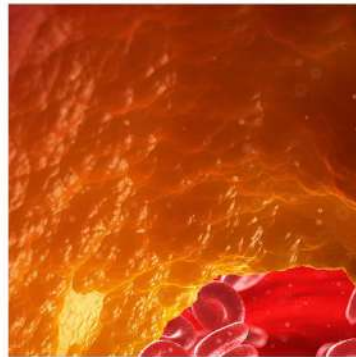
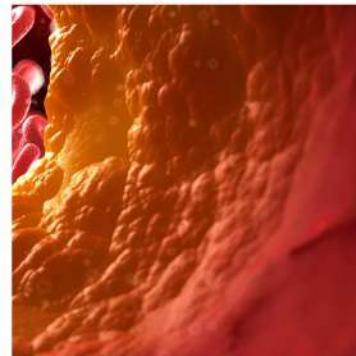
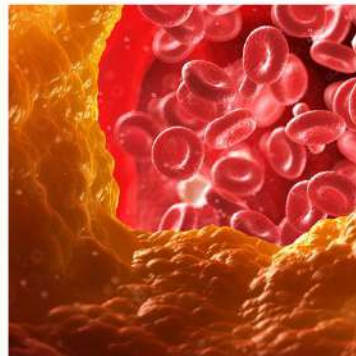


The 2019 EMEA Cardiometabolic Workshop



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From Hypertension to Heart Failure: prevention strategies

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Disclosures

Declared receipts of grants and contracts from Merck Darmstadt, receipt of honoraria or consultation fees from Novartis, to be member of Merck and Novartis Advisory Boards and to participate in Merck and Novartis sponsored speakers' bureaus

Learning objectives

- HTN & HF Risk
- Importance of sympathetic activation
- Prevention strategies in HTN
- Which drugs to use?

Hypertension (HTN) is the Major Risk Factor for Heart Failure (HF)

HTN increases the risk for HF:

HF with reduced ejection fraction (HFrEF) and

HF with preserved ejection fraction (HFpEF)

Chronically increased left ventricular (LV) workload in HTN triggers cardiac remodeling, which results in:

LVH, impaired LV relaxation, left atrial enlargement, increased risk of arrhythmias, especially AF.

Moreover, production of reactive oxygen species by coronary microvascular endothelial cells, reduced nitric oxide bioavailability, and decreased protein kinase G activity is known. **This proinflammatory state results in myocyte hypertrophy, titin hypophosphorylation, increased collagen deposition, and decreased left ventricular compliance.**

Some Epidemiological Facts on Hypertension

1. In the US 33% (in DE 50%) of the adults have BP >140/90
2. The prevalence of HTN rises in direct proportion with the age
3. ≥ 60 years = 65%, ≥ 75 years = 76% have HTN (in Europe)
4. Until 45 years, more men have HTN, >65 more women have HTN
5. 75% of individuals with **type 2 DM** have HTN
6. Hypertensive individuals have a 3 times higher risk for DM
7. Approximately 60% of HTN is ascribable to adiposity
8. 85% of patients with **CKD** are hypertensive
9. HTN is a leading cause of CKD
10. **HTN accounts for 50% of ischemic events (CAD)**
11. **HTN is the strongest major risk factor in HF**
12. **Some 75% of patients with HF have pre-existing HTN**

