Efficacy of Beta-Blockers for First-line Antihypertensive; All Beta-Blockers Same?

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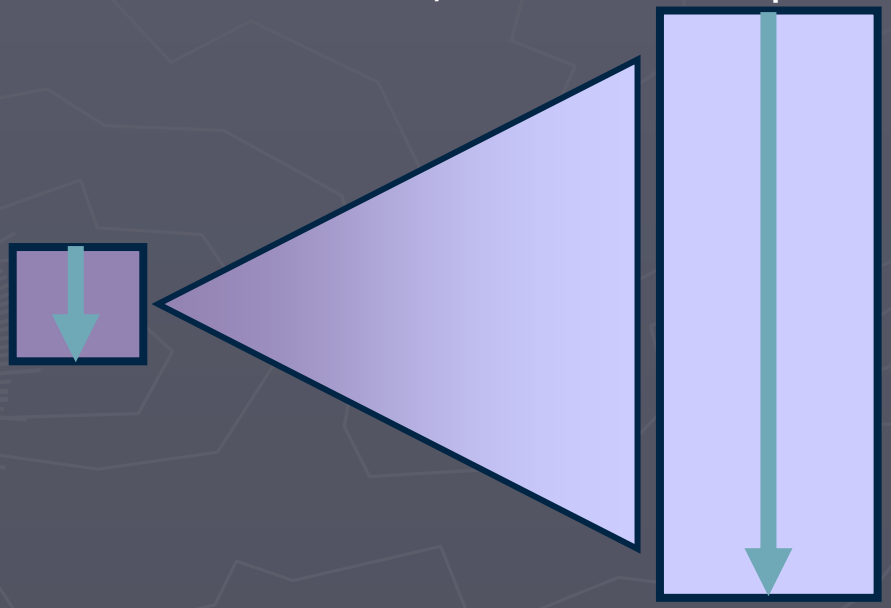
Efficacy of Beta-Blockers for First-line Antihypertensive; All Beta-Blockers Same?

- Current issue with beta-blocker in Hypertension
- Comparisons between old and new drugs
- Logical Practice

Lowering blood pressure reduces cardiovascular risk

Small SBP reductions yield significant benefit

Meta-analysis of 61 prospective, observational studies
One million adults, 12.7 million person-years



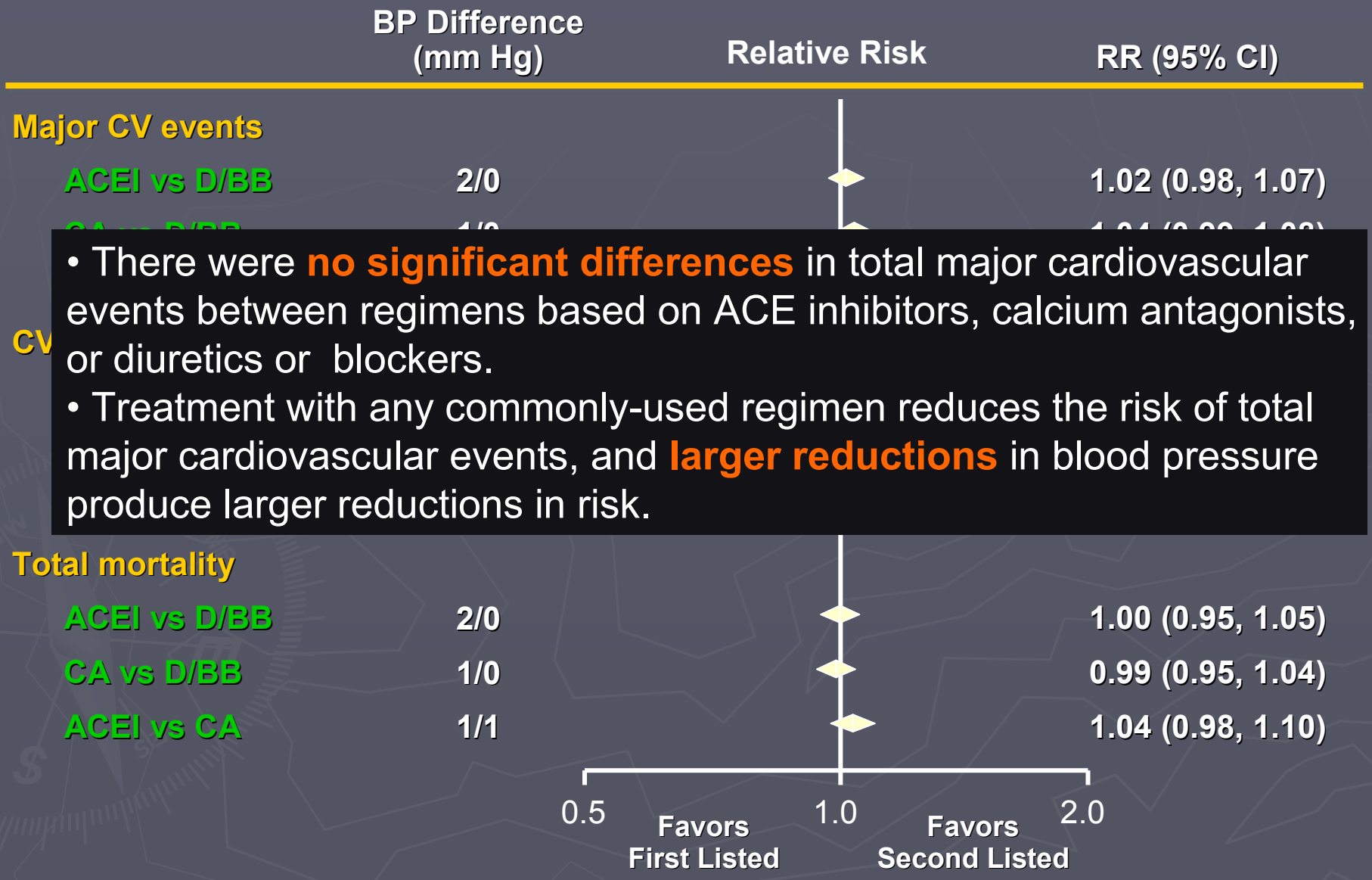
2 mmHg decrease in mean SBP

7% reduction in risk of ischaemic heart disease mortality

10% reduction in risk of stroke mortality

Lewington et al. *Lancet.* 2002;360:1903–1913

Comparisons of Different Drugs



- There were **no significant differences** in total major cardiovascular events between regimens based on ACE inhibitors, calcium antagonists, or diuretics or blockers.
- Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events, and **larger reductions** in blood pressure produce larger reductions in risk.

Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet. 2003;362:1527-1535.

Current Issue

- Atenolol in hypertension: is it a wise choice? Carlberg B, Lancet. 2004 ;364:1684-9.
- Should beta-blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lindholm LH, Lancet 2005;366:1545-53.
- Do Beta-blockers Have a Role in Hypertension Any Longer?
  Henry Black, Medscape Medical News August 11, 2006

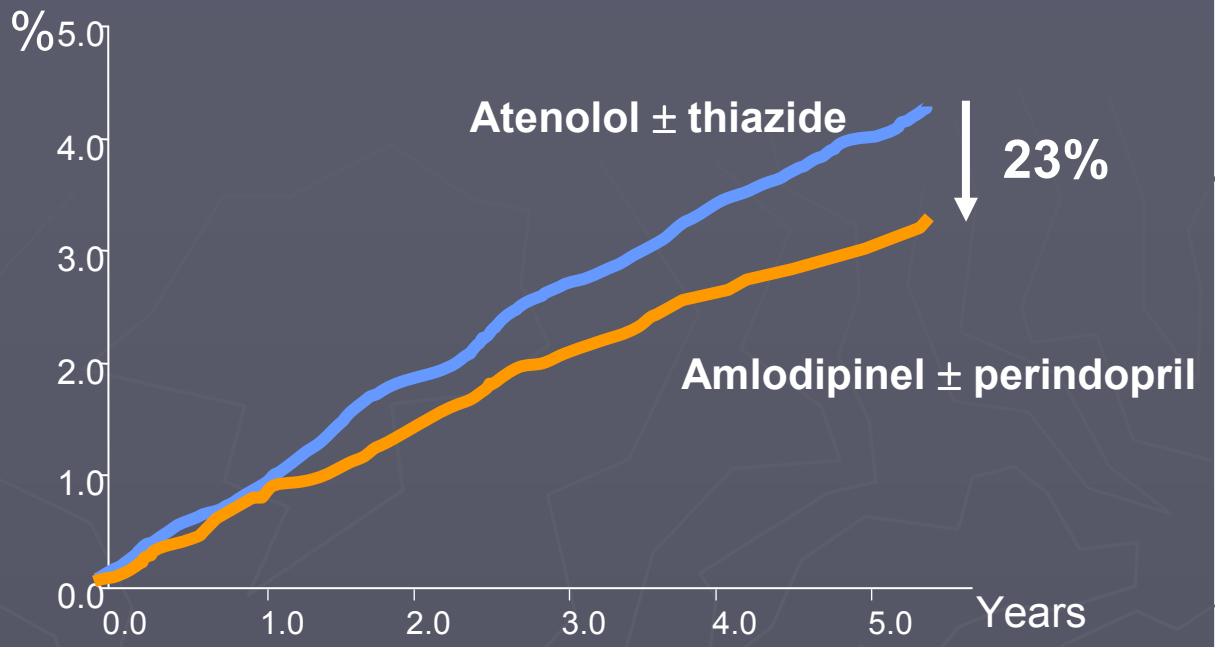
Atenolol vs. other antihypertensives

Outcome	Relative risk with atenolol	95% CI
Stroke	1.26	1.15–1.38
MI	1.05	0.91–1.21
All-cause mortality	1.08	1.02–1.14

