Updates in Hypertension Management

By

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Global Hypertension Facts

PREVALANCE

1 Billion

Estimated people worldwide have hypertension[1]

GLOBAL INCIDENCE

60%

Expected increase in the global incidence of hypertension by 2025[1]

CURRENT TREATMENTS

10 Million

~~Estimated people worldwide who have high blood pressure despite taking 2 or more medications[1]~~

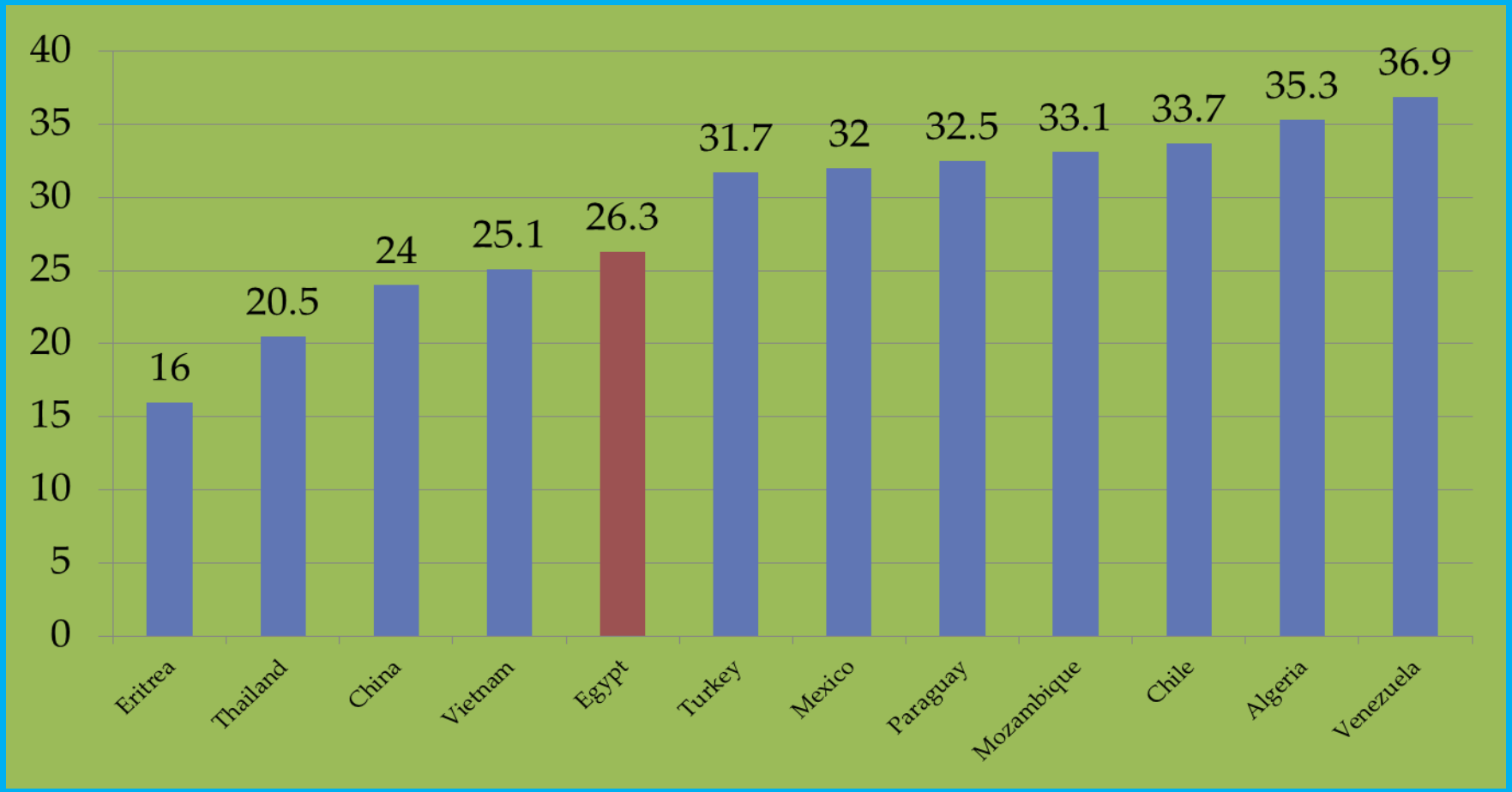
COST

~10% of all global healthcare spending is attributable to high blood pressure[2]

1.Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005 Jan 15 21;365(9455):217 23.

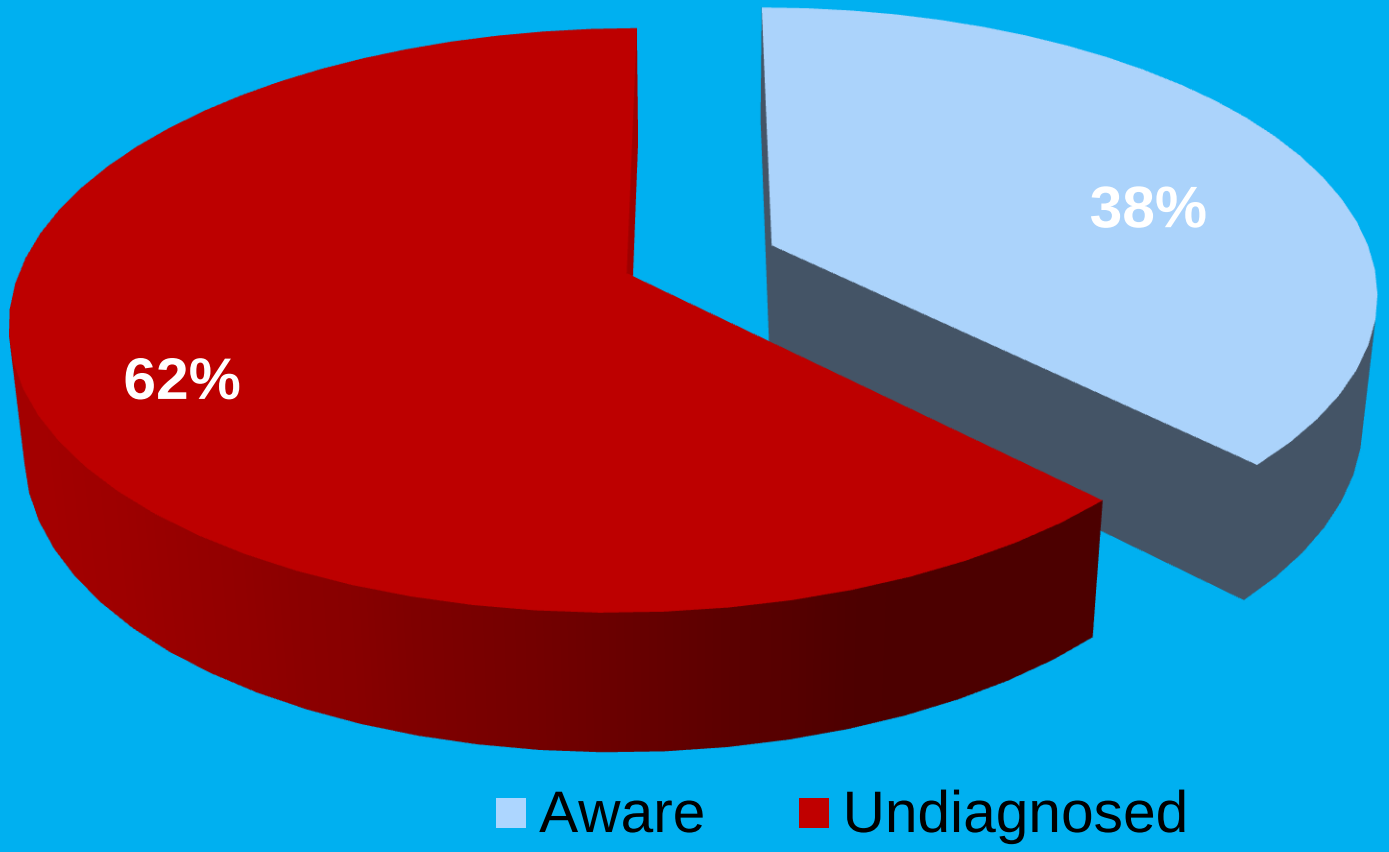
2. Gaziano TA, Asaf B, S Anand, et.al. The global cost of nonoptimal blood pressure. J Hypertens 2009; 27(7): 1472-1477.

Prevalence of hypertension in developing countries



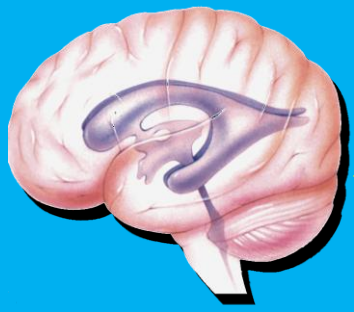
M Mohsen Ibrahim, Albertino Damasceno ; www.thelancet.com ***Vol 380 August 11, 2012***

Only 38% of hypertensive Egyptians are aware of their high BP



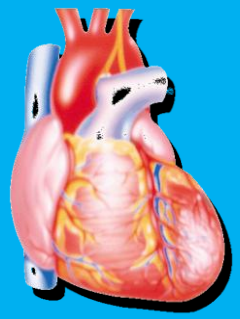
M Mohsen Ibrahim, Albertino Damasceno ; www.thelancet.com ***Vol 380 August 11, 2012***

