 (0.48, 0.71)
β_1-selective β-blockers	563/4179	398/4235	0.67 (0.58, 0.77)
β-blockers with intrinsic sympathomimetic activity	457/1579	447/1852	0.90 (0.77, 1.06)

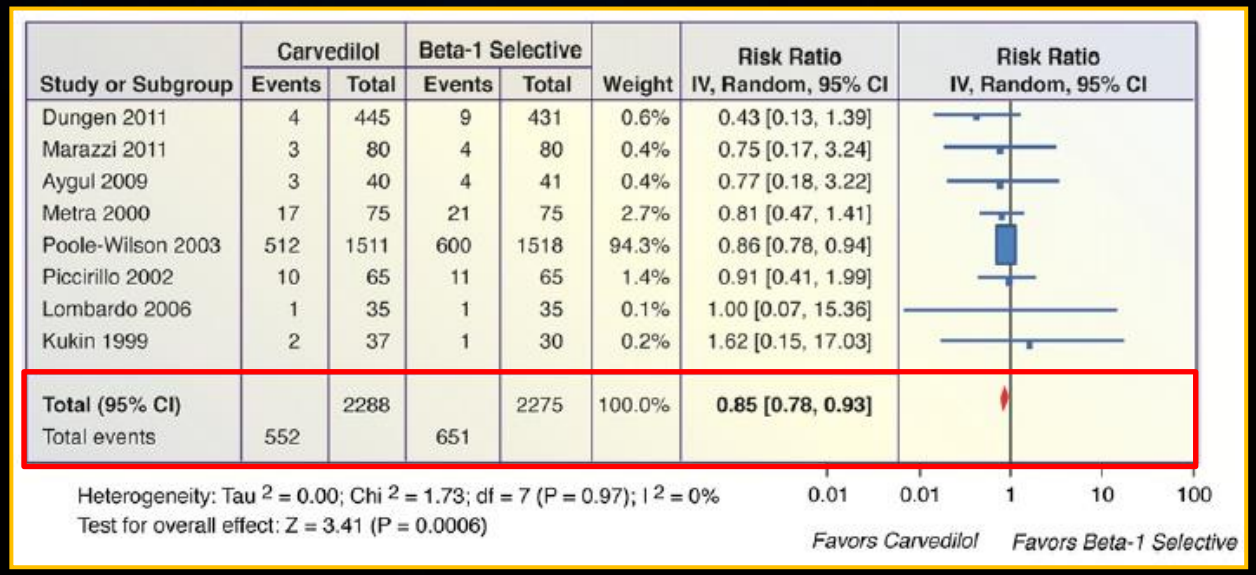
- In the post-infarction trials, the risk of death was reduced by 21% with selective β_1-blockers; by 31% with agents that had additional β_2 or α_1-blocking effects.
- In the heart failure trials, the risk of death was reduced by 33% with selective β_1-blockers; by 42% with agents that had additional β_2 or α_1-blocking effects.

Ref. J Card Fail., 2003;9(6):429-443

Comparison with β_1 selective BBs

- **Systematic review & Meta-analysis II**
  - Relative risk for all-cause mortality

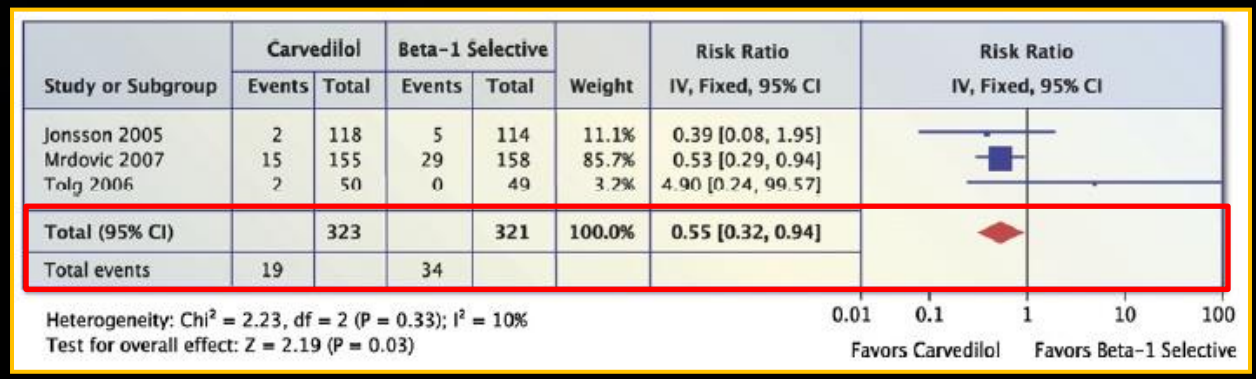
1) HF



Study or Subgroup	Carvedilol Events	Carvedilol Total	Beta-1 Selective Events	Beta-1 Selective Total	Weight	Risk Ratio IV, Random, 95% CI
Dungen 2011	4	445	9	431	0.6%	0.43 [0.13, 1.39]
Marazzi 2011	3	80	4	80	0.4%	0.75 [0.17, 3.24]
Aygul 2009	3	40	4	41	0.4%	0.77 [0.18, 3.22]
Metra 2000	17	75	21	75	2.7%	0.81 [0.47, 1.41]
Poole-Wilson 2003	512	1511	600	1518	94.3%	0.86 [0.78, 0.94]
Piccirillo 2002	10	65	11	65	1.4%	0.91 [0.41, 1.99]
Lombardo 2006	1	35	1	35	0.1%	1.00 [0.07, 15.36]
Kukin 1999	2	37	1	30	0.2%	1.62 [0.15, 17.03]
Total (95% CI)		**2288**		**2275**	**100.0%**	**0.85 [0.78, 0.93]**
Total events	552		651			

Heterogeneity: Tau ^{2} = 0.00; Chi ^{2} = 1.73; df = 7 (P = 0.97); I ^{2} = 0%
Test for overall effect: Z = 3.41 (P = 0.0006)

2) AMI



Study or Subgroup	Carvedilol Events	Carvedilol Total	Beta-1 Selective Events	Beta-1 Selective Total	Weight	Risk Ratio IV, Fixed, 95% CI
Jonsson 2005	2	118	5	114	11.1%	0.39 [0.08, 1.95]
Mrdovic 2007	15	155	29	158	85.7%	0.53 [0.29, 0.94]
Tolg 2006	2	50	0	49	3.2%	4.90 [0.24, 99.57]
Total (95% CI)		**323**		**321**	**100.0%**	**0.55 [0.32, 0.94]**
Total events	19		34			

Heterogeneity: Chi^2 = 2.23, df = 2 (P = 0.33); I^2 = 10%
Test for overall effect: Z = 2.19 (P = 0.03)

Ref. Am J Cardiol 2013;111:765-769

Comparison with β_1 selective BBs

- **Indication of β-blocker in Korea**

Drug	Strength	Indication		
		Hypertension	Angina pectoris	Heart Failure
Dilatrend® (Carvedilol)	3.125mg	V	V	V
	6.25mg	V	V	V
	12.5mg	V	V	V
	25mg	V	V	V
Atenolol	25mg	V	V	
	50mg	V	V	
Bisoprolol	2.5mg			V
	5mg	V	V	V
Nebivolol	5mg	V		V (elderly≥70years)

Comparison with β_1 selective BBs

- **Indication of β-blocker in USA**

Drug	Hypertension	Myocardial Infarction	Heart Failure
Carvedilol	V	V (LVD following MI)	V
Atenolol	V	V (Acute MI)	
Bisoprolol	V		
Nebivolol	V		

Ref. PDR 2012

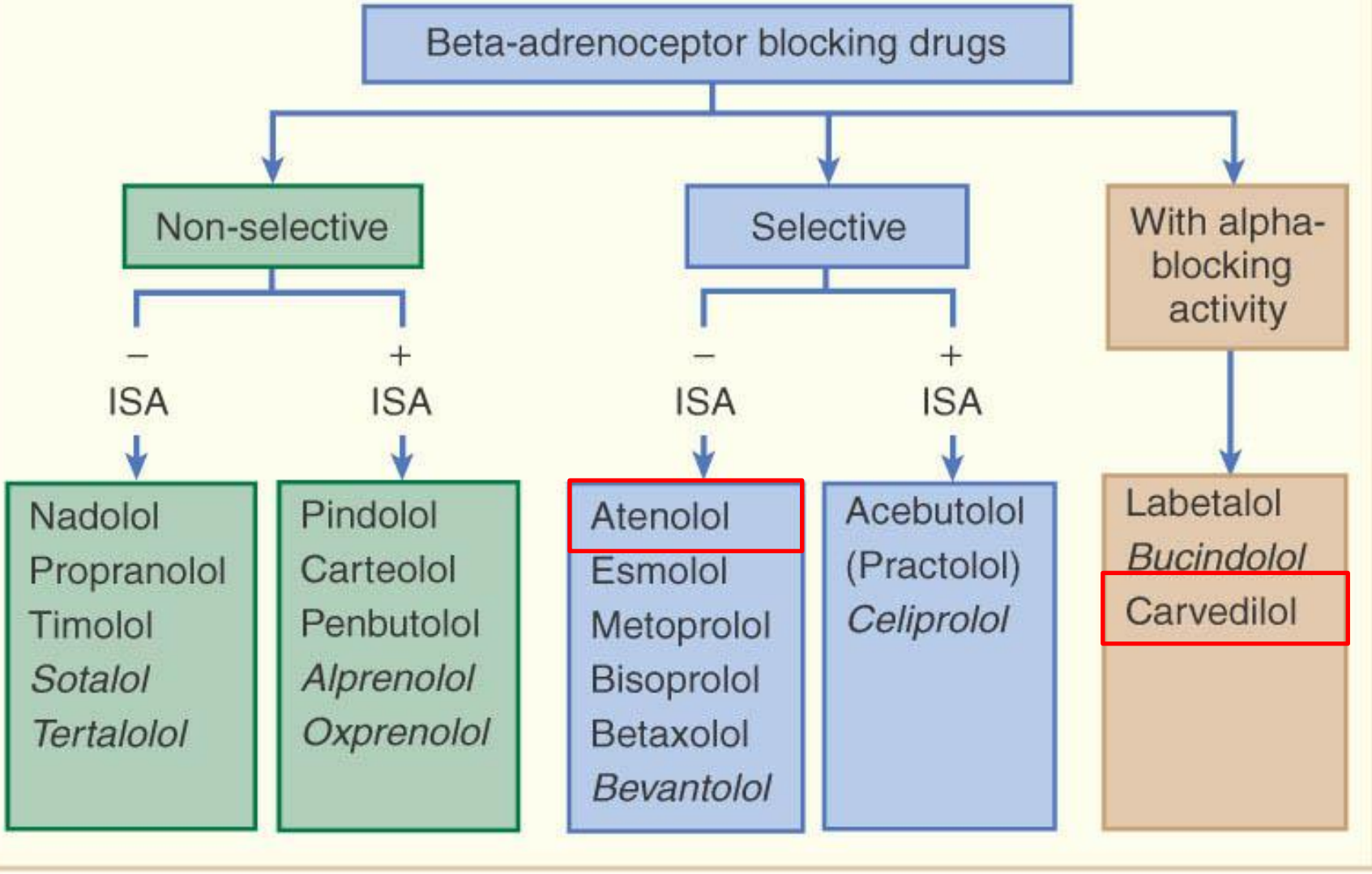
Contents

2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients With Chronic Stable Angina

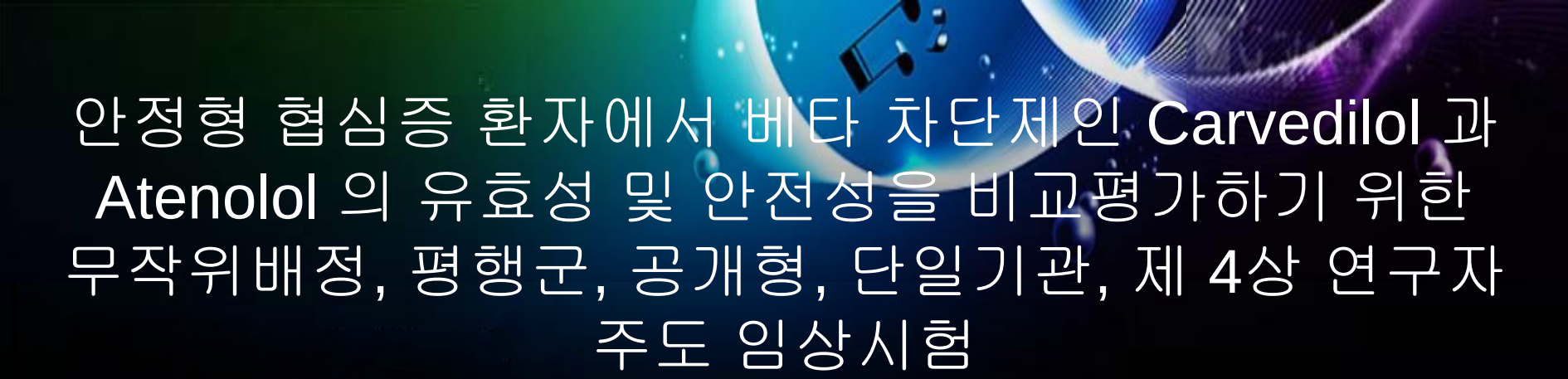
Beta Blockers	
It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.	*I (A)*

JACC 2007;50:2264–74

Beta-adrenergic blocking agents



(Modified from Kaplan NM: Kaplan's Clinical Hypertension, 8th ed. Baltimore, Lippincott Williams & Wilkins, 2002, p 262.)



