당뇨병이 있는 고혈압환자에서 Beta-Blockers 의 사용

영남의대 내분비내과
이 형 우

HYPERTENSION IN DIABETES

	% with BP ≥140/90
General population	31.3%
All patients with DM	65%
Type 1 DM, normal AER	≥30%
Type 2 DM:	
At Dx	50%
Microalbuminuria	40-83%
Macroalbuminuria	78-96%

Hypertension 2004; 44: 398, Am J Kid Dis 2004; 43 (May Suppl): S142

EFFECTS OF ↑BP ON DM COMPLICATIONS

- **CVD: 75% of all DM deaths**
  - **3X ↑in CAD**
  - **2X ↑in stroke**
  - **2X ↑in mortality**
- **Microvascular Complications**
  - **↑retinopathy, nephropathy, neuropathy**

JAMA 2002; 287: 2570 Hypertension 2001; 37: 1053

Multifactorial Intervention and Cardiovascular Disease in Patients with T2 DM (Steno-2 Study)

Gæde P et al. NEJM 2003; 348: 383

	△ Parameters		
	Conventional Rx	Intensive Rx	P Value
N	63	67	
FBS (mg/dl)	-18	-52	<0.001
HbA1c(%)	+0.2	-0.5	<0.001
LDL-C(mg/dl)	-13.0	-47.0	<0.001
SBP (mm Hg)	-3.0	-14.0	<0.001

CVD Risk	↓53%
Nephropathy Progression	↓61%
Retinopathy Progression	↓58%
Autonomic Neuropathy Progression	↓63%

EFFECTIVE BP DRUGS IN DM RCTs

	↓CVD	↓Microvascular Events
Thiazides	**Yes**	**Yes**
ACE-Is	**Yes**	**Yes**
ARBs	**Yes**	**Yes**
Non-DHP-CCBs	**Yes**	**Yes**
DHP-CCBs	**Yes**	**Yes**
B-Blockers	**Yes**	**Yes**

- **BP reduction of 9-11/2-9 mm Hg over 2-5 y**
  - **↓ CVD 34-70%**
  - **↓ Microvascular disease 26-46%**

Hypertension 2003; 42: 1206 Am J Kid Dis 2004; 43 (May Suppl): S142

Poor quality of blood pressure control amongst hypertensive diabetic patients

- **The majority of hypertensive diabetic patients will need a combination of several antihypertensive agents to control BP.**
- **However, most patients are given a single drug therapy, predominantly ACEI.**

The fear of beta blocker-associated side effects(?)

poor quality of BP control

Not decline in cardiovascular mortality

- **EURODIAB Study; 3250 T1DM, 24% hypertension, 11% achieved target BP(130/85)**

- 기간: 2004년 9월 ~ 2005년 2월, CARD PROGRAM
- 실시 병원: 총 36개 종합병원 내분비내과
- 참여 환자수: 총 3,678명

Total patients	**3678**
Diabetes	**1699**
Hypertension	**1243 (73%)**
Medication	**759 (61%)**
↓130/80	**200 (26%)**

*고혈압 환자 : BP가 130/80 이상인 자, 환자 설문 시 고혈압 약물 복용자라고 응답한 자

Conventional treatment with Beta-blockers; Negative Images

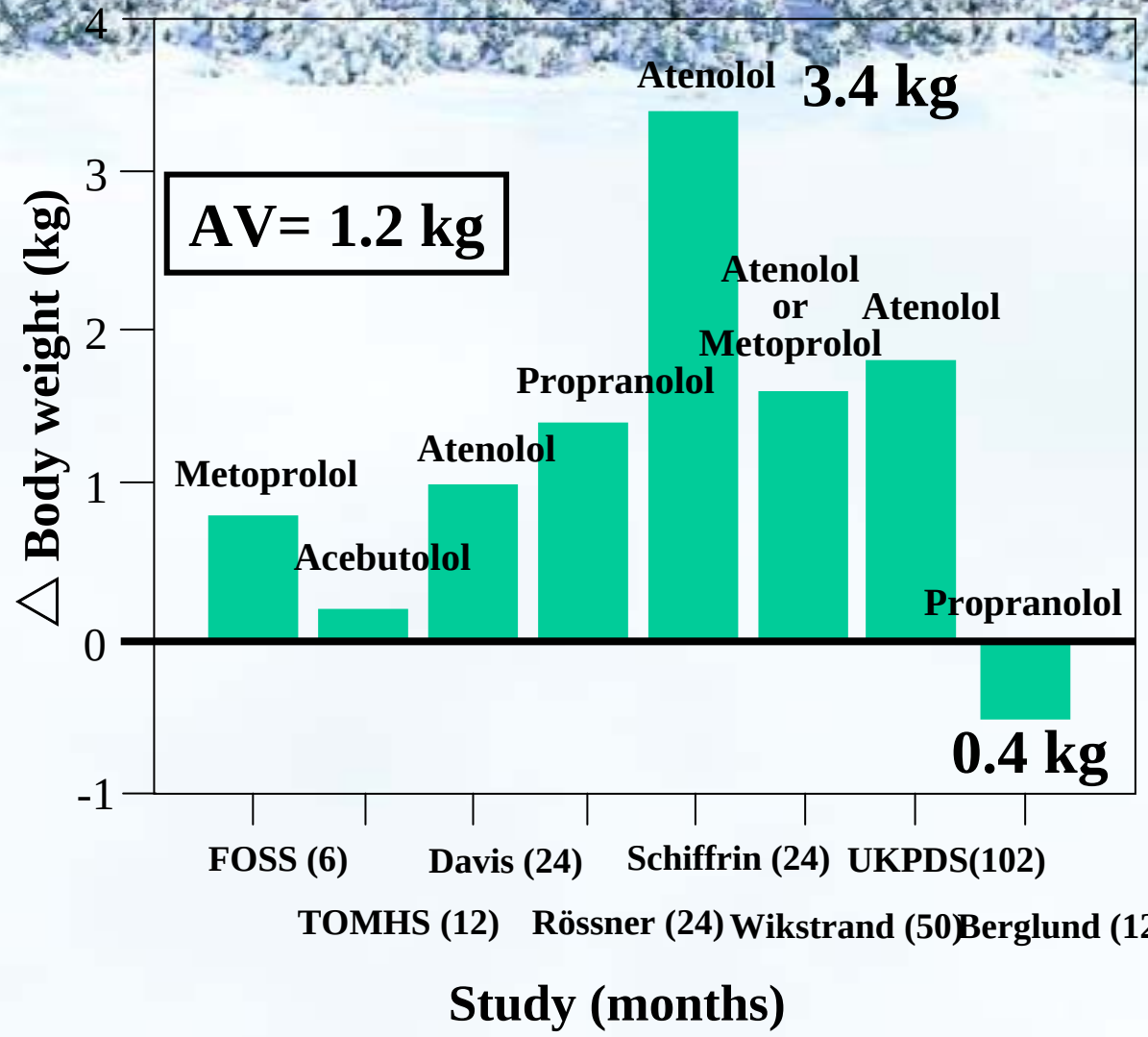
- **Do Beta Blockers have adverse effect on blood glucose and lipid metabolism?**
- **Do Beta Blockers mask symptoms of hypoglycemia and prolong hypoglycemia?**
- **Are Beta Blockers less nephroprotective antihypertensive agents?**

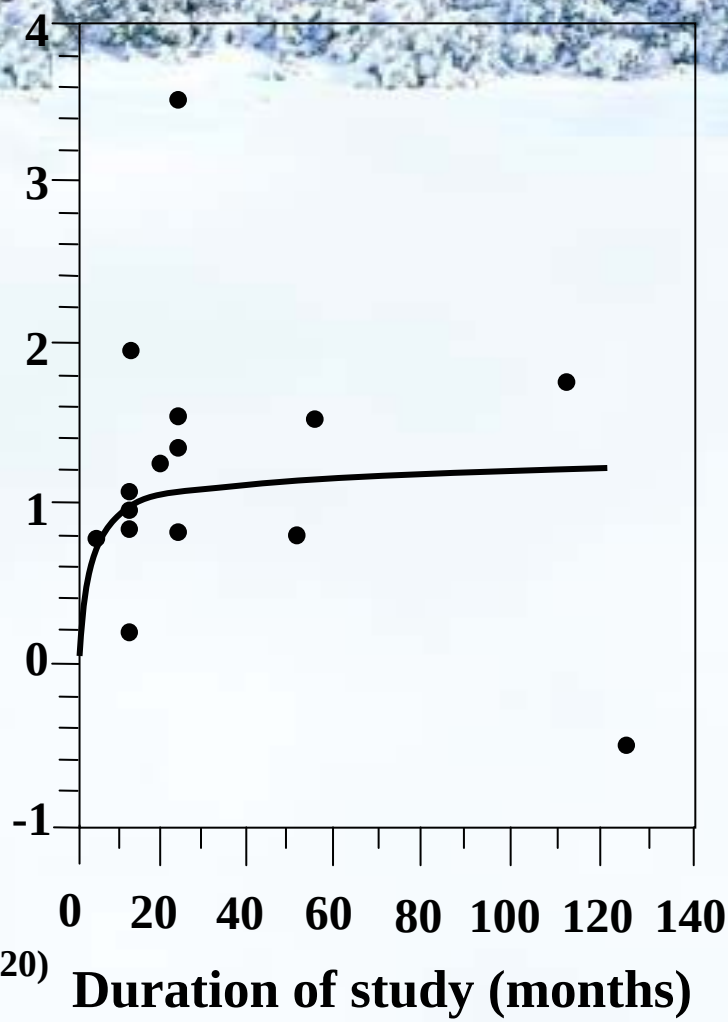
Do Beta Blockers have adverse effect on blood glucose metabolism?