Complications of Hypertension: End-Organ Damage



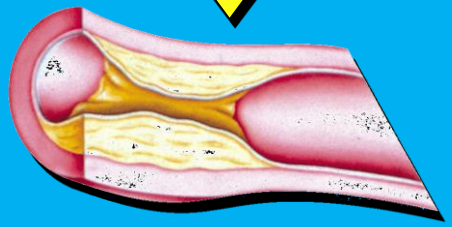
Hemorrhage, Stroke

Hypertension



LVH, CHD, CHF

Retinopathy



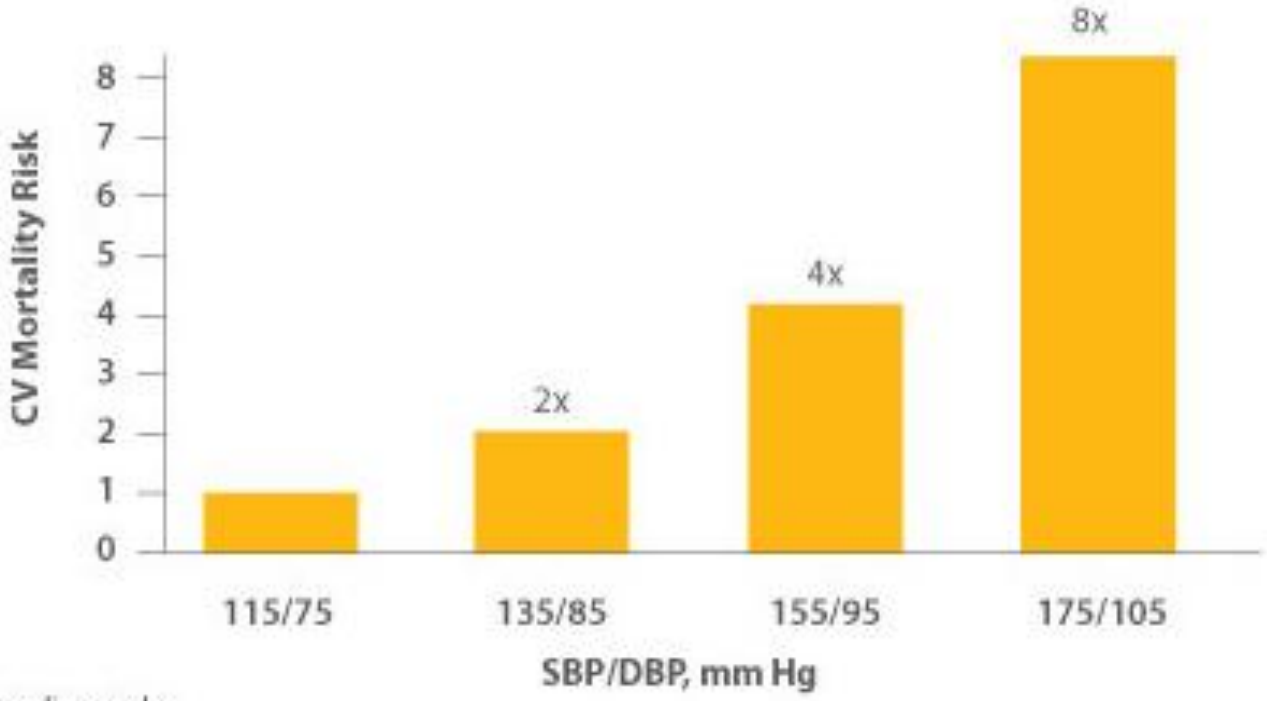
Peripheral Vascular Disease

Renal Failure, Proteinuria

CHD = coronary heart disease
CHF = congestive heart failure
LVH = left ventricular hypertrophy

Chobanian AV, et al. *JAMA*. 2003;289:2560-2572.

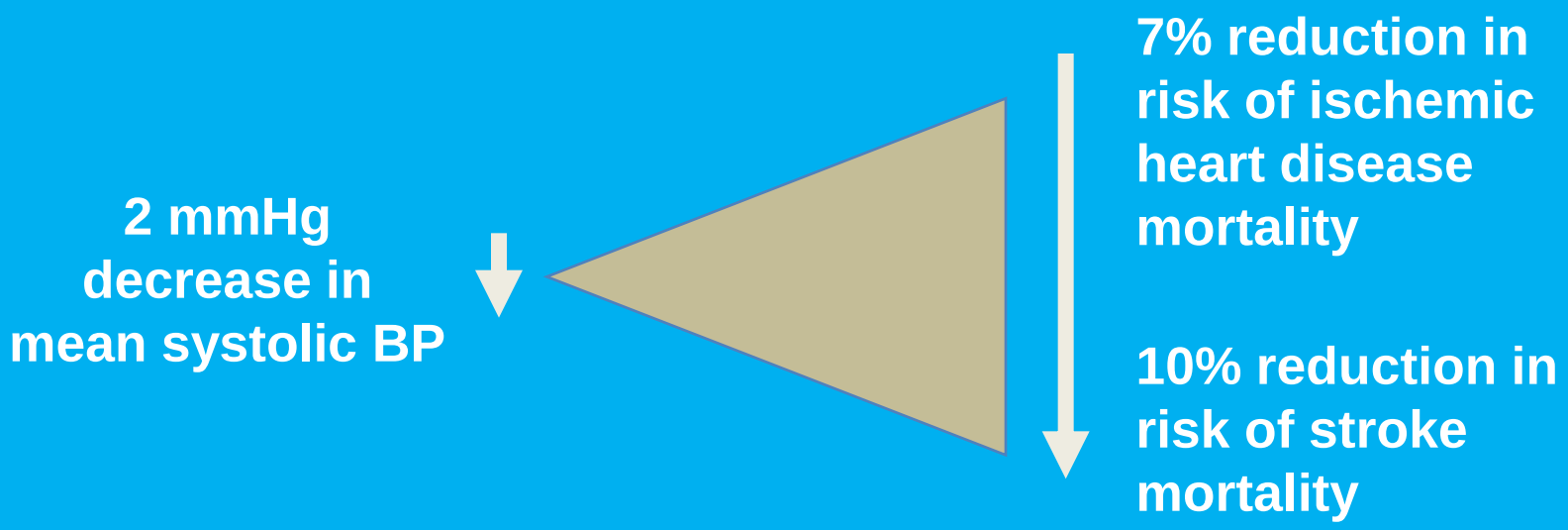
Cardiovascular Mortality Risk Doubles With Each 20/10 mm Hg Increase in BP*



CV = cardiovascular.
SBP = systolic blood pressure.
DBP = diastolic blood pressure.
*In individuals aged 40 to 69 years (10-year study period), starting at BP 115/75 mm Hg.
Lewington S, et al. *Lancet*. 2002;360:1903-1913.

Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%

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

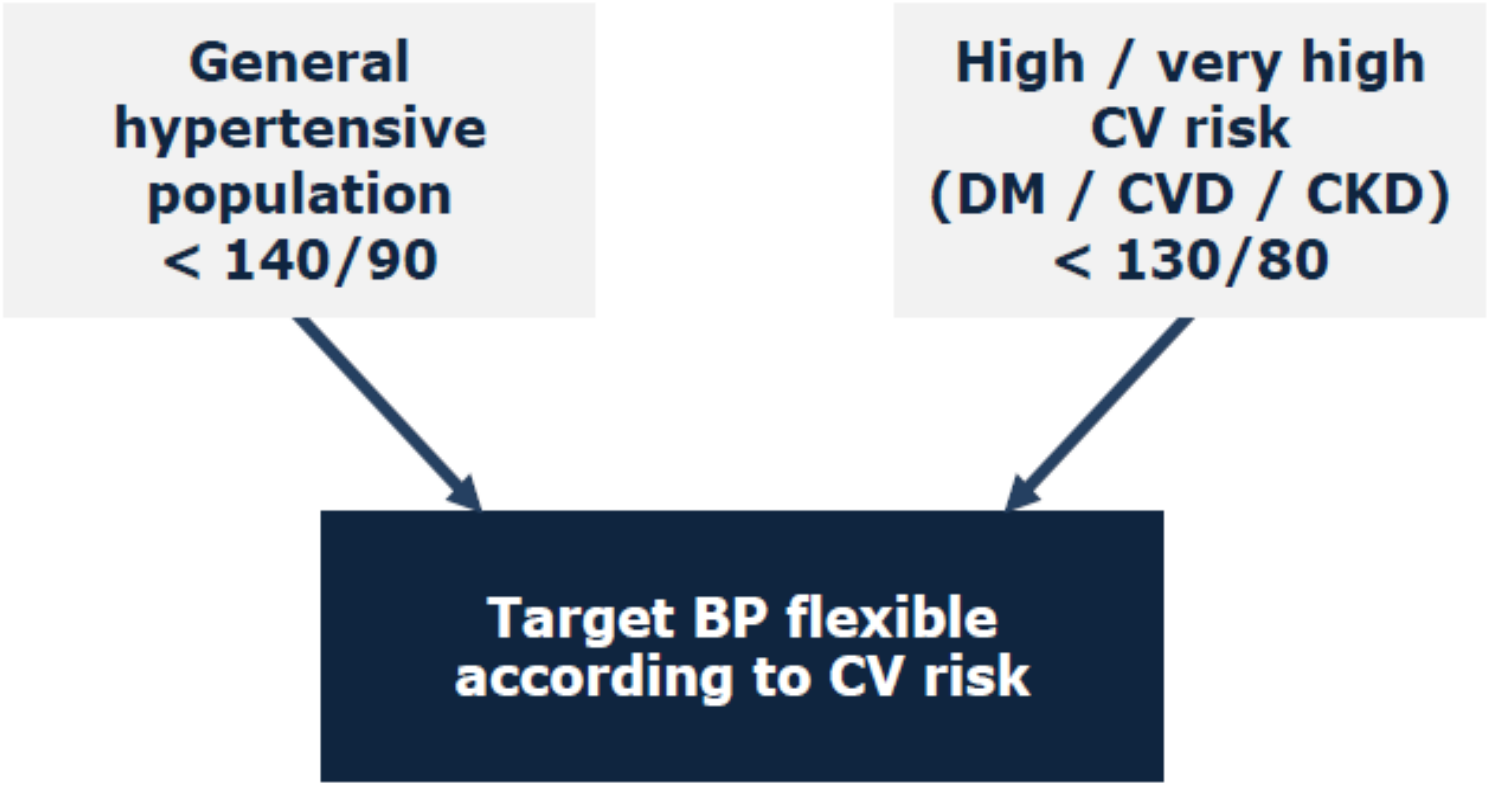


. Lancet 2002;360:1903–13

Lewington et al. Lancet 2002;360:1903–13

New BP goals

2007 ESC/ESH hypertension guidelines



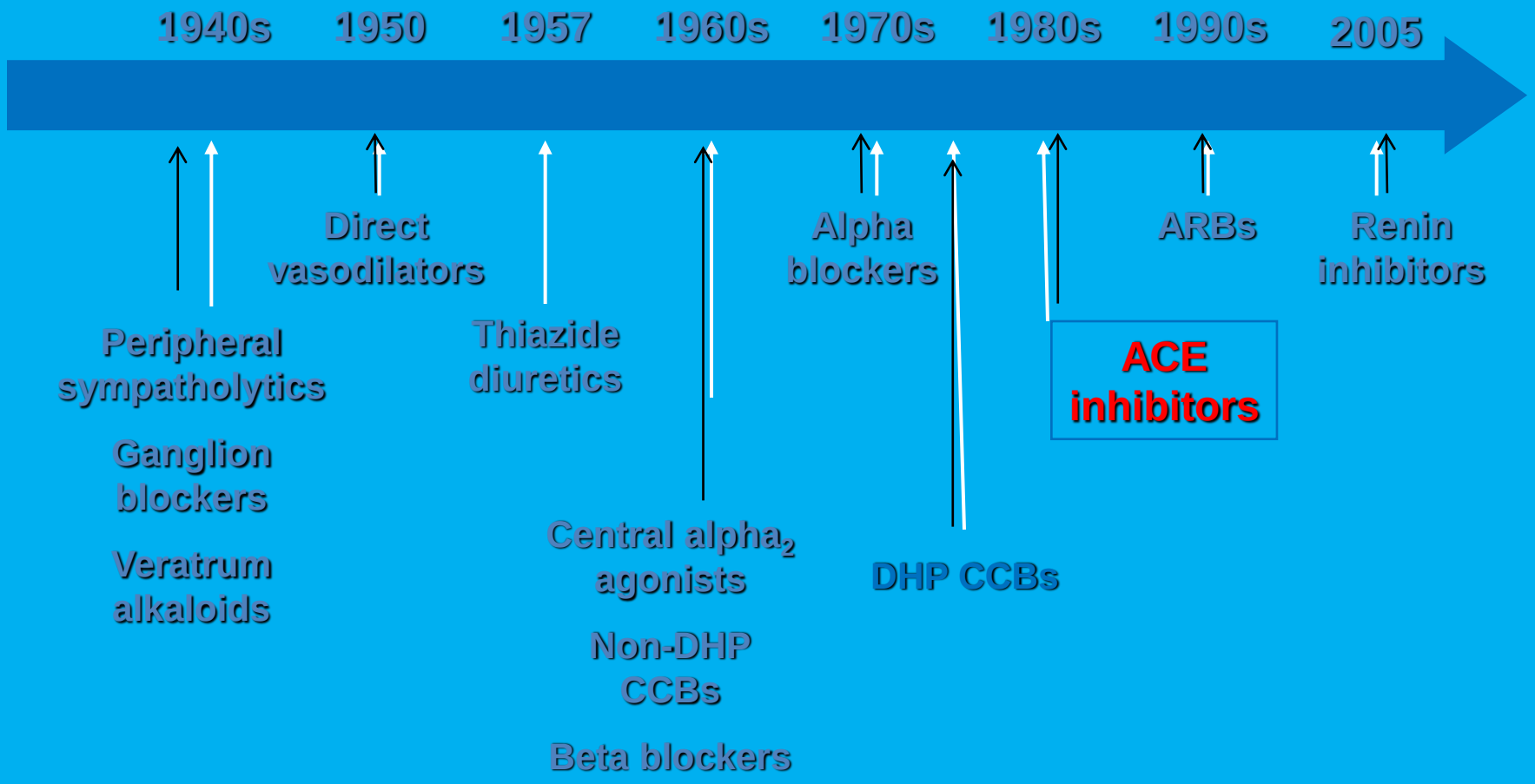
Target BP in recent guidelines

Guideline	Population	Goal BP, mm Hg
2014 Hypertension guideline	General ≥60 y	<150/90
	General <60 y	<140/90
	Diabetes	<140/90
	CKD	<140/90
ESH/ESC 2013[37]	General nonelderly	<140/90
	General elderly <80 y	<150/90
	General ≥80 y	<150/90
	Diabetes	<140/85
	CKD no proteinuria	<140/90
	CKD + proteinuria	<130/90
CHEP 2013[38]	General <80 y	<140/90
	General ≥80 y	<150/90
	Diabetes	<130/80
	CKD	<140/90
ADA 2013[39]	Diabetes	<140/80

A single SBP target for almost all patients

- **JNC VIII (BP target)**
  - In patients with CKD, initiate treatment at SBP ≥140 mmHg or DBP ≥90 mmHg, and treat to achieve SBP <140 mmHg and DBP <90 mmHg.

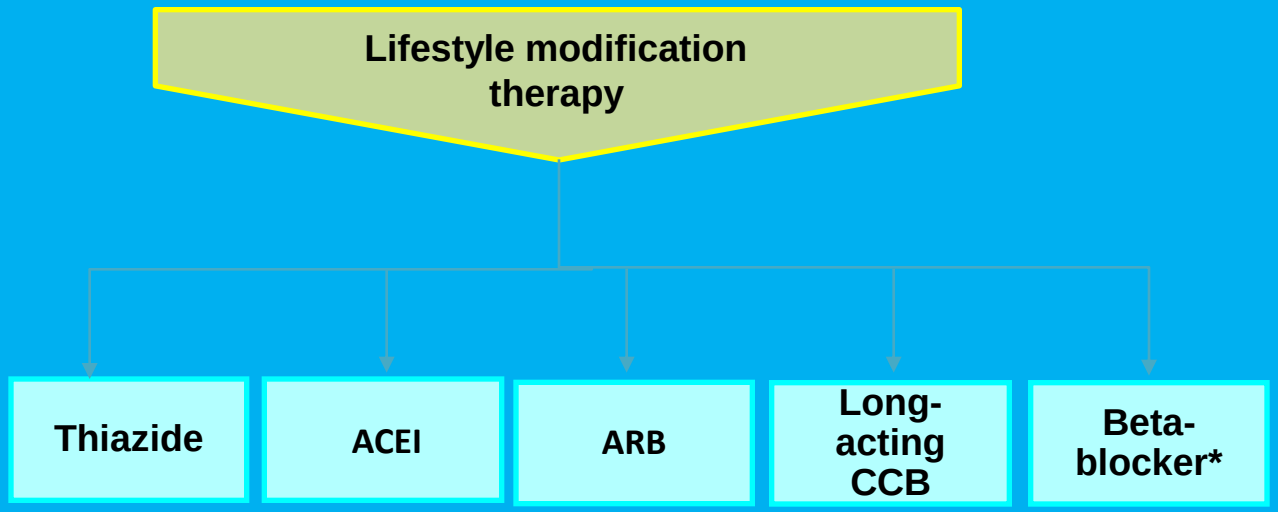
Development of Antihypertensive Therapies


1940s
1950
1957
1960s
1970s
1980s
1990s
2005
Peripheral sympatholytics
Ganglion blockers
Veratrum alkaloids
Direct vasodilators
Thiazide diuretics
Central alpha2 agonists
Non-DHP CCBs
Beta blockers
Alpha blockers
DHP CCBs
ACE inhibitors
ARBs
Renin inhibitors

Treatment of Adults with Systolic/Diastolic Hypertension without Other Compelling Indications

TARGET <140/90 mmHg

INITIAL TREATMENT AND MONOTHERAPY



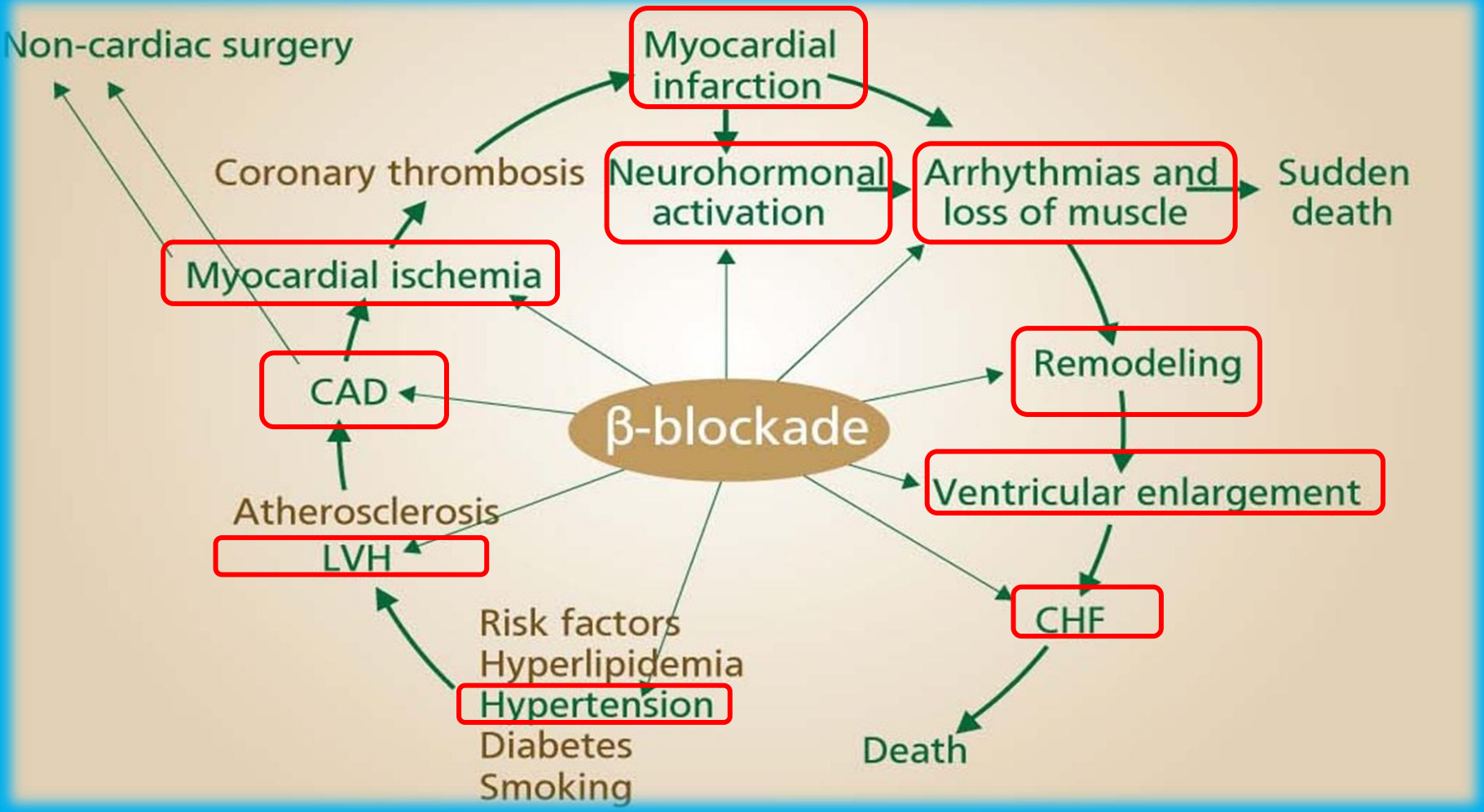
A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target