**13. HTN occurs with multiple comorbidities
that amplify the cardiovascular risk**

Bromfield et al., J Clin Hypertens 2014;16:270

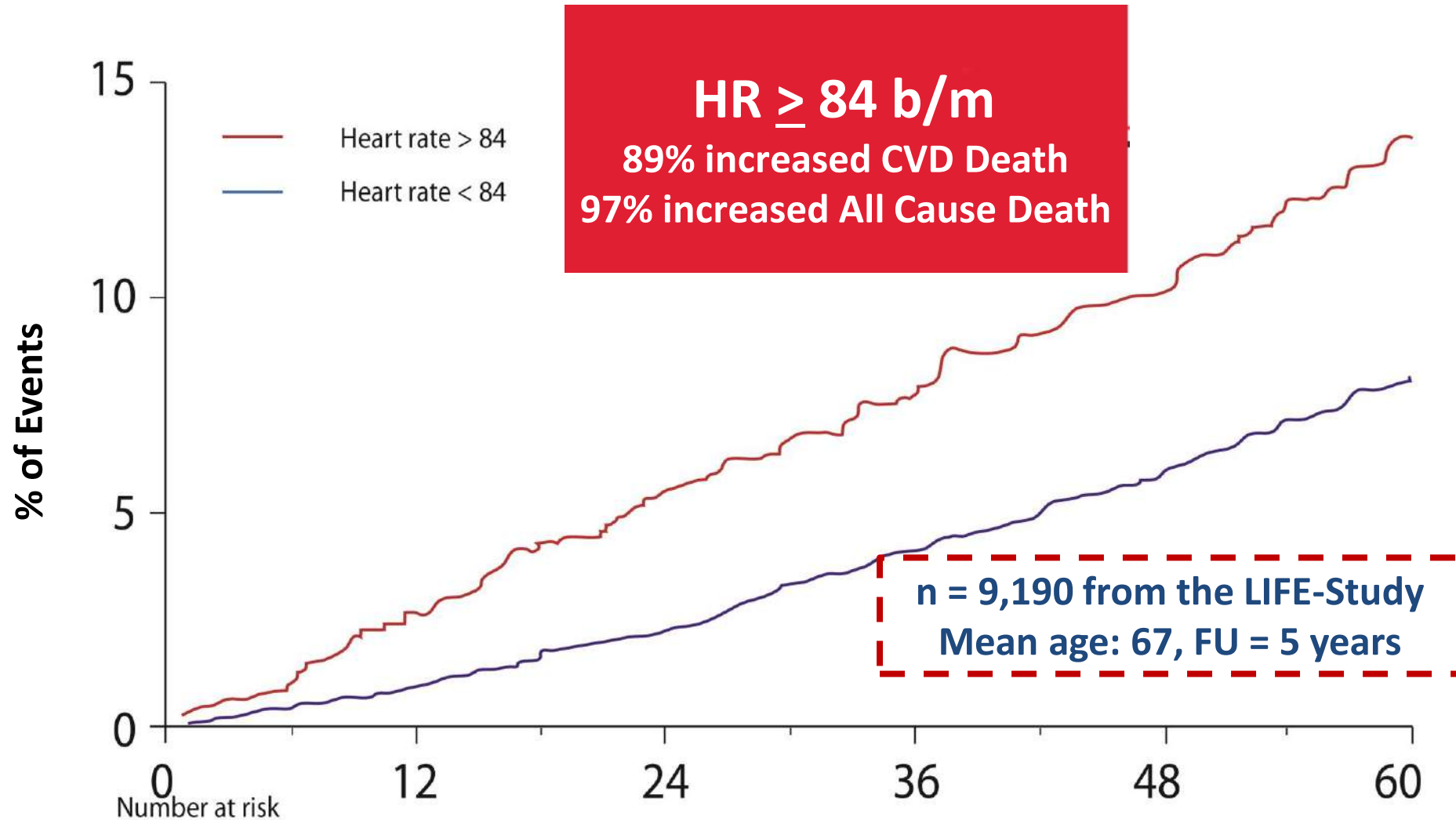
Shrestha et al., Curr Opin Cardiol 2016;31:376

ESC-Classification of office blood pressure and definitions of hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension ^b	≥ 140	and	<90

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP $\geq$ 180 or DBP $\geq$ 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	$\geq$ 3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade $\geq$ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

CV Risk & Heart Rate in Hypertension with LVH



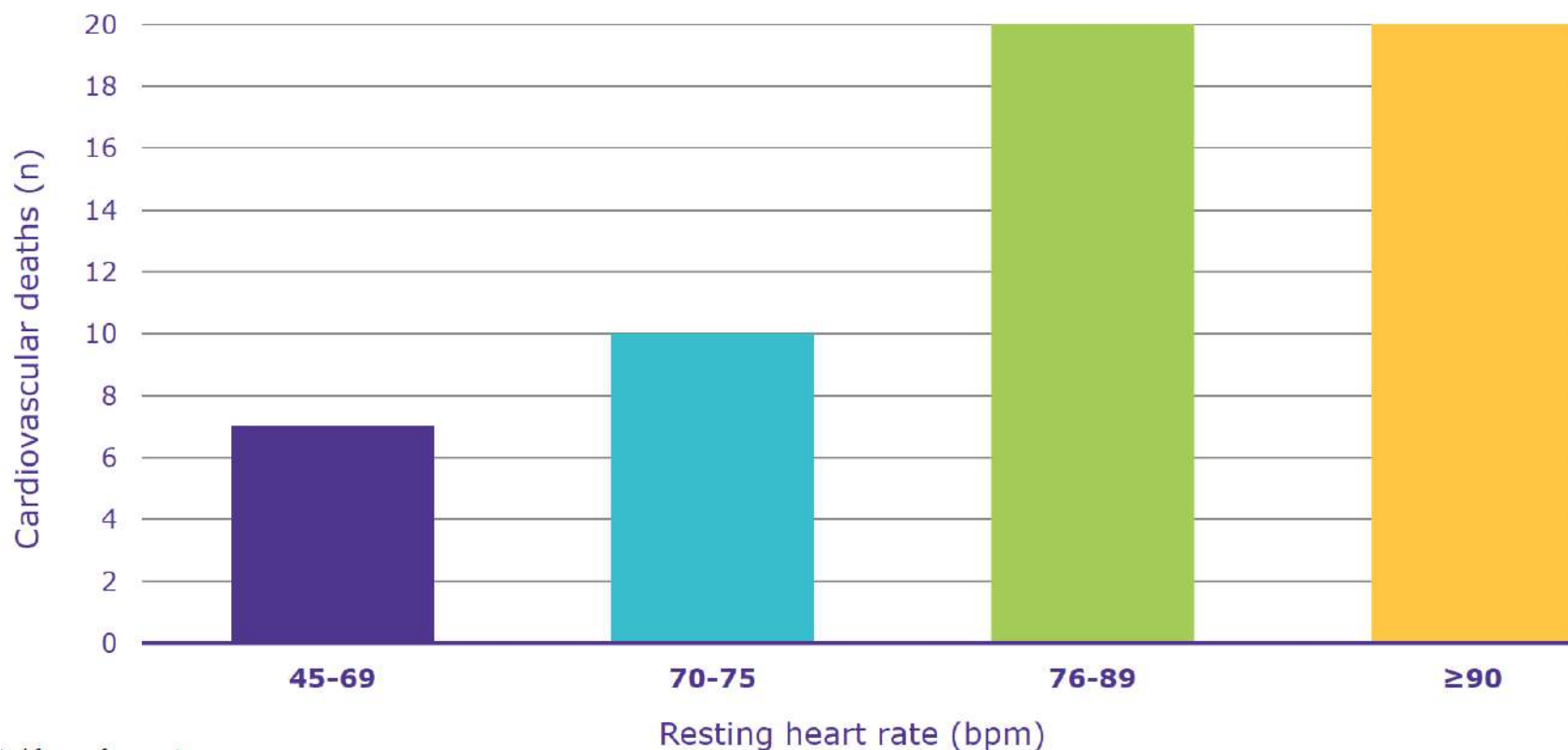
CV Risk & Heart Rate in Hypertension with LVH