- **Weight gain**
- **Insulin sensitivity and DM**

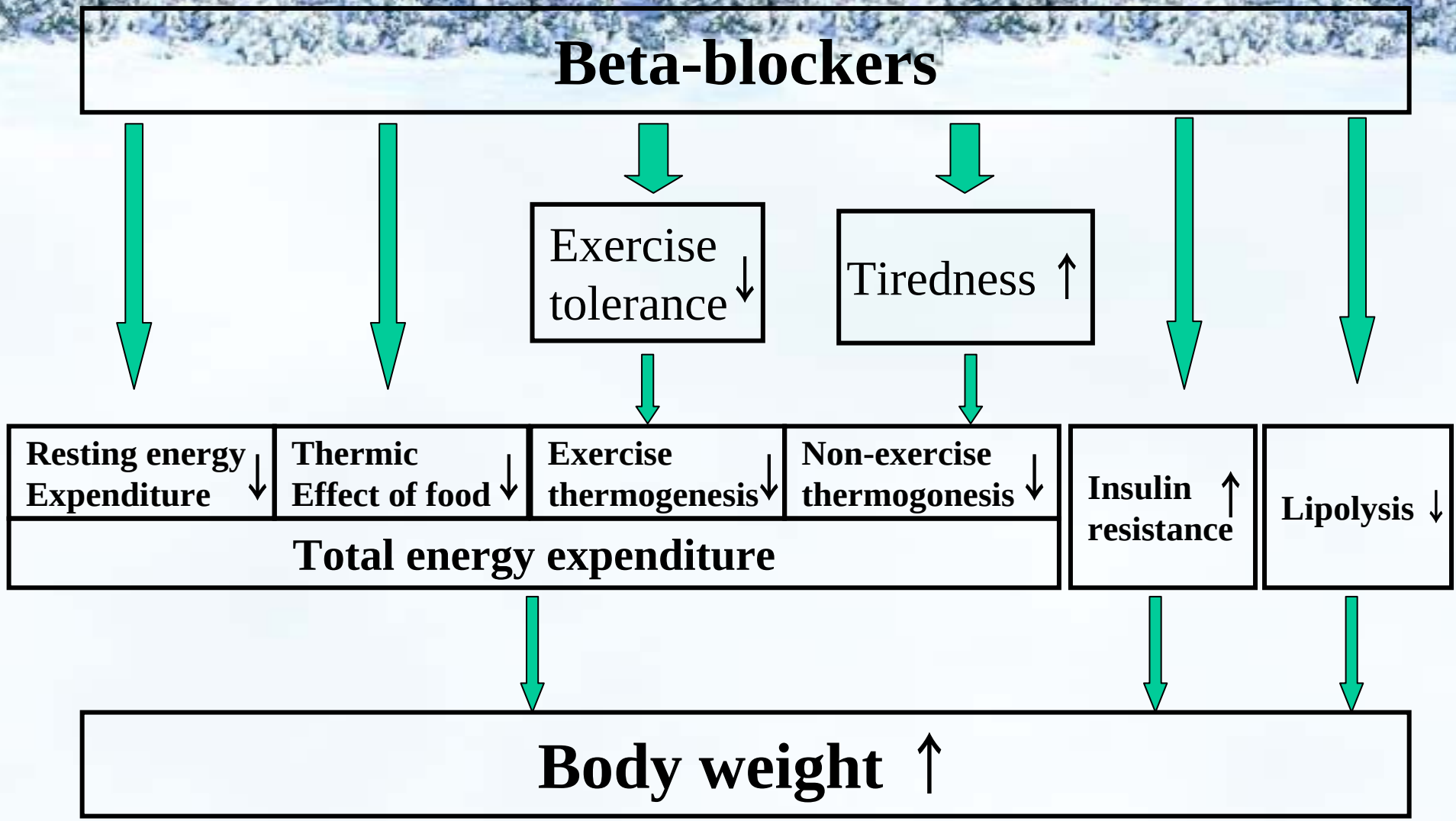
Gain in body weight

Time course





Mechanisms


Beta-blockers
Exercise tolerance ↓
Tiredness ↑
Resting energy Expenditure ↓
Thermic Effect of food ↓
Exercise thermogenesis ↓
Non-exercise thermogonesis ↓
Total energy expenditure
Insulin resistance ↑
Lipolysis ↓
Body weight ↑

↓ Insulin sensitivity; Possible mechanism

- **Lower activity of LPL**
- **Reduce LCAT activity**
- **Increase body weight**
- **Impair first phase insulin secretion**
- **Reduce insulin clearance**
- **Reduce peripheral blood flow and increase TPR**

Jacob S et al. *Am J Hypertens.* 1998;11:1258–1265.

Influence of Beta-Blockers on glucose metabolism in 10 Hypertensives with T2DM

Groop L. et al, Acta Med Scand 211; 7-12, 1982

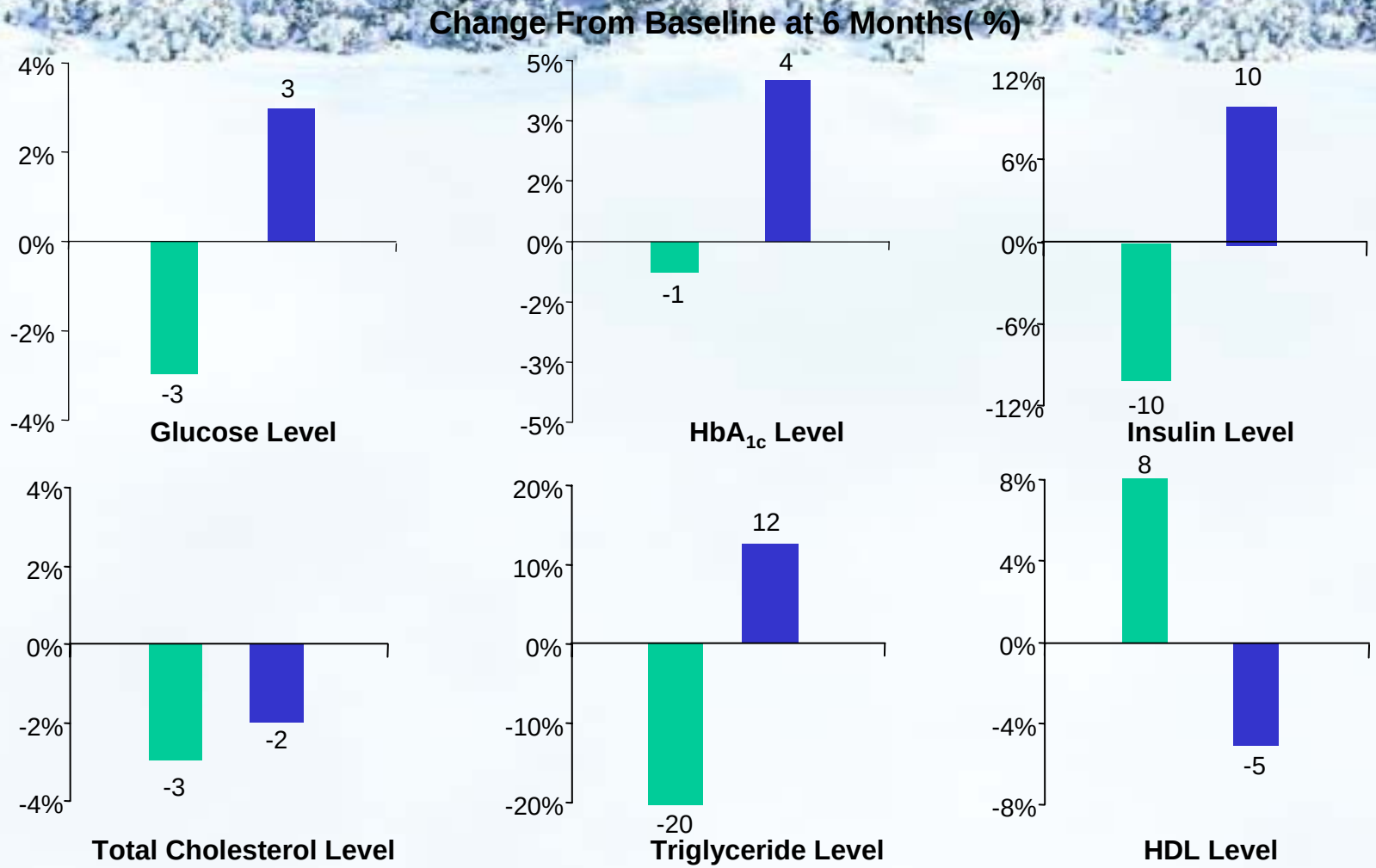
	placebo	Propranolol	Metoprolol
FBG (mmol/L)	7.4±0.4	8.6 ±0.4 *	7.9 ±0.3
Serum insulin (μU/mL)	19.1 ±2.6	27.2 ±4.6	22.6 ±4.1
K_G (%/min)	0.61 ±0.06	0.88 ±0.15	0.78 ±0.09

Significance of the difference compared with placebo; * P < 0.02

Metabolic changes according to three agents (Mean ± S.E.)

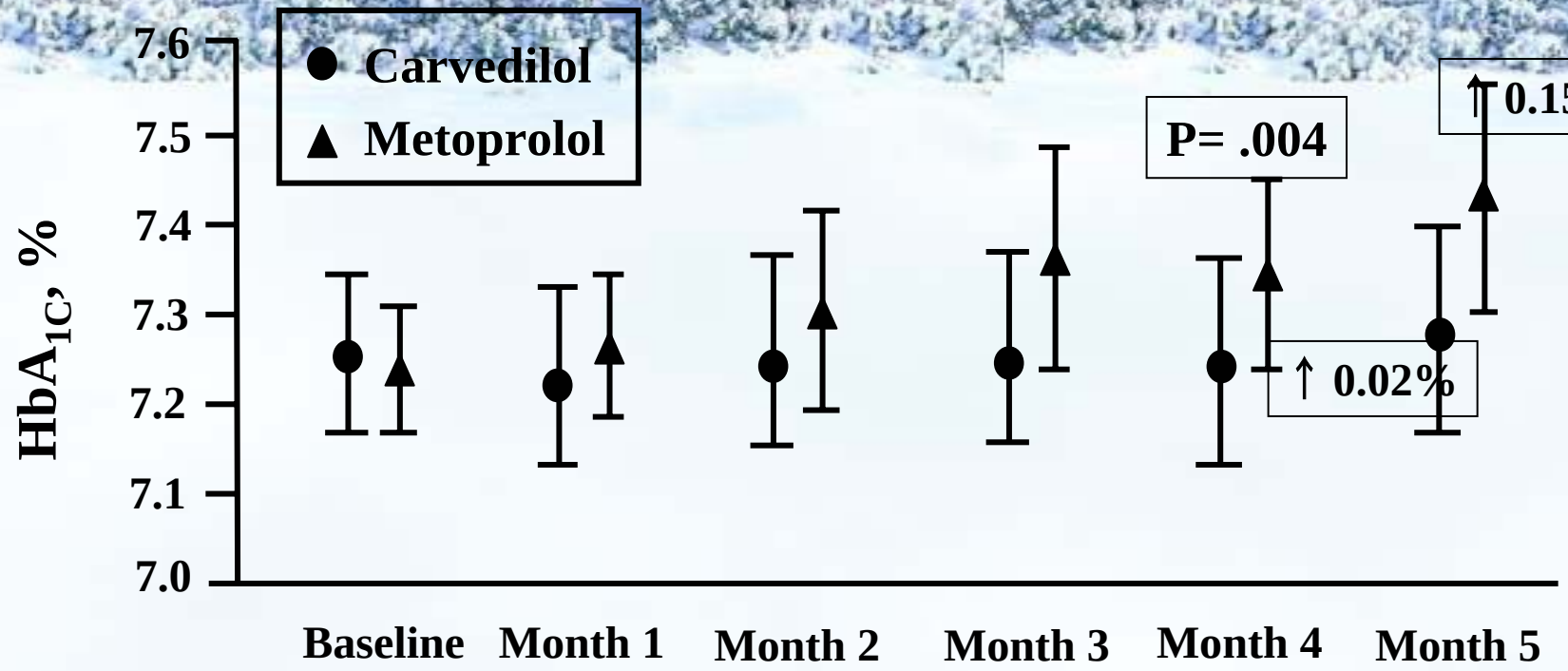
Effect of β-Blockade on Metabolic Parameters in Diabetic Hypertensive Patients

Giugliano D. *Ann Intern Med*. 1997;126:955–959.