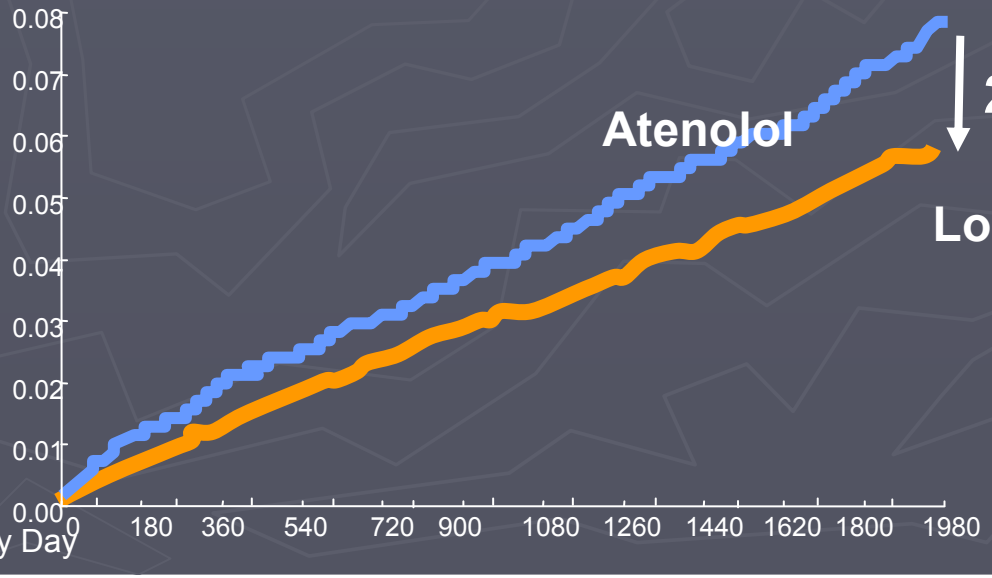
Lindholm LH, et al. *Lancet* 2005

β-Blockers vs. Fatal/Nonfatal Stroke

Anglo-Scandinavian ascot Cardiac Outcomes Trial

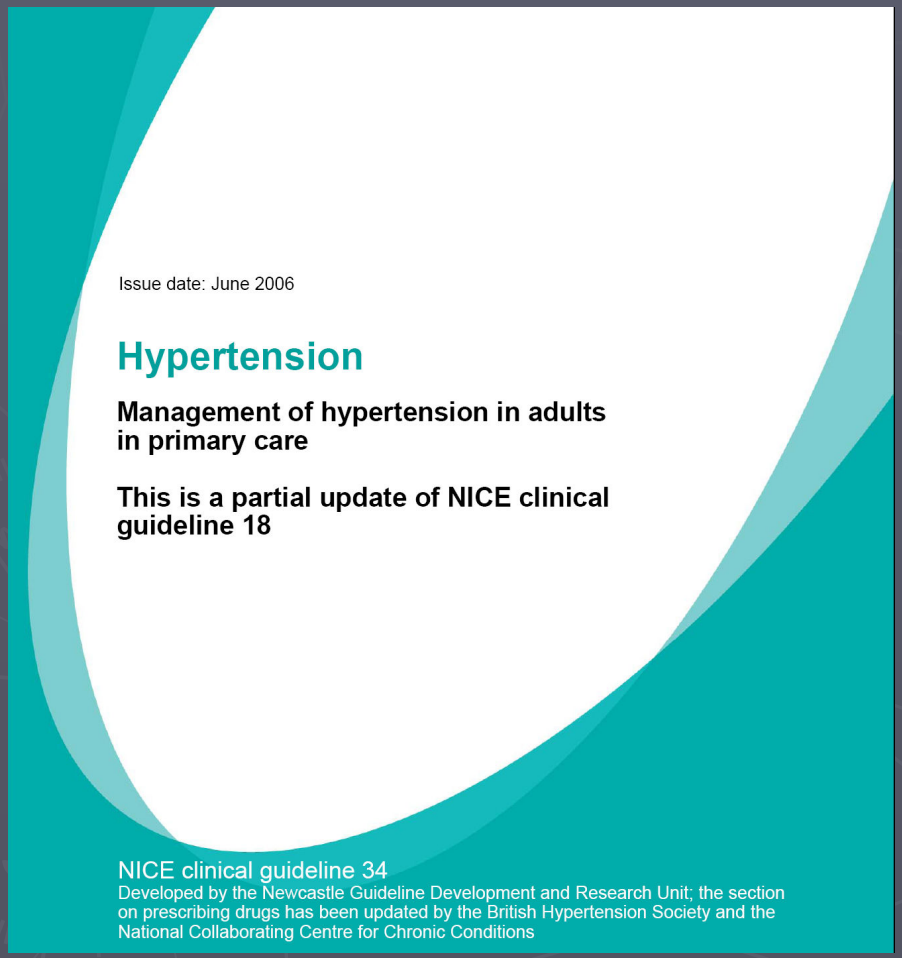


LIFE



Current Issue

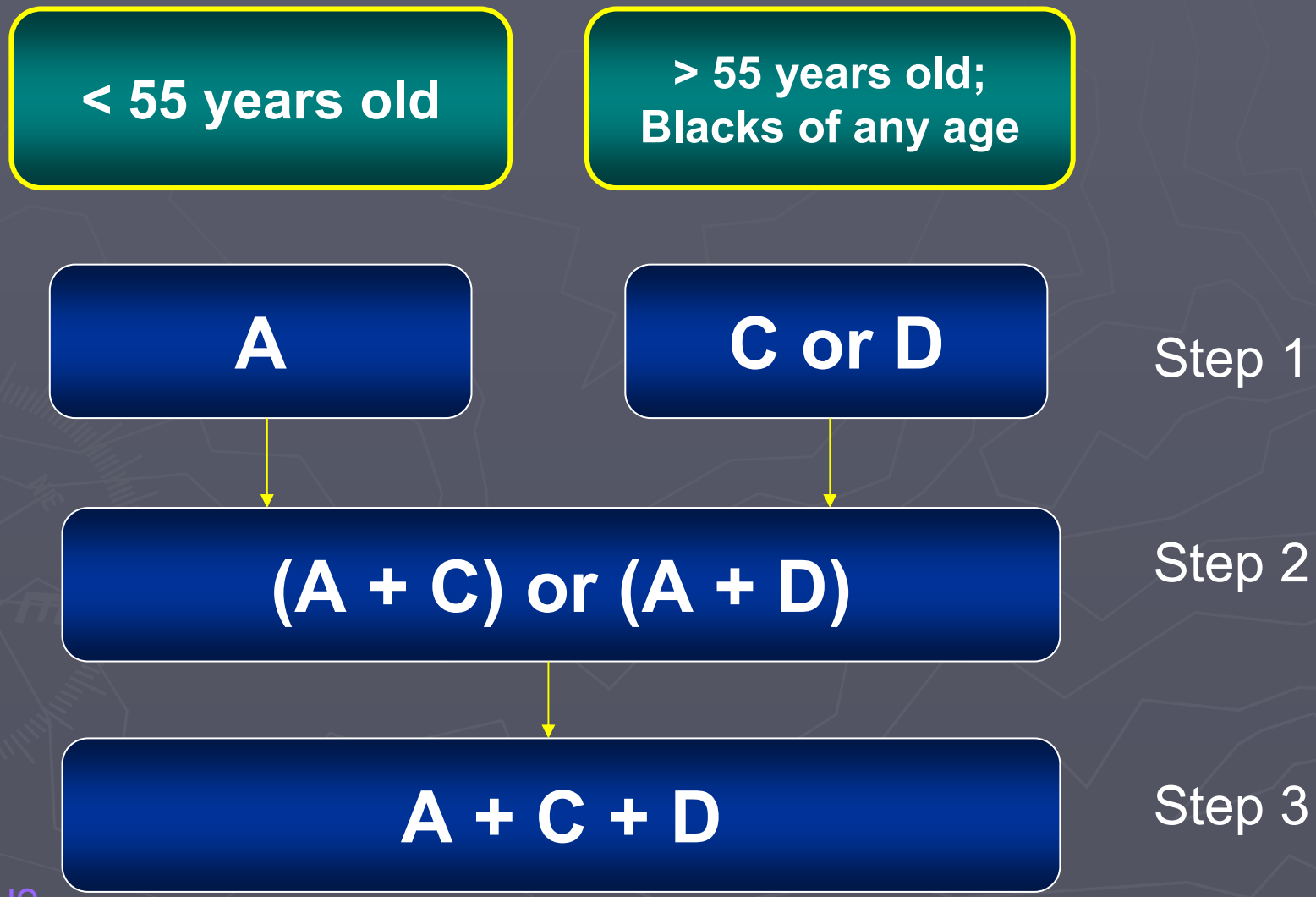
How was the guideline developed? (Why do rapid update?)



- Focusing primarily on **head-to-head** comparisons
- The principal efficacy **outcomes** ; MI, stroke and all-cause mortality.
- Because of the efficiency of **beta blocker**-based treatment at reducing cardiovascular events, especially **stroke**.

Current Issue

BHS/NICE Guideline on Treatment of Hypertension in Adults in Primary Care



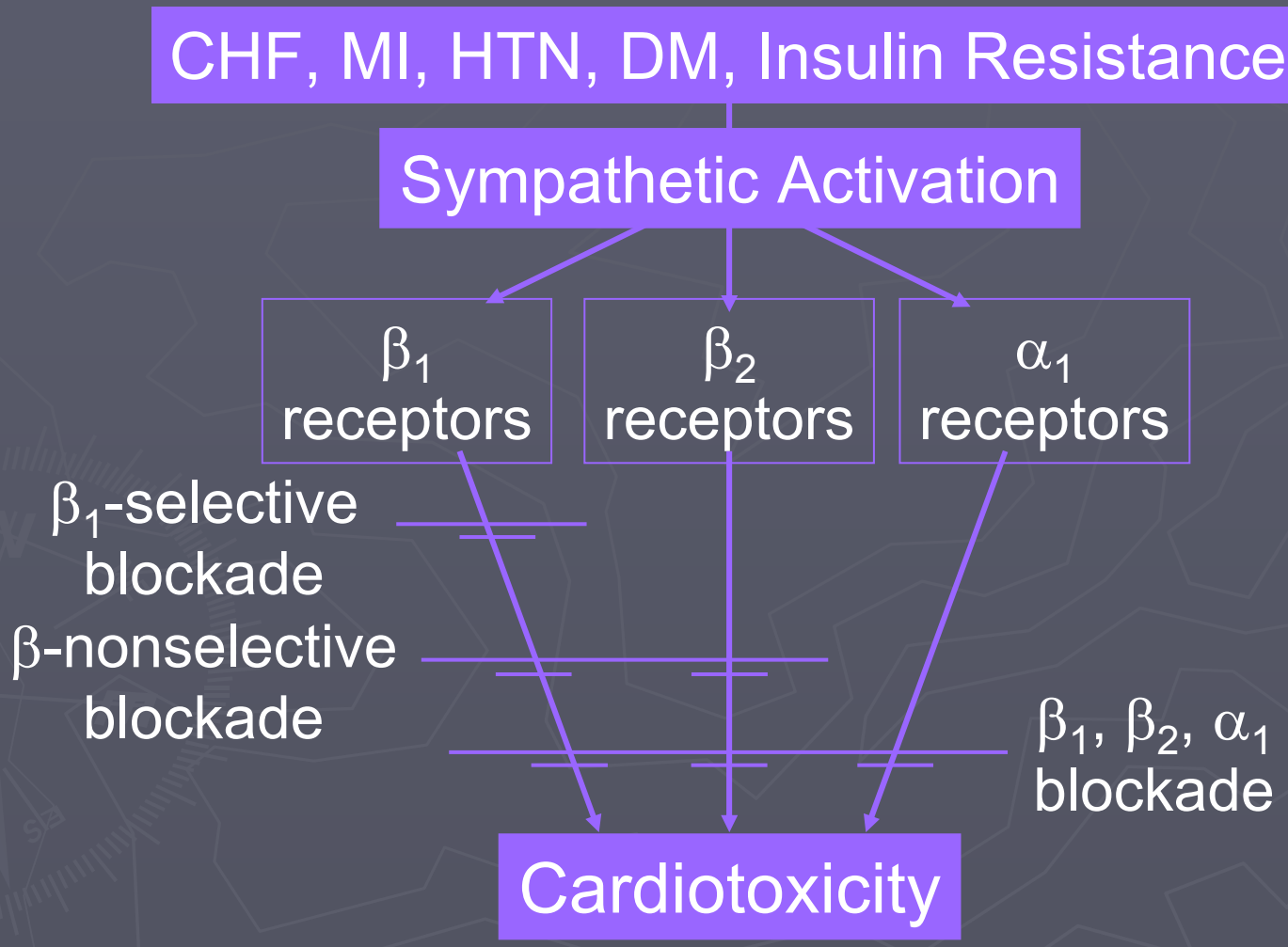
Efficacy of Beta-Blockers for First-line Antihypertensive; All Beta-Blockers Same?

- Are all beta blockers equally ineffective?
- Other beta blockers might give different results.

Efficacy of Beta-Blockers for First-line Antihypertensive; All Beta-Blockers Same?

- Current issue with beta-blocker in Hypertension
- Comparisons between old and new drugs
- Logical Practice

Selectivity of β-Blocking Agents



Bristow MR. *Circulation*. 2000;101:558-569

Comparison

Potential Cardiovascular Benefits of β-Blockade

- Anti-atherogenic
  - Reduces inflammation, shear stress, endothelial dysfunction, and lesion progression
- Anti-arrhythmic
  - Decreases HR and sympathetic activity
  - Reduces sudden death risk
- Anti-ischemic
  - Decreases HR and BP
  - Prolongs diastole (filling coronary arteries)
- Cardio-protective
  - Reverses cardiac remodeling
  - Prevents HF

Tse WY, Kendall M. *Diabet Med*. 1994;11:137-144.

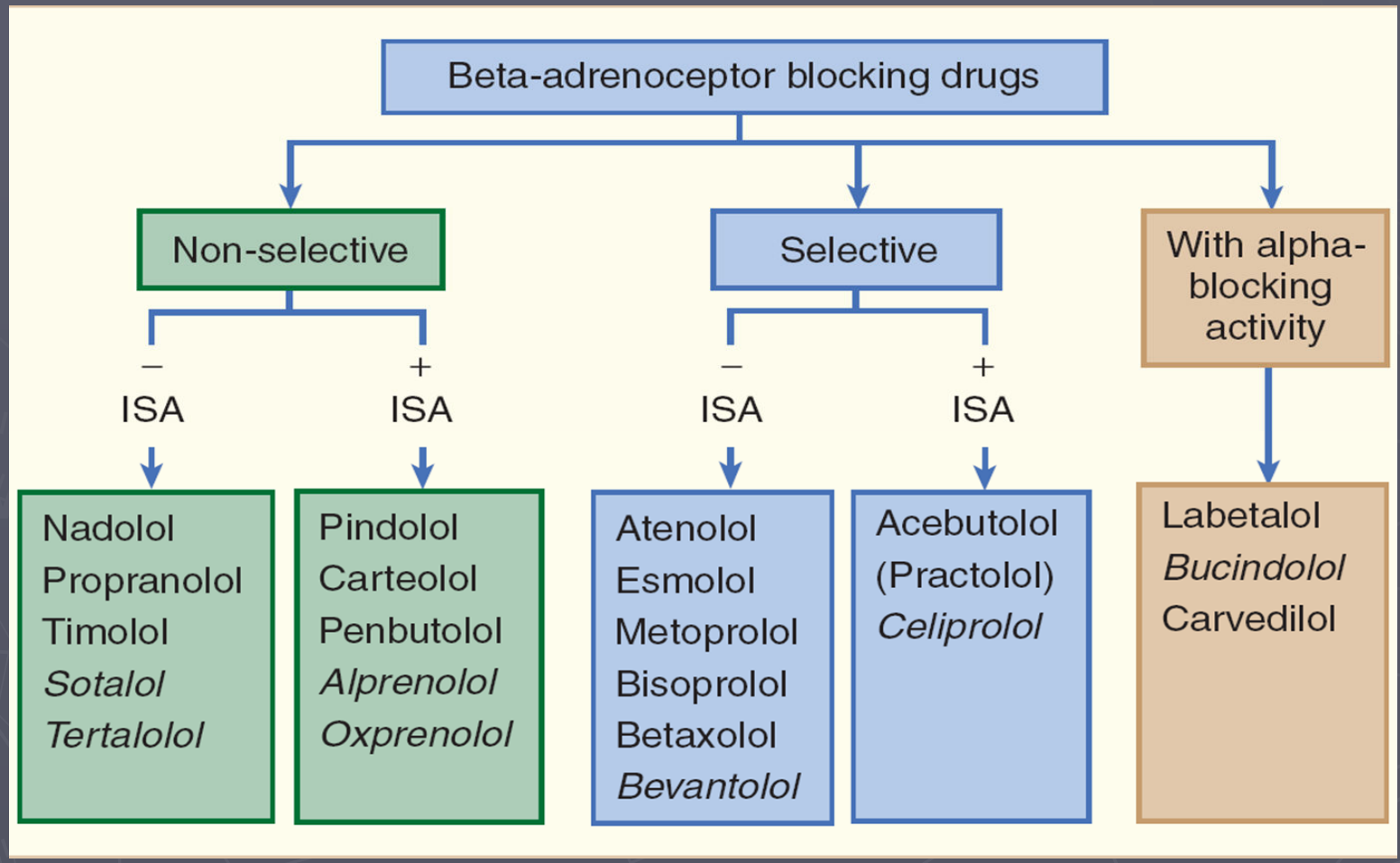
Comparison

β-Blockers : Pharmacological Effects

- β1-Selectivity
- Intrinsic sympathomimetic activity or partial agonist activity
- Solubility, elimination, and duration of effects
- Combined α, β-adrenergic blocking activity
- Extended-release preparations

Comparison

β-Blocking Agents ; Classification



Comparison

Properties of selected β- blockers

	β_1 blockade	β_2 blockade	α_1 blockade	ISA	Ancillary effects*
Carvedilol	+++	+++	+++	-	+++
Metoprolol	+++	-	-	-	-
Bisoprolol	+++	-	-	-	-
Bucindolol	+++	+++	-	++	-
Nebivolol	+++	-	-	-	++

*anti-oxidant, inhibit apoptosis, inhibit endothelin, NO generation

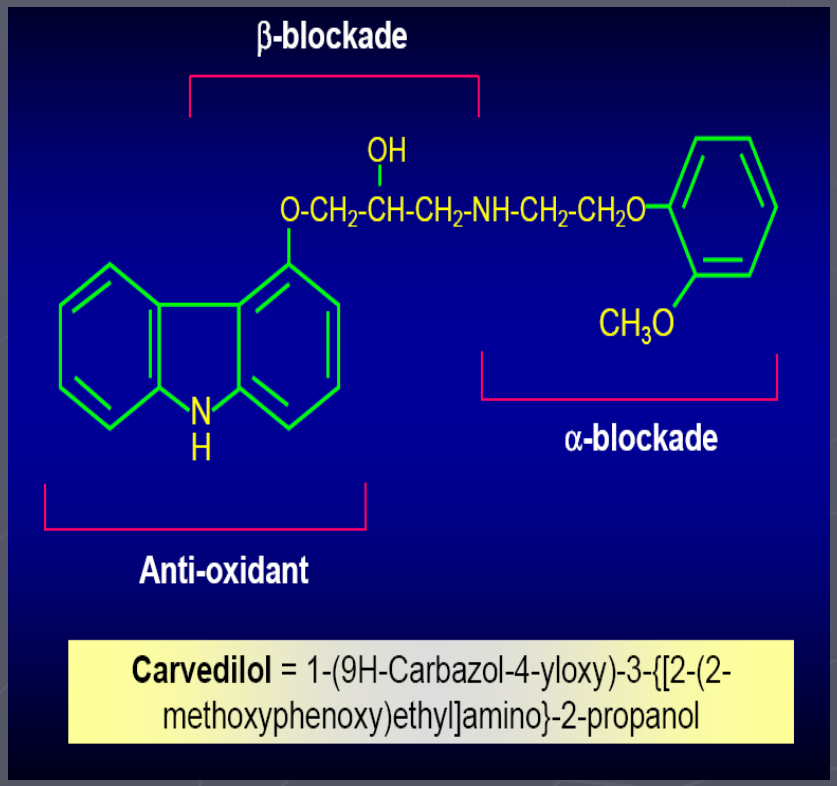
Comparison

Bisoprolol

- Beta-1 receptor selective
  - No adverse effect on lipid metabolism
  - No adverse effect on glucose metabolism
- Better than atenolol; as good as newer drugs
- Better 24 hour coverage
- Sustained BP control over long term
- No sudden changes during exercise

Carvedilol

- β-and α1-adrenergic receptor blocker
- Potent antioxidant effect ; 10-fold more potent than Vit-E
- Blocks the production of angiotensin II
- Suppresses the synthesis of endothelin
- Antiproliferative activity



Comparison

Nevibolol

- Nebivolol is a vasodilating β-blocker, vasodilating effect mediated by the endothelial NO pathway,
- BP lowering effect is linked to a reduction in PVR
- Endothelium-derived NO: the regulation of large arterial stiffness

Do β-blockers differ in their efficacy and safety in Hypertension?