Every **10 bpm** higher HR on in-treatment ECGs was associated with a **25% increased risk of CV death** and a 27% greater risk of all-cause mortality

persistence or development of a HR ≥ 84 bpm was associated with an 89% greater risk of CV death and a **97% increased risk of all cause mortality**

A link between sympathetic overdrive and risk of CV death has been shown in patients with DM type 2

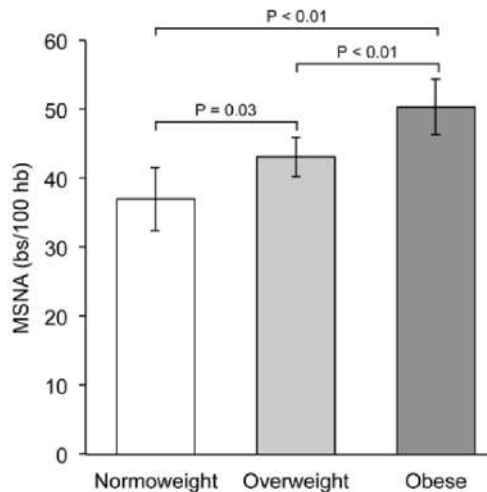
5-year observational study to characterize patients at high risk for death and cardiovascular complications



The Neurohormonal Activation is Characteristic of HTN, HF, and of CAD

(renin–angiotensin– aldosterone axis, sympathetic nervous system)

Sympathetic activation is responsible for ischemia,
Sympathetic activation is involved in the initiation,
the symptoms, progression and outcome of HF
Sympathetic activation can be considered as a
surrogate marker for the management of HF