Glycemic Effects in DM; Carvedilol –Metoprolol Comparision in Hypertensives(GEMINI) trial

Bakris GL et al., JAMA 2004; Vol 292, No 18: 2227



No. of Participants						
Carvedilol	454	390	449	452	453	454
Metoprolol	654	550	643	655	655	657

Glycosylated Hemoglobin (HbA1c) at Baseline and Each Maintenance Month by Treatment in the Modified Intention-to-Treat Population

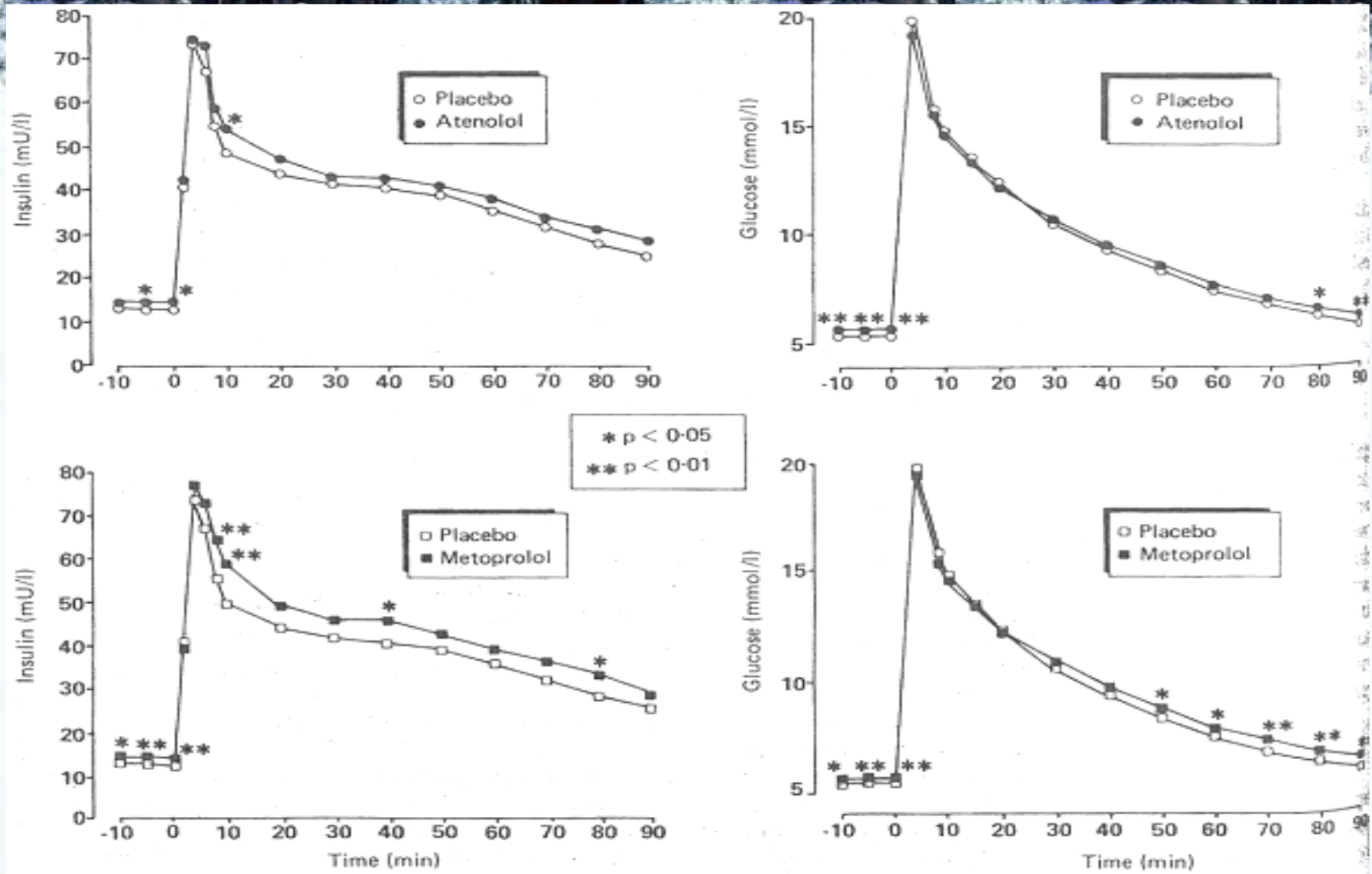
Glycemic Effects in DM; Carvedilol –Metoprolol Comparision in Hypertensives(GEMINI) trial

	Carvedilol (n=454)			Metoprolol (n=657)			Treatment Difference	
Parameter	Baseline	After 5Mo	%change	Baseline	After 5Mo	%change	%change	p-value
HR/min	73.7	67	-6.7	74.5	66.0	-8.3	1.6	<.001
Mean ACR(mg/g)	13.3	11.1	-14.0	12.0	13.3	2.5	-16.2	.003
Mean HOMA-IR	6.0	5.8	-9.1	5.8	6.2	-2.0	-7.2	.004
Mean plasma glucose(mg/dL)	147.0	154.7	6.6	147.4	158.6	10.6	-4.0	.10
Mean serum insulin(µIU/mL)	21.6	19.6	-19.4	21.2	20.2	-15.1	-4.2	.51
Mean BW(kg)	98.2	97.2	0.17	97.0	98.2	1.2	-1.0	<.001

Bakris GL et al., JAMA 2004; Vol 292, No 18: 2227

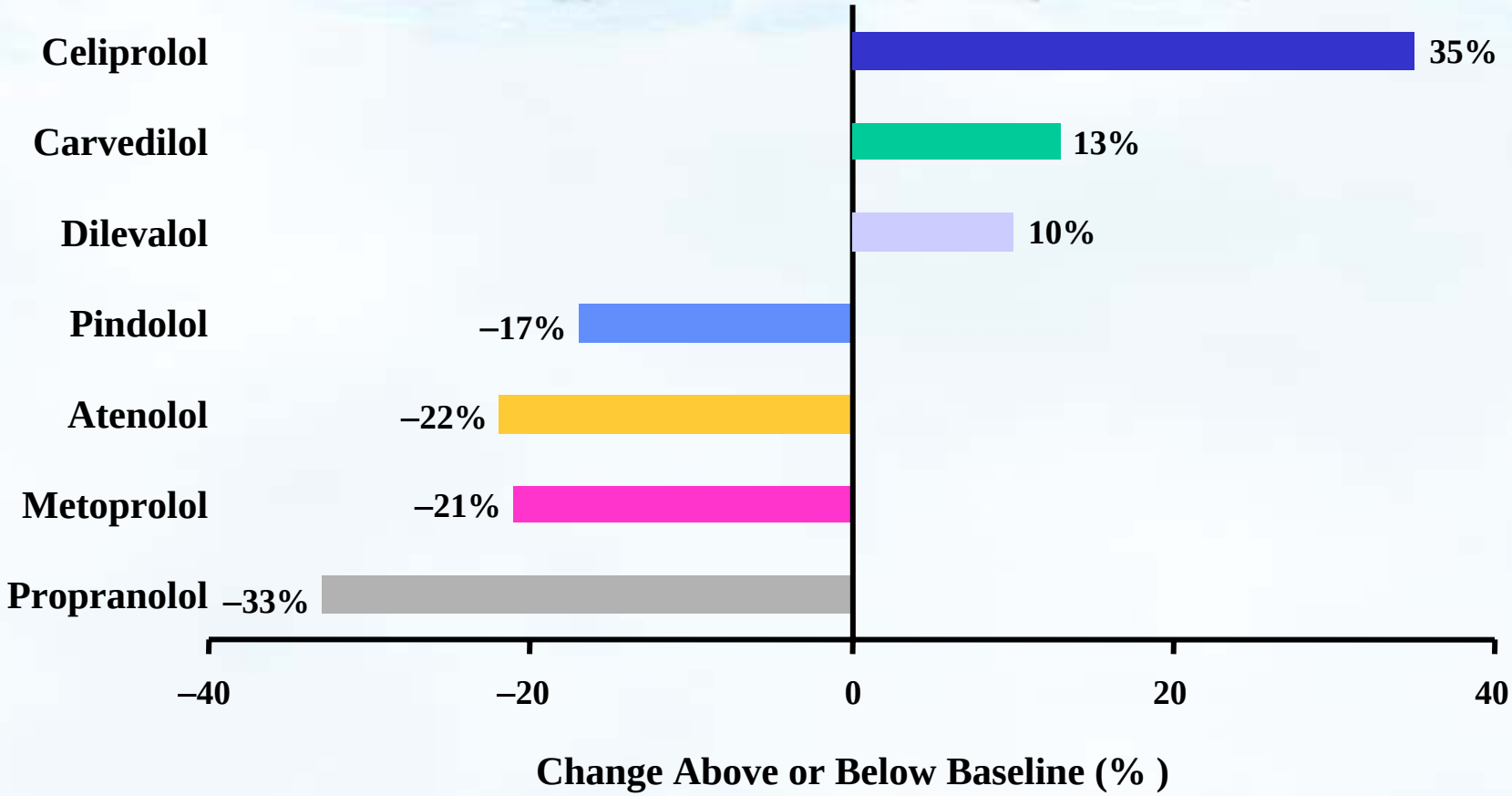
Sensitivity to insulin during treatment with atenolol and metoprolol

Thomas P et al, BMJ vol 298, 29 April 1989



Plasma insulin and glucose concentrations during intravenous glucose tolerance test in 60 hypertensive patients receiving atenolol (top) and metoprolol (bottom)

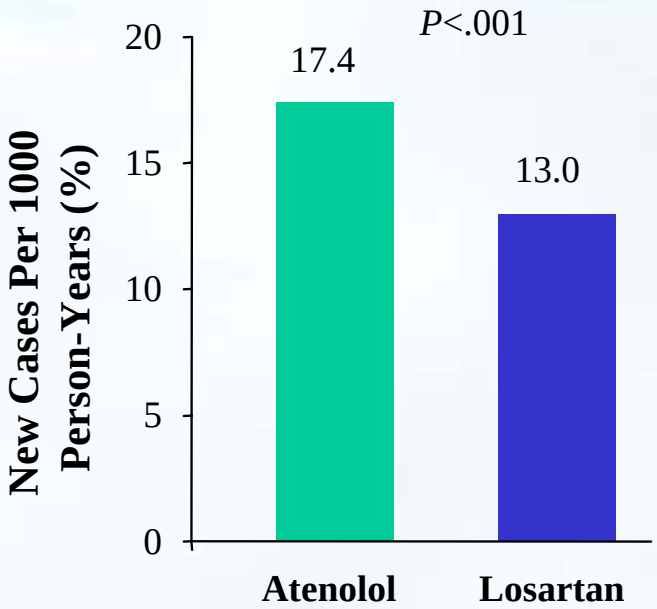
Effect of Beta-Blockers on Insulin Sensitivity in Hypertensive Patients



Jacob S et al. *Am J Hypertens.* 1998;11:1258–1265.

β-Blockers and the Risk of Developing New-Onset Diabetes Mellitus

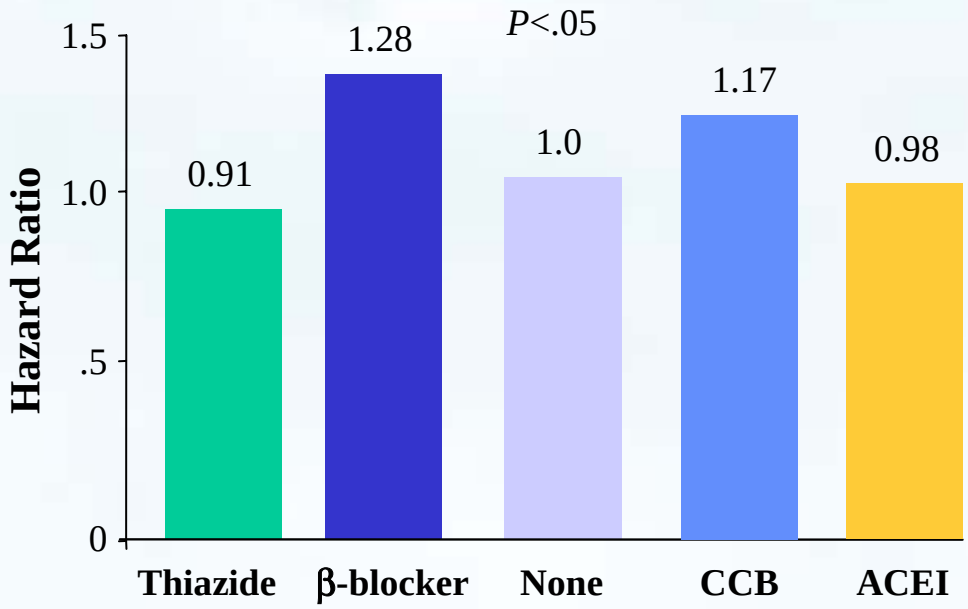
25% Increased Risk
Atenolol RR 1.25 (1.12-1.37)



LIFE[1]

Prospective study of 9193 patients with hypertension aged 55 to 80 and followed for 4.8 years. Analysis of 7998 without diabetes at baseline.