안정형 협심증 환자에서 베타 차단제인 Carvedilol 과 Atenolol 의 유효성 및 안전성을 비교평가하기 위한 무작위배정, 평행군, 공개형, 단일기관, 제 4상 연구자 주도 임상시험

안정형 협심증 환자에서 베타 차단제인 Carvedilol 과 Atenolol 의 유효성 및 안전성을 비교평가하기 위한 무작위배정, 평행군, 공개형, 단일기관, 제 4상 연구자 주도 임상시험

안정형 협심증 환자를 대상으로 6개월 동안 시험군인 Carvedilol (50mg/일, N=50) 과 대조군인 Atenolol (100mg/일, N=50) 을 투여 후 치료 효과 및 안전성을 비교 평가하고자 함

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1) 1차 목적
Carvedilol (50mg/일)이 대조군인 Atenolol(100mg/일) 보다 협심증 치료에 있어서 운동부하검사를 통한 협심증 지표가 향상되는지 확인

안정형 협심증 환자에서 베타 차단제인 Carvedilol 과 Atenolol 의 유효성 및 안전성을 비교평가하기 위한 무작위배정, 평행군, 공개형, 단일기관, 제 4상 연구자 주도 임상시험

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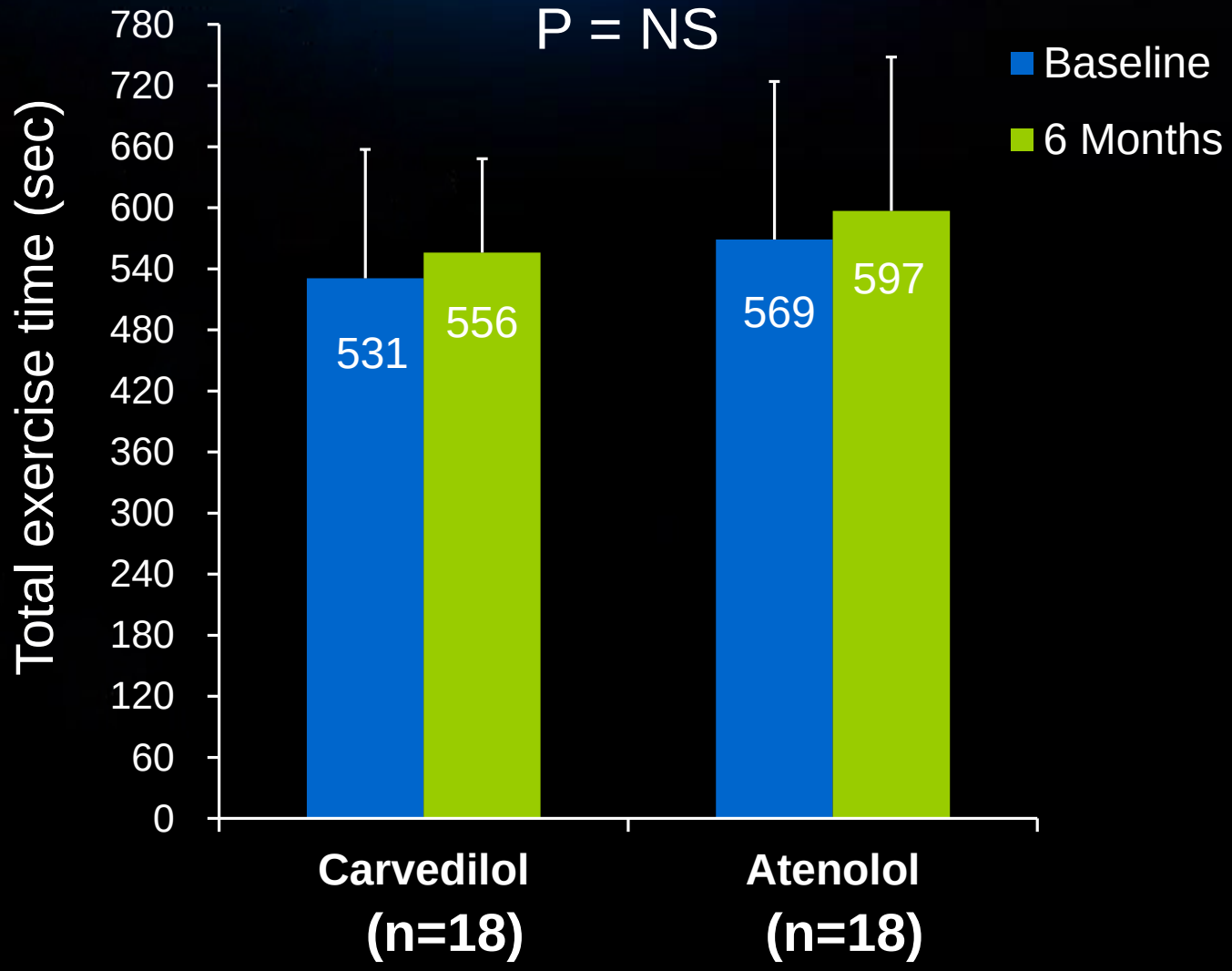
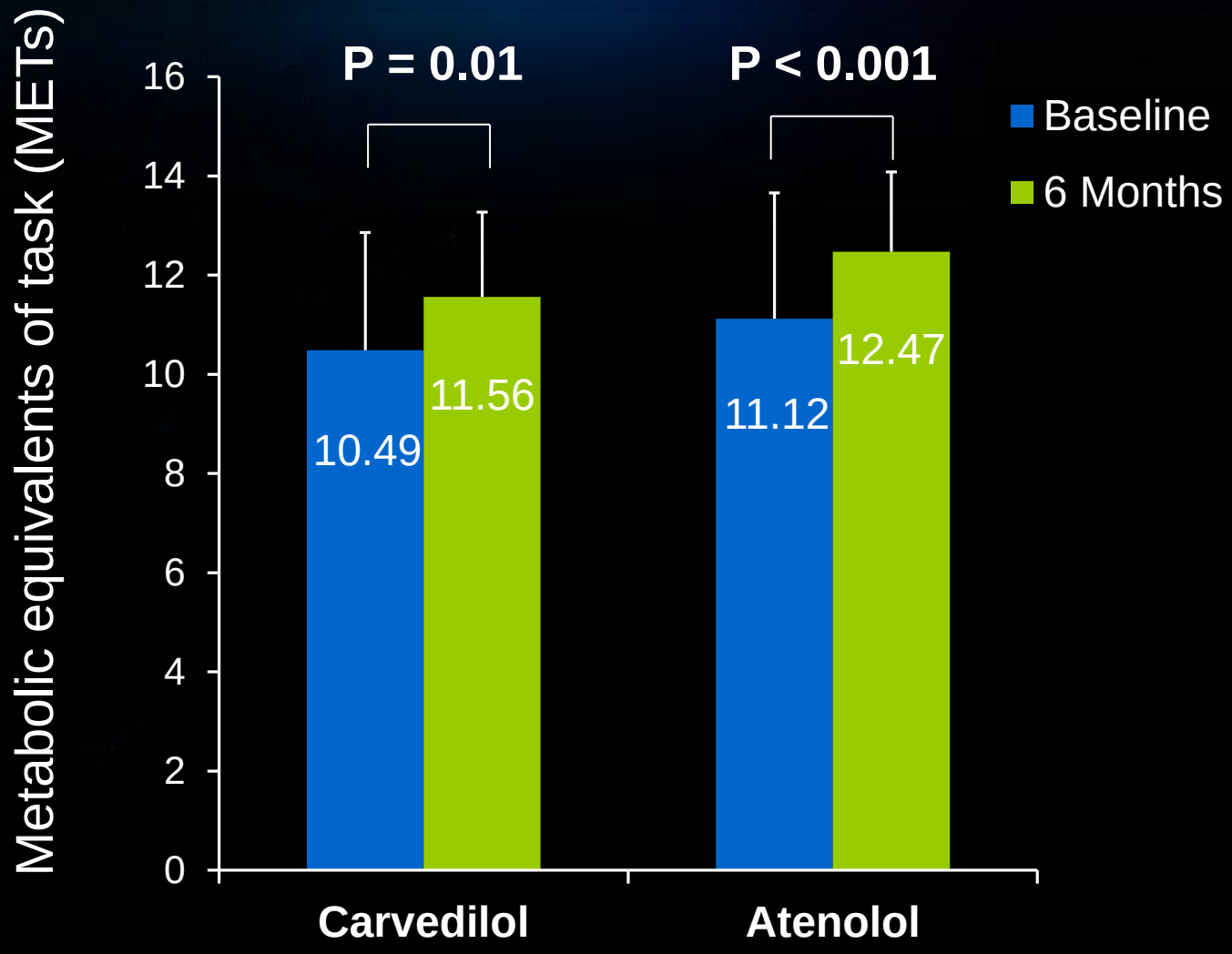
2) 2차 목적
Carvedilol (50mg/일)이 대조군인 Atenolol(100mg/일) 에 비해 긍정적인 대사효과 (지질 개선, insulin 저항성 개선, 항염증 효과) 를 보이는지 확인

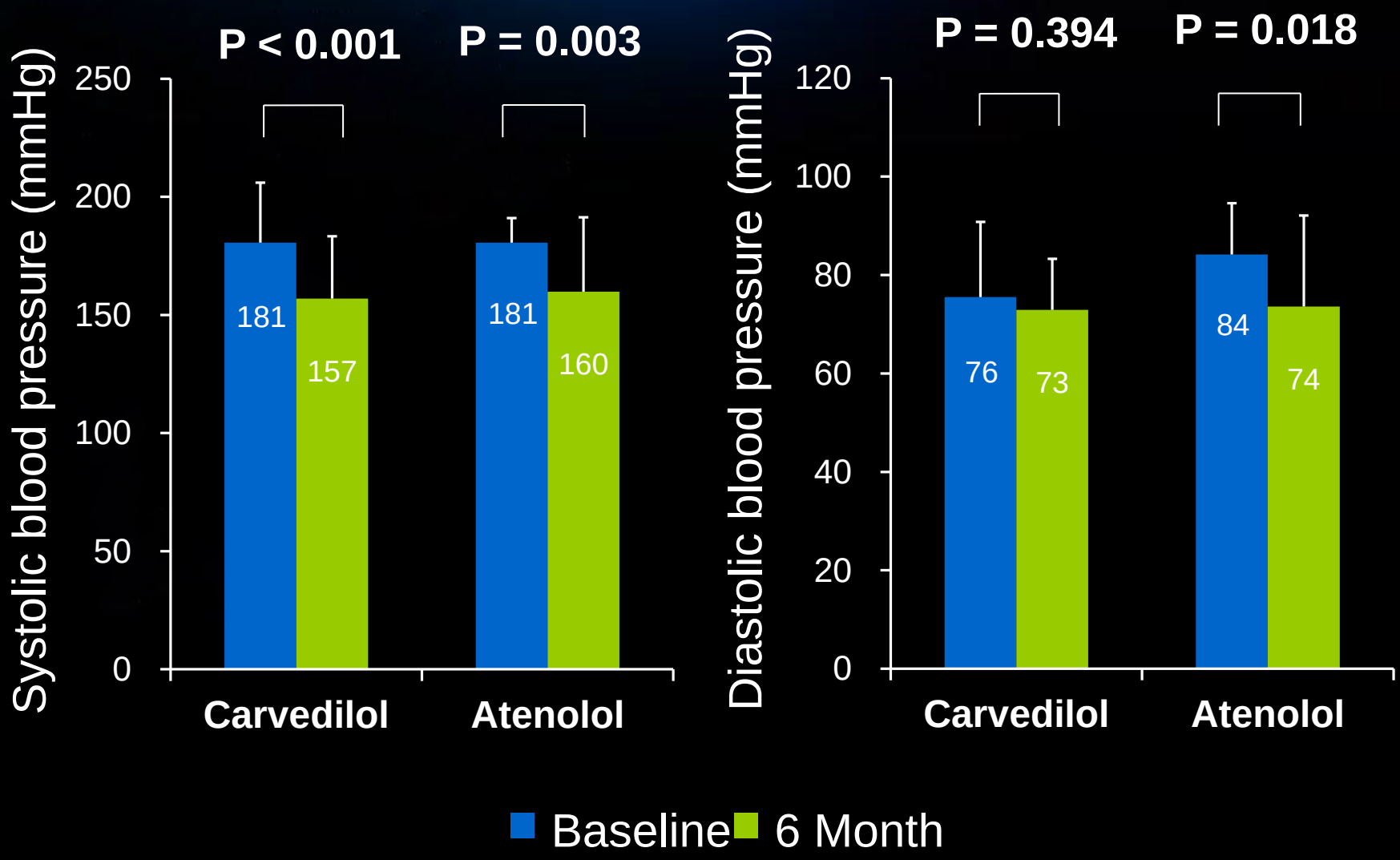
Effect on Total Exercise Time during TMT