***BBs are not indicated as first line therapy for age 60 and above**

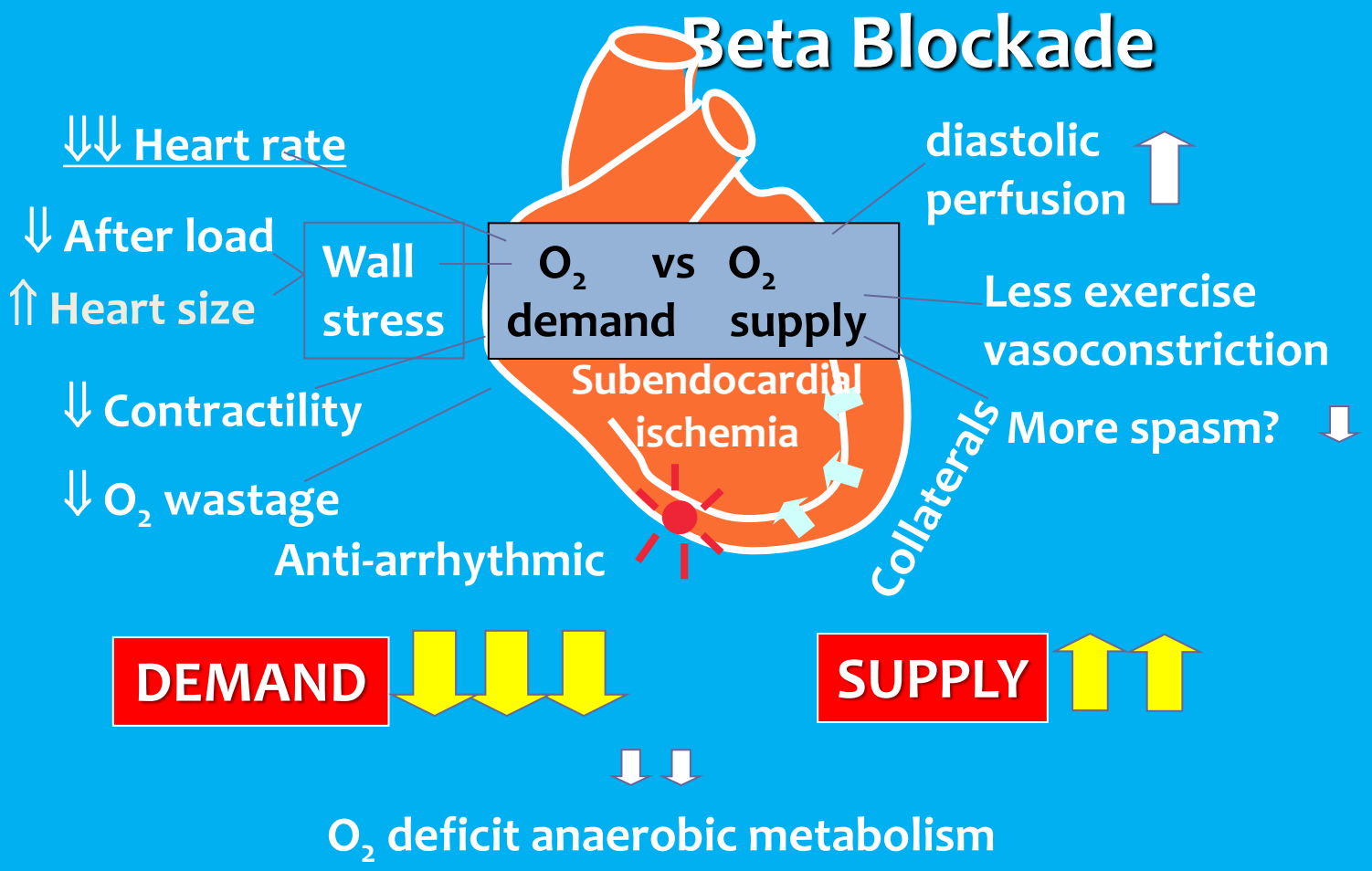
ACEI, ARB and direct renin inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential

Why Beta Blockers?

β-blockers intervene effectively in all stations within the Cardiovascular Continuum from Hypertension to HF.



How BB Works?


Beta Blockade
⇓⇓ Heart rate
⇓ After load
⇑ Heart size
Wall stress
⇓ Contractility
⇓ O_2 wastage
Anti-arrhythmic
O_2 demand vs O_2 supply
Subendocardial ischemia
diastolic perfusion
Less exercise vasoconstriction
More spasm?
Collaterals
DEMAND
SUPPLY
O_2 deficit anaerobic metabolism

Beta Blockers Possess properties other than B.P lowering

1. Anti-ischaemic.
2. Anti-arryhthymic.
3. Anti-RAS.
4. Promoting coronary diastolic filling.
5. Upregulating cardiac B1 receptors. (H.F)
6. Lowers plasma endothelin.
7. Inhibit catecholamine induced Cardiac Neurosis.
8. Other Effects May Include Anti-atherogenic and Anti-Thrombotic effects

BB are CARDIOPROTECTIVE

26 Indications for Beta-Blockers

CARDIAC

1- Angina
2- Unstable Angina
3- Silent Ischaemia
4- Hypertension
5- Heart Failure
6- A.MI.
7- Aortic Dissection
8- HOCM
9- M.V. Prolapse
10- Marfans Synd
11- Prolonged Q.T int.
12- Peri-operative.
13- VPBTS, V.T. (S/NS)
14- AVNRT
15- A. Fib
16- DM. (high Risk)
17- Elective PCI

26 Indications for Beta-Blockers

NON-CARDIAC

1- Migraine Prophylaxis.

2- Glaucoma

3- Portal HTN.

4- Thyrotoxicosis.

5- Insulinoma.

6- Narcolepsy.

7- Situational anxiety.

8- Barther's Synd. (Juxta-Glomerular hyperplasia).

9- Essential Tremor.

Types of Beta Blockers

Table 1[10] : 3 Generations of beta-blockers

	Properties	Drugs
1st Generation	Non-selective No vasodilatation	Propranolol, Timolol, Pindolol, Nadolol, Sotalol
2nd Generation	β1-selective without vasodilation β1selective with vasodilation	Atenolol, Bisoprolol, Metoprolol Nebivolol, Acebutolol
3rd Generation	Non-selective with vasodilation	Carvedilol, Bucindolol

BB Have a Different Pharmacological Profiles matching Different Needs and Indications

	Relative ß1 - Selectivity	VD	ISA	Lipid solubility	Average daily oral dose
Carvedilol	0	+*	0	moderate	3.125–50 mg twice
Labetalol	0	+*	0	low	200–800 mg twice
Celiprolol	+	+	+	moderate	200–600 mg once
Timolol	0	0	0	high	5–40 mg twice
Propranolol	0	0	0	high	40–180 mg twice
Atenolol	++	0	0	low	25–100 mg once
Bisoprolo	++	0	0	moderate	2.5–20 mg once
Metoprolol	++	0	0	high	12.5–200 mg once
Nebivelol	++	+(↑NO)	0	high	1.25-10 mg once

ISH=Intrensic sympathomimetic activity *α-blocker

European Heart Journal (2004) 25, 1341–1362
Progress in Cardiovascular Diseases, 47(1) 2004: 11-33

Guidelines recommendations for choice of anti-hypertensive pharmacological treatment

ESH and ESC Guidelines

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

List of authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy)*, Robert Fagard (Chairperson) (Belgium)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redón (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis Miguel Ruilope (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viigimaa (Estonia), Bernard Waeber (Switzerland), and Faiez Zannad (France)

Recommendations on treatment strategies and choice of drugs (1)

Recommendations	Class	Level
Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combination with each other.	I	A
Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage.	IIa	C

β-blockers ***can all be considered for initiation & maintenance for antihypertensive treatments***

should be avoided.

www.escardio.org/guidelines

Eur Heart J, 2013; 34: 2159-2219
J Hypertens, 2013; 31: 1281-1357
Blood Pressure, 2013: 193-278