- β blockers differ in their pharmacological properties

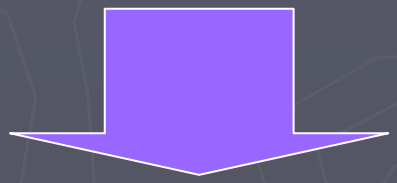
- β blockers differ in their clinical effects:
  Atenolol, Metoprolol, Bisoprolol,
  Carvedilol, Nevibolol,

Why not Beta Blocker?

- **Major Reason 1:**
  - increased risk of **new-onset diabetes**, especially when used in combination with thiazide diuretic
- **Major Reason 2:**
  - compared with other agents, BB generally less effective in reducing cardiovascular events, especially **stroke**.

Comparison

- Are all beta blocker equally ineffective?
- Other beta blocker might give different results.



Soft Endpoint : Metabolic Effect, DM
Hard Endpoint : Stroke or CVD

Comparison

Adverse metabolic effects of β - blockers

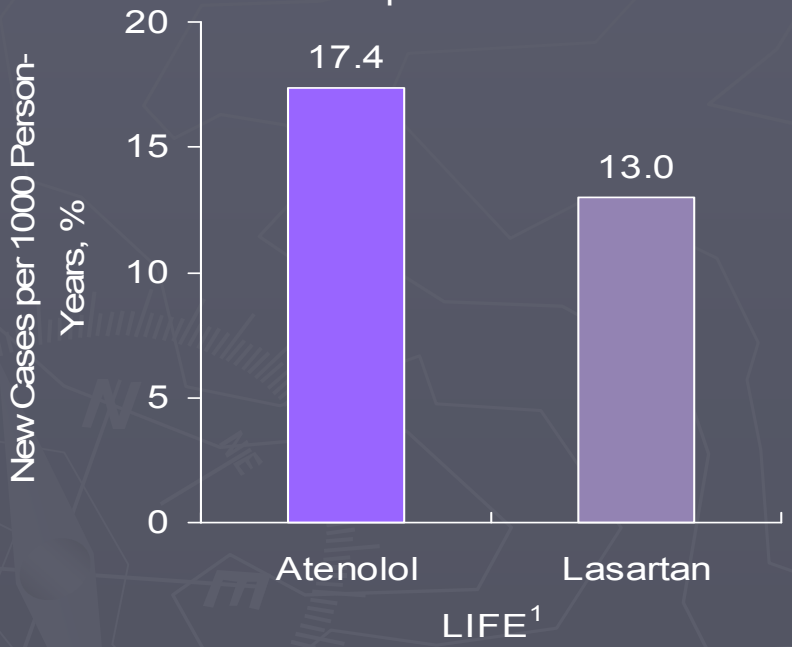
- Lower activity of LPL
- Reduce LCAT activity
- Increase body weight
- Impair first phase insulin secretion
- Reduce insulin clearance
- Reduce peripheral blood flow and increase TPR

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

Comparison

β-Blockers and the Risk of Developing New-Onset DM

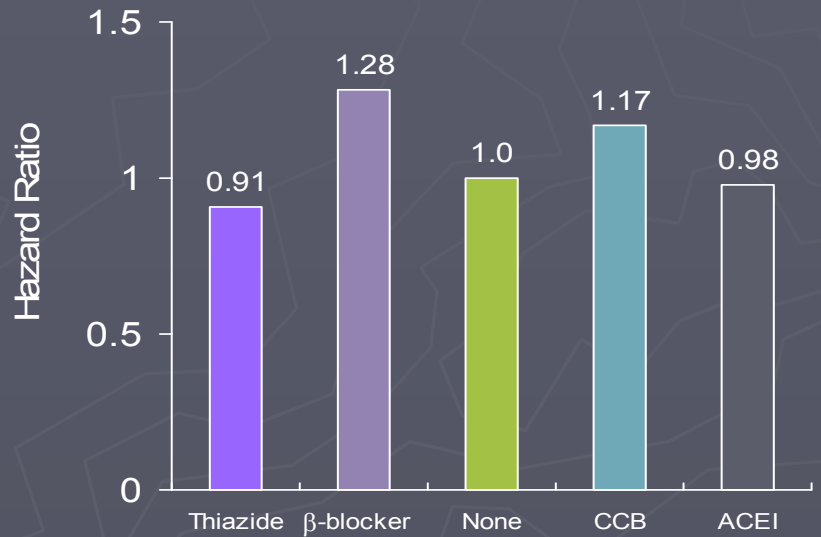
25% Increased Risk
Atenolo RR 1.25 (1.12-1.37)
p<.001



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)
p<.05



ARIC[2]

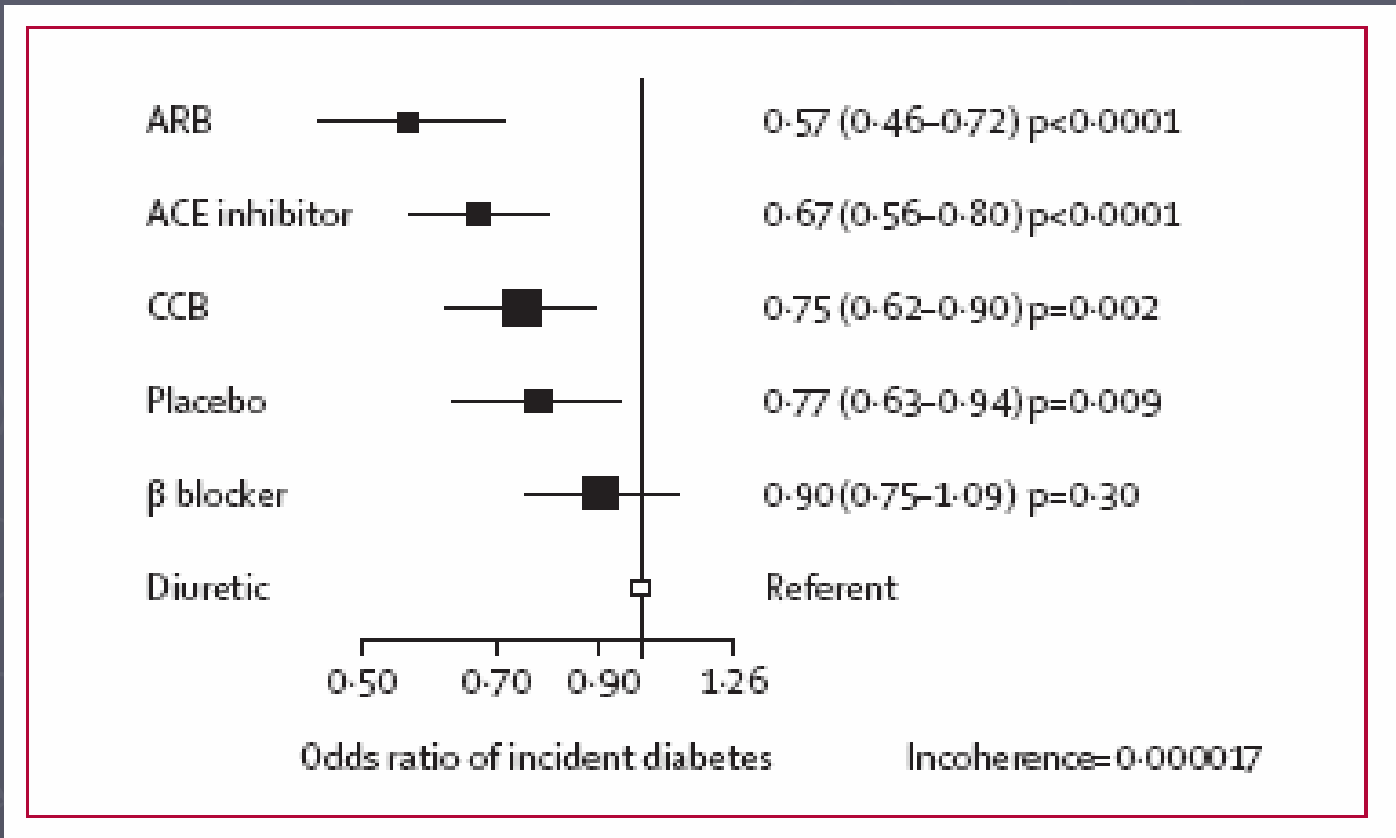
Prospective study of 12,550 patients with diabetes aged 45 to 64 and followed for 6 years. Multivanate analysis of 3804 who had hypertension at baseline.

LIFE. Losartan intervention For Endpoint Reduction; ARIC. Atherosclerosis Risk in Communities.

[1]Dahiof B, et al. *Lancet*. 2002;359:995-1003. [2]Gress TW. Et al. *N Engl J Med*. 2000;342:905-912.

Comparison

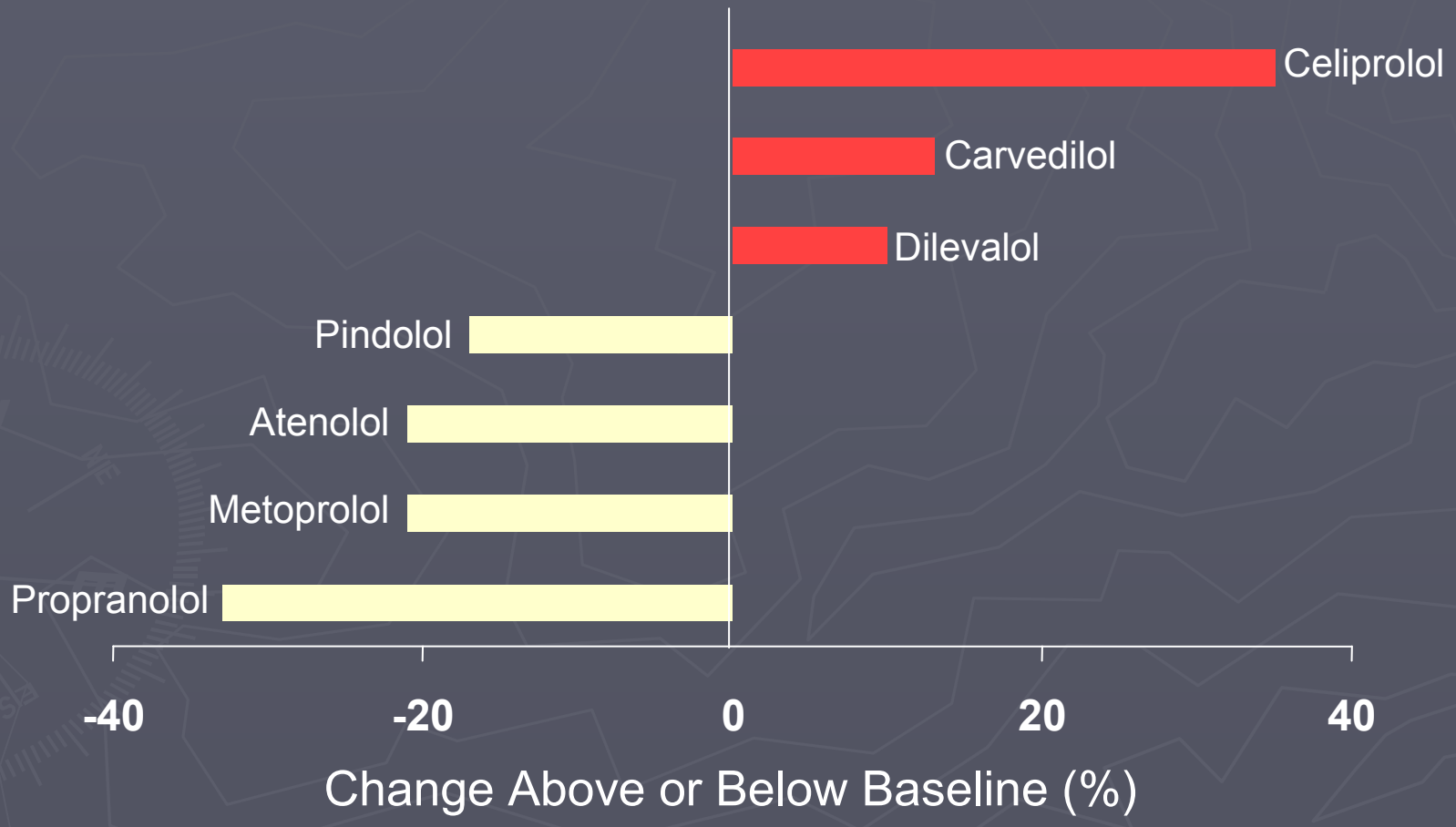
Incident diabetes of network meta-analysis of 22 clinical trials