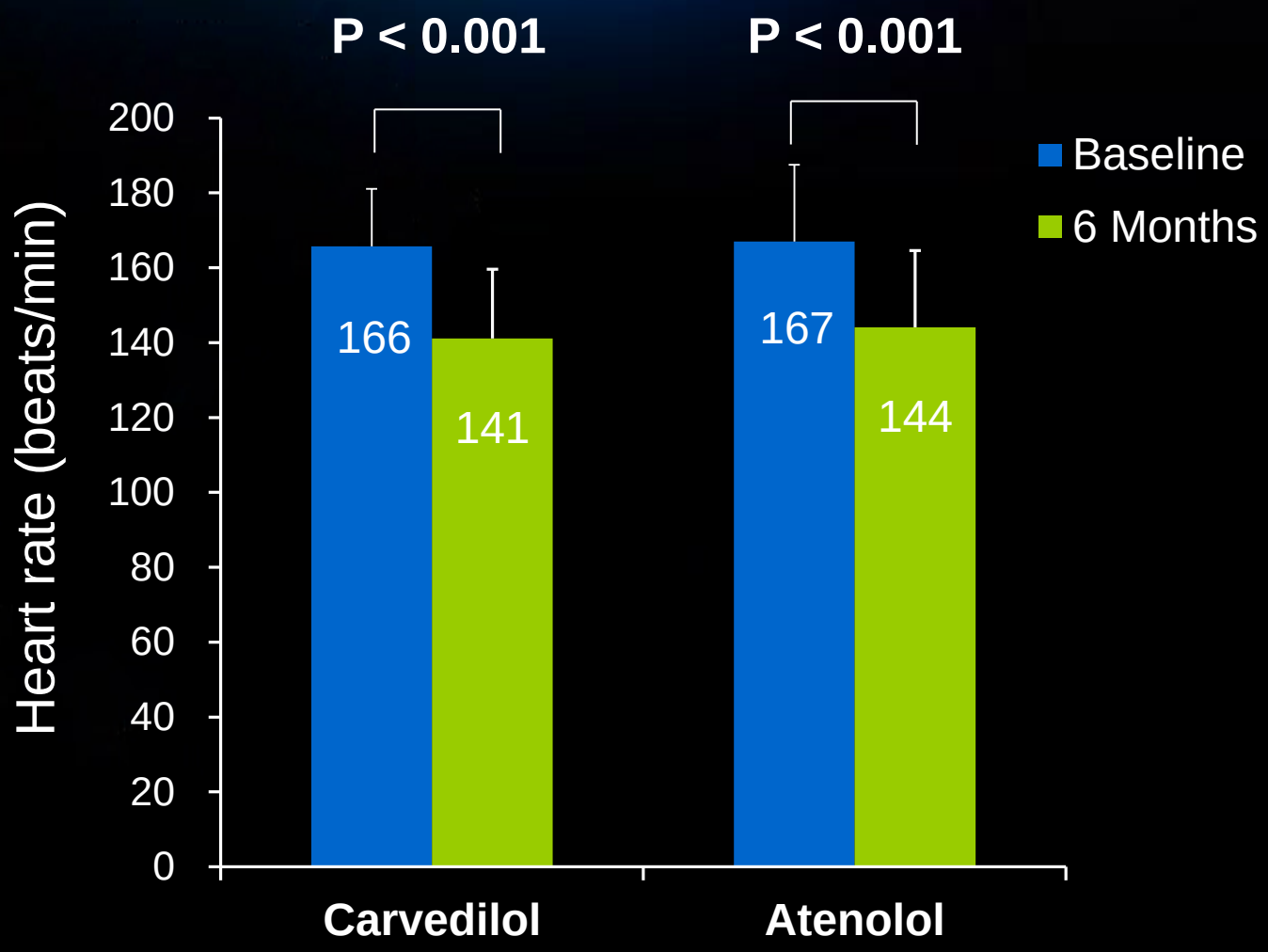
Effect on METs during TMT



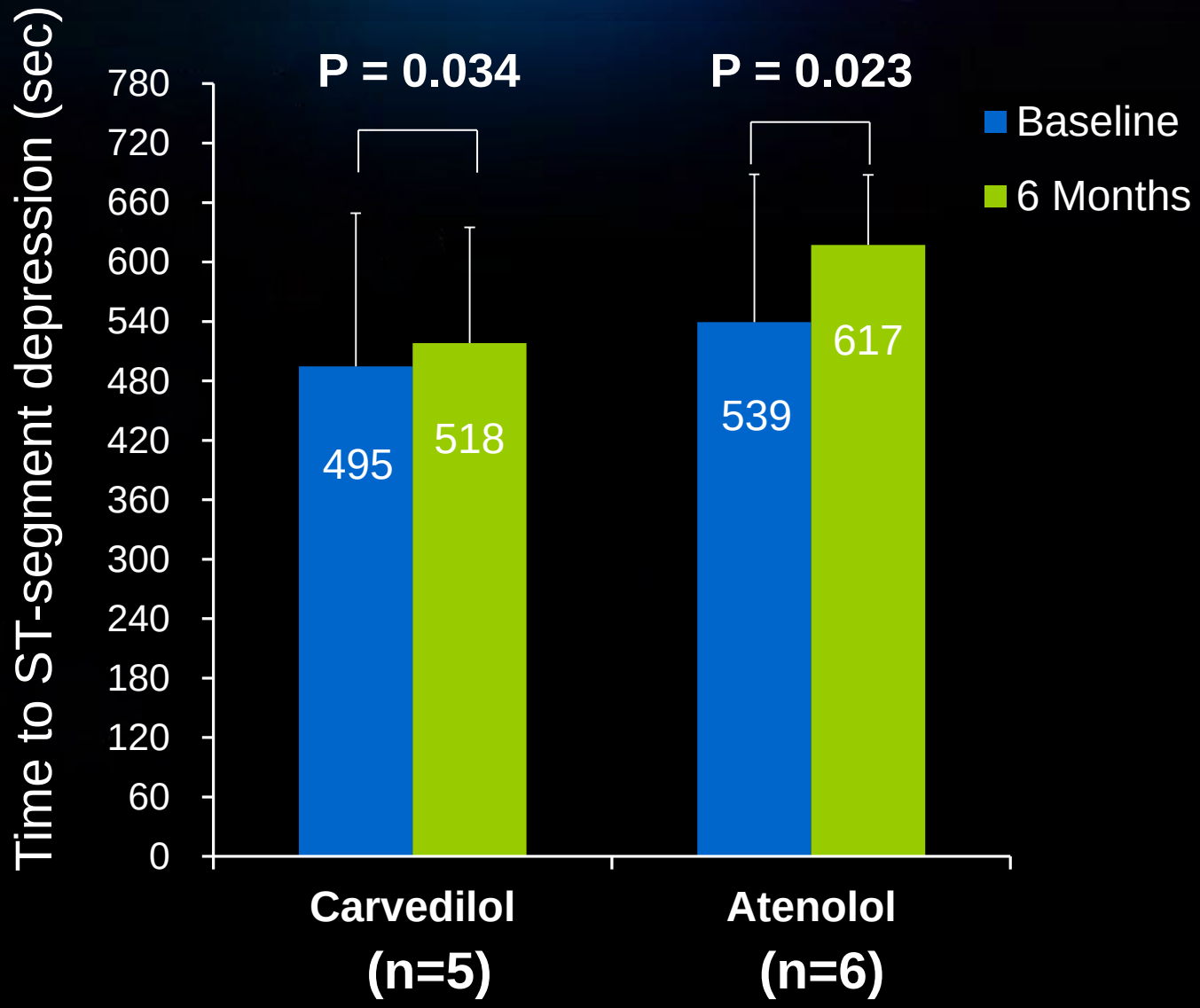
Effect on Maximal BP during TMT



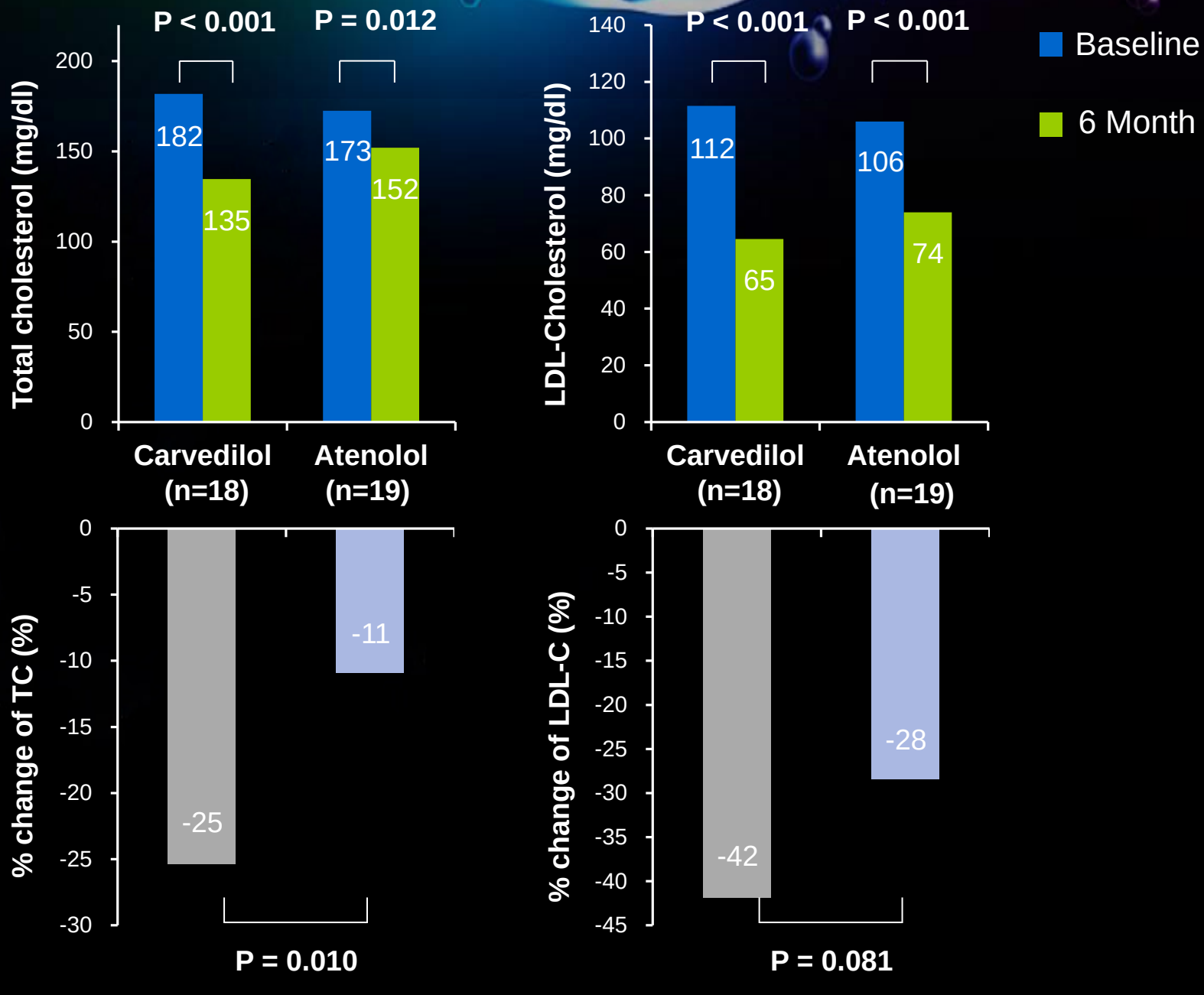
Effect on Maximal Heart Rate during TMT



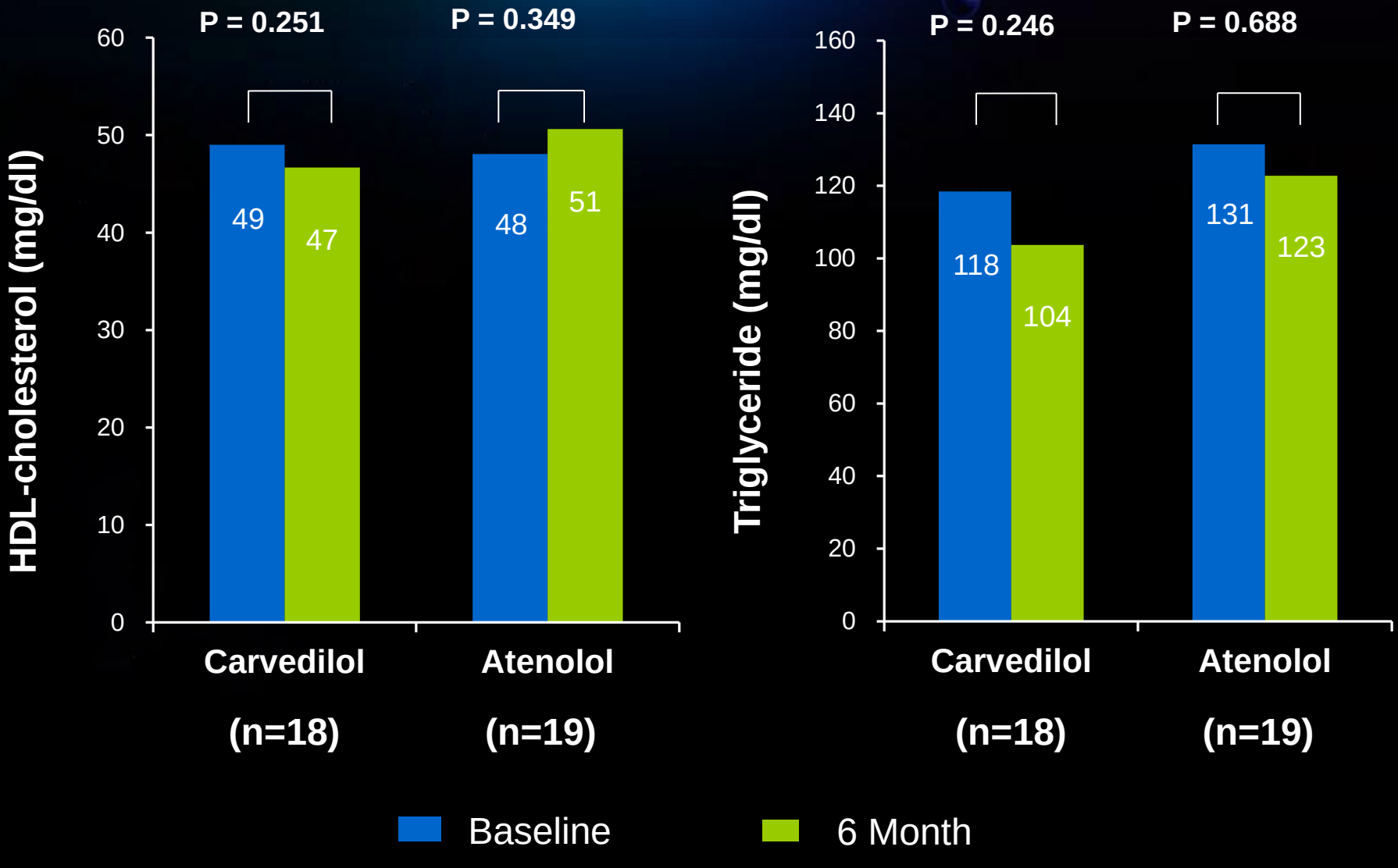
Effect on Time to ST-segment depression during TMT