European Society of Hypertension

EUROPEAN SOCIETY OF CARDIOLOGY®

Compelling Indications for β-blockers

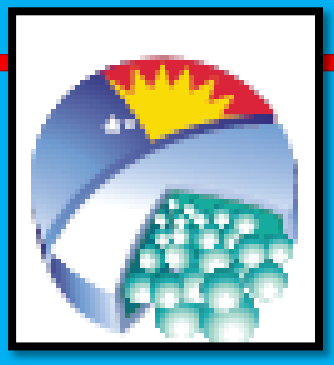
- Angina Pectoris
- Post MI
- Heart Failure
- Tachyarrhythmia
- Hyperkinetic Heart
- Pregnancy
- Glaucoma

Summery of Guidelines recommendations for Hypertension drug therapy initiation

Guideline	Population	Goal BP mm Hg	Initial Drug Treatment Options
EHS 2014	< 65 y	<140/90	diuretics, **BB** , CCB, ACEIs, ARBs
	> 65 y or blacks	<150/95	diuretic or CCB
ESH/ESC 2013	General nonelderly <80 y	<140/90	Diuretic, **BB ,** CCB, ACEI, or ARB
	General elderly ≥80 y	<150/90	
CHEP 2014	General <80 y	<140/90	Diuretic, **BB** (>\60 years) , ACEI (nonblack), or ARB
	General ≥80 y	<150/90	
ADA 2014	Diabetes	130–140 /80	ACEIs, ARBs, **BB,** diuretics, CCB
NICE 2011	General <55 y:	<140/90	ACEI or ARB
	General ≥55 y or black	<150/90	CCB
JNC-8 2014	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	

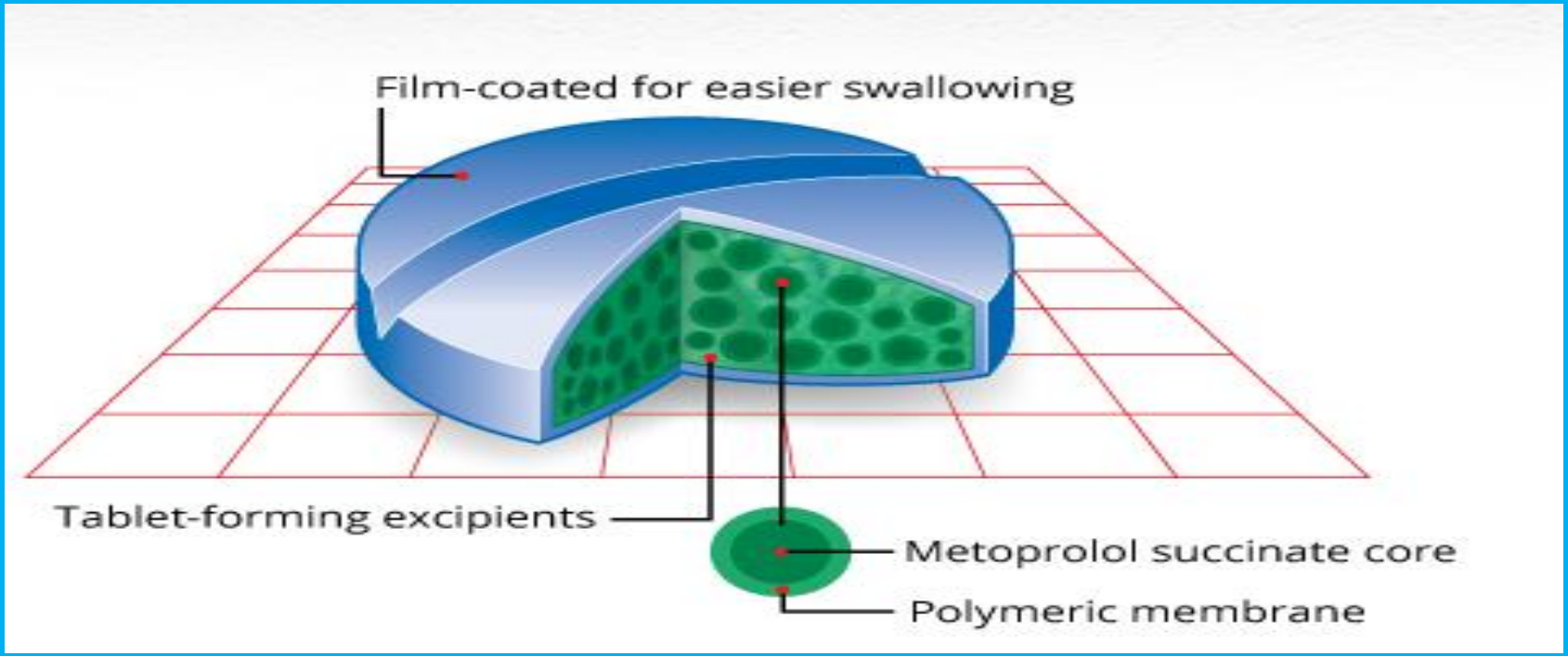
SelokenZOC

β_1 metoprolol succinate



SelokenZOC Metoprolol Succinate, a selective ß1- receptor blocking agent

In Advanced Extended Release formulation



The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval with Once Daily Regimen.

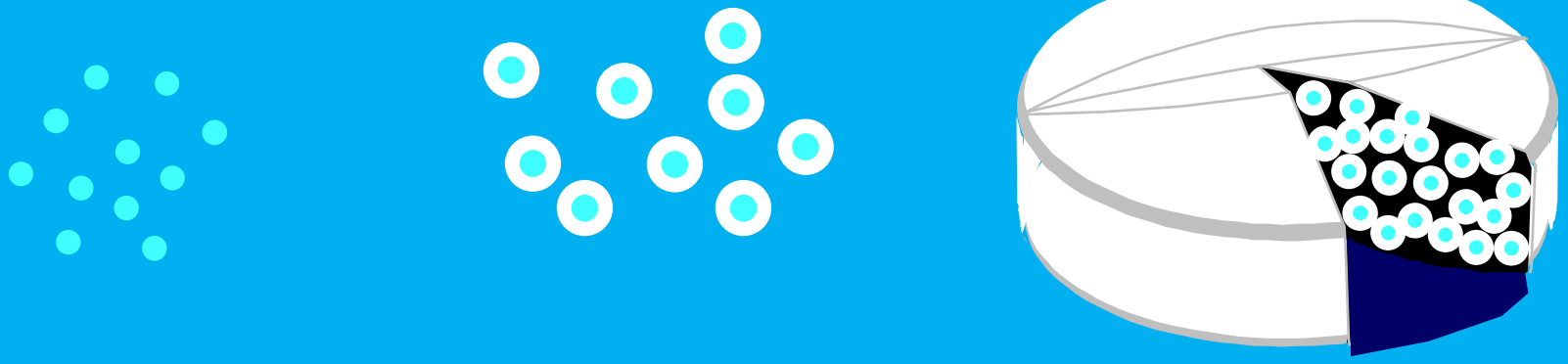
ZOC: Zero Order Kinetics

What is Metoprolol?

- Metoprolol is a cardio selective ß1- selective, adrenoceptor blocking drug.

An Advanced Constant Release Formulation

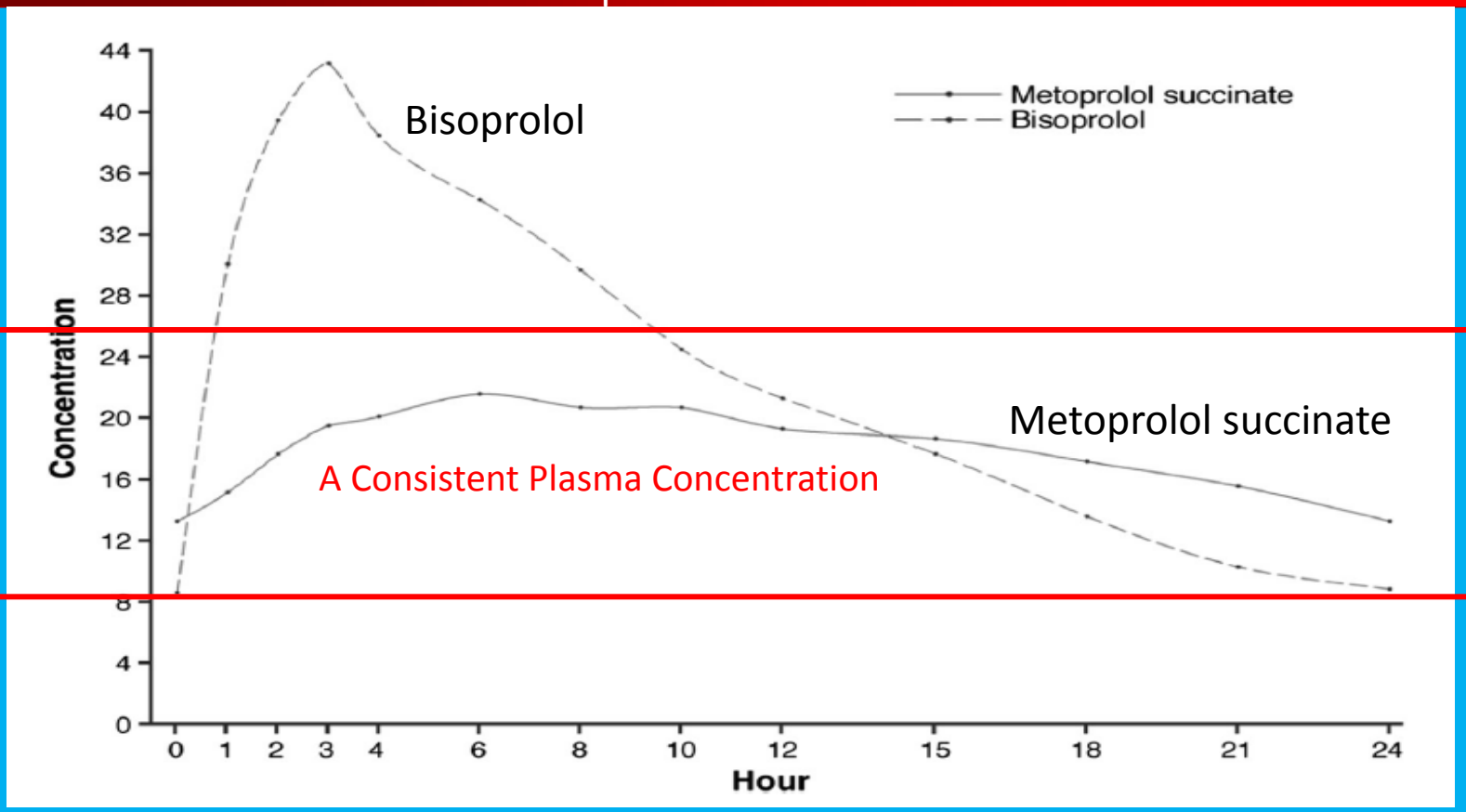
Pellets → Microcapsules → Tablet



Sandberg A et al, J Clin Pharmacol 1990;30:S2-16

SelokenZOC® vs Bisoprolol Plasma Profiles

Plasma concentrations at steady state over the 24-h dose interval: bisoprolol and metoprolol succinate



SelokenZOC have a less varying blood pressure-lowering effect over the 24-h day.