28% Increased Risk
β-blocker RR 1.28 (1.04-1.57)



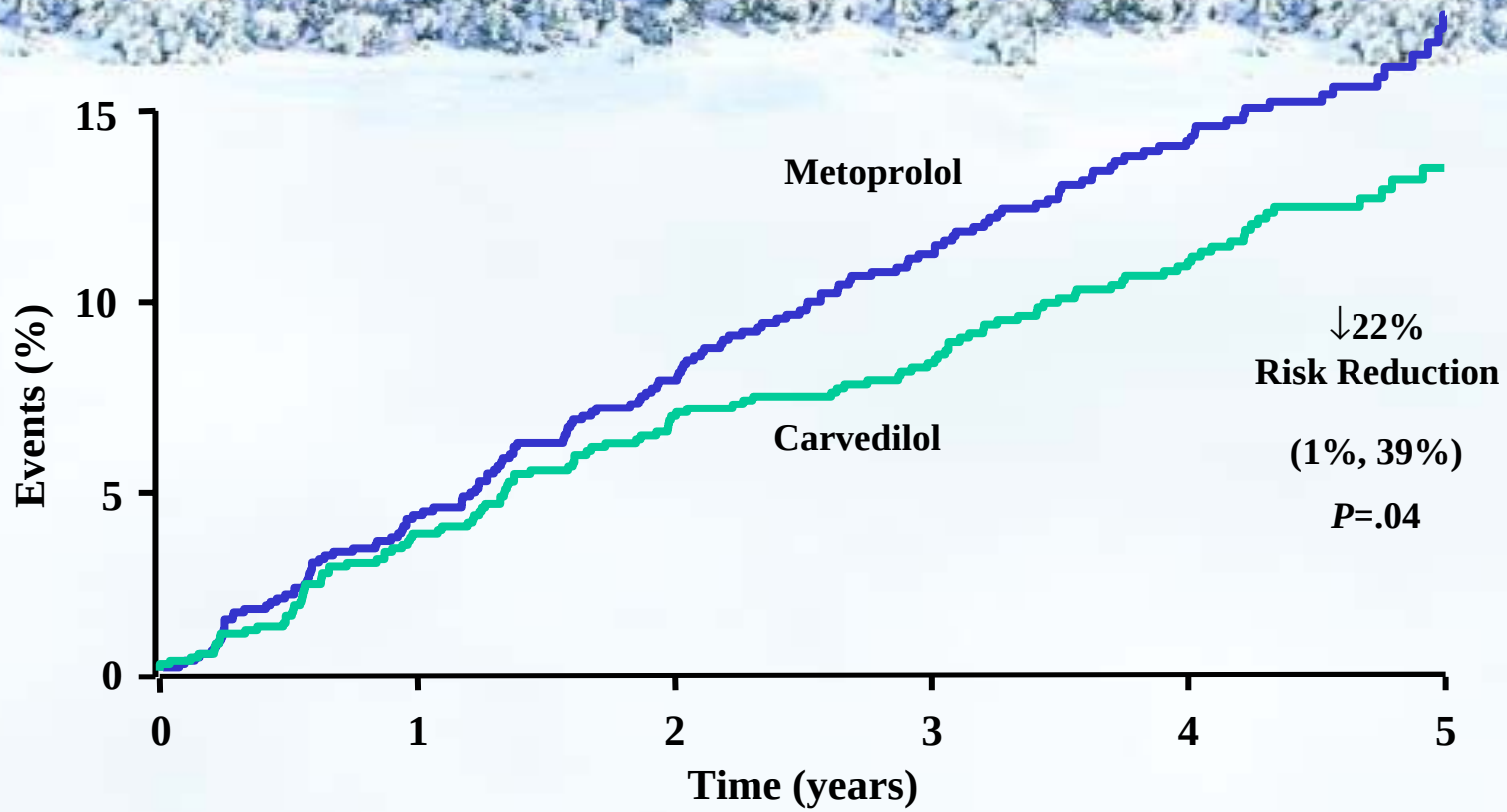
ARIC[2]

Prospective study of 12 550 patients without diabetes aged 45 to 64 and followed for 6 years. Multivariate analysis of 3804 who had hypertension at baseline.

RR, relative risk.

1. Dahlöf B et al. *Lancet.* 2002;359:995–1003.
2. Gress TW et al. *N Engl J Med.* 2000;342:905–912.

COMET: New-Onset Diabetes Related Adverse Events in CHF



Endpoints include adverse events of diabetic coma, diabetes mellitus, peripheral gangrene (diabetic foot), decreased glucose tolerance, or hyperglycemia in a patient classified as not having diabetes at baseline. COMET, Carvedilol or Metoprolol European Trial. 3029 CHF patients randomized to carvedilol (n=1511, mean dose 42 mg) or metoprolol tartrate (n=1518, mean dose 85 mg) and followed for a mean of 58 months.Event rates: metoprolol 13.0%, carvedilol 10.6%. Data on file. GlaxoSmithKline.

Do Beta Blockers have adverse effect on Lipid metabolism?

Carvedilol vs metoprolol effects on fasting cholesterol and TG in hypertensives

	Metoprolol		Carvedilol	
	Week 0	Week 12	Week 0	Week 12
HDL cholesterol	52.2 ±2.6	46.2 ±2.7*	49.5 ±3.2	49.1 ±3.1
LDL cholesterol	155.5 ±9.2	155.8 ±9.4	148.3 ±9.9	149.0 ±9.9
Triglycerides	155.5 ±12.1	174.5 ±27.4*	157.5 ±24.6	158.2 ±27.2

*$p<0.05$ versus week 0. HDL, high-density lipoproteins; LDL, low-density lipoproteins
All values in mg/dl.

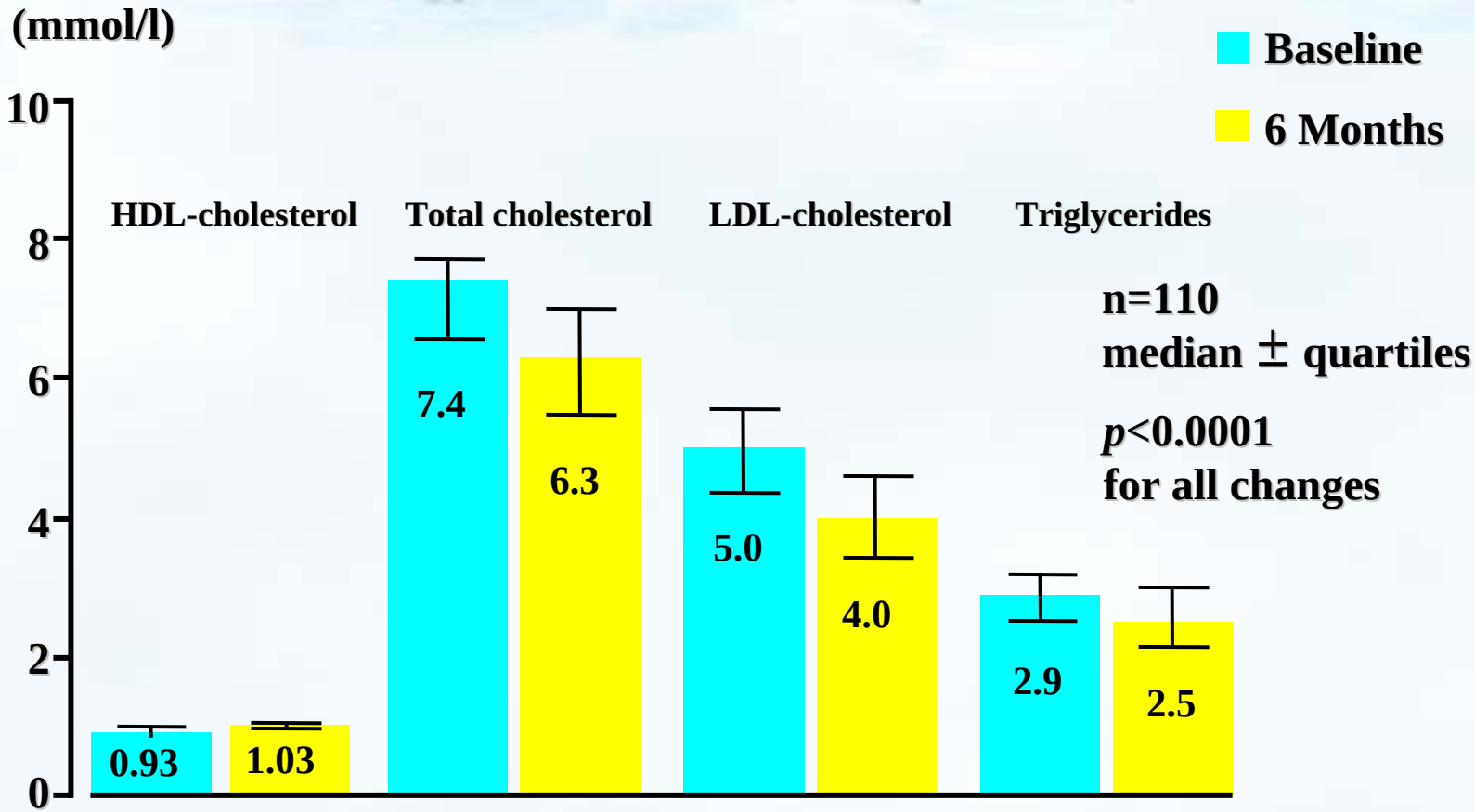
Jacob (1996)

EFFECTS OF β-BLOCKER TREATMENT ON METBOLIC RISK FACTORS

	Triglycerides	HDL Cholesterol	Total Cholesterol
Propranolol	+25%	-10%	+9%
Metoprolol*	+30%	-7%	-1%
Atenolol*	+18%	-9%	=
Pindolol	=	=	=
Dilevalol	-22%		-6%
Carvedilol	=	=	=
Celiprolol	-15%	+5%	=