Elliott WJ, Lancet 2007; 369: 201–07

Comparison

Effect of β - Blockers on Insulin Sensitivity



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

Comparison

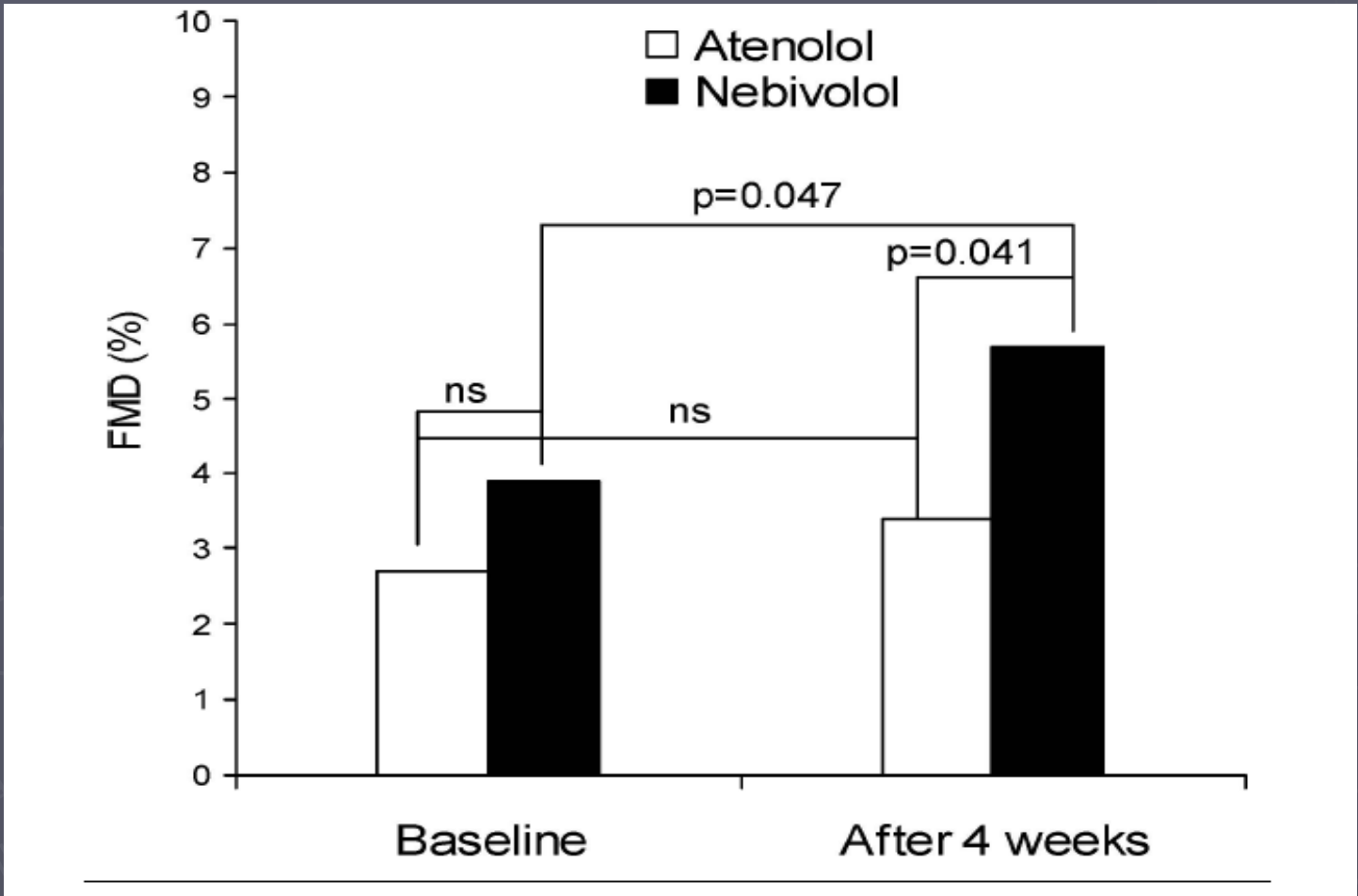
Beneficial metabolic effects of third generation β - blockers

	Insulin sensitivity	Triglyceride(%)	HDL(%)	T.Chol(%)
Propranolol	- 33%	+ 25%	- 10%	+ 9%
Metoprolol	- 21%	+ 30%	- 7%	- 1%
Atenolol	- 22%	+ 18%	- 9%	=
Pindolol	- 17%	=	=	=
Carvedilol	+ 13%	=	=	=
Celiprolol	+ 35%	- 15%	+ 5%	=

Comparison

Jacobs S et al. Am J Hypertens 1998;11:1258-1265

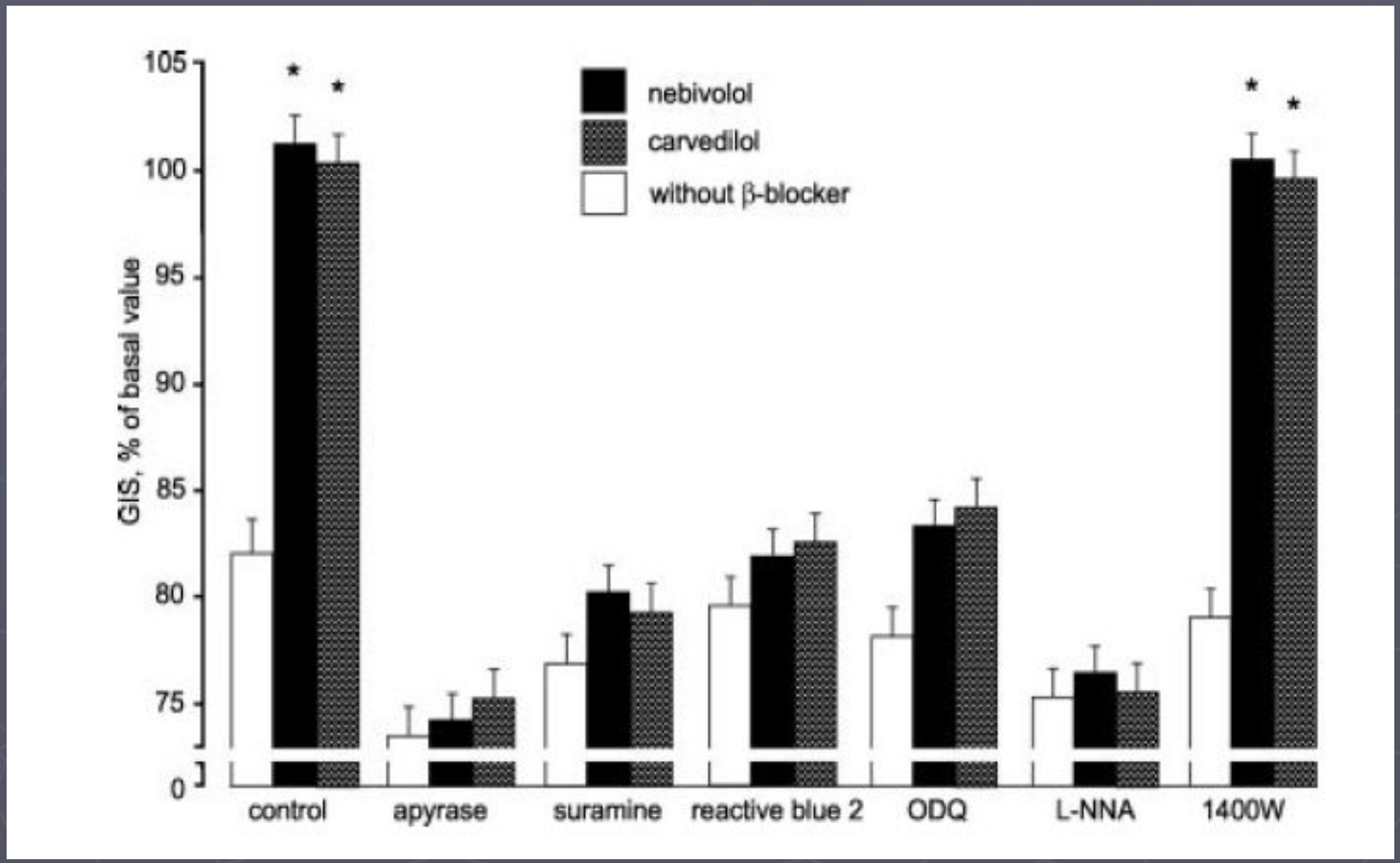
3rd generation β - blockers & endothelial function



Lekakis JP. Cardiovasc Drugs Ther 2005;19:277-281

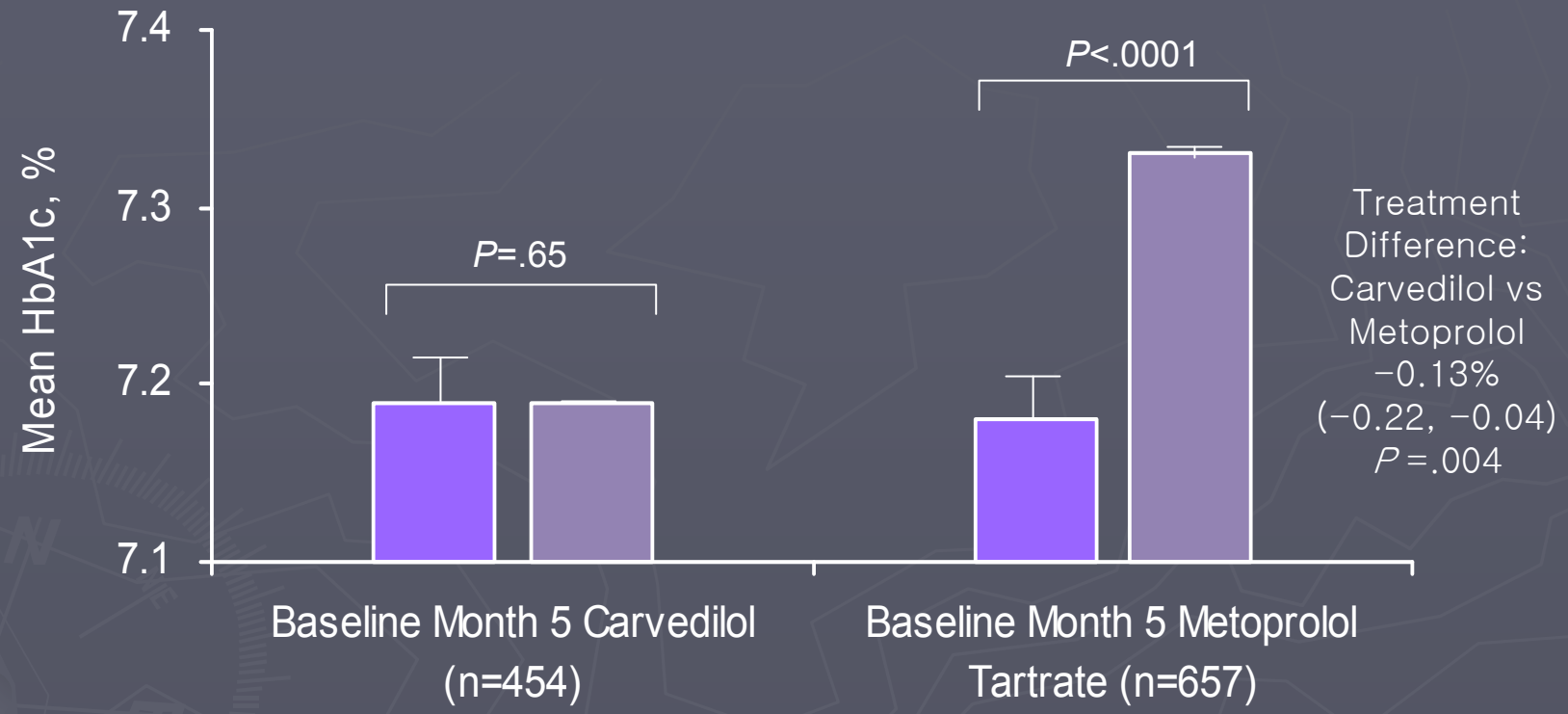
Comparison

3rd generation β - blockers & endothelial function



Kalinowski L et al. Circulation 2003;107:2747-2752

GEMINI: Hemoglobin A_{1c}

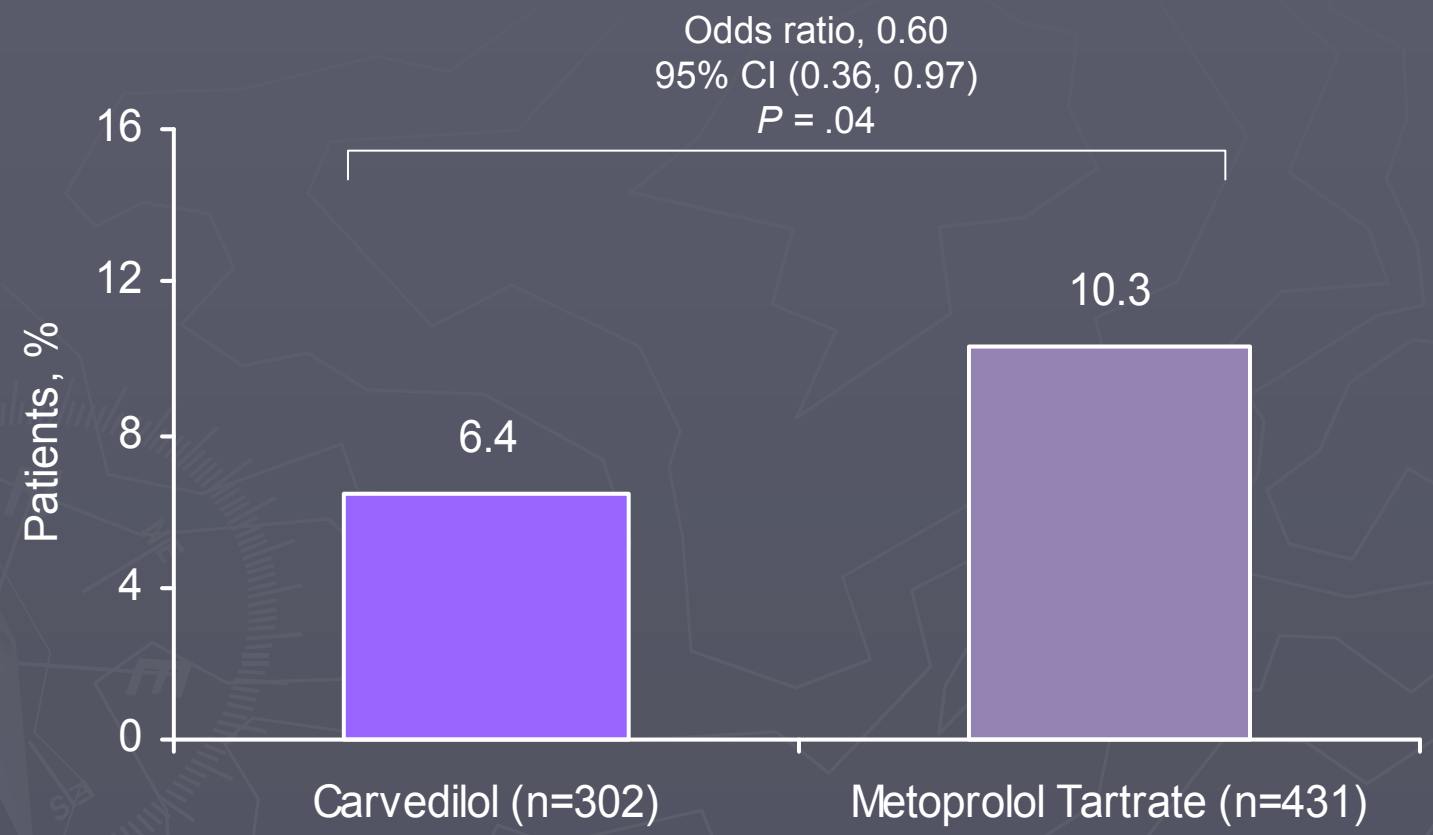


1111 patients (90%) were evaluable for efficacy, having both a valid baseline and at least one on-therapy HbA1c assessment.