Metoprolol/ SelokenZOC®
Landmark Outcome Studies

Primary Prevention

Hypertension
- MAPHY

Atherosclerosis Development
- BCAPS
- ELVA

Secondary Prevention

AMI/PMI
- Amsterdam
- Belfast
- Gothenburg
- LIT (PMI)
- Stockholm (PMI)
- MIAMI (AMI)

Heart Failure
- MDC
- MERIT-HF

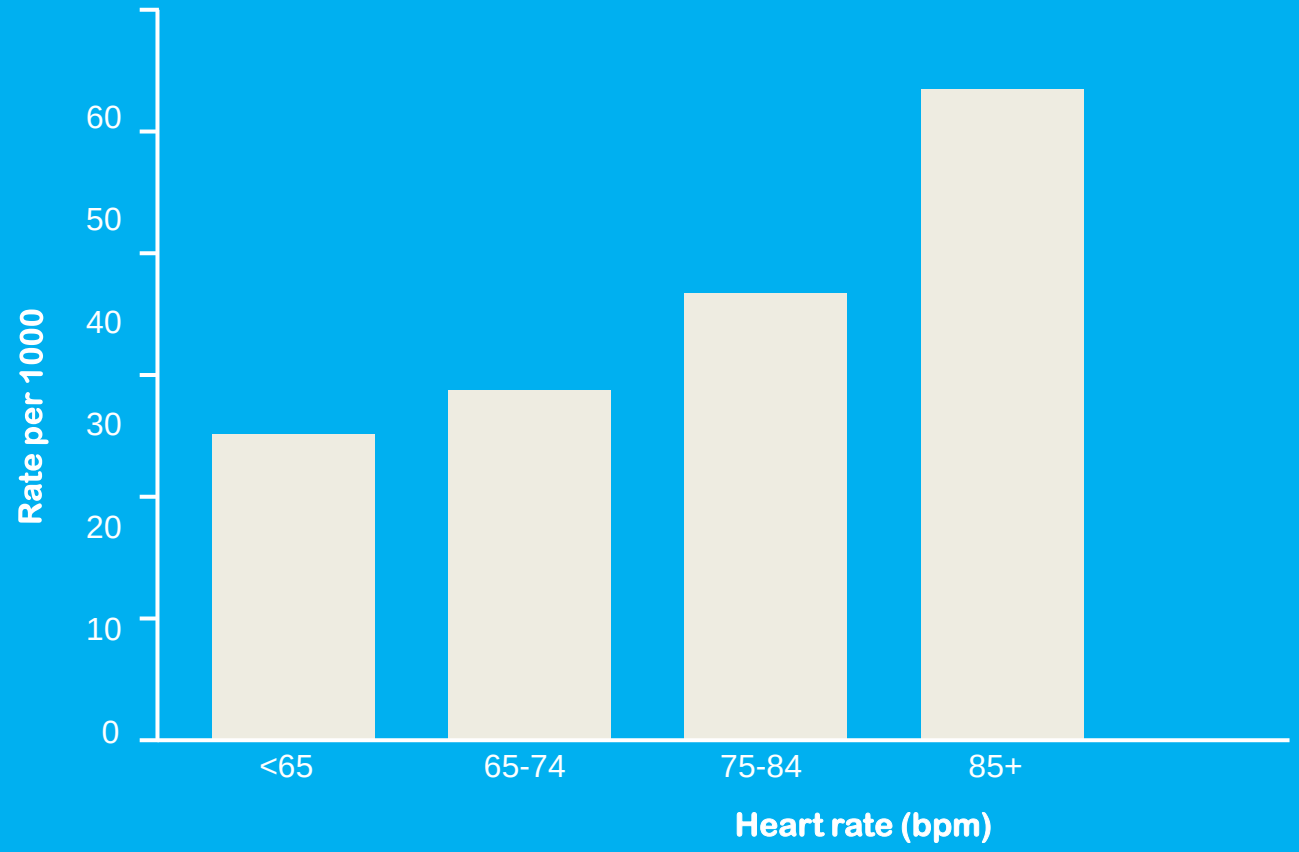
SelokenZOC®

&

“Heart Rate Control”

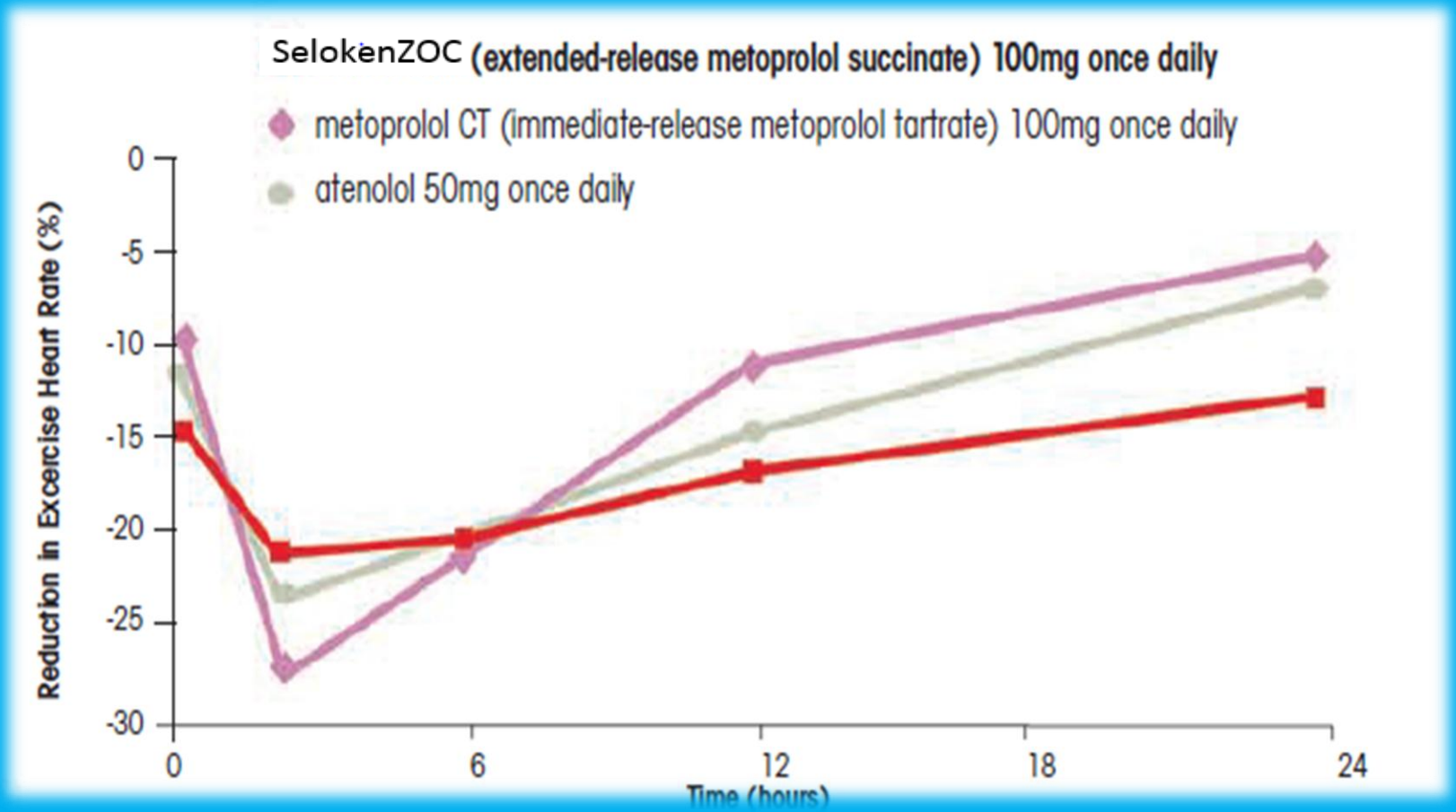
Heart Rate as a Predictor of All-Cause Mortality in Hypertension

Framingham study: 2,037 men; 36-year follow-up



Gillman MW, et al. Am Heart J. 1993;125:1148-1154.