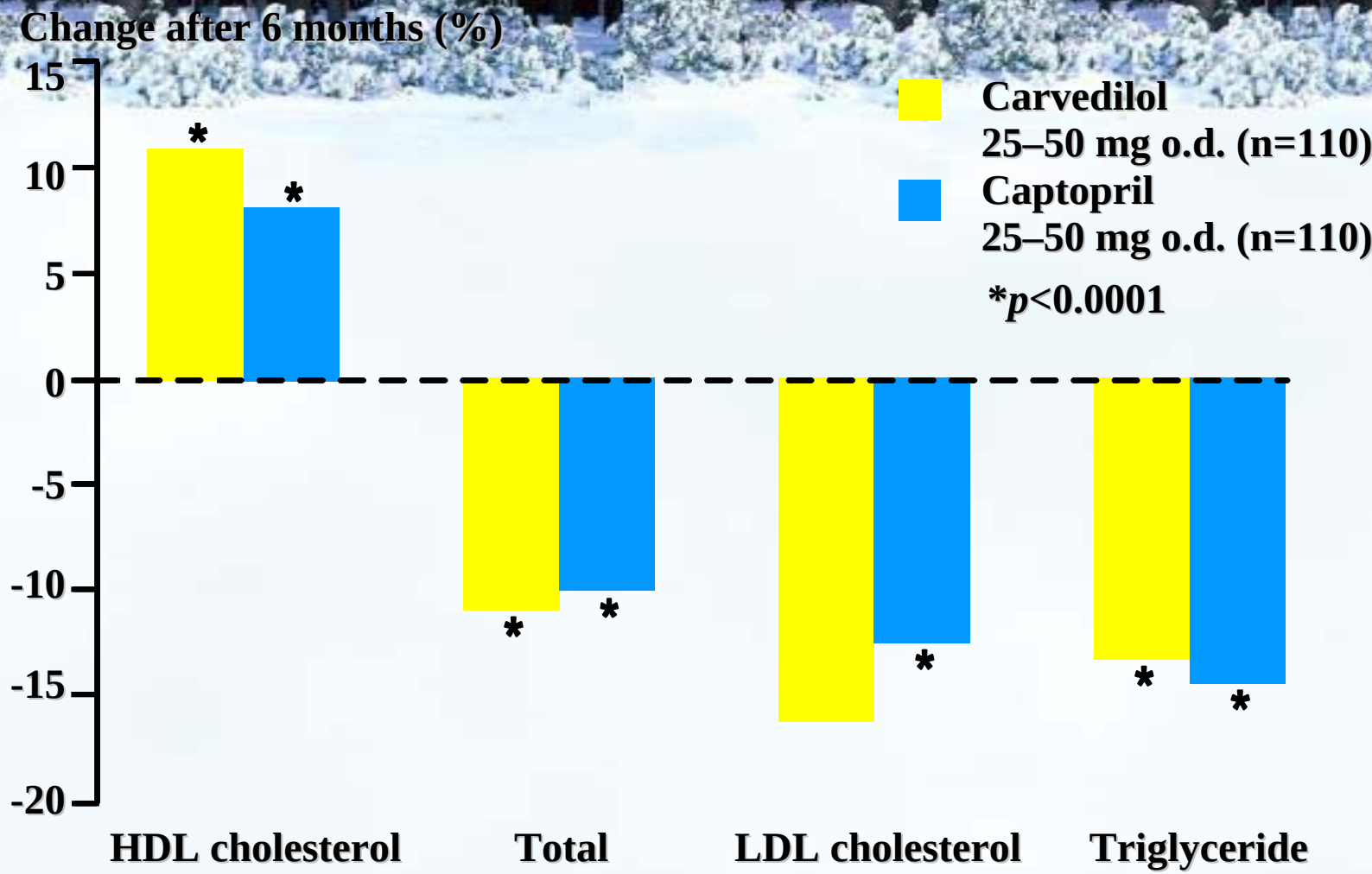
Jacob S et al. *Am J Hypertens.* 1998;11:1258–1265.

Influence of carvedilol on lipid metabolism in patients with dyslipidaemia



Hauf-Zachariou (1993)

Changes in lipid profiles after 6 months treatment with carvedilol and enalapril



Hauf-Zachariou (1993)

Do Beta Blockers mask symptoms of hypoglycemia ?

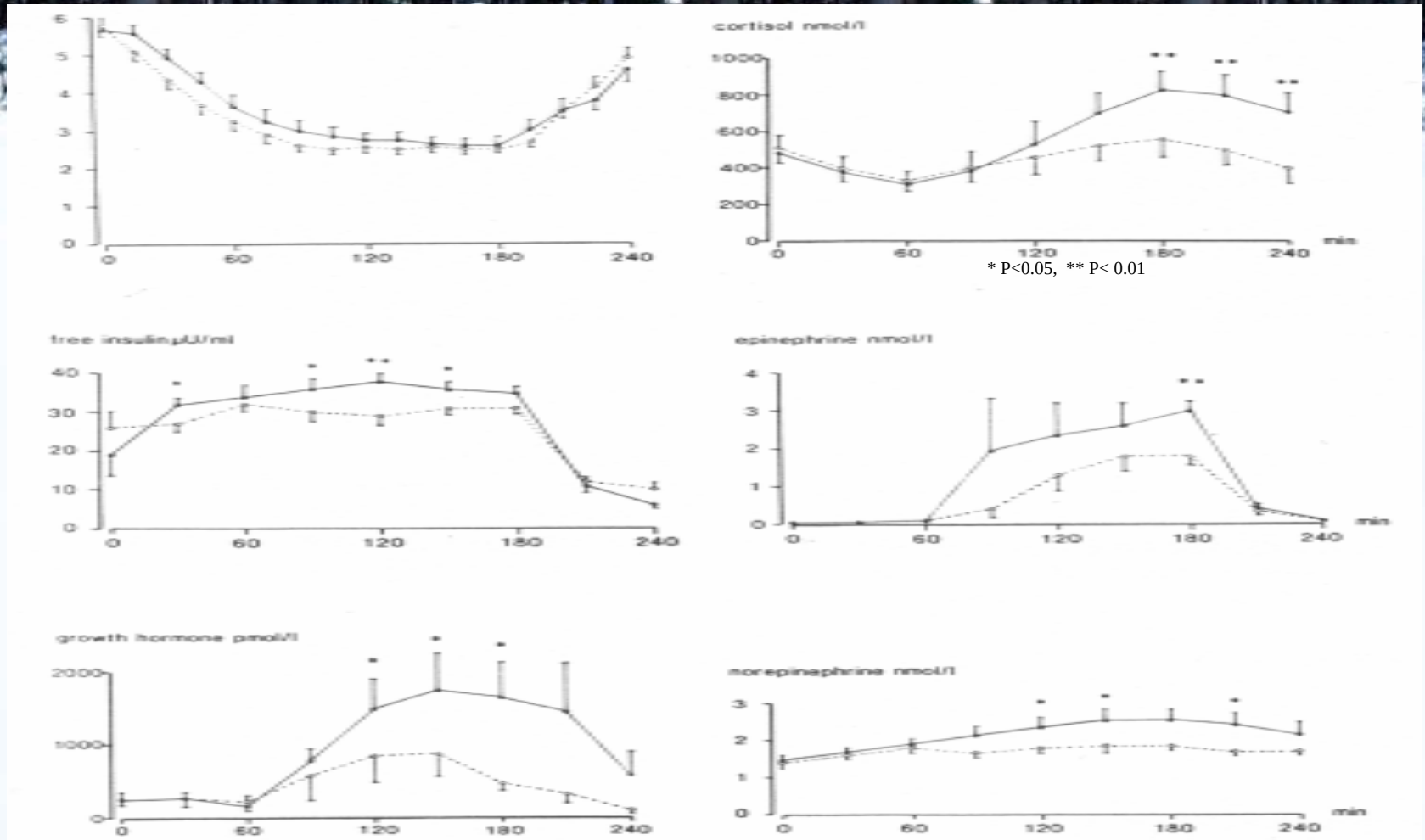
- **Beta blockers could diminish the adrenergic counter reaction to low BG concentrations.**
- **Some of these studies ; diminished of tremor and palpitation most of them ; increased sweating.**
- **Four recent studies ; beta 1 blockers are not associated with an increased risk of severe hypoglycemia.**

Beta-1 blockers do not mask hypoglycemia but may change the pattern of symptoms by increasing the sweating.

Clausen SN et.al. Acta Med Scand 222; 57-63, 1987, Barnett AH, BMJ,2;976, 1980

Effect of Metoprolol on the counter regulation and Recognition of Prolonged hypoglycemia in TIDM

Clausen SN et al, Acta Med Scand 1987; 222; 57-63



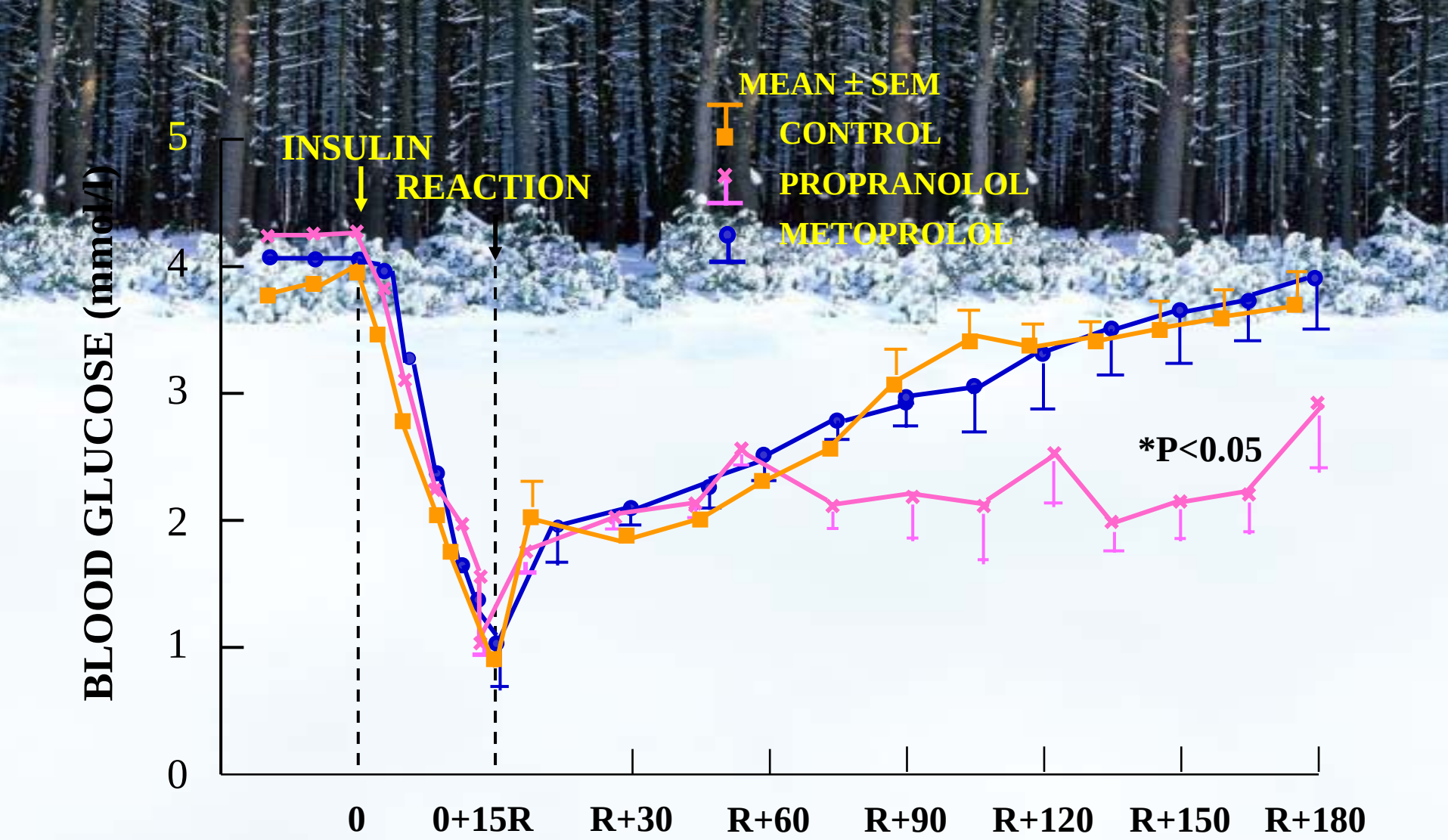
Glucose, freee insulin, GH, cortisol, epinephrine and nor-epinephrine levels during infusion of insulin (2.4U/h) between 0 and 180 min, in eight insulin dependent diabetes (mean ∓ SEM), metoprolol experiment (●-●), control experiment (○-○)

Do Beta Blockers prolong hypoglycemia?