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

Comparison

Development of Microalbminuria in Previously Normoalbuminuric Participants

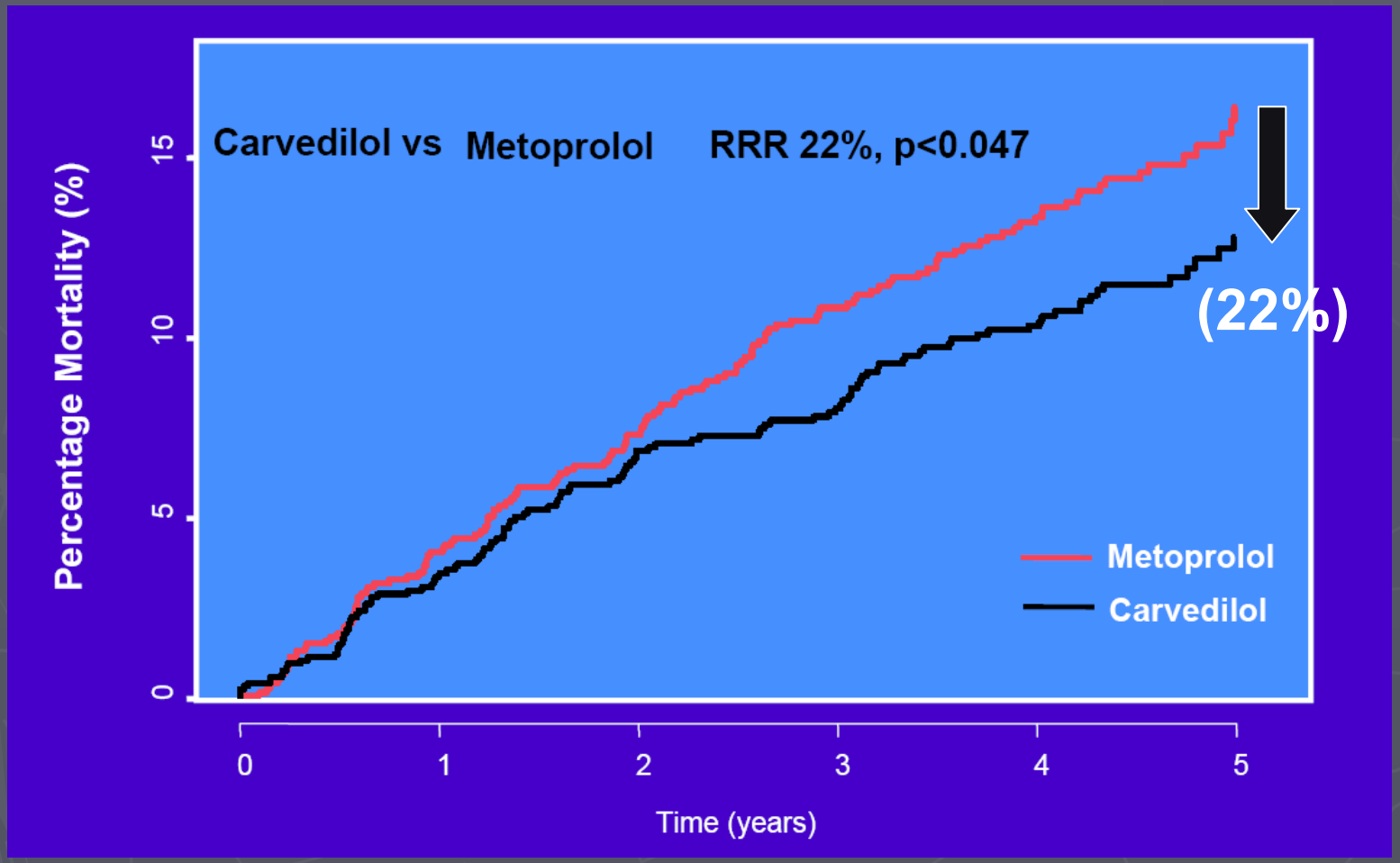


*81% of patients did not have microalbuminuria at screening.

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

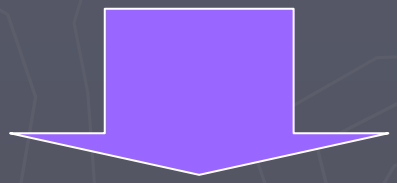
Comparison

COMET; New Diabetes Endpoint



Comparison

- Are all beta blocker equally ineffective?
- Other beta blocker might give different results.



Soft Endpoint : Metabolic Effect, DM
Hard Endpoint : Stroke or CVD

Comparison

Atenolol vs. other antihypertensives

Outcome	Relative risk with atenolol	95% CI
Stroke	1.26	1.15–1.38
MI	1.05	0.91–1.21
All-cause mortality	1.08	1.02–1.14

Atenolol is less useful than other drugs in reducing cardiovascular events (especially strokes) amongst hypertensive patients

Lindholm LH, et al. *Lancet* 2005

Comparison

Non-atenolol beta blockers vs. other antihypertensives

Outcome	Relative risk with beta blockers	95% CI
Stroke	1.20	0.30–4.71
MI	0.86	0.67–1.11
All-cause mortality	0.89	0.70–1.12

Non-atenolol β blockers may be equivalent to other antihypertensive drugs in cardiovascular protection

Lindholm LH, et al. *Lancet* 2005

Clinical Evidence ?

- β blockers differ in their pharmacological properties.
- Carvedilol, nebivolol, or other new generation beta-blocker may have good biologic properties.
- Clinical Evidences for CV outcomes ?

NO !

Comparison

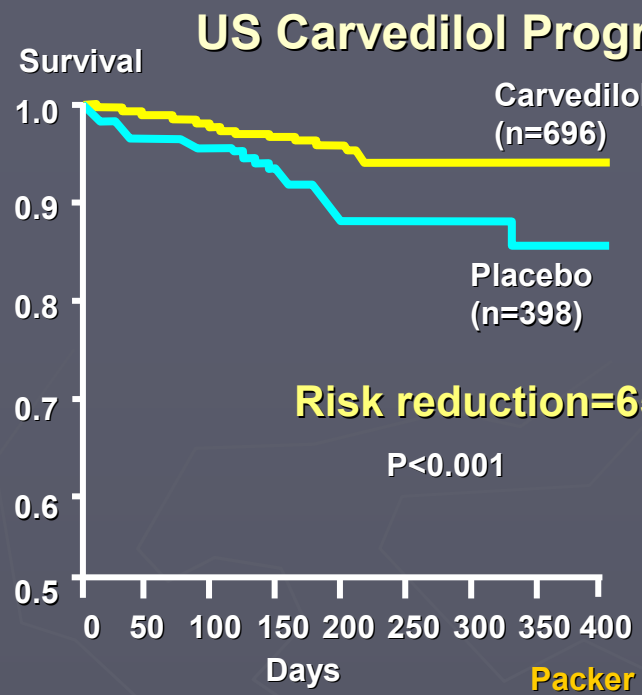
Do β-blockers differ in their efficacy and safety in heart failure?

- β blockers differ in their pharmacological properties
- β blockers differ in their clinical effects:
  Metoprolol, Bisoprolol ,Carvedilol

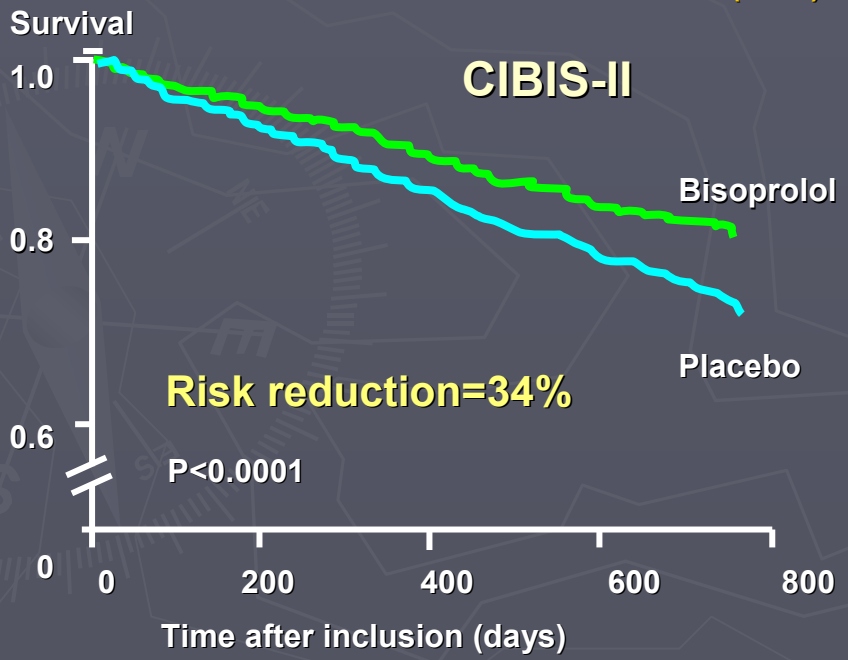
Comparison

β – blockers in CHF ; all-cause mortality

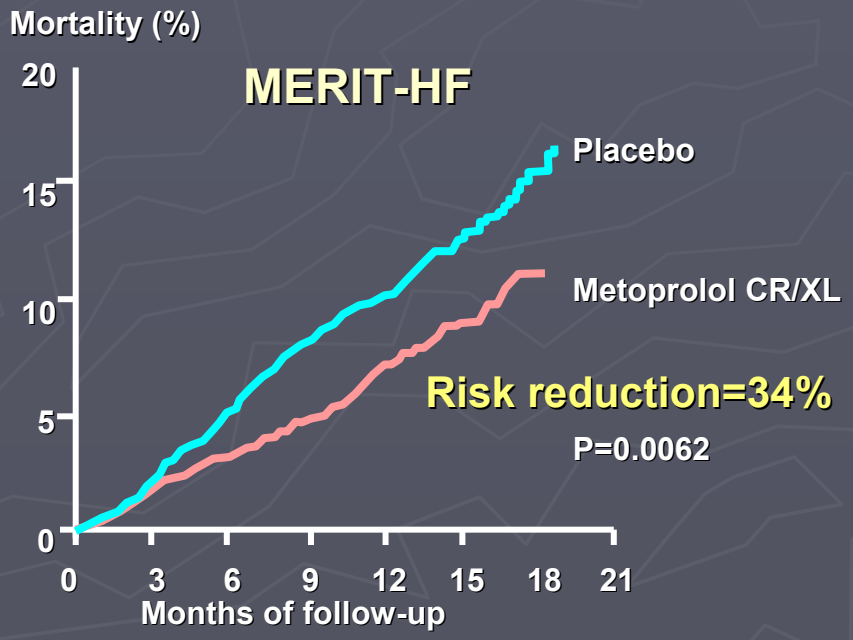
(Atenolol, Propranolol : Not Approved)



Packer et al (1996)



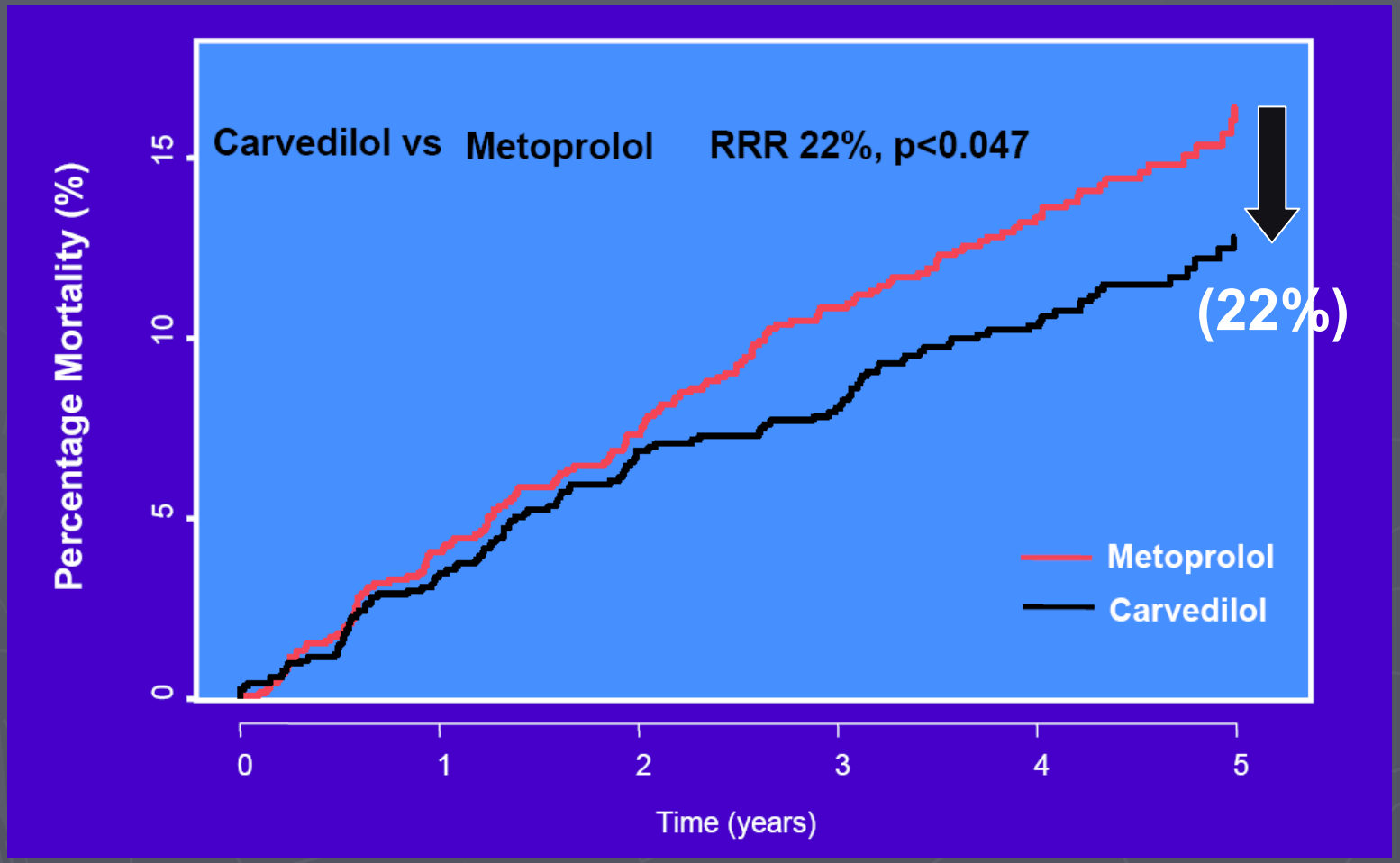
CIBIS-II Investigators (1999)