SelokenZOC® provides consistent 24hr reduction in exercise Heart Rate vs Atenolol



Dermansjah I et al, J Cllin Pharmacol 1990;30:S39-S45E

SelokenZOC

&

“Hypertension”

Beta-blockers a Characteristic Level of Evidence in Hypertension

Table 2. Trials with β-blockers in hypertension

Drug	Year	Study
Propranolol	1985	MRC, trial of mild hypertension[17]
Oxprenolol	1985	IPPSH[18]
Pindolol	1991	STOP-Hypertension[19]
Pindolol	1999	STOP-2[20]
Metoprolol	1987	HAPPHY[21]
Metoprolol	1988	MAPHY[22]
Metoprolol	1991	STOP-Hypertension[19]
Metoprolol	1999	STOP-2[20]
Metoprolol	1999	CAPPP[23]
Metoprolol	2002	AASK[24]
Atenolol	1986	HEP[25]
Atenolol	1987	HAPPHY[21]
Atenolol	1991	STOP-Hypertension[19]
Atenolol	1999	STOP-2[20]
Atenolol	1992	MRC, treatment of hypertension in older adults[26]
Atenolol	1999	CAPPP[23]
Atenolol	1998	UKPDS[27]
Atenolol	2002	AASK[24]
Atenolol	2002	ELSA[28]
Atenolol	2002	LIFE[29]
Atenolol	2003	INVEST[30]
Atenolol	2003	CONVINCE[31]
Atenolol	2005	ASCOT-BPLA[32]

In Hypertension

MAPHY trial

(Metoprolol Atherosclerosis Prevention in Hypertensives)

Hypertension
Journal of the American Heart Association

American Heart Association®

Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY Study.

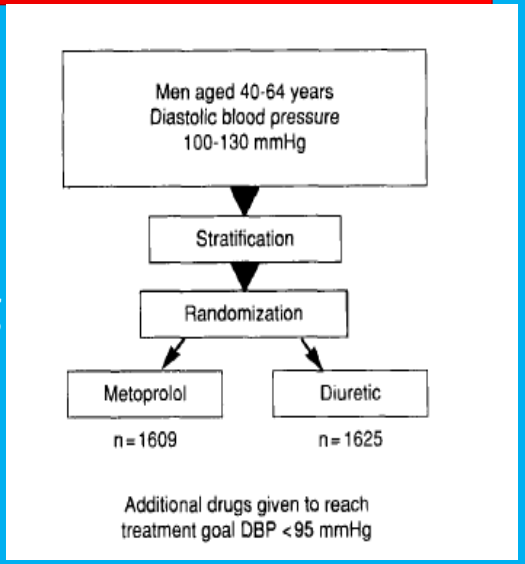
J Wikstrand, I Warnold, J Tuomilehto, G Olsson, H J Barber, K Eliasson, D Elmfeldt, B Jastrup, N B Karatzas and J Leer

Hypertension. 1991;17:579-588
doi: 10.1161/01.HYP.17.4.579
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

MAPHY Study

- **Objective:** to compare the effects of metoprolol, given as initial antihypertensive treatment, and thiazide diuretics in reducing cardiovascular complications of high BP



- **Study design:** randomised, open, parallel-group Study. Enrolling 3234 men Patients (1609 metoprolol, 1625 placebo), aged 40-64 years. DBP at entry: 100-130 mm Hg
  Follow-up: 842 days to 10.8 years (mean 5 years)

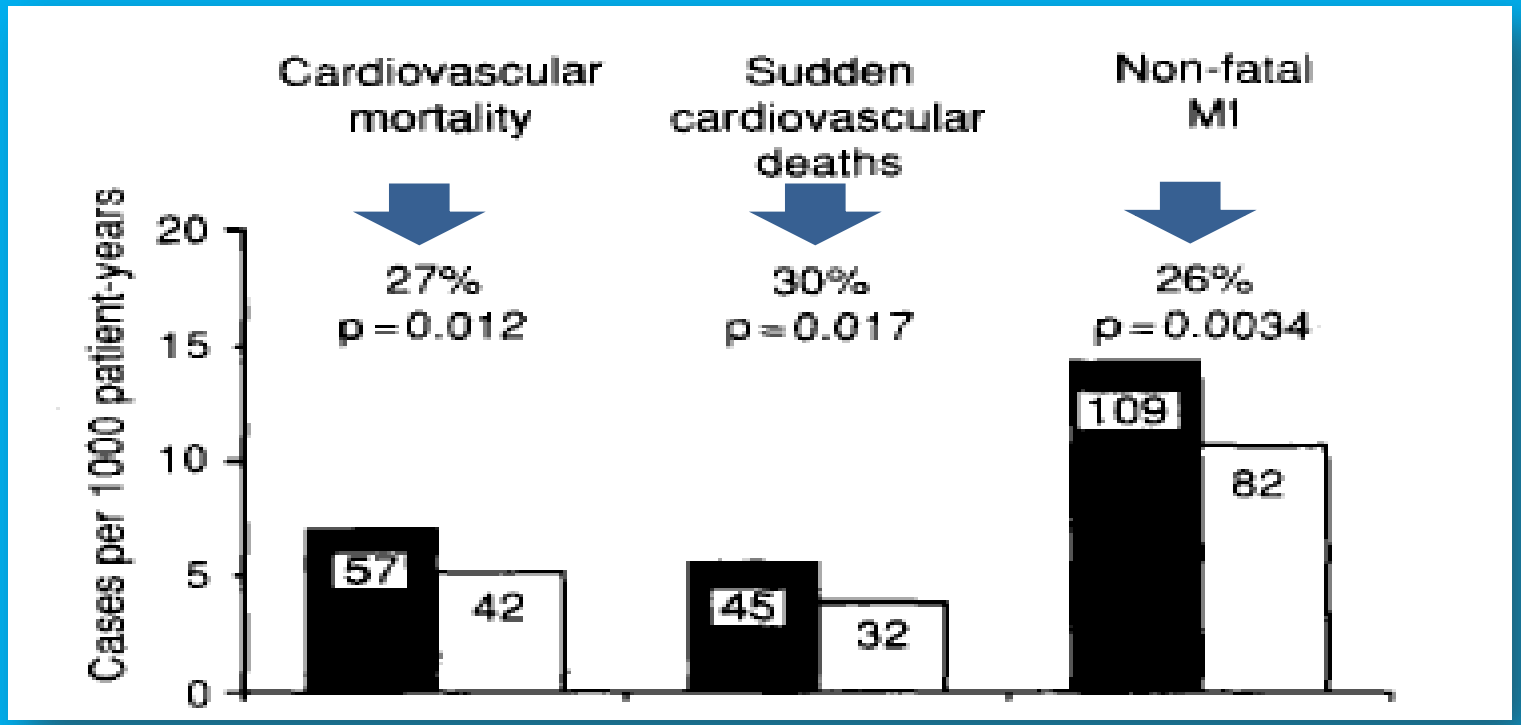
- **Treatment regimen:** metoprolol, 200 mg/day maximum (mean 174 mg/day), hydrochlorothiazide, 50 mg/day maximum (mean 46 mg/day), or bendroflumethiazide, 5 mg/day maximum (mean 4.4 mg/day)

Wikstrand et al, Hypertension 1991;17;579-88

- **Concomitant therapy:** additional drugs (eg hydralazine, spironolactone) given, if necessary, to reduce DBP to < 95 mm Hg

Study Outcomes Primary Prevention

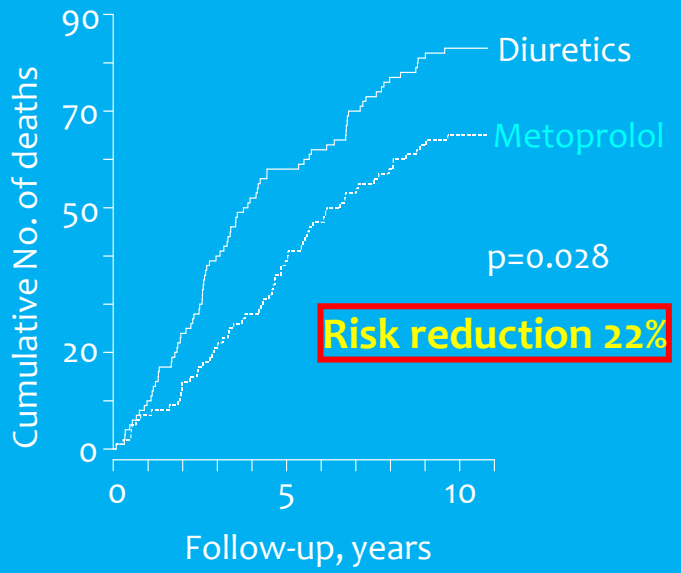
Metoprolol Reduced both CV Mortality, Sudden CV death & Non Fatal MI



Clin. Cardiol. Vol. 14 (Suppl. III), July 1991

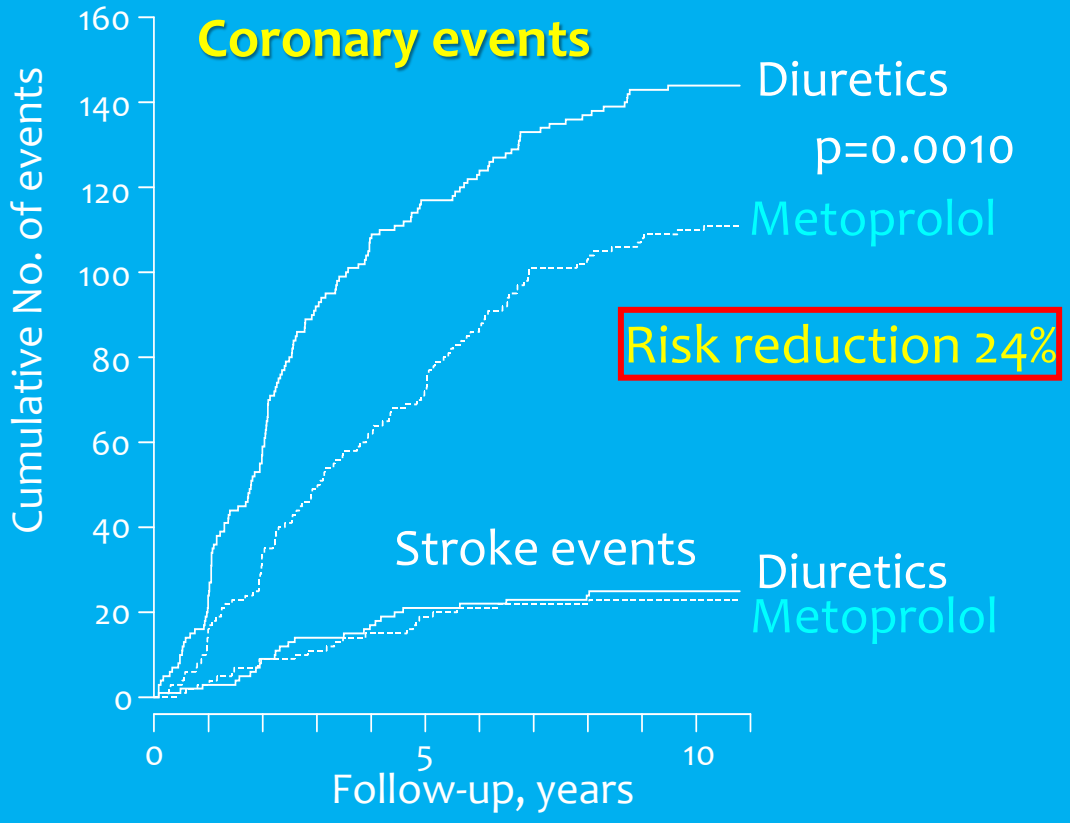
Study Outcomes: Primary Prevention – Metoprolol