- **Under <u>unselective beta blocker</u> treatment, prolongation of hypoglycemia has been described .**

- **Under <u>selective beta-1 blocker</u> treatment, the recovery from hypoglycemia <u>was not</u> impaired amongst patients with insulin or OHA**

Corrall R. et al, Eur J Cli Invest ,1981, 11, 279-283



Glucose levels in response to hypoglycaemia in control, propranolol and metoprolol studies.

Corrall R. et al, Eur Cli Invest ,1981, 11, 279-283

Are Beta Blockers less nephroprotective antihypertensive agents?

- **ACEI ; more effective than beta-blockers to the reduction of proteinuria, equally effective to the decline of GFR in diabetic nephropathy.**
- **The selective beta-1 blocker metoprolol had equal beneficial nephroprotective effects on all histological parameters as compared with the ACEI enalapril .**
- **No evidence for a less pronounced nephroprotective effect of beta blockers on progression of diabetic nephropathy as measured by valid clinical parameters, i.e. the decline of GFR or renal histology**

PSG **Sawicki PT, Nephrol Dial Transplant 1997; 12; 1890,** ***Rudberg S.et.al.Diabetologia, 1999, 42: 589***

Effects of different antihypertensive drugs on human diabetic proteinuria

Weidmann P., Nephrol Dial Transplant,1993 8; 582-584

Type of therapy	Number of patients	Average changes (%) in	
		Mean systemic blood pressure	Urinary albumin or protein excretion
Conventional (diuretics and/or β blocker)	131	-10	-17
ACE inhibitors	589	-15	-52
Ca antagonists			
all	191	-13	-4
nifedipine	85	-13	+21
all except nifedipine	106	-12	-24
diltiazem + verapamil	52	-17	-23

Synthesis of reported effects of different antihypertensive treatments on proteinuria in diabetic patients with incipient or clinical nephropathy

Overview of controlled, randomized, prospective studies of at least 2years duration comparing β-blockers with ACEI on T1DM patients with Diabetic Nephropathy

	Decline of GFR in the (mL/min/year)	
Study	**ACEI group**	**β-blocker group**
Björck et al.	**Enalapril; -2**	**Metoprolol; -6**
Elving et al.	**Captopril; -5**	**Atenolol; -4**
Sawicki et al.	**Ramipril; +1**	**Metoprolol; ±0**

Björck S,et al BMJ. 8;304:339,1992
Elving LD,et al Diabetologia. 37:604,1994
Sawicki PT,et al. Nephrol Dial Transplant 12:1890,1997

Compare histological parameters between ACEs ,Beta- Blocker & reference groups

	Enalapril Group1		Metoprolol Group2		Reference Group3	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
BMT(nm)	570(120)	593(94)	610(93)	602(84)	562(90)	702(173)[b]
Vv(mes/glom)(%)	19.6(5.0)	19.3(5.3)	21.3(2.5)	23.8(2.8)	21.2(2.9)	28.2(7.2)
Vv(met/glom)(%)	10.7(2.6)	11.2(4.0)	11.2(1.2)	12.9(1.6)	12.2(1.3)	13.3(1.9)
Matrix star volume(μm^3)	26.8(9.5)	30.8(14.7)	29.5(5.6)	35.7(10.1)	28.2(7.2)	37.1(15.7)[a]
Index DGP	94.4(22.6)	101.2(27.1)	101.7(13.2)	108.8(17.1)	96.6(13.2)	120.6(30.9)[b]

BMT, Vvmes/glom; Vvmat/glom, matrix star volume, index DGP at baseline and follow-up
[a]: p = 0.04, [b]: p = 0.007 vs baseline Mean (SD)

BMT : Basement membrane thickness
Vvmes/glom; Vvmat/glom : mesangial and matrix volume fractions
overall diabetic glomerulopathy index : index DGP + matrix star volume

Rudberg S.et.al.Diabetologia, 1999, 42: 589

The incidence of renal failure in T2DM patients treated with the Beta-Blocker or The ACEI

	Patients with clinical end points		Absolute risk (events per 1000 patient years)			
	Captopril (n=400)	**Atenolol (n=358)**	Captopril	Atenolol	P value	Relative risk for captopril (99% CI)
Renal failure	**4**	**4**	1.3	1.4	0.90	0.91 (0.15 to 5.64)
microalbuminuria	**31%(16)**	**26%(20)**				

The number of patients with renal failure after 8 years of follow-up was <u>exactly the same</u> in the atenolol and the captopril group

UKPDS* ,*BMJ VOL. 317 12 SEPTEMBER 1998

Beta Blockers and Diabetics with CAD

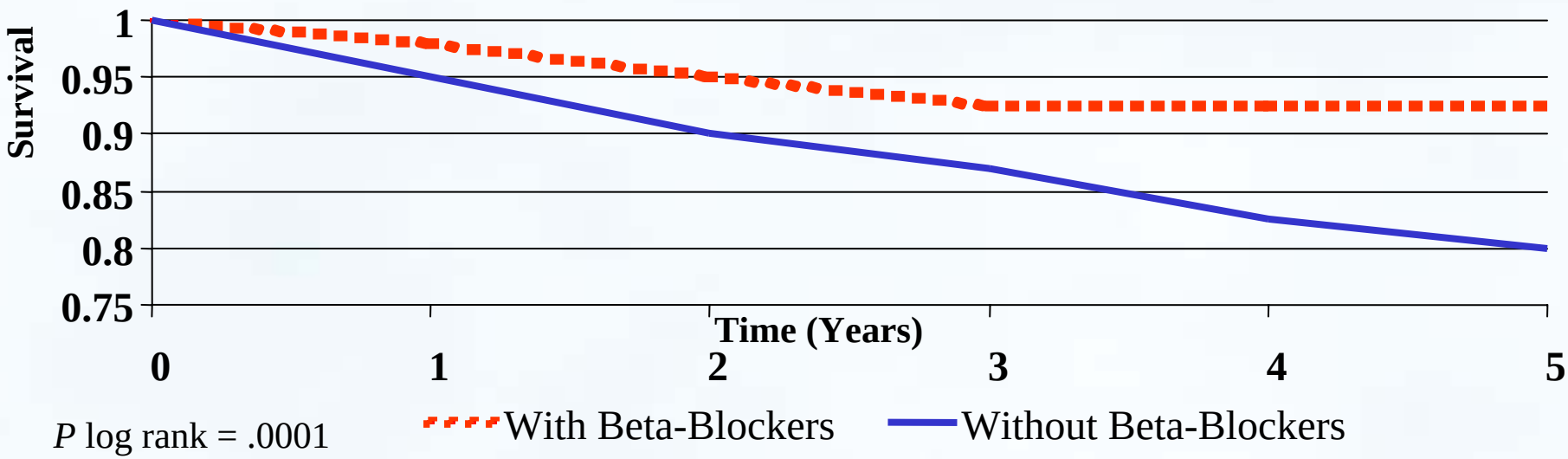
Beta- Blocker treatment of Diabetics after AMI is more effective than of Non Diabetics

Study	Nondiabetic patients	Diabetic Patients
Beta-Blockers and acute reduction of mortality after AMI (Relative risk reduction. %)		
Goteborg Metoprolol Trial (1395)	36	58
MIAMI Trial(5778,metoprolol)	12	50
ISIS I(16,000 ,atenolol)	15	22
Malmberg et al.(metoprolol)	29	69
Betablockers and long-term reduction, of mortality after AMI (Relative risk reduction. %)		
BHAT (propranolol)	25	35
Gundersen et al.(timolol)	34	63
Kjekshus at al. (2024)	49	56

Overview of acute (up to 3 months) and long-term (more than 1 year) effects of beta blocker treatment after acute myocardial infarction (AMI) on relative mortality in patients with and without diabetes.

• Bezafibrate Infarction Prevention Study

- 19% of the 14,417 recruits , 2723 Patients with T2DM and CAD which one third received beta-blockers.
- After 3 years, a 43% reduction in cardiac events with beta-blockers (7.8% vs 14%)
- 42% reduction in cardiac mortality compared to the no-beta-blocker groups.
- Increasing divergence of survival curves with time



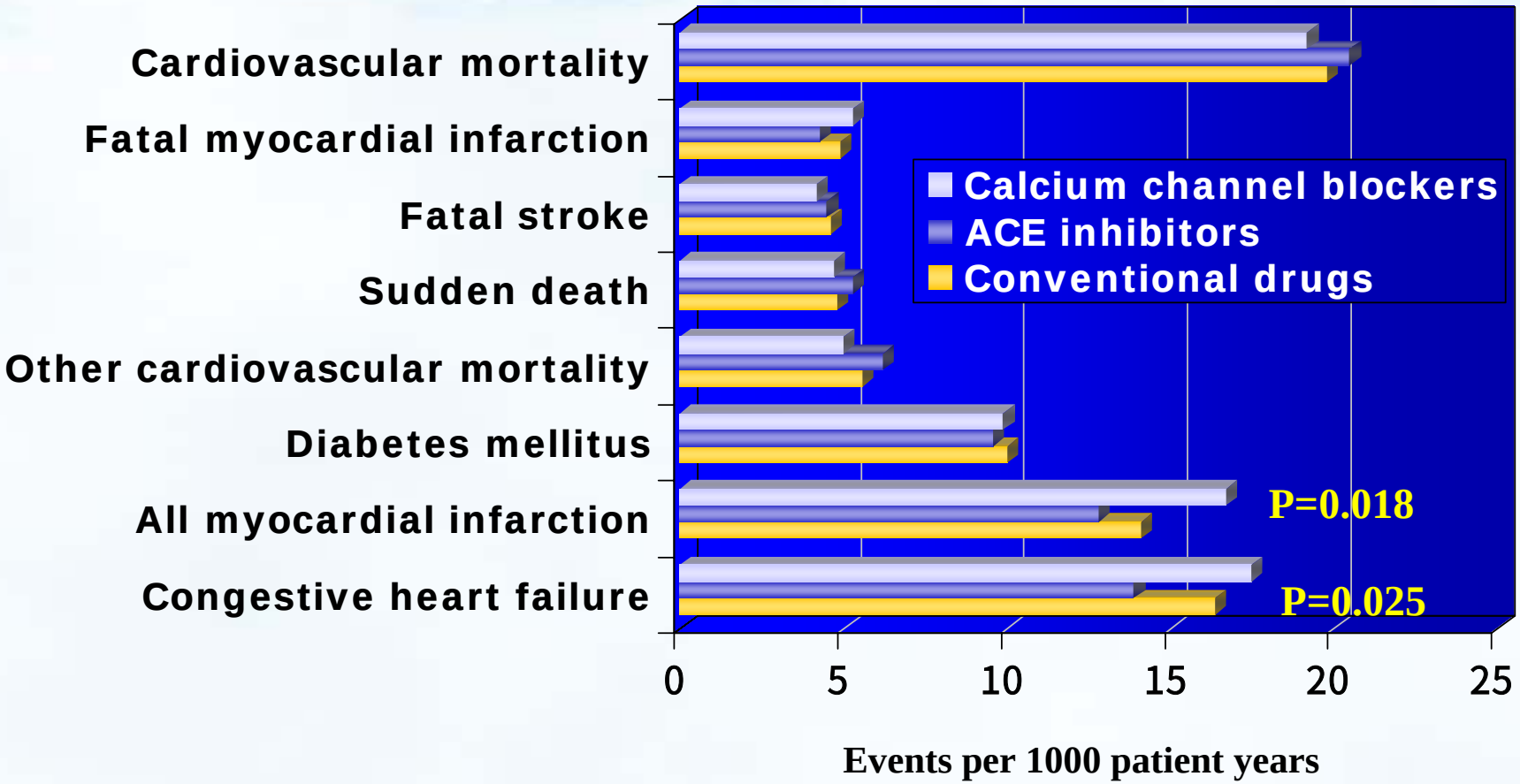
P log rank = .0001

Jonas M et al. *Am J Cardiol*. 1996;77:1273-1277.