Effect on Lipid Profiles



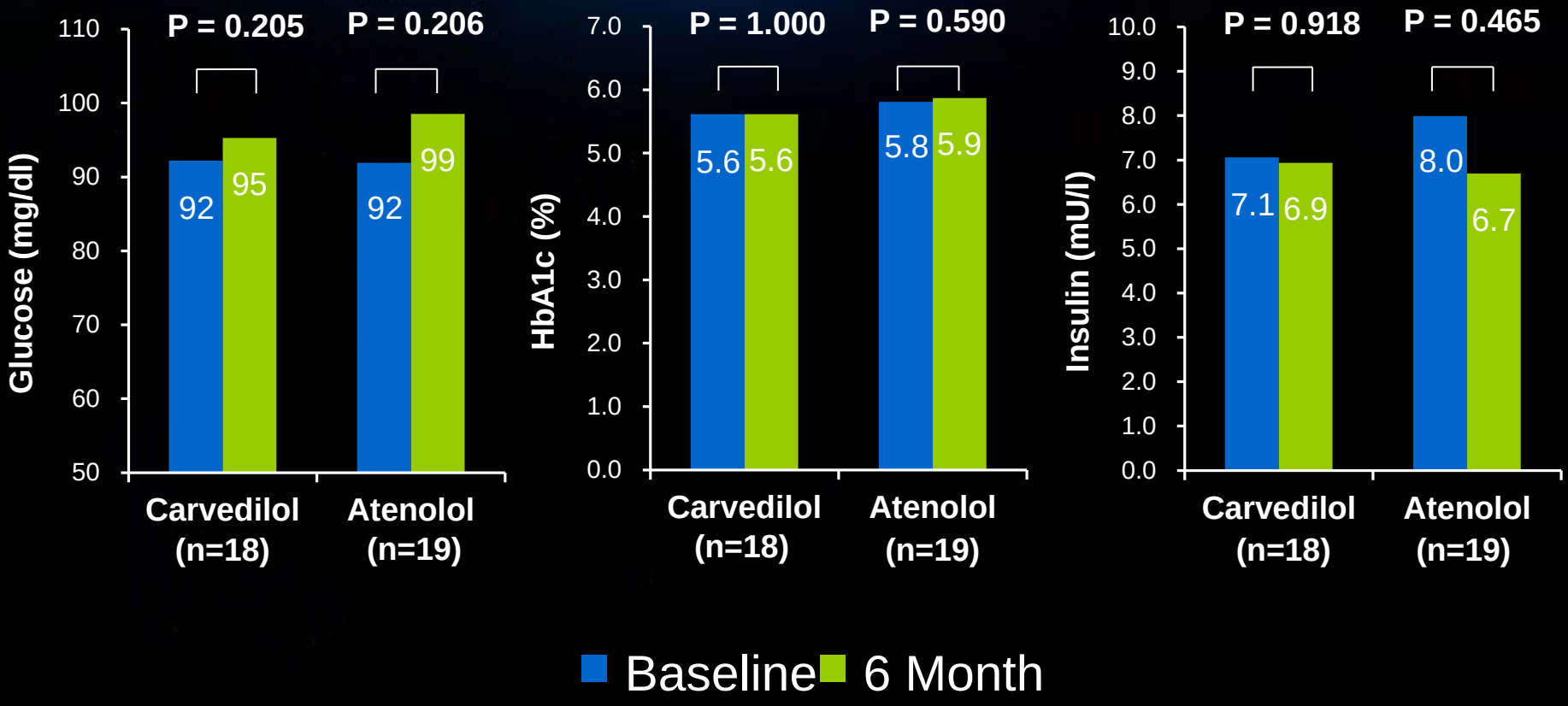
Effect on Lipid Profiles



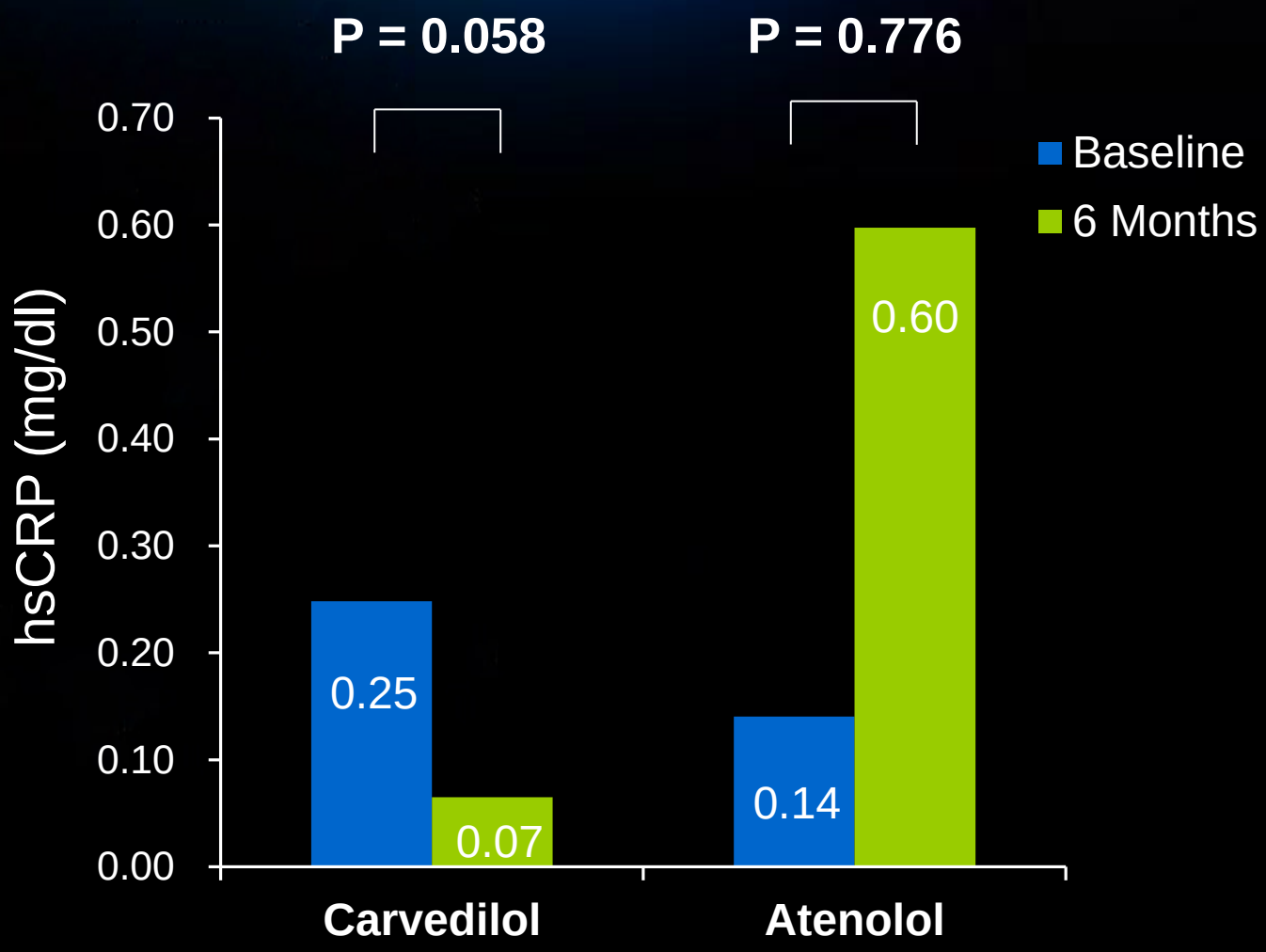
Statin Use Between Both Groups

	Carvedilol (n=18)	Atenolol (n=19)
Statin Use, n (%)	15 (83)	16(84)

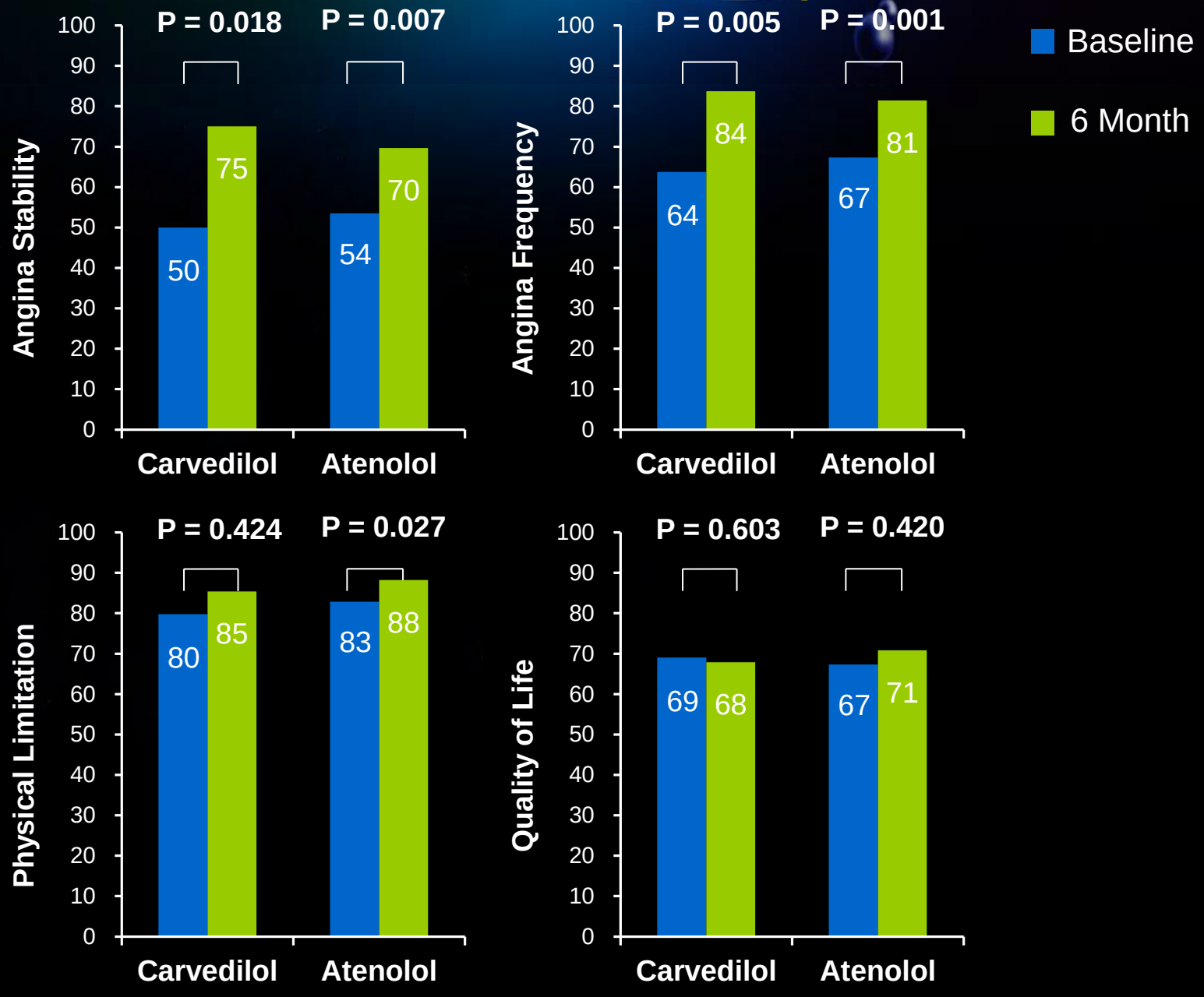
Effect on Glucose, HbA1c After 6 Months



Effect on hs-CRP After 6 Months



Effect on Seattle Angina Questionnaire (SAQ) scoring

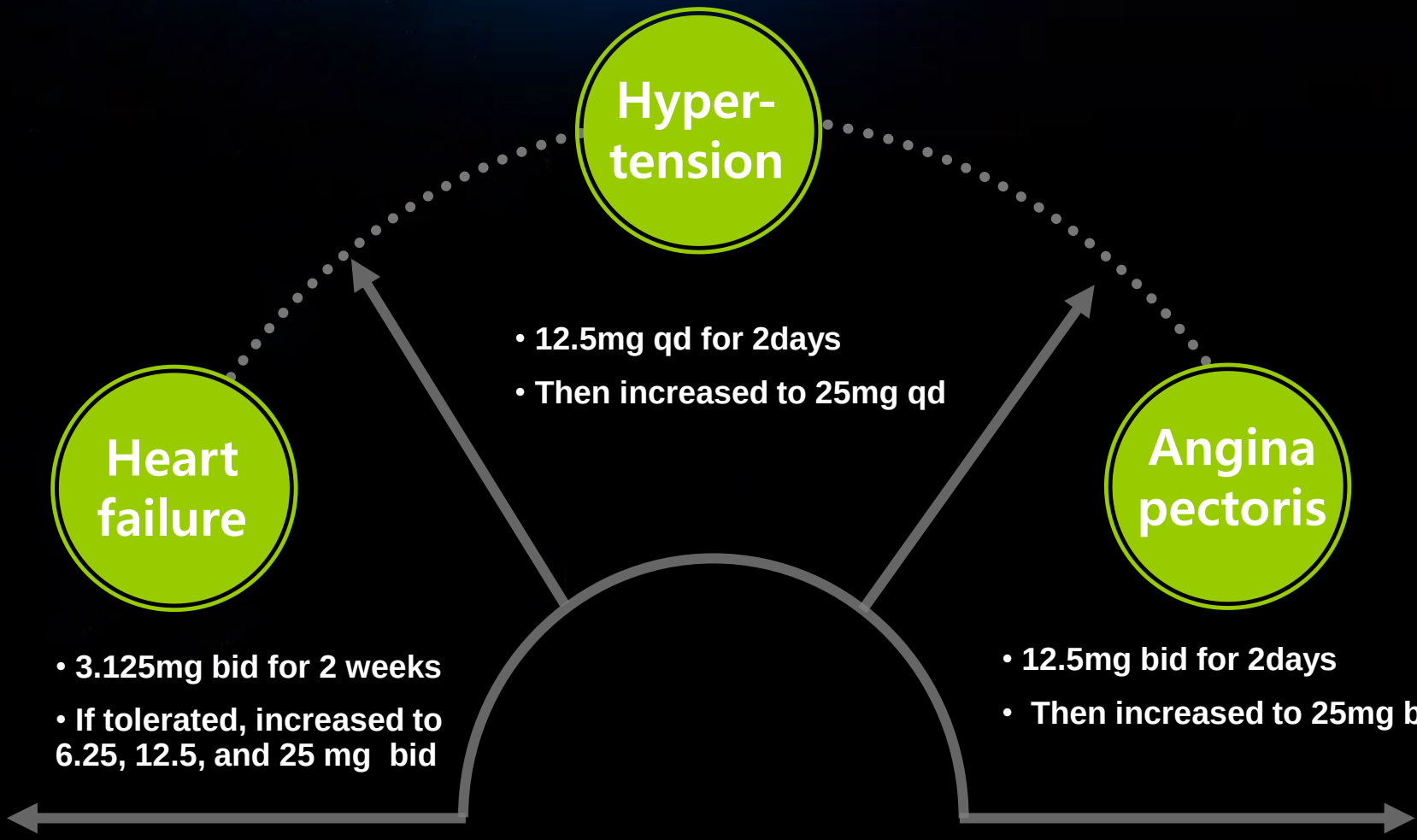


Our preliminary data showed…

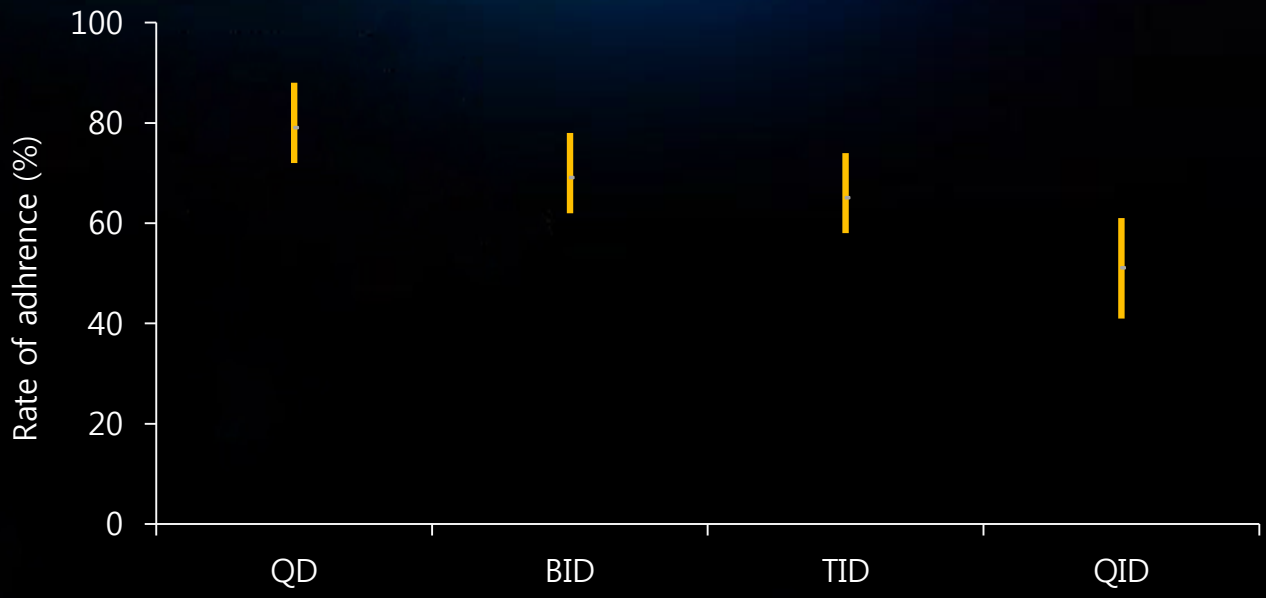
- Similar anti-angina effects are showed between both medication.
- Anti-metabolic and anti-inflammatory effect, however, are more favorable in carvedilol than atenolol.
- More data are needed.