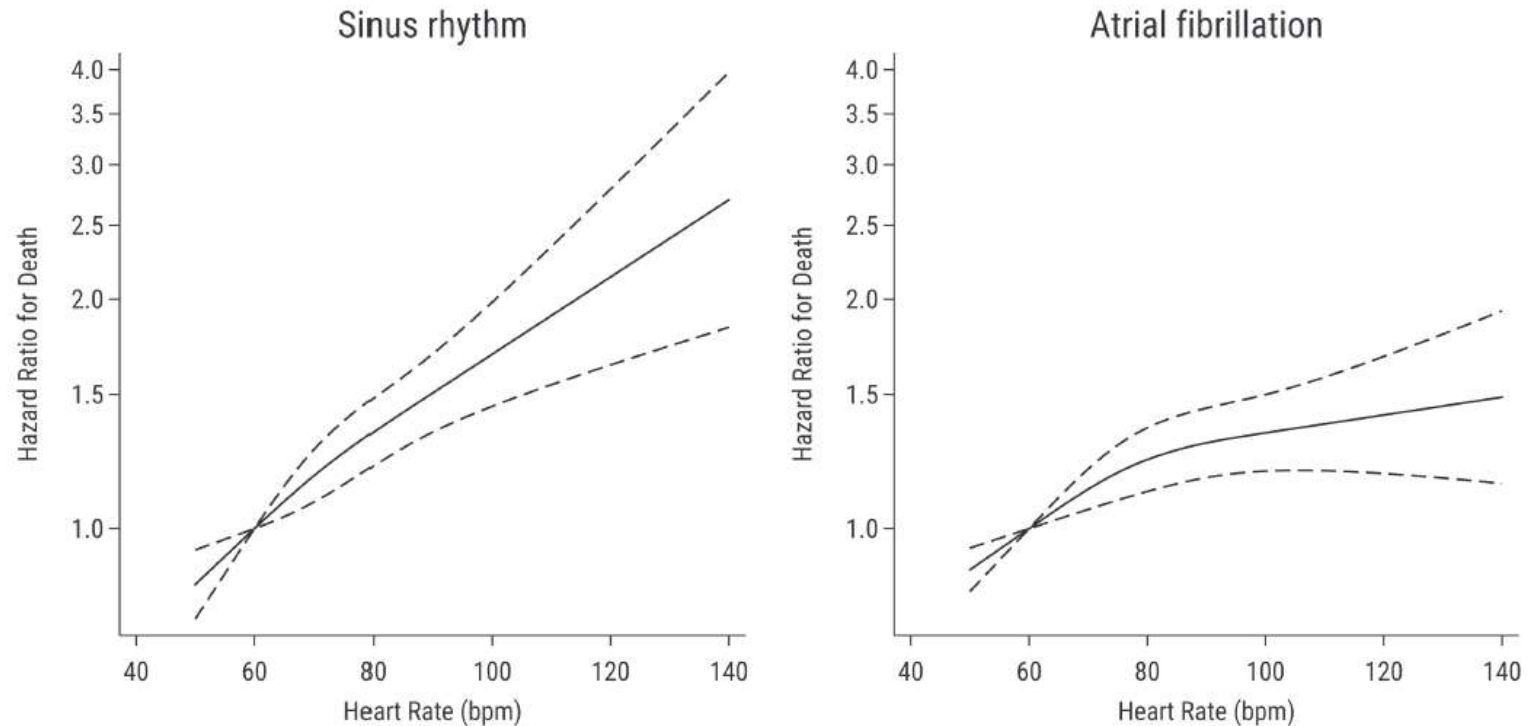


Sympathetic Neural Overdrive in the Obese and Overweight State

Heart Rate and Risk for Death in HFpEF

9090 patients with HFpEF, 47% had SR and 53% had AF

lower HR = lower sympathetic tone = lower risk of arrhythmic death



Pathophysiology of Heart Failure

Myocardial Injury

(Ischemia, MI, Cell Death, HTN, Hypertrophy, Fibrosing)



Counter-Regulations

Sympathetic activation

Na⁺/Waterretention, Edema, Congestion of Liver & Lungs



Secondary Organ Dysfunction

Renal Failure, Pneumonia, Multi-Organ Failure



Final Stage (NYHA III or IV)

There are two well-established strategies to lower BP:

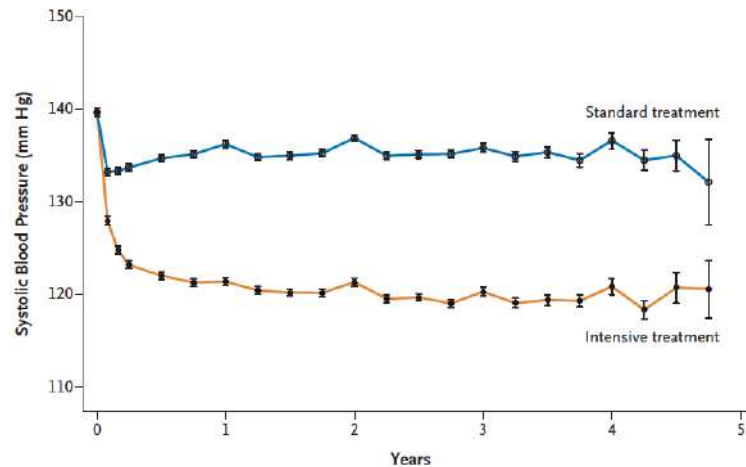
lifestyle interventions

drug treatment

Meta-analyses of RCTs including several hundred thousand patients have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP is associated with significant reductions in all major CV events by 20%, all-cause mortality by 10 - 15%, stroke by 35%, coronary events by 20%, and heart failure by 40%.

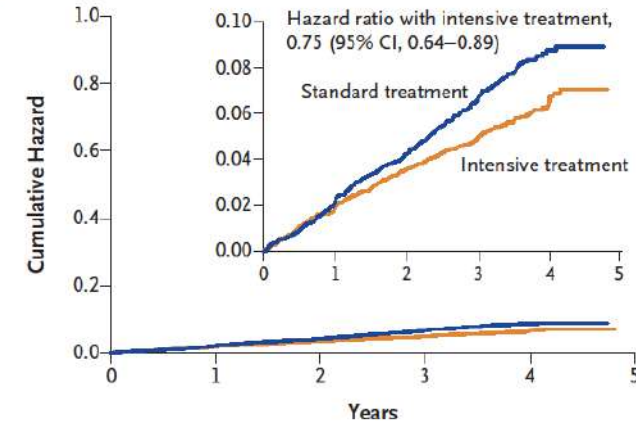
These relative risk reductions are consistent, irrespective of baseline BP within the hypertensive range, the level of CV risk, comorbidities (e.g. diabetes and CKD), age, sex, and ethnicity.