Beta-Blockers and Diabetics with Hypertension

- **STOP-2**
- **UKPDS**
- **LIFE**

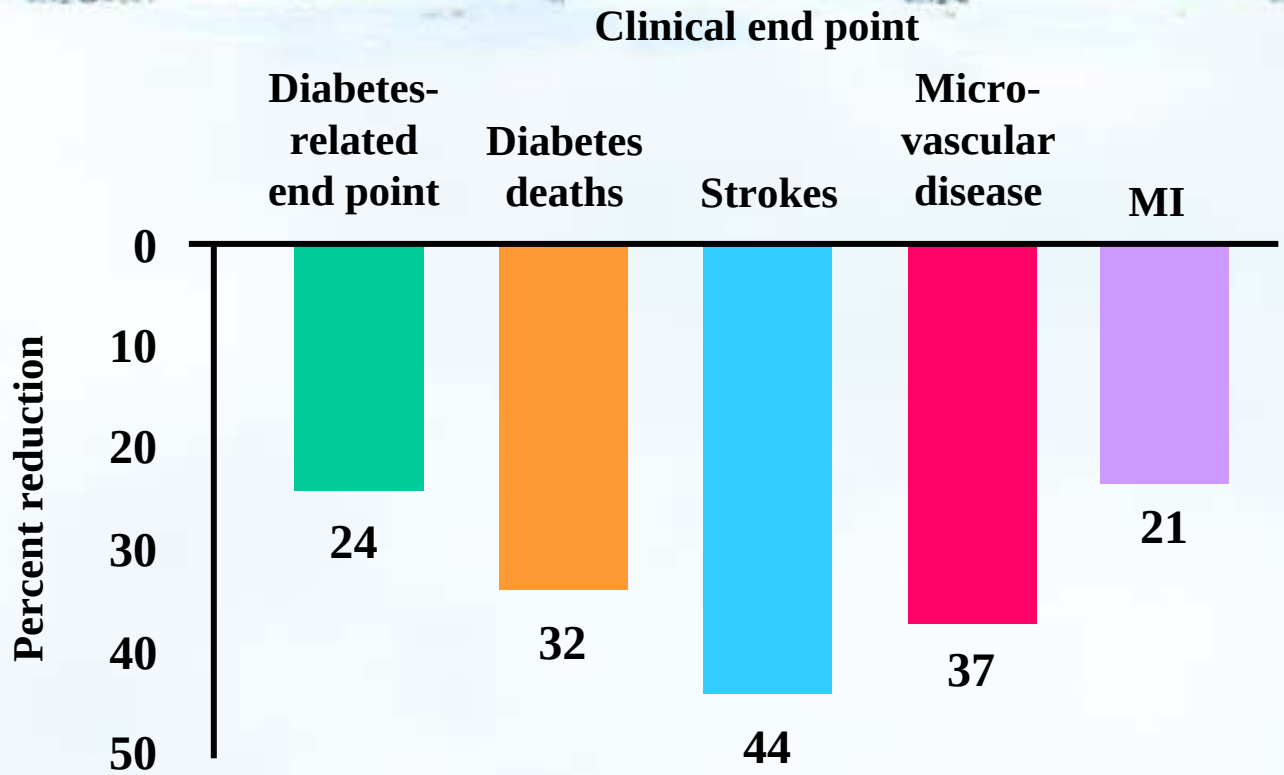
STOP-2(719 hypertensive diabetics); Frequency of Events Per 1000 Patient Years



Hansson L, et al. Lancet. 1999;354:1751-1756.

Clinical End-Point Risk Reduction in1148 Type 2 Diabetes by UKPDS trial(38)

"Tight" vs "Less Tight" BP Control

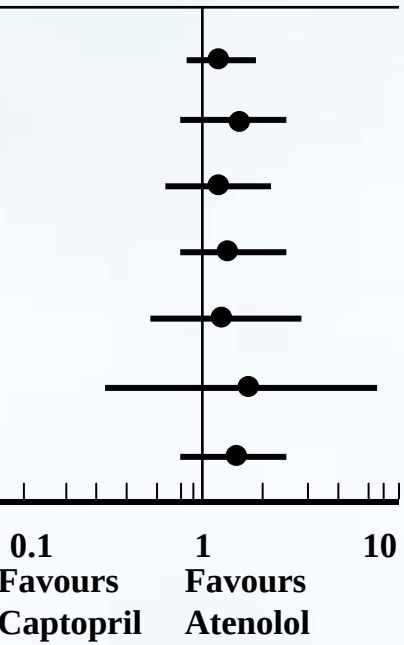


BP reduction with "tight" control = 10/5 mm Hg (144/82 vs 154/87 mm Hg).
29% of "tight control" patients required three or more drugs.

UK Prospective Diabetes Study Group. BMJ, 317:703, 1998

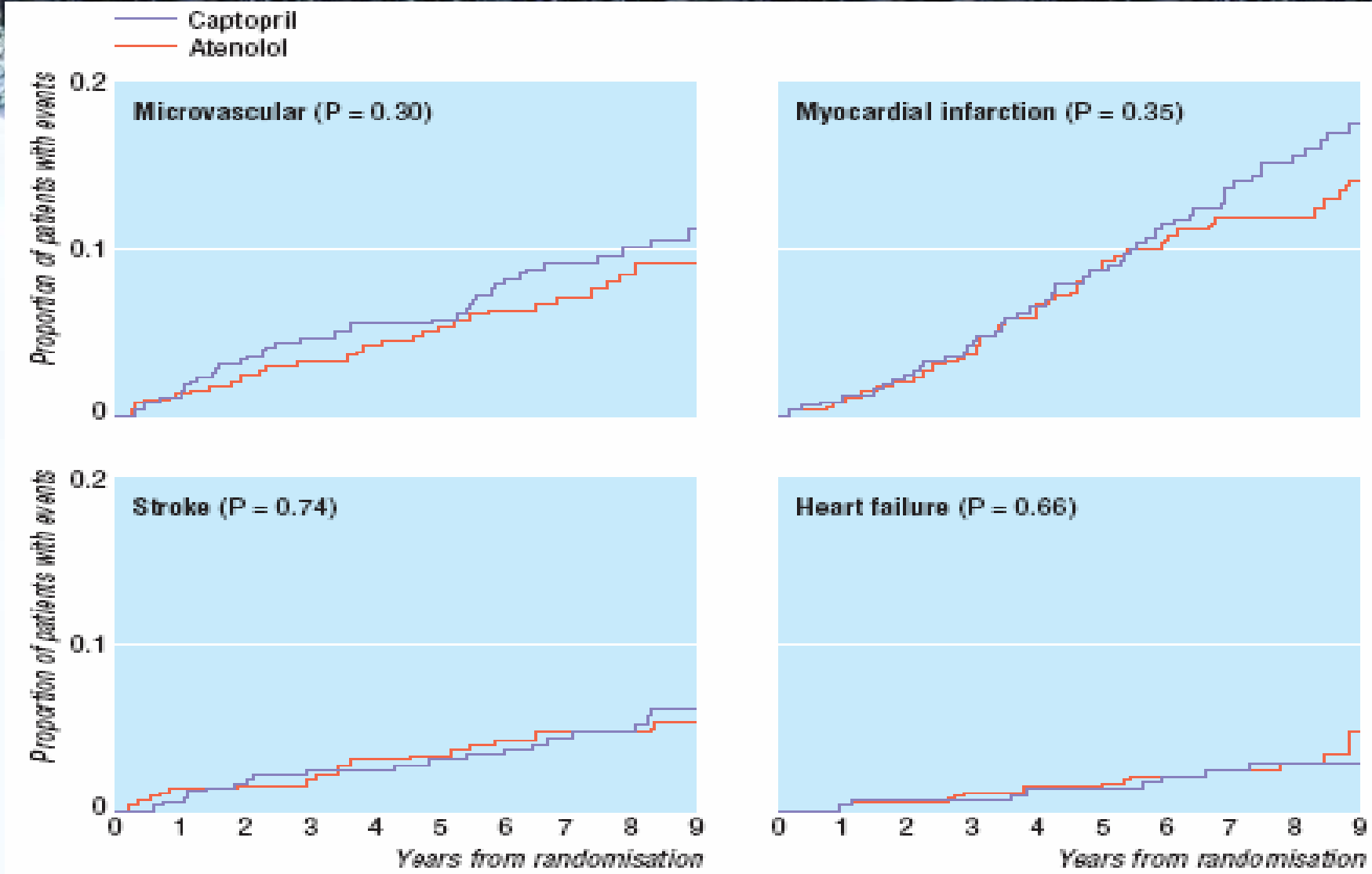
UKPDS 39. In diabetics, tight control of BP result in fewer cardiovasrcular event.

Clinical end point	Absolute risk (events per 1000 patient years)		P value	Relative risk for tight control (95% CI)
	Captopril (n=400)	Atenolol (n=358)		
Any diabetes related end point	53.3	48.4	0.43	1.10 (0.86 to 1.41)
Deaths related to diabetes	15.2	12.0	0.28	1.27 (0.82 to 1.97)
All cause mortality	23.8	20.8	0.44	1.14 (0.81 to 1.61)
Myocardial infarction	20.2	16.9	0.35	1.20 (0.82 to 1.76)
Stroke	6.8	6.1	0.74	1.12 (0.59 to 2.12)
Perpheral vascular disease	1.6	1.1	0.59	1.48 (0.35 to 6.19)
Microvascular disease	13.5	10.4	0.30	1.29 (0.80 to 2.10)



UKPDS Group. BMJ. 1998;317:713–720.