Contents

Dosage & Administration of Dilatrend®



Adherence to medication according to frequency of doses



[Rate of adherence by frequency of regimen in long-term clinical studies]

Frequency of regimen	Mean dose-taking adherence (%)	Range(%)
QD	79	35-97
BID	69	38-90
TID	65	40-91
QID	51	33-81

Ref. Cardiol Rev. 2007;15(5):257-263.

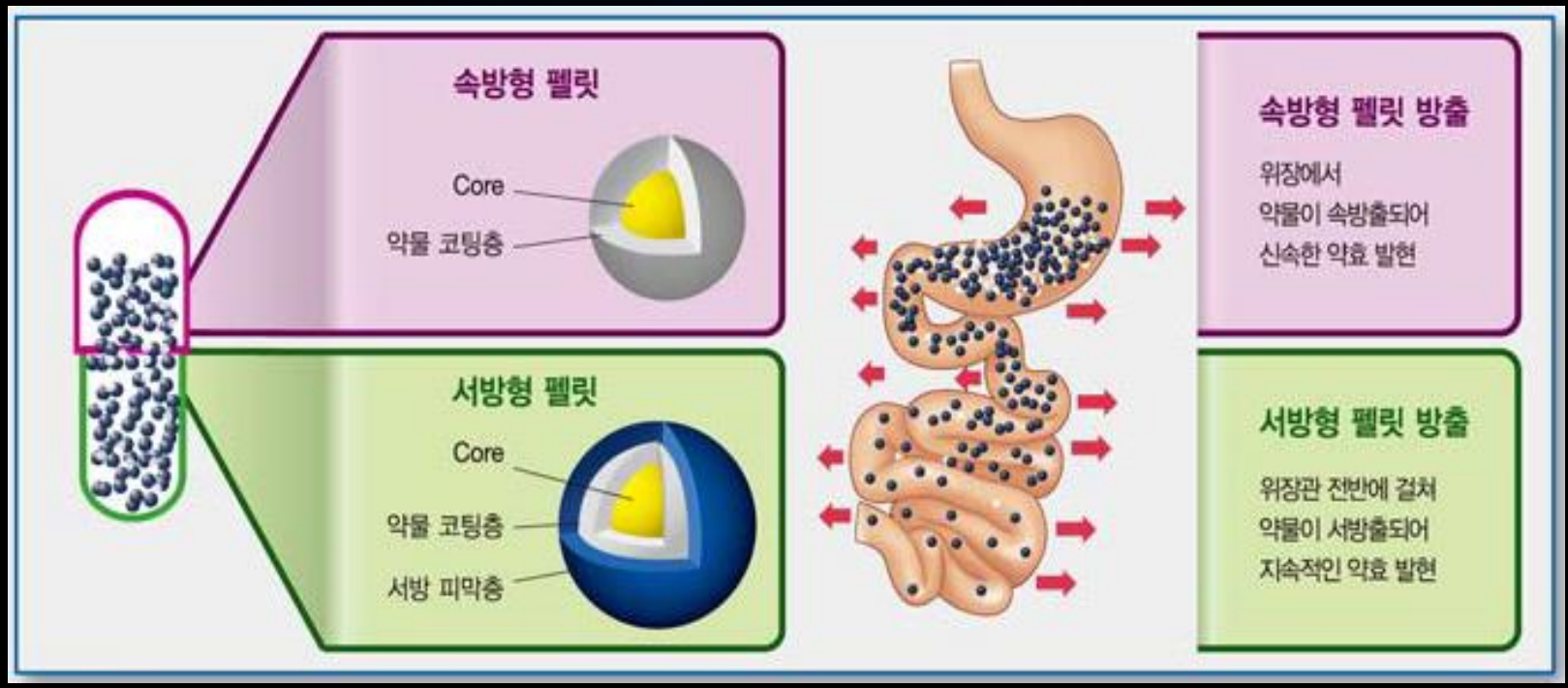
Dilatrend® SR

A new once-daily Sustained-Release (SR) capsule formulation of carvedilol is now available.

- Nonadherence to cardiovascular medications is a major barrier to the achievement of optimal clinical outcomes.
- A sustained-release (SR) once-daily capsule formulation of carvedilol has been developed and is now approved in the Korea.
- This new formulation of carvedilol allows for once-daily administration, which may simplify treatment and which is expected to improve patient adherence.

Dilatrend® SR

- Sustained – Release Formulation



Ref. data on file

Dilatrend® SR

Dosing equivalence

Dilatrend® Tab.	Dilatrend® SR Cap.
Carvedilol 3.125mg bid	Carvedilol 8mg qd
Carvedilol 6.25mg bid	Carvedilol 16mg qd
Carvedilol 12.5mg bid	Carvedilol 32mg qd
Carvedilol 25mg bid	Carvedilol 64mg qd

- Dilatrend® SR contains additional carvedilol compared with the twice-daliy formulation to adjust for bioavailability.

Ref. data on file

Dilatrend® SR

Repeated dosing study

Randomized, open-labeled, repeated dosing study to compare the pharmacokinetic characteristics of carvedilol IR and carvedilol SR in healthy male participants

Single dosing study

Randomized, open-labeled, single dosing study to compare the pharmacokinetic characteristics of carvedilol SR 32 mg 2 capsules and carvedilol SR 64 mg 1 capsule in healthy male participants

Dose–proportionality study

A randomized, open-label, single dose, dose-rising 10-sequence, 3-period balanced incomplete blocked clinical trial to evaluate dose–proportionality of Dilatrend SR in healthy male volunteers

Food effect study

A randomized, open-label, single-dose, crossover clinical trial to evaluate the food effect on the pharmacokinetics of Dilatrend SR 64mg capsule after oral administration in healthy male volunteers

Ref. data on file

Dilatrend® SR

Repeated dosing study : PK bioequivalence

Randomized, open-labeled, repeated dosing study to compare the pharmacokinetic characteristics of carvedilol IR and carvedilol SR in healthy male participants

Objective

To compare the pharmacokinetic characteristics of Dilatrend® 25mg and Dilatrend® SR 64mg

Method

- Design : phase I, open-label, randomized, 2-way crossover study
- Center : Korea University Anam Hospital
- Subjects : healthy male volunteers (n=48)
- Administration : Dilatrend® SR 64mg qd or Dilatrend® 25mg bid q 12hr for 7 days

Ref. data on file

Dilatrend® SR

Repeated dosing study : PK bioequivalence

Randomized, open-labeled, repeated dosing study to compare the pharmacokinetic characteristics of carvedilol IR and carvedilol SR in healthy male participants

Results

[Comparison of carvedilol pharmacokinetic parameters]

	Dilatrend®	Dilatrend® SR	T / R Ratio	p value
C_{max} (ng/mL)	39.74	42.01	1.06	0.739
C_{min} (ng/mL)	6.23	6.24	1.02	0.532
$AUC_{0\text{-}192hr}$ (ng·h/mL)	1089.32	1132.92	1.04	0.945

* T/R ratio : test/reference ratio

Ref. data on file

Dilatrend® SR

Dose–proportionality study

A randomized, open-label, single dose, dose-rising 10-sequence, 3-period balanced incomplete blocked clinical trial to evaluate dose–proportionality of Dilatrend® SR in healthy male volunteers

Objective

To evaluate dose-proportionality of Dilatrend® SR in healthy male volunteers

Method

- Design : phase I, open-label, randomized, single-dose ,10-sequence, 3-period balanced incomplete block design
- Center : Asan Medical Center
- Subjects : healthy male volunteers (n=30)
- Test drug : Dilatrend® SR 8, 16, 32, 64, 128mg (64mgx2)

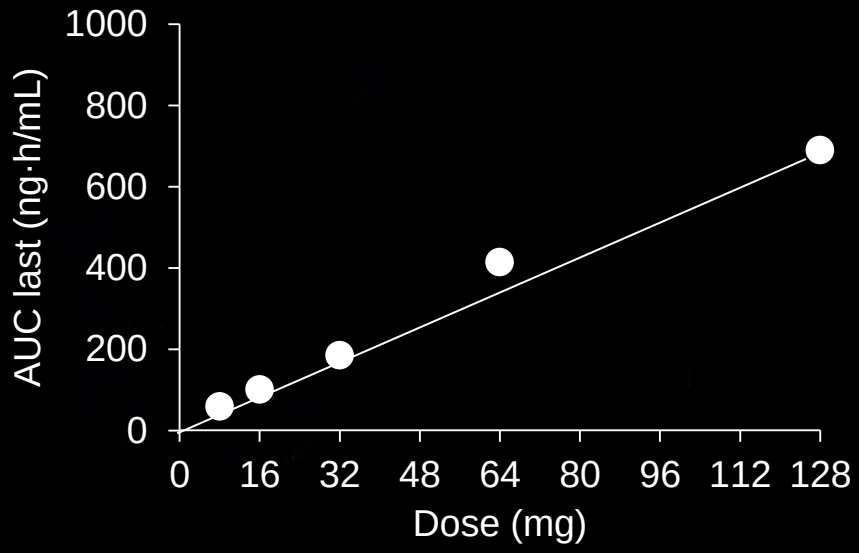
Ref. data on file

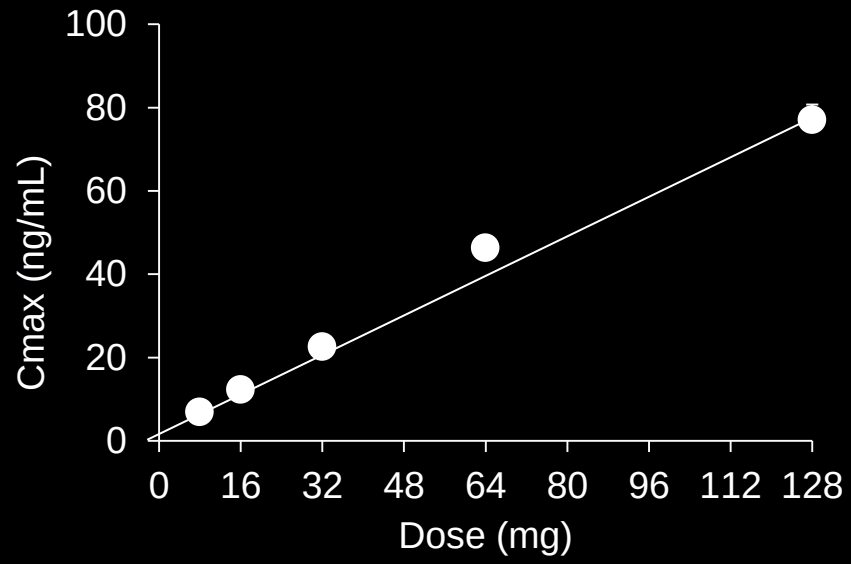
Dilatrend® SR

Dose–proportionality study

A randomized, open-label, single dose, dose-rising 10-sequence, 3-period balanced incomplete blocked clinical trial to evaluate dose–proportionality of Dilatrend® SR in healthy male volunteers

Results





Ref. data on file

Dilatrend® SR

□ Adverse Drug Reaction

Variable		Repeated dosing study		Dose–proportionality study
		Carvedilol IR (n=44)	Carvedilol SR (n=43)	Carvedilol SR (n=31)
ADR		Headache, Dizziness	Headache, Dizziness	Headache, Dizziness Light headedness, Paresthesia
Serious / Unexpected ADR		-	-	-
Severity	mild	V	V	V
	moderate	-	-	-
	severe	-	-	-

Ref. data on file

Conclusion

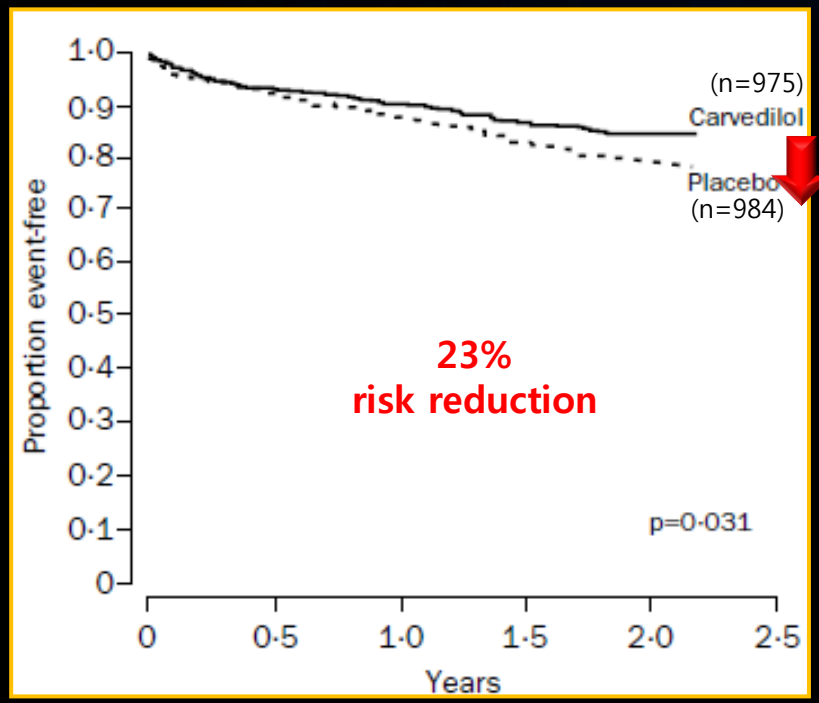
- Carvedilol has a much broader adrenergic inhibition as well as vasodilating and antioxidative properties not shared by traditional β1-selective β-blockers .
- These advantageous properties have translated into better outcomes in clinical trials.
- Taken together, the better therapeutic profile of carvedilol compared with β1-selective β-blockers should make carvedilol a first-choice treatment in cardiovascular disease.