A Randomized Trial of Intensive versus Standard Blood-Pressure Control



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286

A Primary Outcome



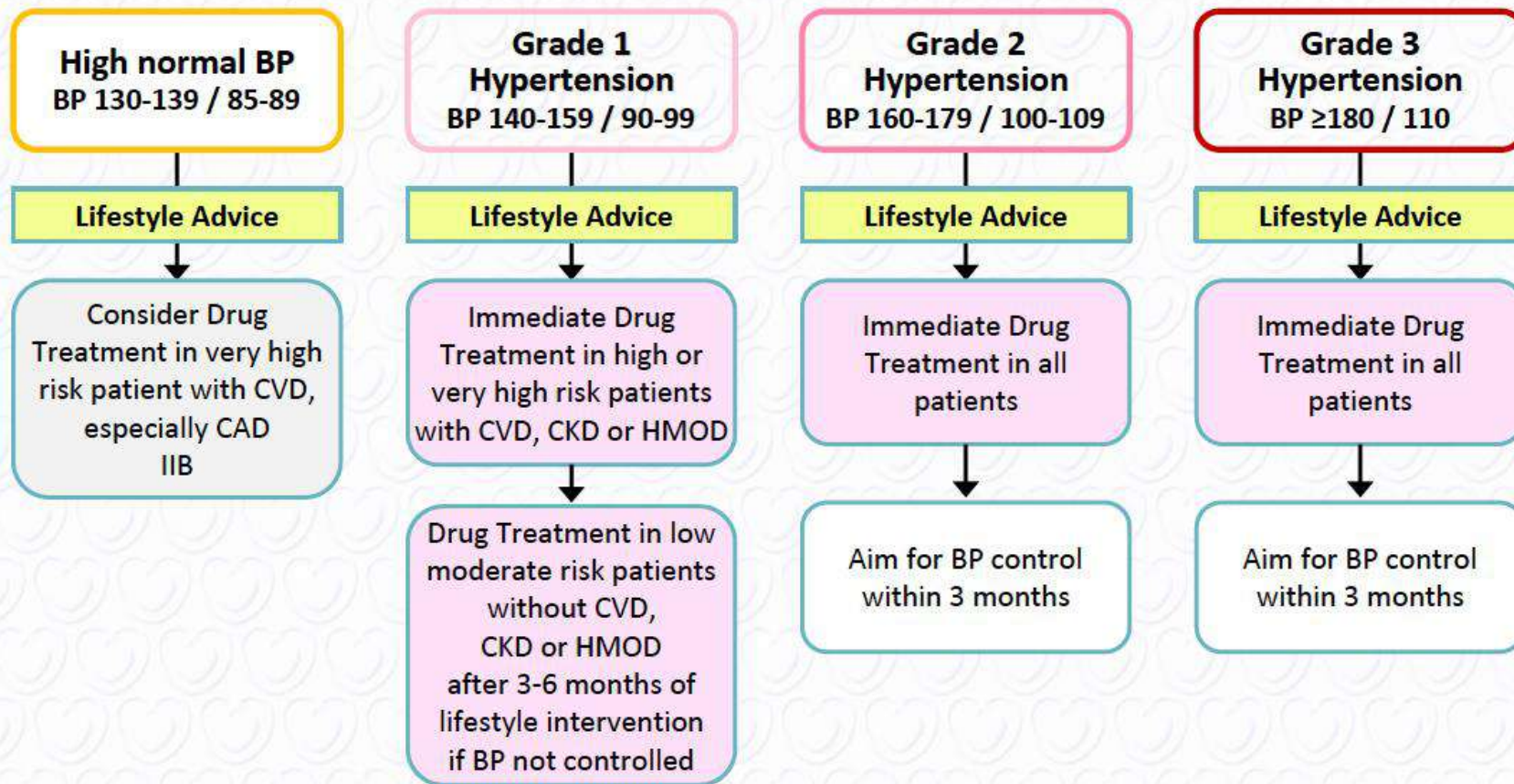
No. at Risk					
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

The SPRINT Research Group N Engl J Med 2015;373:2103-16.

Hypertension Leads to Heart Failure

1. HF is the final common pathway of almost all cardiovascular diseases, including DM
2. prevention of HF largely involves the prevention and treatment of HTN and modifiable risk factors of CAD.
3. Benefits of antihypertensive treatment have been clearly shown.
4. In the **SPRINT trial** targeting SBP to less than 120 in patients with hypertension who were at a high risk of cardiovascular events had lower rates of important outcomes: HF (-38%), death from cardiovascular causes (-43%), and death from any cause (-27%).