Effect of the ACEI captopril and the cardioselective betablocker atenolol within the tight-control group

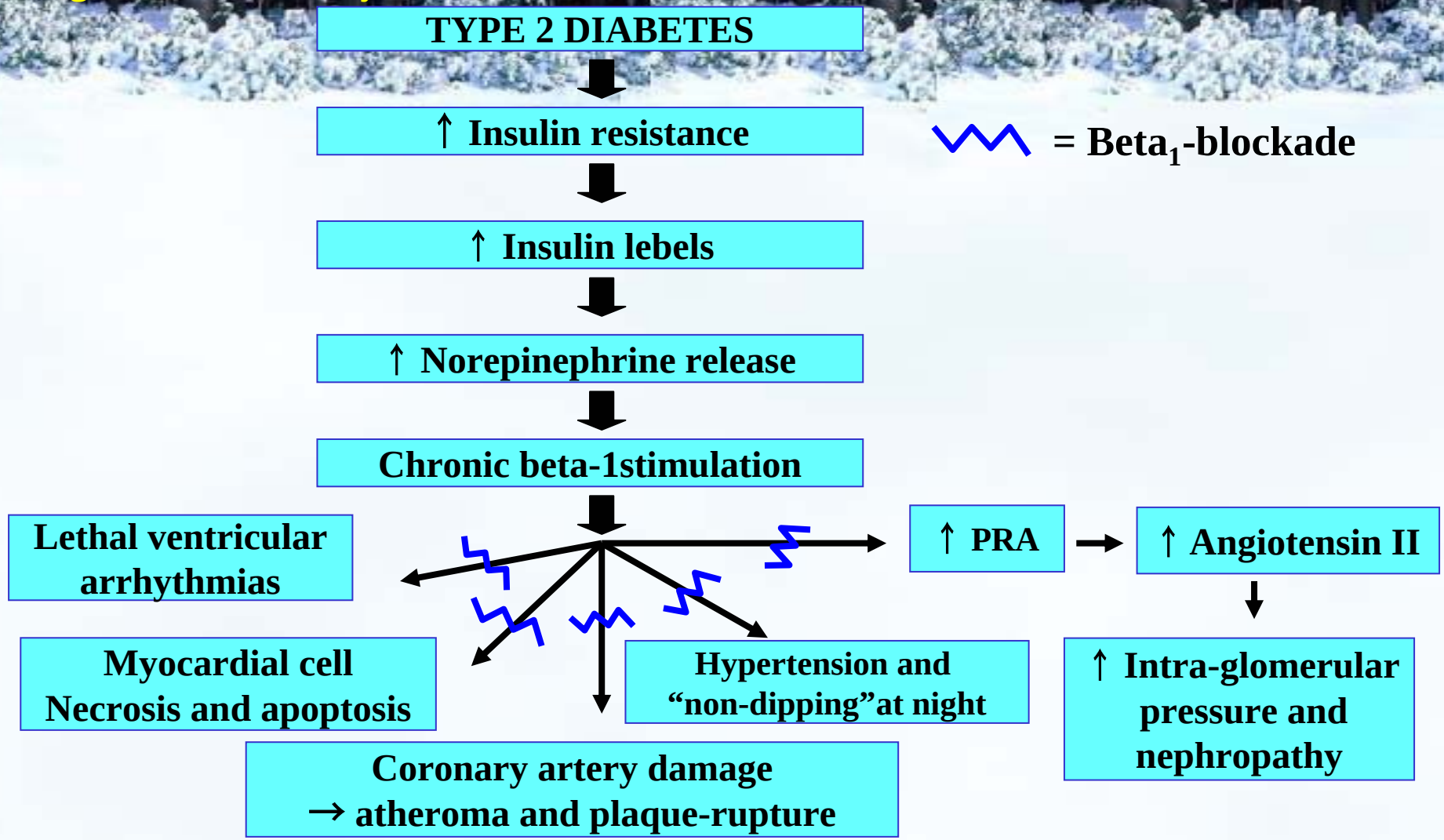


UK Prospective Diabetes Study Group. BMJ, 317:713, 1998

Can we explain the surprising result of the UKPDS ?

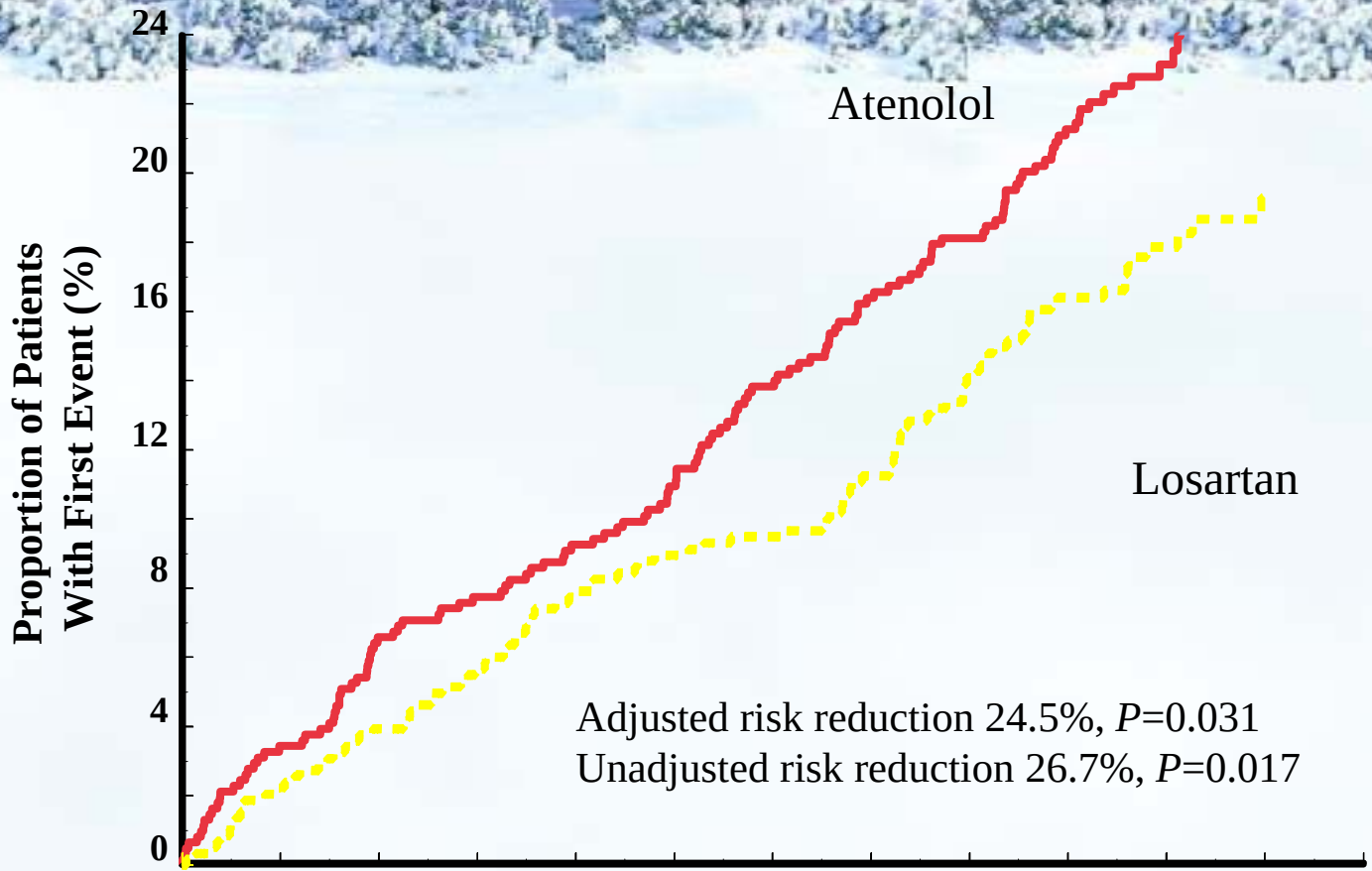
SNS Pathophysiology

Beta-1 selective blockade is an alternative way of breaking the norepinephrine /angiotensin vicious cycle



Cardiovascular Drug & Therapy 2002; 457-470

LIFE: 1195 Diabetes Subgroup
Composite of CV death, stroke, and MI



Study Month	0	6	12	18	24	30	36	42	48	54	60	66
Losartan (n)	586	569	558	548	532	520	513	501	484	459	237	127
Atenolol (n)	609	588	562	552	540	527	507	486	472	434	204	99

Lindholm LH et al. *Lancet.* 2002;359:1004-1010.

Prospective Hard-event Trials in Hypertension involving Beta Blockers

Trial	Drugs	Mean age (yr)	Starting BP (mmHg)	Pulse-Pressure (mmHg)
Studies with favouable to beta-blockers				
IPPPSH	oxyprenolol	52	173/108	65
MRC-mild	Propranolol	51	161/98	63
MAPHY	Metoprolol	52	167/108	59
UKPDS	Atenolol	56	159/94	65
Studies with unfavouable to beta-blockers				
HEP	atenolol	69	196/99	97
MRC-elderly	atenolol	70	185/91	94
LIFE(whole)	atenolol	67	174/98	76
LIFE(DM)	atenolol	67	177/96	81

Why happen the different result between UKPDS & LIFE Study ?

	UKPDS	LIFE
Age	Younger & middle age	Elderly
Mean age	56.3(56)	67.4(Around 70 years)
Vascular system	Relatively compliance	non- compliant, stiff
pulse pressure(mmHg)	65	81
ß1 receptor response	Relatively preserve	Decreased

Summary

Beta-1 selective blocker,vasodilating betablocker;

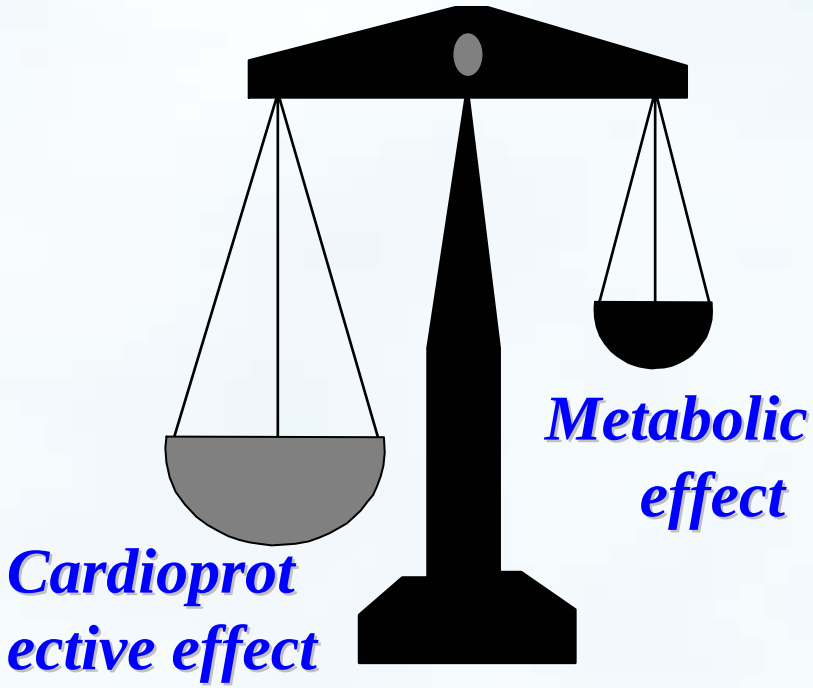
- *less adverse effects on glucose and lipid metabolism*
- *not mask hypoglycemic symptom &prolong hypoglycema*
- *not less nephroprotective than ACEI*
- *primary and secondary cardioprotective effect in antihypertensive treatment and after MI*

There is no evidence-based reason to withhold these agents from diabetic patients with hypertension.

Conclusion

The Bad Guys Come good.

- **ß1 selective blockers should be considered for the first line therapy in younger/middle age hypertensives with T2DM**



•1st line Rx with ACE-I if post-MI, CHF

in Diabetic Hypertensives


THANK YOU FOR YOUR ATTENTION
by H. Iwabuchi