Thank you

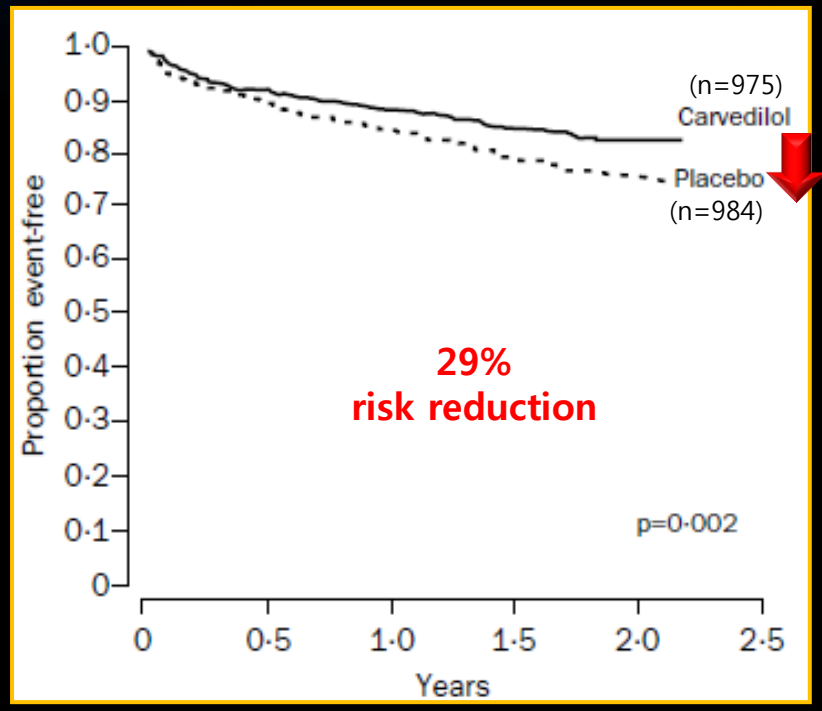
Landmark trial

- **CAPRICORN** (Effect of carvedilol on outcome after MI in patients with LV dysfunction)

[All-cause mortality]



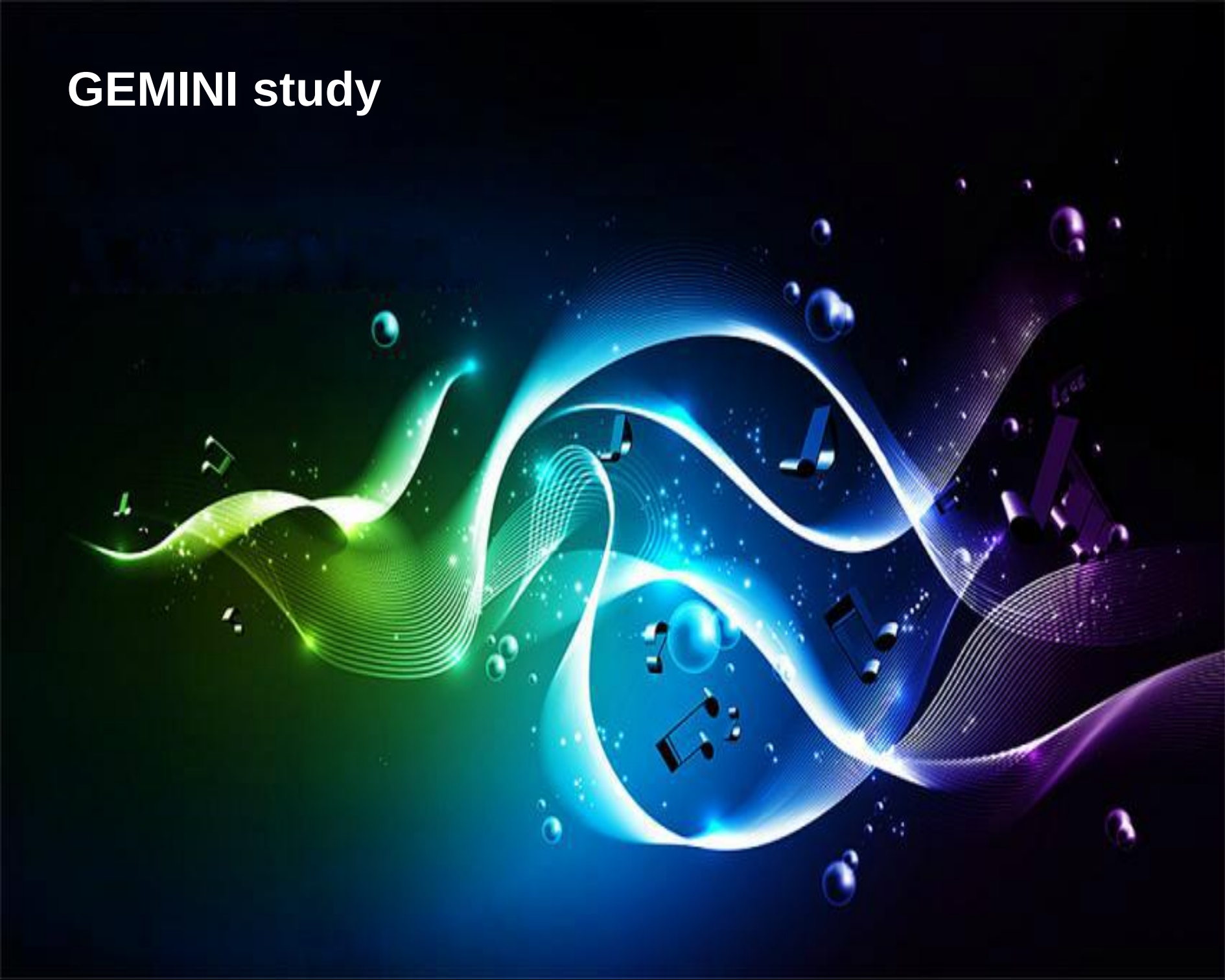
[All-cause mortality or Non-fatal MI]



- All-cause mortality alone was lower in the carvedilol group than in the placebo group (116 [12%] vs 151 [15%], 0·77 [0·60–0·98], p=0·03).
- Fewer patients on carvedilol than on placebo died from cardiovascular causes or had a non-fatal myocardial infarction.

Ref. Lancet 2001; 357: 1385–1390

GEMINI study



Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension

A Randomized Controlled Trial

George L. Bakris, MD
Vivian Fonseca, MD
Richard E. Katholi, MD
Janet B. McGill, MD
Franz H. Messerli, MD
Robert A. Phillips, MD, PhD
Philip Raskin, MD
Jackson T. Wright, Jr, MD, PhD
Rosemary Oakes, MS
Mary Ann Lukas, MD
Karen M. Anderson, PhD
David S. H. Bell, MD
for the GEMINI Investigators

Context β-Blockers have been shown to decrease cardiovascular risk in patients with hypertension and type 2 diabetes mellitus (DM); however, some components of the metabolic syndrome are worsened by some β-blockers.

Objective To compare the effects of β-blockers with different pharmacological profiles on glycemic and metabolic control in participants with DM and hypertension receiving renin-angiotensin system (RAS) blockade, in the context of cardiovascular risk factors.

Design, Setting, and Participants A randomized, double-blind, parallel-group trial (The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives [GEMINI]) conducted between June 1, 2001, and April 6, 2004, at 205 US sites that compared the effects of carvedilol and metoprolol tartrate on glycemic control. The 1235 participants were aged 36 to 85 years with hypertension (>130/80 mm Hg) and type 2 DM (glycosylated hemoglobin [HbA_{1c}], 6.5%-8.5%) and were receiving RAS blockers. Participants were followed up for 35 weeks.

Interventions Participants were randomized to receive a 6.25- to 25-mg dose of carvedilol (n=498) or 50- to 200-mg dose of metoprolol tartrate (n=737), each twice daily. Open-label hydrochlorothiazide and a dihydropyridine calcium antagonist were added, if needed, to achieve blood pressure target.

Bakris, et al. *JAMA*. 2004;292:2227-2236.

Rationale

- HTN is common in pts with DM; coexistence confers increased risk for development of CV and renal disease
- Medical management of DM and HTN is complex and multiple agents are needed, including β-blockers
- HTN and DM are also recognized risk factors for CHF, in which β-blockers are part of the standard therapy
- But many MDs are afraid to use β-blockers
  - β_1-selective blockers reportedly increase insulin resistance and worsen glycemic control
- Are there differences among β-blockers (selective vs non-selective) with respect to reducing BP without compromising glycemic control?

GEMINI

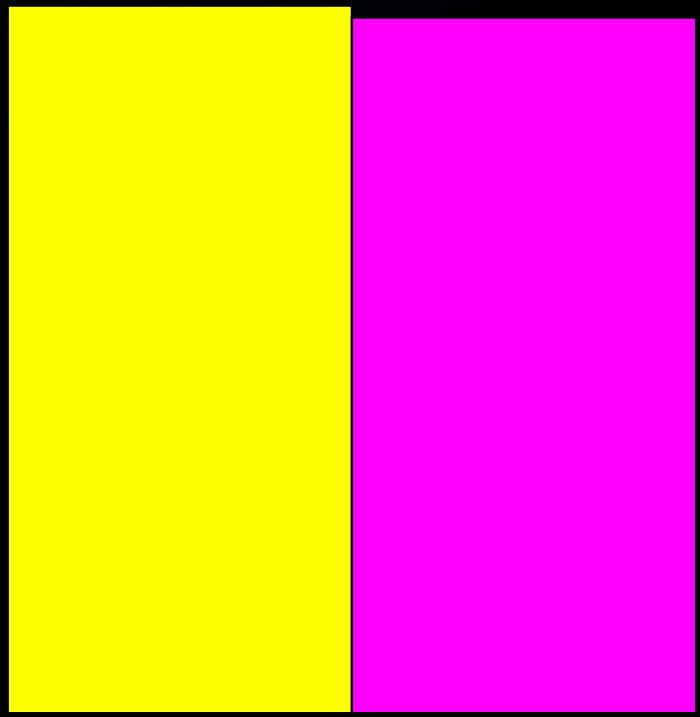
- Objective
  - To compare the effects of carvedilol and metoprolol on glyce mic control in diabetic hypertensives
- Population
  - 1235 participants (aged 36-85)
  - 205 US sites
  - hypertension (>130/80 mmHg) and type 2 DM ([HbA_{1c}] 6.5%-8.5%)
  - receiving RAS blockers
- Design
  - Randomized, double-blind, parallel-group trial

Endpoints

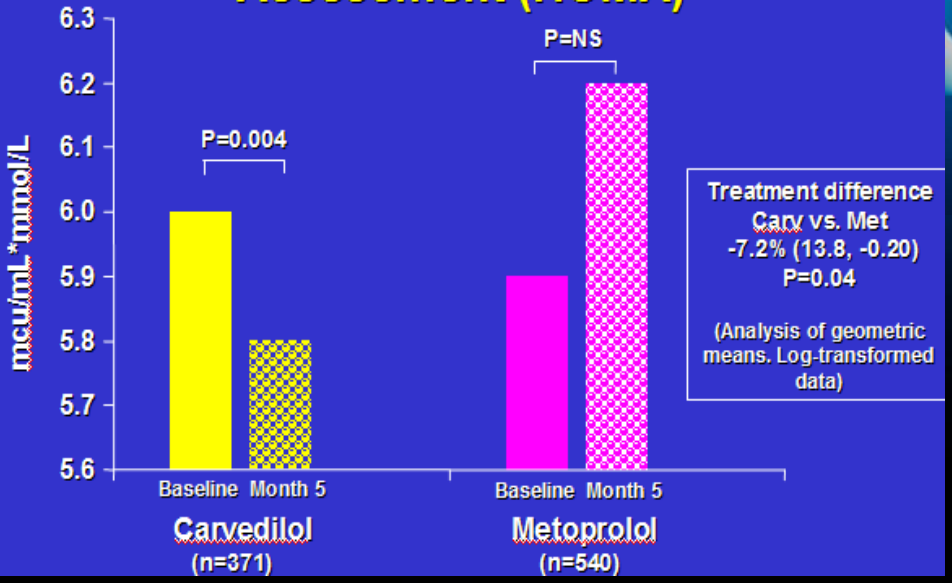
- Primary Endpoints
  - Difference in change of HbA_{1c} between treatment groups following 5 months of therapy

- Secondary Endpoints
  - Changes from baseline HbA_{1c} in the individual treatment groups
  - Changes in systolic and diastolic BP
  - Insulin and fasting glucose
  - Insulin resistance using HOMA
  - Cholesterol, tryglicerides, urinary albumin/creatinine ratio (mg/g), weight gain
  - Drop due to worsening glycemic control