Office Blood Pressure Thresholds for Treatment



Office Blood Pressure Treatment Target Ranges

Recommendations	Class	Level
It is recommended that the first objective of treatment should be to lower BP to < 140/90 mmHg in all patients, and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower, in most patients.	I	A
In patients < 65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120 to < 130 mmHg in most patients. ^a	I	A
In older patients (aged ≥ 65 years) receiving BP-lowering drugs:		
• It is recommended that SBP should be targeted to a BP range of 130 to < 140 mmHg.	I	A
• Close monitoring of adverse effects is recommended.	I	C
• These BP targets are recommended for patients at any level of CV risk and in patients with and without established CVD.	I	A

^aLess evidence is available for this target in low–moderate-risk patients.

In the 2018 ESC Guidelines,

Five major drug classes are recommended for the treatment of hypertension:

ACE inhibitors,

ARBs,

beta-blockers,

CCBs, and

Diuretics (preferably chlortalidone and indapamide),

based on:

(a) proven ability to reduce BP;

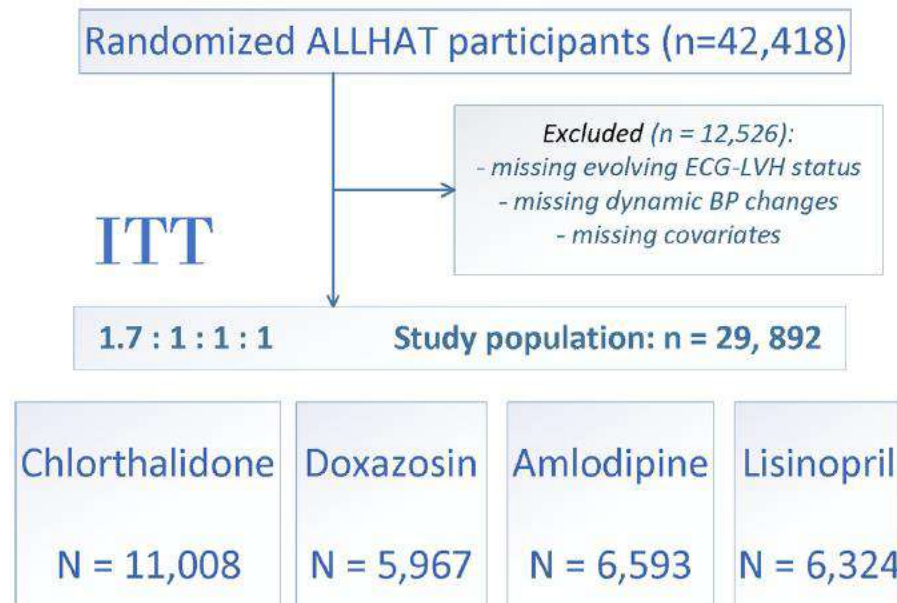
(b) evidence from RCT that they reduce CV events;

(c) Evidence of broad equivalence on CV morbidity and mortality,

with the conclusion that benefit from their use predominantly derives from BP lowering.

Prevention of Heart Failure in Hypertension

Johnson et al., J Am Heart Assoc. 2019;8: e011961



1. Evolving ECG LVH was associated with incident HF.
2. Progressing ECG LVH carried a larger risk,
3. Resolving ECG LVH was correlated with beneficial effects

- a. **Chlorthalidone** was the most effective agent to prevent HF.
- b. The mechanisms by which the **thiazide diuretic prevented HF** were not restricted to BP lowering and prevention of LVH.

Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Suchard et al., Lancet published online October 24, 2019

Using 4.9 million patients, we generated 22 000 calibrated, propensity-score-adjusted hazard ratios comparing all drug classes and outcomes across databases.

Most estimates revealed no effectiveness differences between classes; however,

**Thiazides showed better primary effectiveness than ACE-Is:
AMI (HR 0.84), HF (HR 0.83), and stroke (HR 0.83).**

Safety profiles also favoured thiazides over ACE-Is

**The non-dihydropyridine calcium channel blockers were
significantly inferior to the other four classes.**

Compelling and possible contraindications to the use of specific antihypertensive drugs

Drug	Contraindications	
	Compelling	Possible
Diuretics (thiazides/thiazide-like, e.g. chlorthalidone and indapamide)	● Gout	● Metabolic syndrome ● Glucose intolerance ● Pregnancy ● Hypercalcaemia ● Hypokalaemia
Beta-blockers	● Asthma ● Any high-grade sinoatrial or atrioventricular block ● Bradycardia (heart rate <60 beats per min)	● Metabolic syndrome ● Glucose intolerance ● Athletes and physically active patients
Calcium antagonists (dihydropyridines)		● Tachyarrhythmia ● Heart failure (HFrEF, class III or IV) ● Pre-existing severe leg oedema
Calcium antagonists (verapamil, diltiazem)	● Any high-grade sinoatrial or atrioventricular block ● Severe LV dysfunction (LV ejection fraction <40%) ● Bradycardia (heart rate <60 beats per min)	● Constipation
ACE inhibitors	● Pregnancy ● Previous angioneurotic oedema ● Hyperkalaemia (potassium >5.5 mmol/L) ● Bilateral renal artery stenosis	● Women of child-bearing potential without reliable contraception
ARBs	● Pregnancy ● Hyperkalaemia (potassium >5.5 mmol/L) ● Bilateral renal artery stenosis	● Women of child-bearing potential without reliable contraception