Total Mortality



Wikstrand J et al
JAMA 1988

Coronary events



Wikstrand et al, Hypertension 1991;17;579-88

Post Myocardial Infarction

The Göteborg Metoprolol Trial

Effects on Mortality and Morbidity in Acute Myocardial Infarction

Å. Hjalmarson, M.D., Ph.D., J. Herlitz, M.D., Ph.D., S. Holmberg, M.D., Ph.D.,
L. Rydén, M.D., Ph.D., K. Swedberg, M.D., Ph.D., A. Vedin, M.D., Ph.D.,
F. Waagstein, M.D., Ph.D., A. Waldenström, M.D., Ph.D., J. Waldenström, M.D., Ph.D.,
H. Wedel, Ph.D., L. Wilhelmsen, M.D., Ph.D., and C. Wilhelmsson, M.D., Ph.D.

treatment, 697 to placebo and 698 to metoprolol

CIRCULATION VOL 67, SUPPL I, JUNE 1983

Study Design

1395 patients, 40-74 years old with suspected acute myocardial infarction were, on admission, randomly allocated to double-blind treatment, 697 to placebo and 698 to metoprolol (15 mg i.v., 5 mg Every 2 Min., followed by 15 mg orally 15 minutes later and every 6 hours during the first 48 hours, followed by 200 mg) for 90 days.

Primary Objective

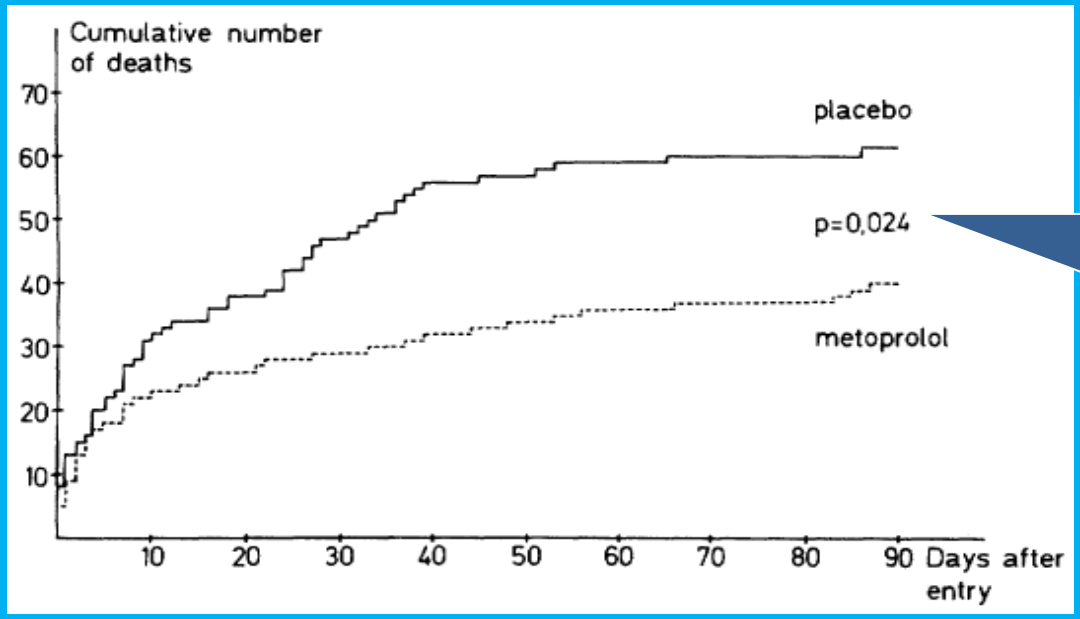
Metoprolol Effect on 3-month mortality.

Secondary Objective

To investigate the effects on infarct size, arrhythmias and tolerance.

Study Outcomes: Primary End Points

Metoprolol significantly reduced 3-month mortality by 36%



RRR 36%

Cumulative number of deaths

Mortality Benefits Sustained Significantly After 3 months and Up to 1 Year

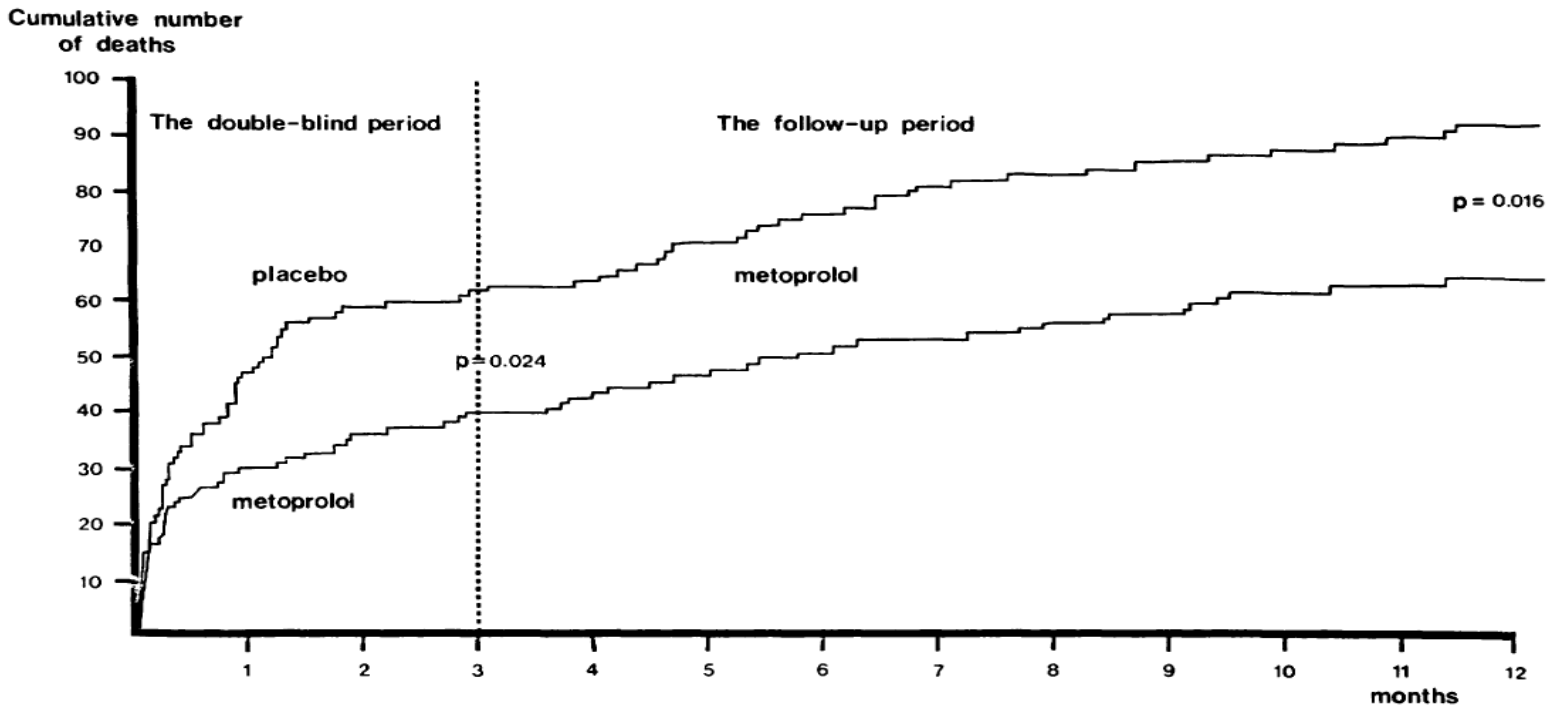


FIGURE 3. *Cumulative number of deaths in all patients randomly allocated to treatment with metoprolol and placebo during the first 3 months. After 3 months, all patients were given open treatment with metoprolol. The* p *values were calculated according to Mantel-Haenszel.*

Take Home Message...

- **Beta Blocker is Considered A corner stone Treatment Modality across Cardivascular disease conntinnum**

- **SelokenZOC** "Metoprolol Succinate", is an Advanced Constant Release Formulation that will be Introduced to the Egyptian Market Soon

- **SelokenZOC** Formulation allows a 24 Hours Steady Release and Consequently a Steady state of Plasma Concentration with Once Daily Dose[1]

1. Wikstrand. Basic Res Cardiol 2000;95(Suppl1):1/46-1/51

Take Home Message...

- Metoprolol Succinate is the only BB that has shown significant reduction of both CV death and coronary Events in Hypertensive patients [1]

- Metoprolol Succinate improved survival and lowered the risk of death from worsening heart failure [2]

- Metoprolol Succinate significantly reduced Total mortality and Sudden Death in post-MI patients[3].

1. *Wikstrand et al, Hypertension 1991;17;579-88*
2. *Lancet 1999;353:2001-7*
3. ***Janosi A et al, for the MERIT-HF Study Group. Am Heart J, Accepted for publication***


Thank You