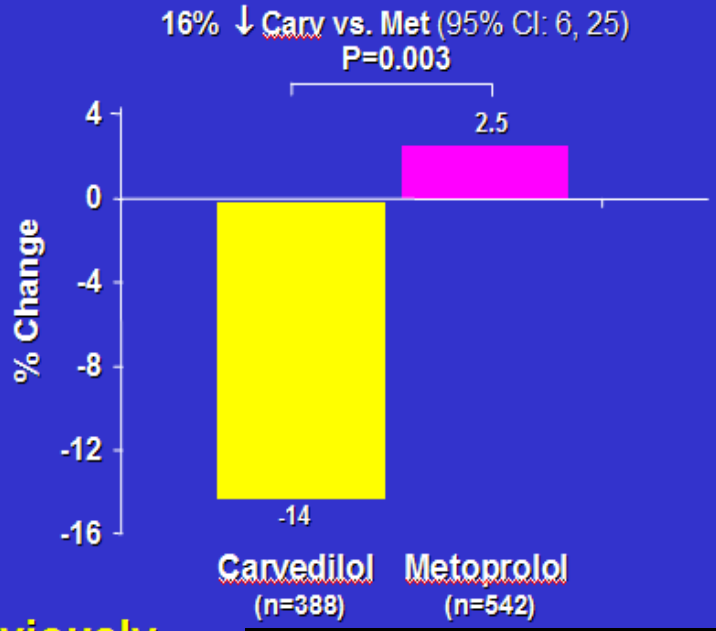
Patients Achieving Blood Pressure <130/80 mmHg



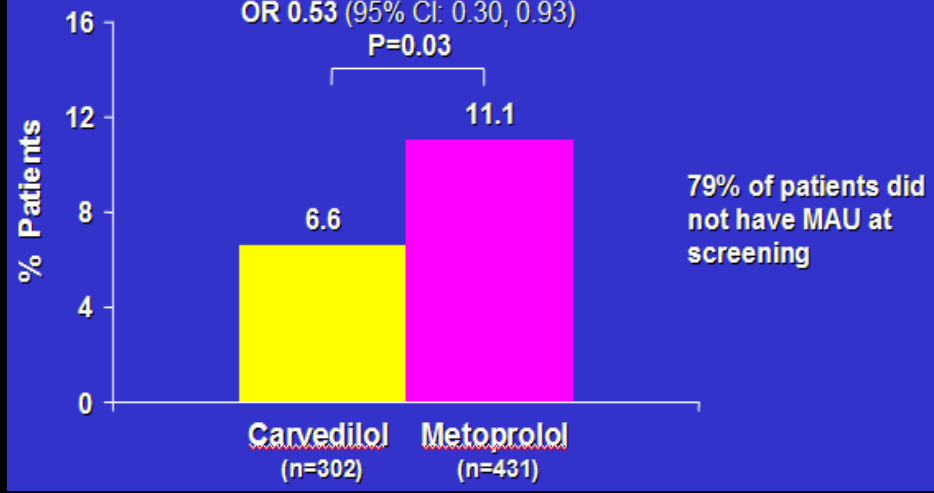
Insulin Resistance by Homeostasis Model Assessment (HOMA)

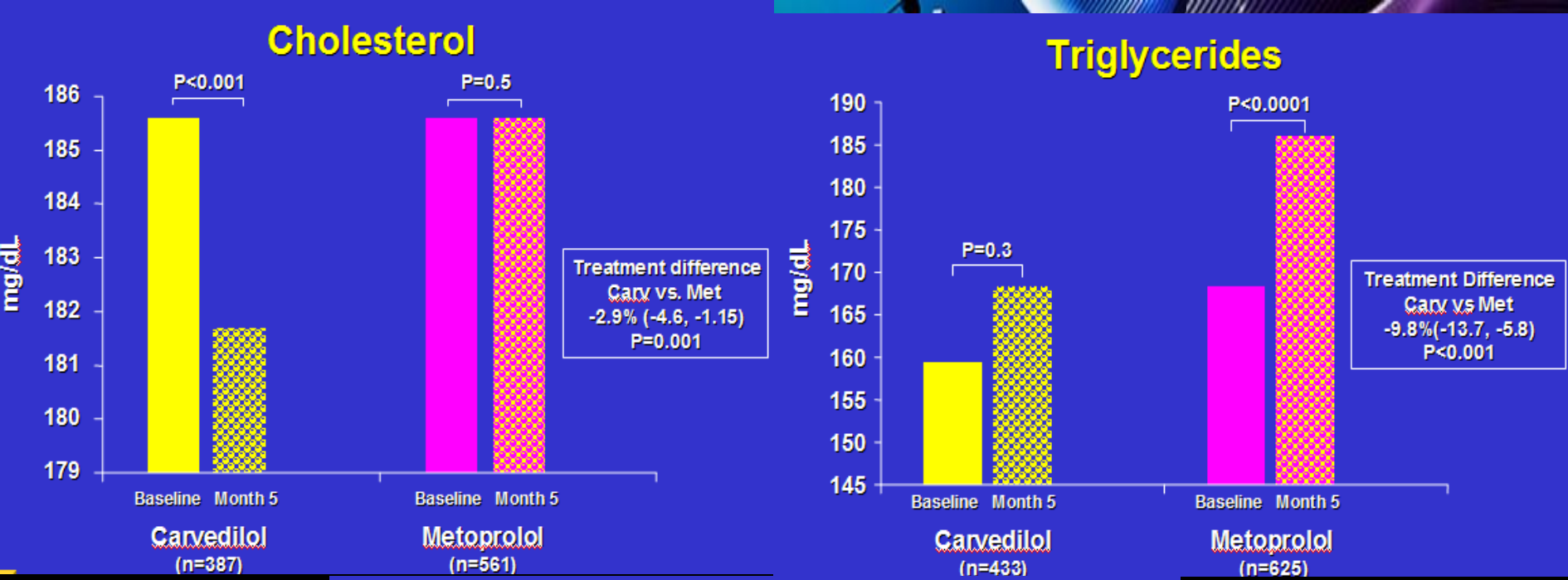


Albumin:Creatinine Ratio

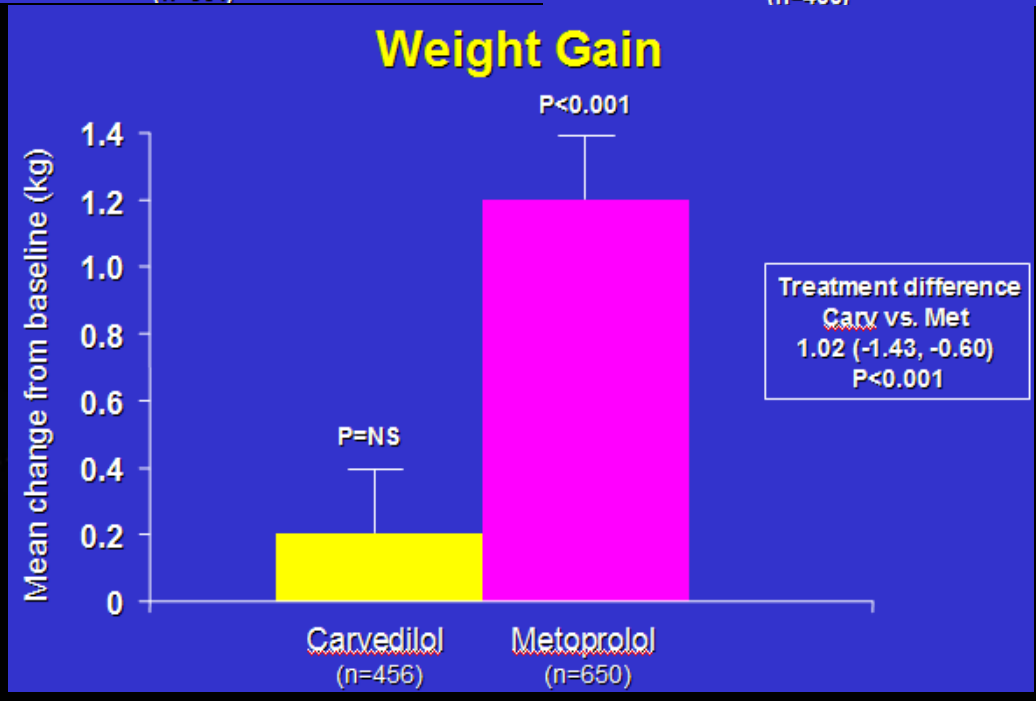


New Microalbuminuria in Previously Normoalbuminuric Patients




Cholesterol
mg/dL
186
185
184
183
182
181
180
179
P<0.001
P=0.5
Baseline
Month 5
Baseline
Month 5
Carvedilol
(n=387)
Metoprolol
(n=561)
Treatment difference
Carv vs. Met
-2.9% (-4.6, -1.15)
P=0.001

Triglycerides
mg/dL
190
185
180
175
170
165
160
155
150
145
P=0.3
P<0.0001
Baseline
Month 5
Baseline
Month 5
Carvedilol
(n=433)
Metoprolol
(n=625)
Treatment Difference
Carv vs Met
-9.8%(-13.7, -5.8)
P<0.001


Weight Gain
Mean change from baseline (kg)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
P=NS
P<0.001
Carvedilol
(n=456)
Metoprolol
(n=650)
Treatment difference
Carv vs. Met
1.02 (-1.43, -0.60)
P<0.001

Quality of Life and GEMINI

Carvedilol
(n=366)

VS

Metoprolol
Tartrate

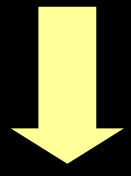
GEMINI Conclusions

- GEMINI is the first large-scale randomised trial evaluating the addition of beta-blockade to ACE inhibition to achieve the recommended BP target of <130/80 mmHg in patients with type 2 diabetes mellitus

- Compared with metoprolol, carvedilol achieved the BP goal, maintained glycaemic control, improved insulin resistance and reduced progression to microalbuminuria in this high risk patient population

FDA label change

Diabetes and Hypoglycemia: In general, β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. In congestive heart failure patients, there is a risk of worsening hyperglycemia (see PRECAUTIONS).



5.6 Glycemic Control in Type 2 Diabetes

In a study designed to examine the effects of carvedilol on glycemic control in a population with mild-to-moderate hypertension and well-controlled type 2 diabetes mellitus, carvedilol had no adverse effect on glycemic control, based on HbA1c measurements *[see Clinical Studies (14.4)]*.

2006년 카베딜롤의 당대사와 관련된 이상반응의 FDA label이 변경되었습니다.

NICE Clinical Guideline

One class which caused particular debate was the beta-blockers. The GDG noted that in head-to-head trials, beta-blockers were usually less effective than the comparator drug at reducing major cardiovascular events, in particular stroke. Atenolol was the beta-blocker used in most of these studies and, in the absence of substantial data with other agents, it is unclear whether this conclusion applies to all beta-blockers. However, if atenolol studies are excluded, the total evidence on the use of beta-blockers for the treatment of hypertension is much less than for the other main drug classes. It was therefore concluded that in the absence of other compelling indications for beta-blockade (for example, angina), beta-blockers should not be a preferred initial treatment for hypertension.

The widely used class of drug which is omitted from this regimen is the beta-blocker. The evidence overall suggests that clinical benefit is least likely (especially for stroke prevention) with these agents. However, given the relative lack of clinical outcome data from trials of treating hypertension with beta-blockers other than atenolol, concern about the generalisability of this conclusion, beyond atenolol, to all beta-blockers remains. The GDG felt that good studies with alternative beta-blockers in people with hypertension are required for this conclusion to be reversed. An additional concern is the increased risk of developing diabetes, particularly with the combination of a beta-blocker with a thiazide-type diuretic. Omitting beta-blockers from the routine treatment algorithm was therefore justified. Nevertheless, the GDG noted that there are certain compelling indications for beta-blockers which have been specified.

2006 Canadian Hypertension Education Program Recommendations

What Are the New Messages?

Beta blocker therapy is strongly recommended in hypertensive patients of all ages who have specific indications such as post MI, angina and congestive heart failure. However, new evidence further supports the use of beta blockers as a first-line therapy in uncomplicated hypertension only in patients younger than 60 years old. These findings were based on recent meta-analysis.[14,15] The

2007 ESH-ESC Guidelines for the management of hypertension

…β-blockers should be avoided in subjects with the metabolic syndrome because of their adverse effect on the incidence of new onset diabetes as well as on body weight, insulin sensitivity and the lipid profile.

However, these effects appear to be less pronounced or absent with the *new vasodilating β-blockers such as* *Carvedilol.*

Conclusions

- Beta-blocker is still recommended in hypertensive patients with compelling indication
- Atenolol is inferior to other antihypertensive drug especially in the elderly and patient with dysmetabolic risk.
- There is no evidence that new vasodilating beta-blocker, carvedilol and nebivolol are inferior to other class of antihypertensive drug
  - Carvedilol and nebivolol should not be removed from the first line drug for the treatment of hypertension
  - Should consider drug effect rather than class effect !!
  - Caution is needed in the interpretation of meta-analysis or systemic reviews!!!

"The [ESH] committee felt this was not an appropriate decision….