The ESC - Rationale for Initial Two-Drug **Combination Therapy** for Most HTN Patients

1. The majority of HTN patients will require combination therapy.
2. Initial combination therapy is invariably more effective than monotherapy,
3. Even low-dose combination therapy is usually more effective
4. The addition of spironolactone for the treatment of resistant hypertension
5. Optimal antihypertensive therapy is optimal HF therapy

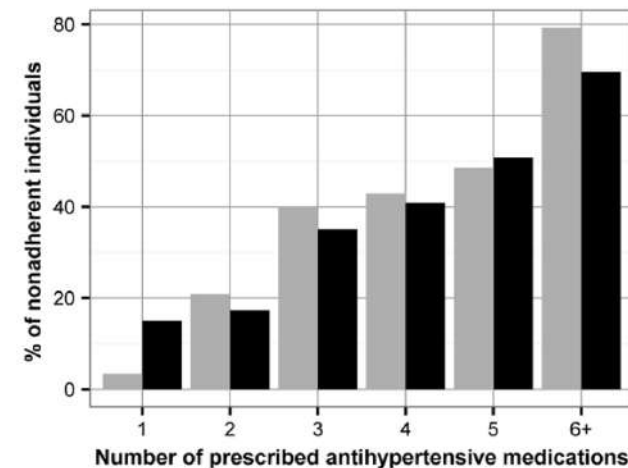
Diuretic + ACE-I

Diuretic + Betablocker

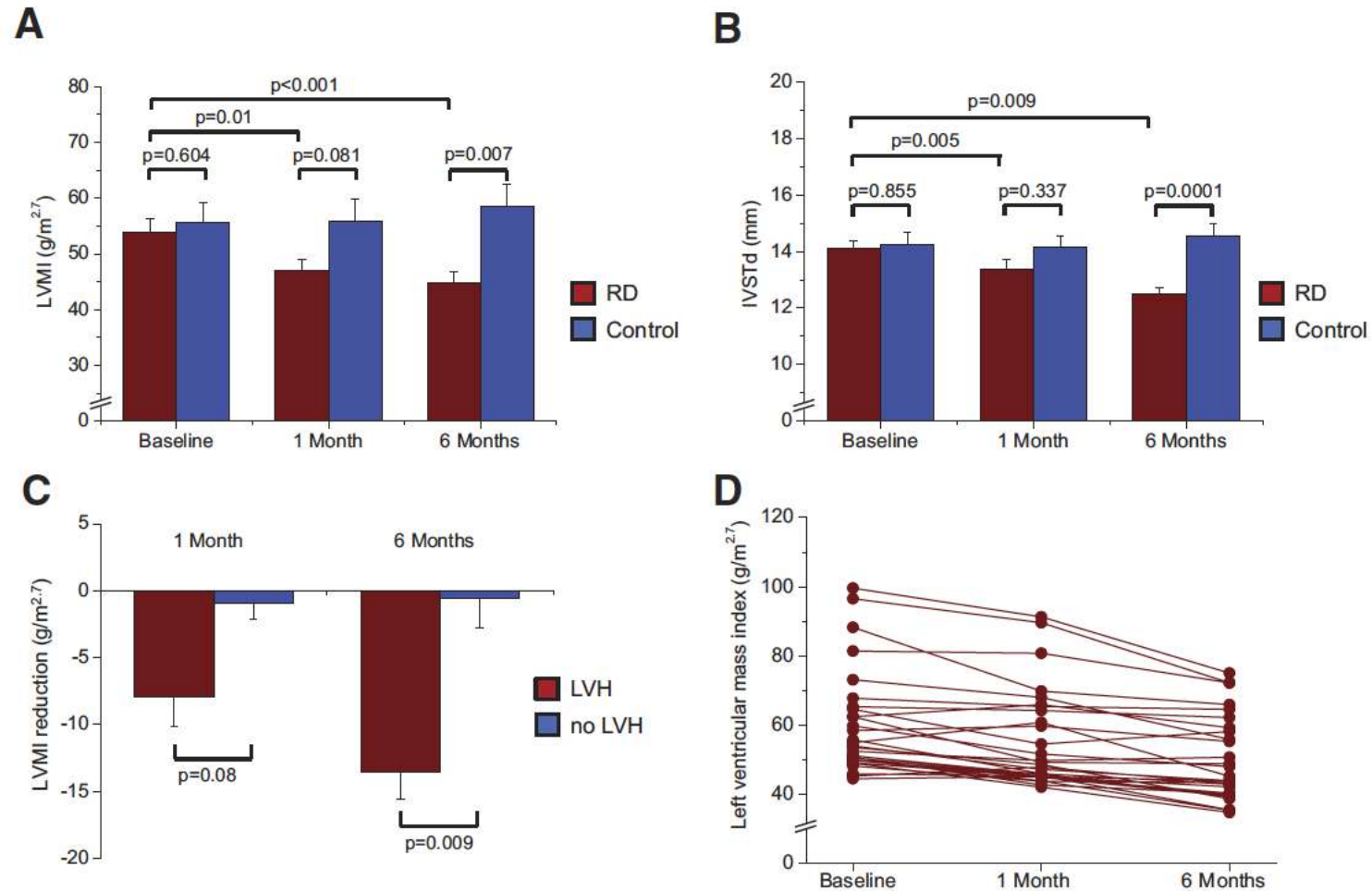
Diuretic + ACE-I + Betablocker +++++

Risk Factors for Nonadherence to Antihypertensive Treatment

1. The rates of nonadherence to antihypertensive treatment were 41.6% and 31.5% in the UK and Czech populations, respectively.
2. Nonadherence was inversely related to age and male sex.
3. Each increase in the number of antihypertensive drugs led to 85% and 77% increase in nonadherence in the UK and Czech populations, respectively.
4. The odds of nonadherence to diuretics were the highest among 5 classes of antihypertensive medications.