The MERIT-HF Study Group (1999)

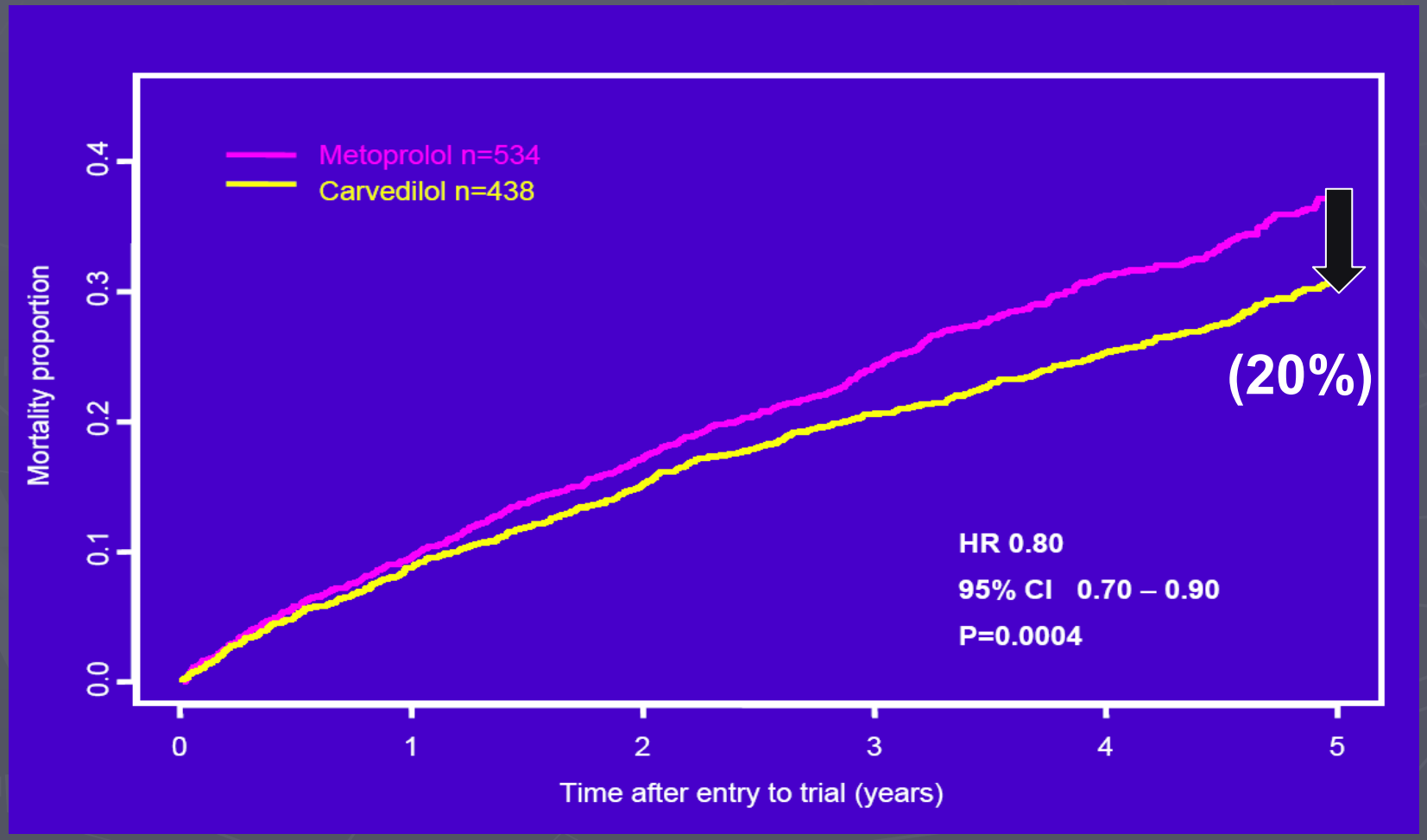
Comparison

COMET; New Diabetes Endpoint

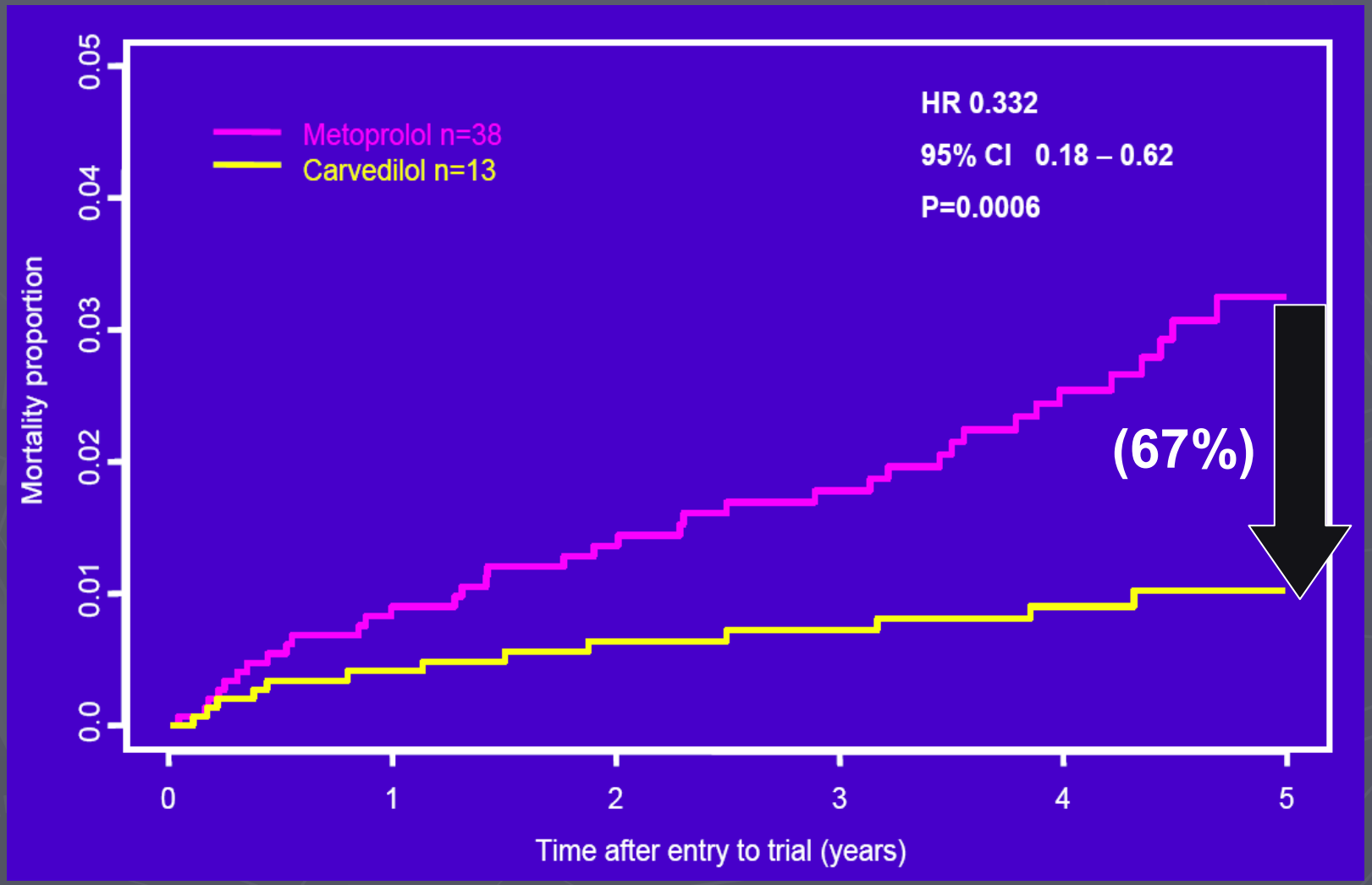


Comparison

COMET : Cardiovascular Mortality



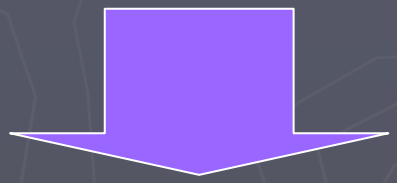
COMET : Stroke Death



Comparison

- Are all beta blocker equally ineffective?
- Other beta blocker might give different results.

Soft Endpoint : Metabolic Effect, DM



Hard Endpoint : Stroke or CVD

Comparison

Effects of Different Antihypertensive Agents on Risk Factors

	Diuretic	β-blocker	α-blocker	CCB	ACEI
Blood Pressure	+	+	+	+	+
Cholesterol	-	NS	+	NS	NS
HDL-cholesterol	NS	-	NS	NS	NS
Glucose Intolerance	-	-	+	NS	+
Hyperinsulinemia	-	-	+	NS	+
Physical activity	NS	-	+	NS	NS
LV hypertrophy	-	+	+	+	+

Kaplan NM. J Hypertens 1990; 8(Suppl.7): S175-9

Comparison

Quality data in ALLHAT (n=42,448)

- Drug Discontinuation, 50% (> 20,000)
- Drug Cross Over, 20% (about 10,000)
- Patient lost to follow-up, 2.6% (1,176)

→ ALLHAT was huge trial with low precision and have numerous problems.

→ Early Stop in patients with Alpha-blocker.

Summary of Attributes of Newer Generation β-Blockers in Hypertension

- Significant reduction in CV events, including in patients with diabetes, post-MI LVD, and HF
- No adverse effect on fasting plasma glucose
- Do not affect lipid and triglyceride metabolism
- Maintain renal blood flow
- Less likely to cause cold extremities
- AE profile comparable to placebo in clinical trials

Clinical Evidence ?

- Carvedilol, nebivolol, or other new generation beta-blocker may contribute to a reduction in CV risk.
- Whether these are clinically beneficial remains undetermined.

Efficacy of Beta-Blockers for First-line Antihypertensive; All Beta-Blockers Same?

- Current issue with beta-blocker in Hypertension
- Comparisons between old and new drugs
- Logical Practice
  - DM & Compelling Indications
  - Young Age
  - Tolerability

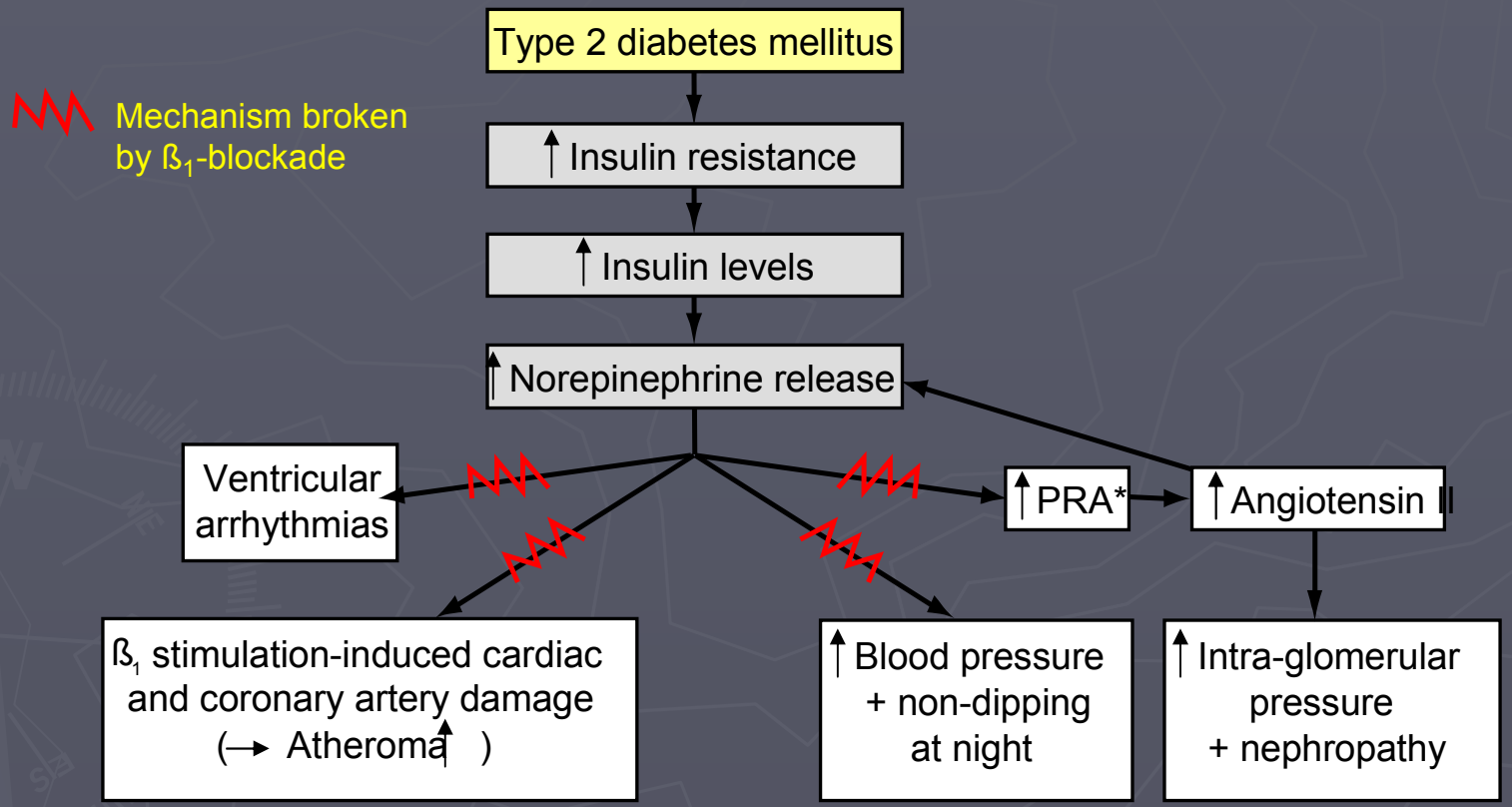
Compelling Indication in β - Blockers

TABLE 12. Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

Compelling Indication*	Recommended Drugs: Diuretic	BB	ACEI	ARB	CCB	Aldo ANT	Clinical Trial Basis†
Heart failure	●	●	●	●		●	ACC/AHA Heart Failure Guideline,[132] MERIT-HF,[133] COPERNICUS,[134] CIBIS,[135] SOLVD,[136] AIRE,[137] TRACE,[138] ValHEFT,[139] RALES,[140] CHARM[141]
Post–myocardial infarction		●	●			●	ACC/AHA Post-MI Guideline,[142] BHAT,[143] SAVE,[144] Capricom,[145] EPHESUS[146]
High coronary disease risk	●	●	●		●		ALLHAT,[109] HOPE,[110] ANBP2,[112] LIFE,[102] CONVINCE,[101] EUROPA,[114] INVEST[147]
Diabetes	●	●	●	●	●		NKF-ADA Guideline,[88,89] UKPDS,[148] ALLHAT[109]
Chronic kidney disease			●	●			NKF Guideline,[89] Captopril Trial,[149] RENAAL,[150] IDNT,[151] REIN,[152] AASK[153]
Recurrent stroke prevention	●		●				PROGRESS[111]