- *Beta blockers were usually employed together with diuretics in virtually all trials*
- *It was difficult to discriminate what was the favorable or unfavorable role of one drug class or another."*

New ESH Guideline Will…

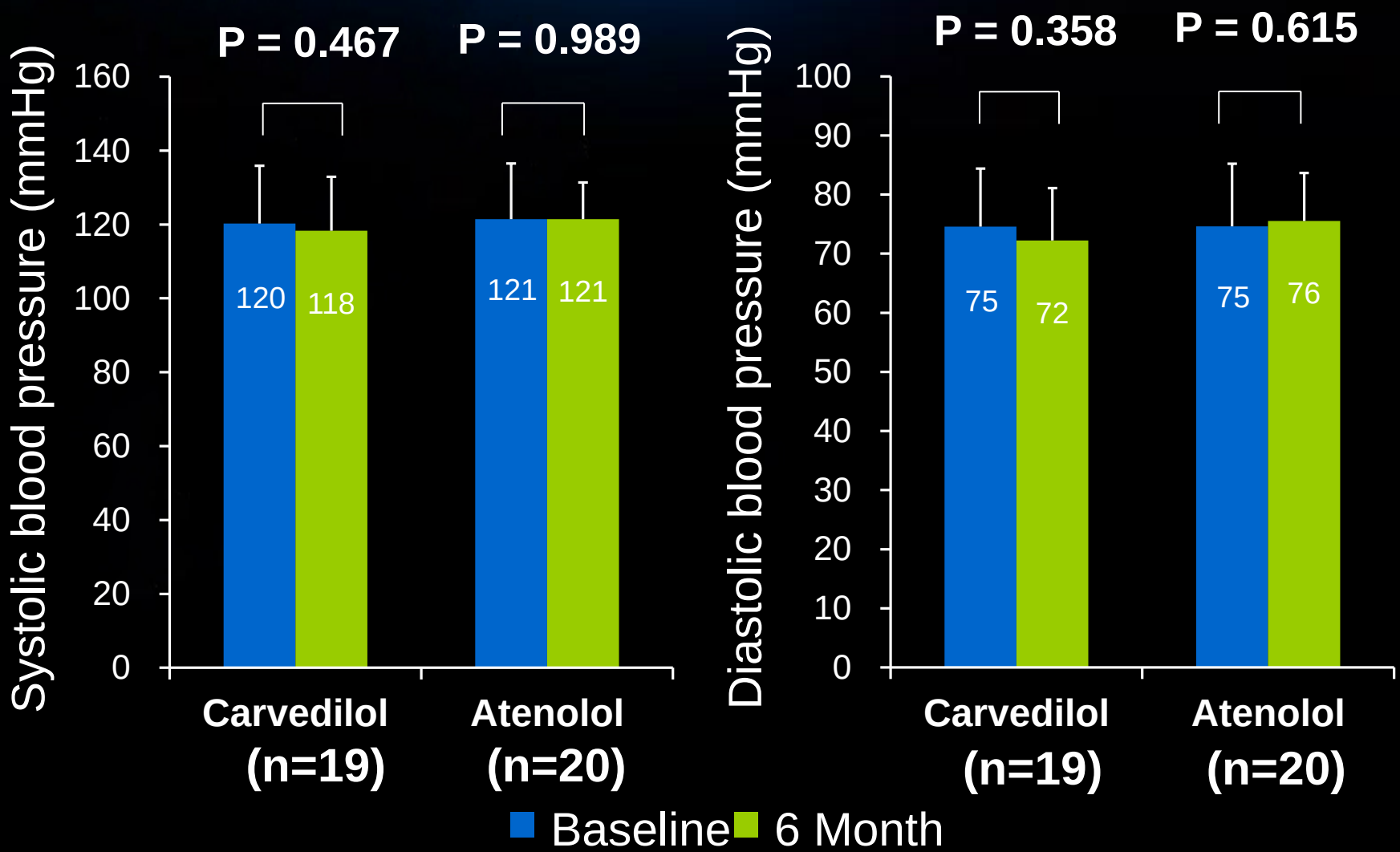
- Reducing the emphasis on the step-by-step approach
- Indicate which drug might be preferred in which patient under which circumstance

- “All drugs have advantages and disadvantages, and we have to try to see in which conditions the

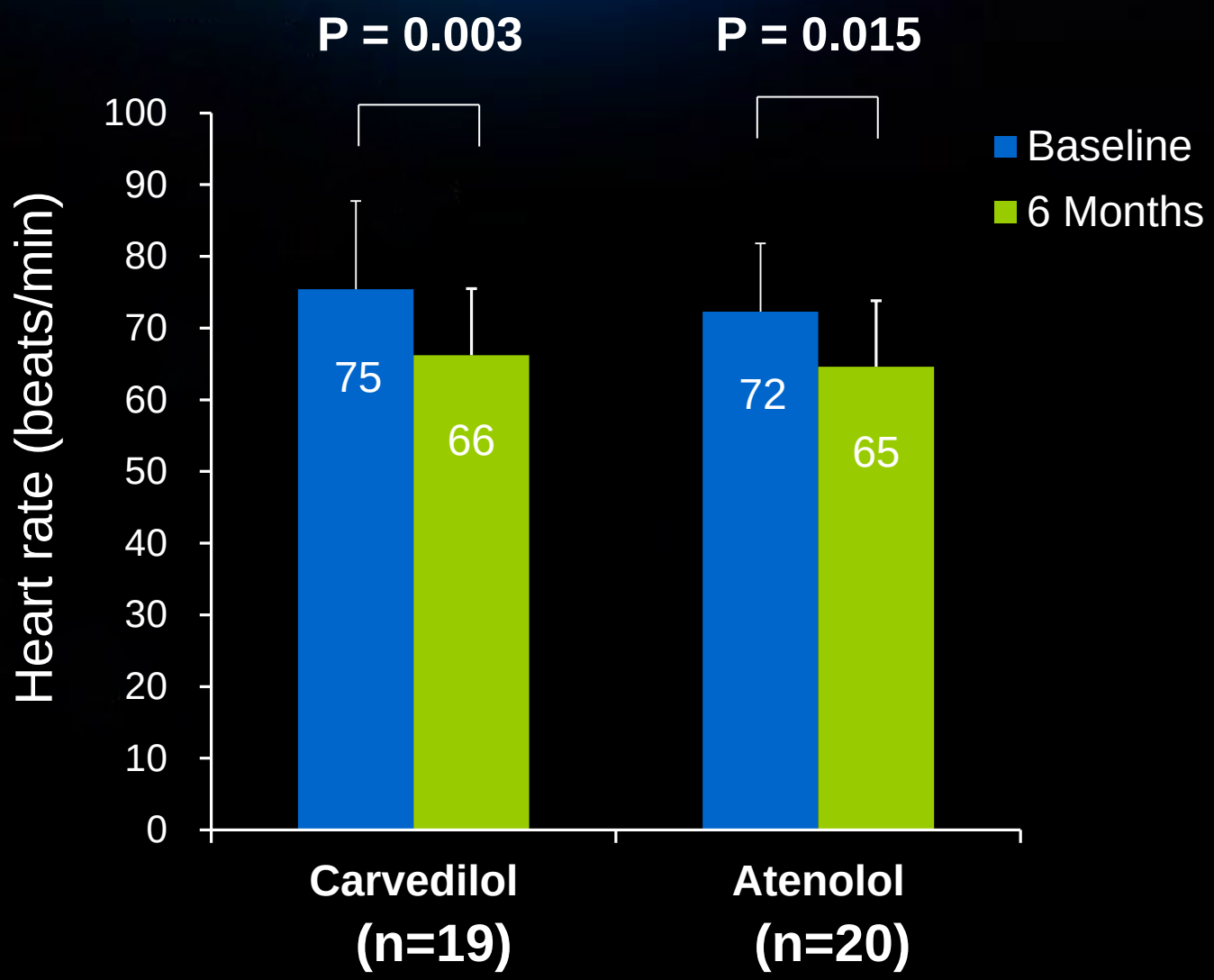
Result of Treadmil Test After 6 Months

	TMT (+)	TMT (-)
Carvedilol (n=18)	5 (27.8)	13 (72.2)
Atenolol (n=18)	6 (33.3)	12 (66.7)

Effect on Office Blood Pressure After 6 Months



Effect on Office Heart Rate After 6 Months



Comparison with β_1 selective BBs

- Systematic review & Meta-analysis I

Table 2. Meta-analysis of β-blockers versus active/placebo trials.

Outcome	Relative risk reduction: mortality and vascular events, respectively (95% CI)
Acute MI	
β1-selective	0.82 (0.67–1.01); nonsignificant 0.68 (0.42–1.11); nonsignificant
β1 and β2	0.73 (0.64–0.82); significant 0.71 (0.59–0.84); significant
Heart failure	
β1-selective	0.76 (0.68–0.87); significant 0.87 (0.67–1.14); nonsignificant
β1 and β2	0.77 (0.69–0.86); significant 0.80 (0.64–1.00); significant

MI: Myocardial infarction.

Ref. Hypertension, 2005;45:980-985

- Although they are effective antihypertensive agents, b-blockers are generally perceived to adversely effect dyslipidemia as well as to decrease insulin sensitivity in hypertensive subjects.
- Beta-blockers without adverse carbohydrate and lipid metabolism effects may provide a significant improvement in long-term therapy of the high-risk hypertensive subject by maintaining the overall metabolic profile.
- b-blockers comprise a heterogeneous drug class having different pharmacologic properties including a-blockade, sympathomimetic activity, effect on myocardial function, and reduction of ventricular remodeling, depending on the inhibition of specific adrenergic receptors, and thus, there may be differences in how they affect various metabolic factors.
- Carvedilol, in doses used to effectively control blood pressure (BP), decreases insulin resistance (improves insulin sensitivity), has no effect on glycemic control, and is lipid neutral.
- This positive metabolic profile comes from a limited number of small studies of hypertensive nondiabetic subjects,9 subjects with type 2 diabetes, 10 and from the large, randomized controlled Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial11 in subjects with hypertension and type 2 diabetes.

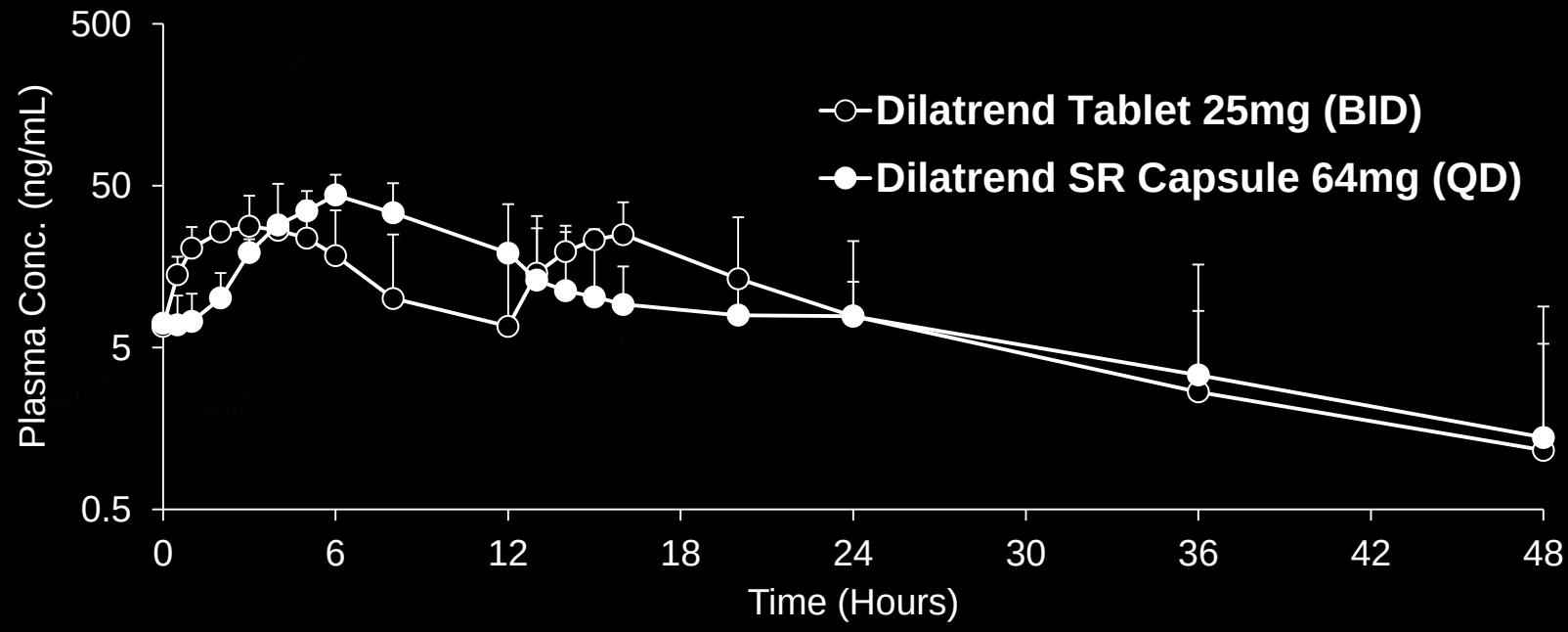
Dilatrend® SR

Repeated dosing study : PK bioequivalence

Randomized, open-labeled, repeated dosing study to compare the pharmacokinetic characteristics of carvedilol IR and carvedilol SR in healthy male participants

Results

[Mean plasma concentration profiles of carvedilol]



Ref. data on file

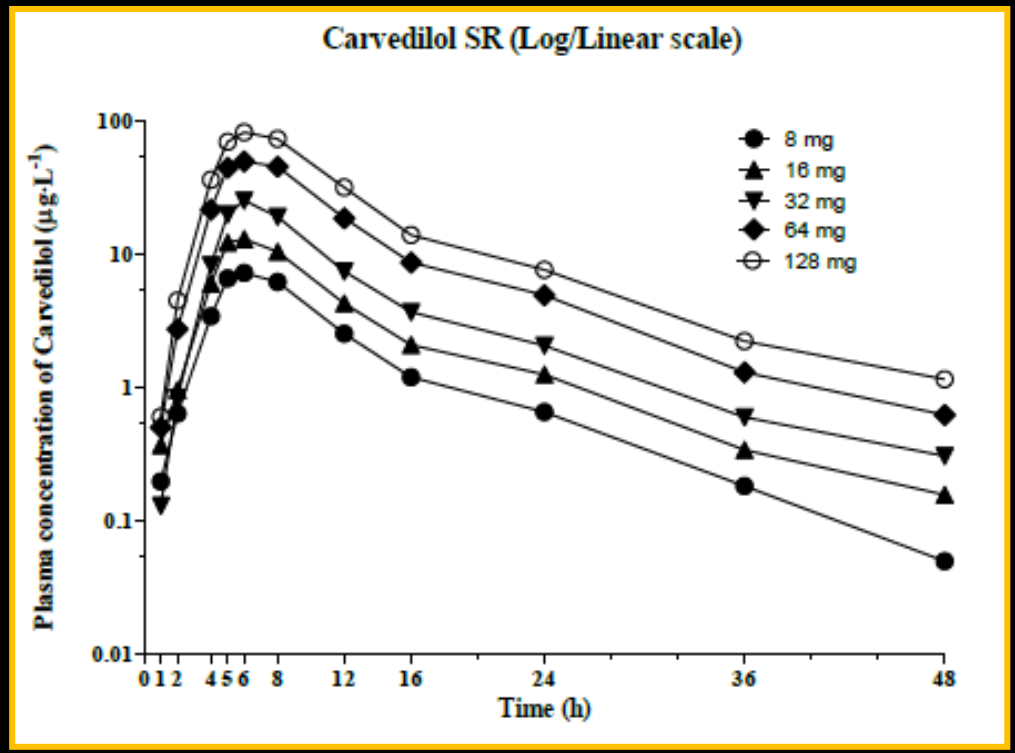
Dilatrend® SR

Dose–proportionality study

A randomized, open-label, single dose, dose-rising 10-sequence, 3-period balanced incomplete blocked clinical trial to evaluate dose–proportionality of Dilatrend® SR in healthy male volunteers

- Results

[Mean plasma concentration-time curves]



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CrystalGraphics