Practice

$ß_1$-blockade benefits patients with type 2 diabetes and hypertension



* PRA = plasma renin activity

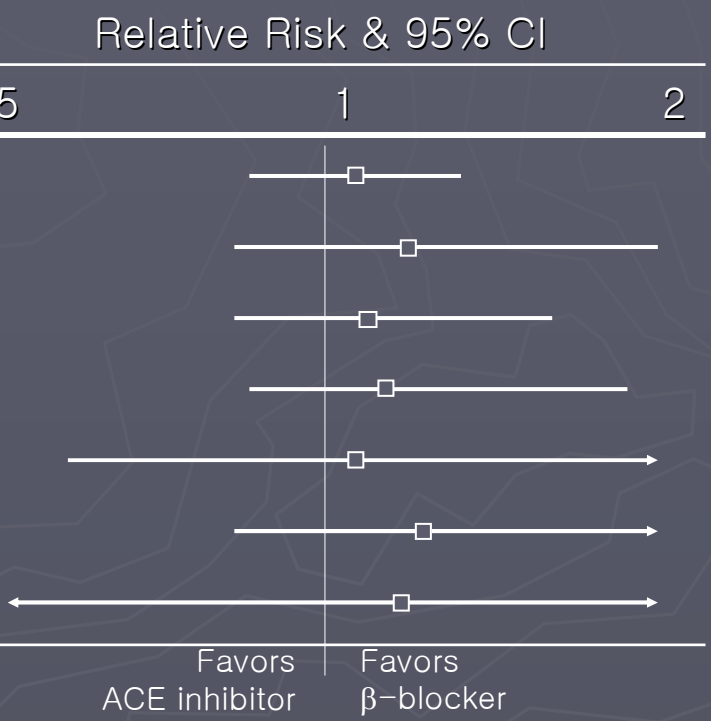
Practice

Cruickshank JM. Hypertension and diabetes: a fateful alliance.
Satellite symposium from the XXII Congress of the ESC. Amsterdam 26-30 August 2000

DM and Beta Blocker in HTN

UKPDS:ACE Inhibitor vs. β-Blocker

	RR	*P*
Any DM-related endpoint	1.10	.43
Diabetes-related deaths	1.27	.28
All-cause mortality	1.14	.44
Myocardial infarction	1.20	.35
Stroke	1.12	.74
Microvascular disease	1.29	.30
Heart failure	1.21	.66



1148 hypertensive patients with type 2 diabetes. Of the 758 patients randomized to tight control of blood pressure. 400 were allocated to captopril and 358 to atenolol. Follow-up was 9 years.

UKPDS Group. *BMJ*. 1998:317:713-720.

Practice

American Association of Clinical Endocrinologists 2006 Guidelines for Type 2 Diabetes With Hypertension

Indication	Recommendation	Highest Level of Evidence	Grade
Type 2 diabetes	Goal BP ≤ 130/80 mm Hg	2	A
	Goal BP ≤ 120/75 mm Hg When severe proteinuria Exists	1	A
	ACEI or ARB as first-or second-line agent	1	A
	Thiazide diuretic as first-or second-line agent (in low dosage with adequate potassium replacement or sparing)	1	A
	BB (preferably drugs that block both α and β receptors) as second-or third-line agent	**1**	**A**
	CCB (preferably nondihydropyridine) as second-, third-, or fourth-line agent	1	A

Torre JJ. et al. AACE Hypertension Guidelines. *Endocr Pract*. 2006;12:193-222.

Practice

Key Messages in the NICE/BHS Hypertension Guideline Update:

- 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.

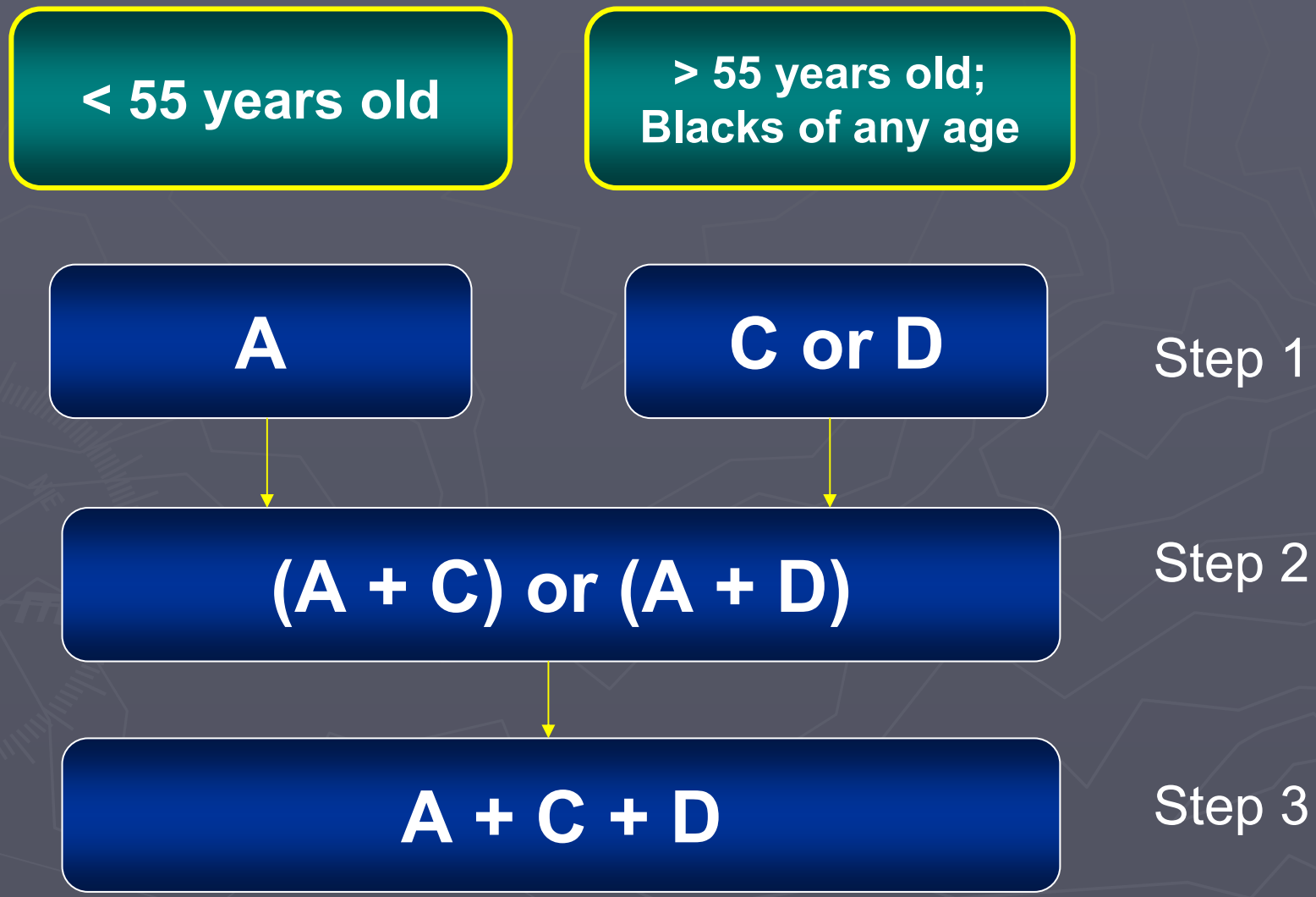
Clinical Results vs. Interpretation

Alcohol consumption vs. CV risk

- France vs. Scotland or English
- Italian vs. English
- Japanese vs. American
- Chinese vs. American

• In an ethnic group with using an English letters, there are higher CV risk than others.

BHS/NICE Guideline on Treatment of Hypertension in Adults in Primary Care



Prospective Hard-event Trials in Hypertension involving β-Blockers

Trial	Drugs	Mean age (yr)	Starting BP (mmHg)	Pulse-Pressure (mm Hg)
Studies with favorable to beta-blockers				
IPPPSH	Oxyprenolol	52	173/108	65
MRC-mild	Prepranolol	51	161/98	63
MAPHY	Metoprolol	52	167/108	59
UKPDS	Atenolol	56	159/94	65
Studies with Unfavorable 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)
Vascular system	Relatively compliance	non-compliant, stiff
Pulse pressure (mmHg)	65	81
β1 receptor response	Relatively	decreased

Practice

Physician Concerns About Adding β-Blockade in Hypertension

Metabolic

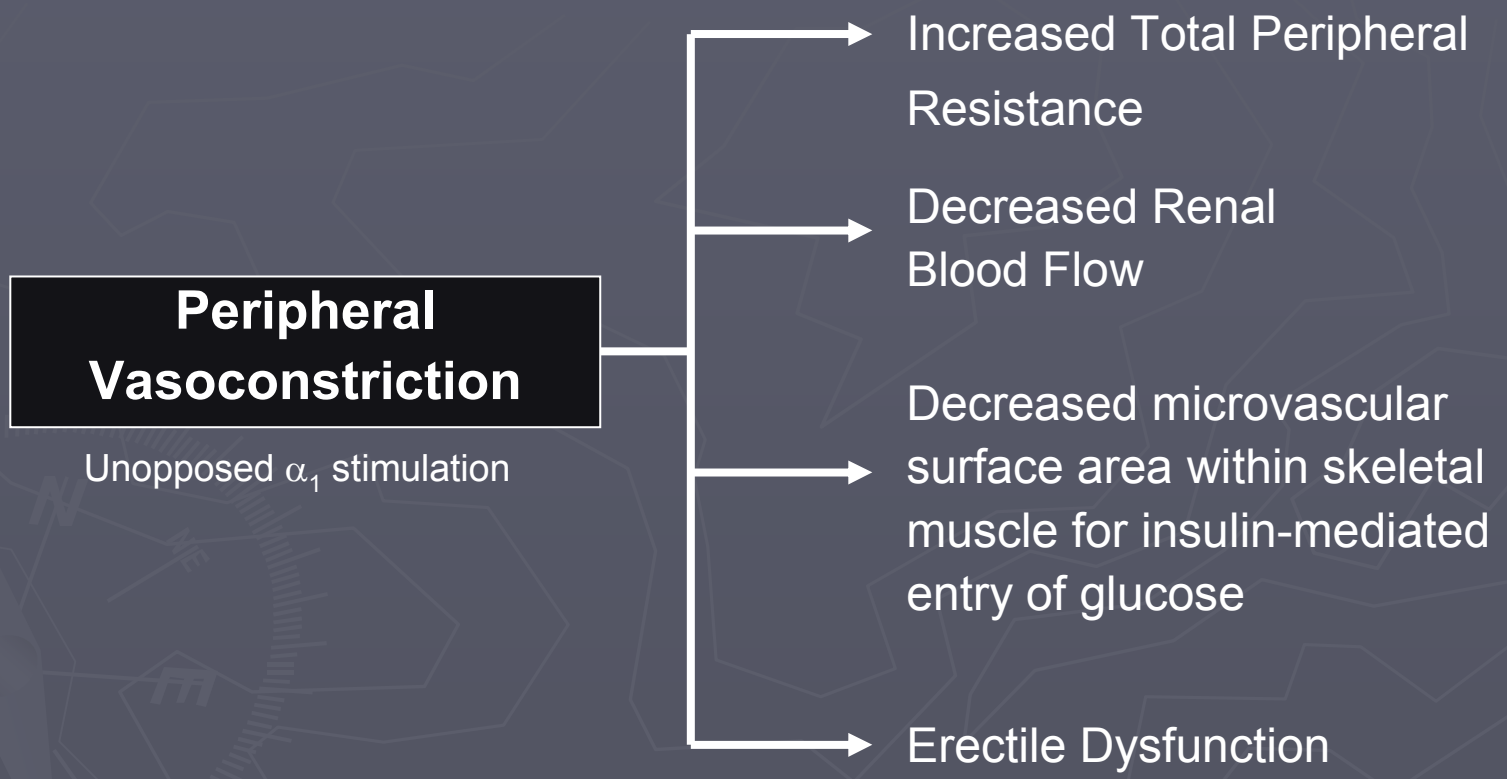
- Worsening HDL
- Increased Apo B
- Negative effects on glucose metabolism
- Negative effects on renal blood flow
- Masked hypoglycemia

Tolerability

- Fatigue
- Impotence
- Weight increase
- Peripheral vasoconstriction (cold extremities)
- Depression

Adapted from: Bell DS. Endocr Pract. 1999;5:51-53.

Traditional β-Blocker Effects on Peripheral Vasculature



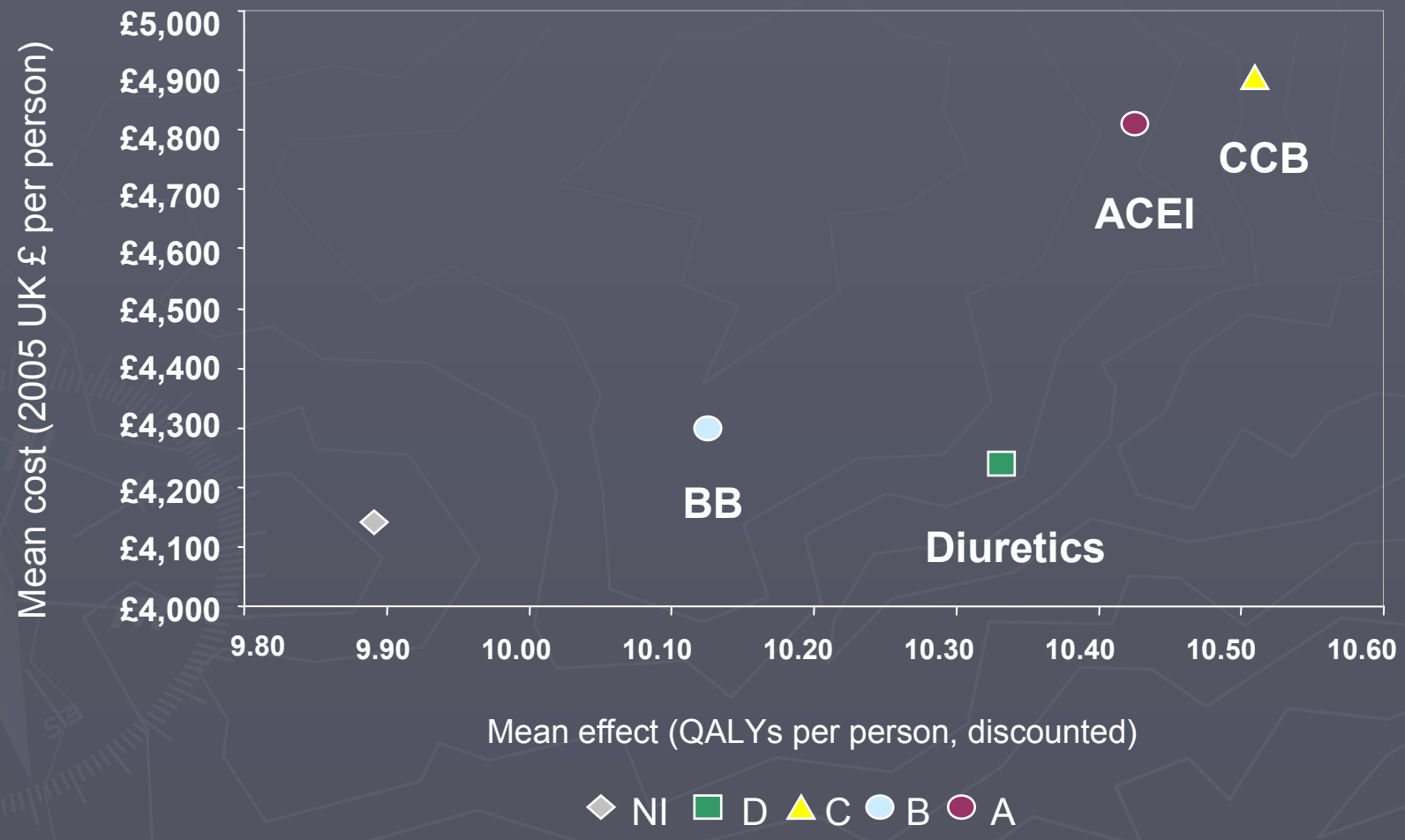
Bell DSH. *Endocrinologist*. 2003;13:116-123. Packer M. *Prog Cardiovasc Dis*. 1998;41:39-52. Man In't Veld AJ. *Am J Hypertens*. 1998;1:91-96.

Tolerability / Cost

- New Generation Beta Blocker : relatively good tolerance
- Extended Release or long half life
- Less side Effect
- In some drugs, drug cost is so high.

Cost effectiveness

Base case results 65-year-old male 2% annual CVD risk, Cost effectiveness plane



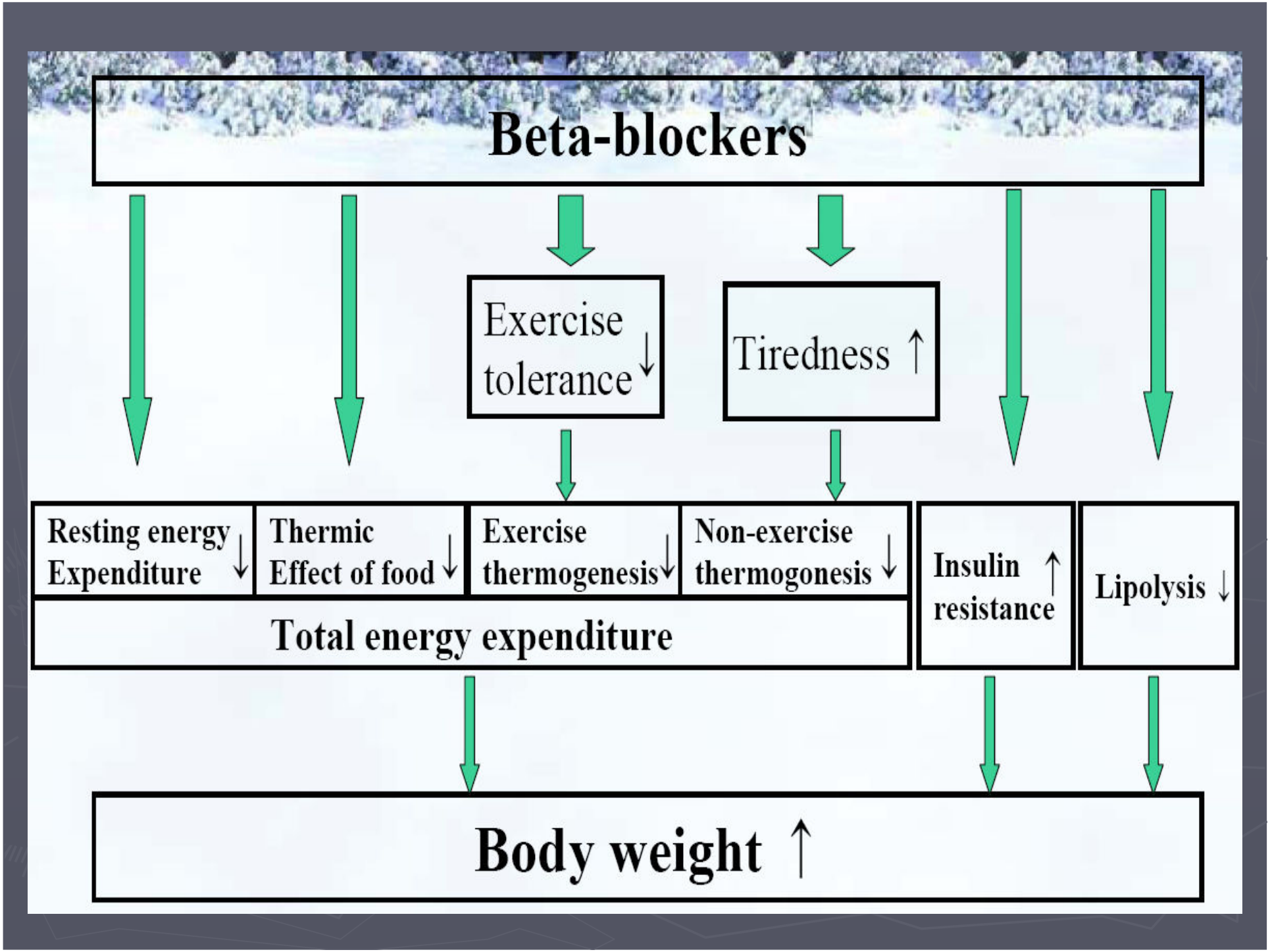
partial update of *NICE Clinical Guideline*

Practice

Conclusions

- The downgrading of beta blockers as a routine initial therapy for hypertension, especially atenolol in primary care. But, it is unclear whether this conclusion applies to all beta- blockers.
- New generation beta blockers have good biologic and metabolic evidences, but further clinical outcome study will be needed.

Thank You for Your Attention


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

Carvedilol' PDs, PKs and Elimination

	Carvedilol	Atenolol
Pharmacodynamics		
β_1-Blackade potency	x10	x1
β_1-selectivity	∅	++
ISA	∅	∅
Memb stabilizing activity	++	∅
Pharmacokinetic		
Absorption	>90%	~50%
Bioavailability	~30%	~40%
Dose-dependent bioavailability	yes	no
Interpt. variation of pl. conc	x 5-10	x 4
Lipid solubility	moderate	weak
Elimination		
Half life	7-10 hr	6-9 hr
Elimination route	hepatic	renal
Active metabolite	yes	no
Drug accumulation in renal ds.	no	yes

Beta Blocker Classification

	GENERATION/CLASS	K(β1)	β1/β2	β1 /α1
Propranolol	1st/nonsel	4.1	2.1	-
Metoprolol	2st/β1-sel	45	74	-
Bisoprolol	2st/β1-sel	121	119	-
Carvedilol	3rd/β-vasod	4	7.3	2.4
Nebivolol	3rd/β-vasod	5.8	1700	66
Bucindolol	3rd/β-vasod	3.6	1.4	-

Beta Blocker Classification

DRUG	β_1-BLOCKADE POTENCY RATIO(PROPRANOLOL=1)	RELATIVE β_1 SELECTIVITY	ISA	Ancillary Effect
Propranolol	1.0	0	0	+
Atenolol	1.0	++	0	0
Bisoprolol	10.0	++	0	0
Carvedilol	10.0	0	0	++
Labetalol	0.3	0	+?	0
Metoprolol	1.0	++	0	0
Nebivolol	10.0	++	0	++

Adverse metabolic effects of beta blockers

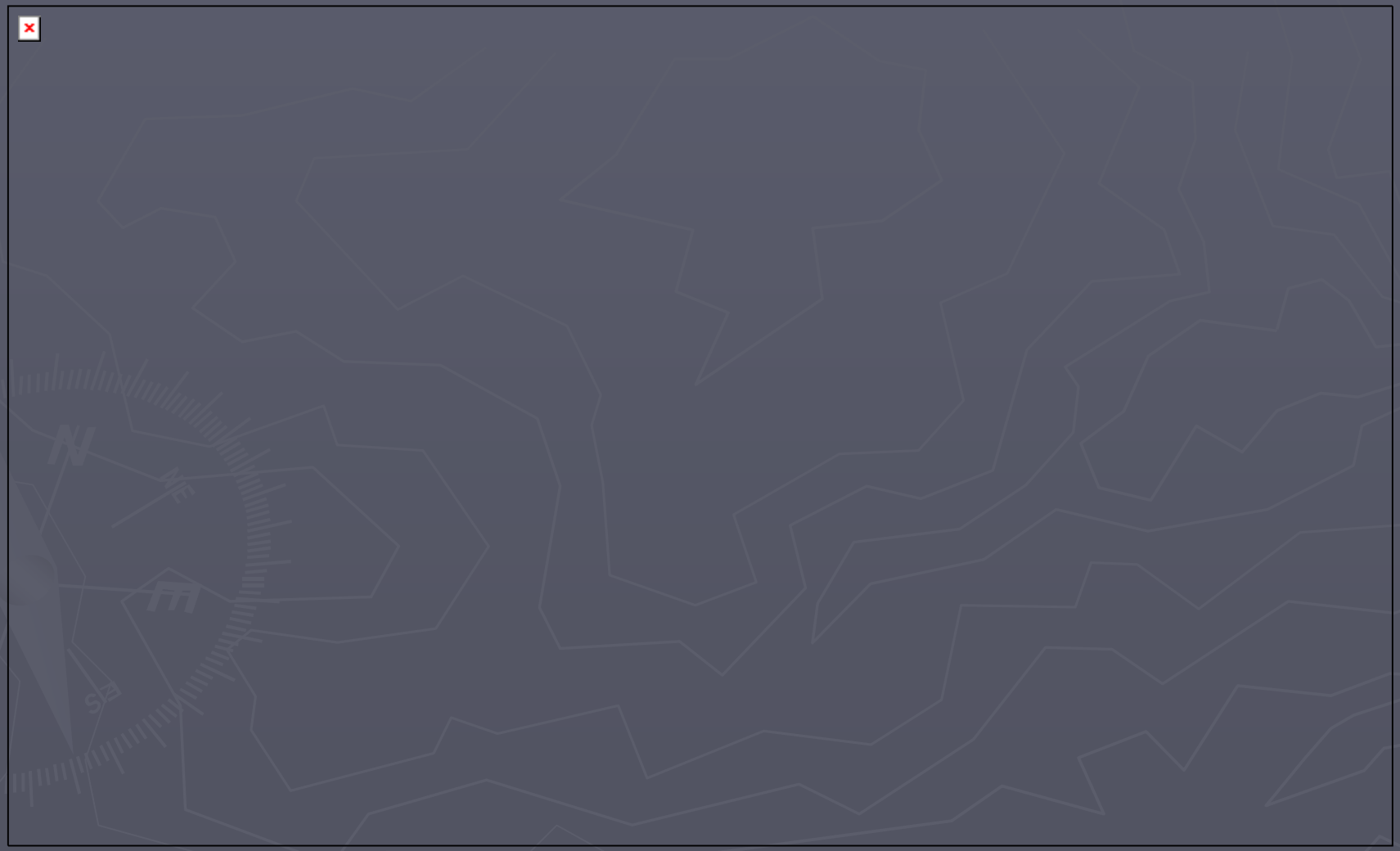
- Peripheral vasoconstriction: increased insulin resistance
- Inhibition of LPL → increase in triglyceride and small dense LDL
- Inhibition of LCAT → decrease in HDL

Bell DSH. Curr Med Res Opn 2005;21:1191-1200

Effect of Stimulating α- and β - adrenoreceptors

	Cardiac	Vascular	Neuroendocrine	Metabolic
α1	Minimal increase contractility	Venous and arterial constriction	Stimulation of renal renin release via arterial contriction	-
α2	Electrophysiological effect?	Venous and arterial constriction (less potent than α1)	Inhibition of norepinephrine release	Antagonises effect of β1-stimulation
β1	HR ↑ Contractility ↑ Excitability ↑ hypertrophy ↑	-	Stimulation of renin release	Lipolysis Platelet aggregation
β2	As β1, but less potent	Coronary and skeletal muscle arterial dilatation	-	Glycogenolysis

COMET : Risk of Death



Beta-blockers are no longer preferred as a routine initial therapy for hypertension

- Beta-blockers may be considered in :

  - younger women of child-bearing potential
  - patients with HTN & evidence of increased sympathetic drive
  - intolerance / contra-indication to ACEI and ARBs

- In these circumstances, if initial therapy is with a BB and a second drug is required, add DHP CCB rather than a thiazide-type diuretic to reduce the risk of developing diabetes.

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