Impact of Renal Sympathetic Denervation on LV Mass



ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Wiviott et al., N Engl J Med 2019;380:347-57

Conclusions: Dapagliflozin did result in a lower rate of cardiovascular death or hospitalization for heart failure. In the first SGLT2i CV outcome trial to evaluate T2DM patients stratified by EF, **dapagliflozin reduced HF in patients with and without HFrEF**, and reduced CV death and all cause mortality in patients with HFrEF.

HHF

Prior HF

No HF

212/8582

87/852

125/7730

286/8578

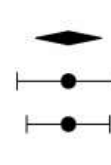
115/872

171/7706

0.73 (0.61-0.88)

0.73 (0.55-0.96)

0.73 (0.58-0.92)

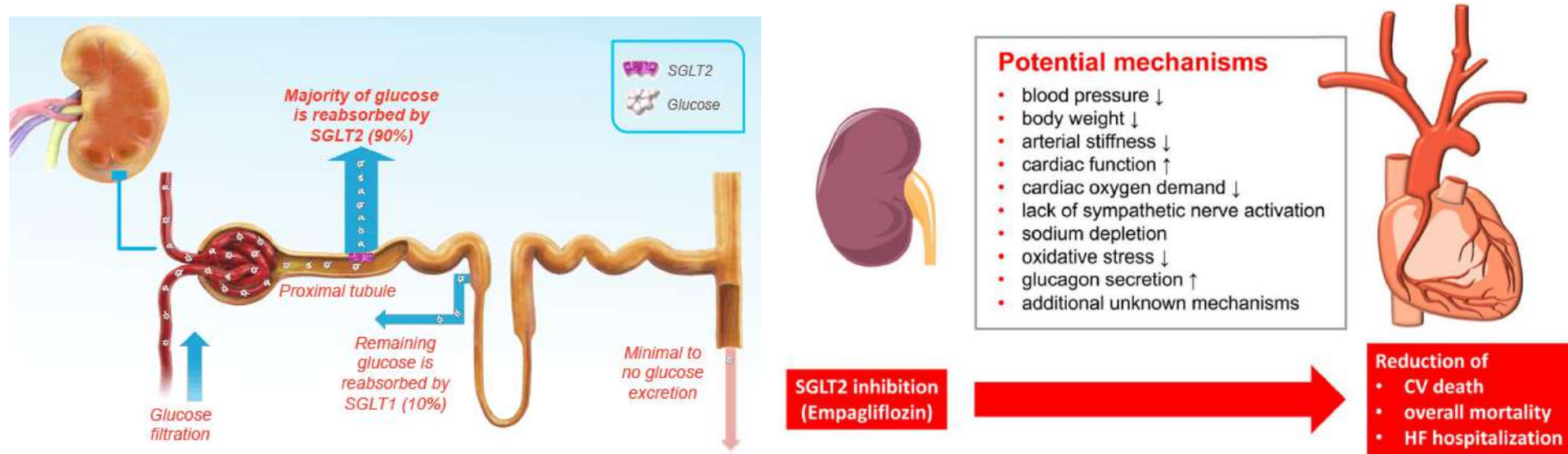


SGLT2 inhibitors decrease blood pressure and body weight

Canagliflozin, Dapagliflozin, Empagliflozin have a diuretic like action, beneficial effects on calcium handling, and they reduce BP and LVH

1. A number of cardioprotective and renoprotective effects of this class of drugs are linked to **HF benefits**
2. Reduction in HF-related admission was seen as a class effect of SGLT2 inhibitors
3. Data is emerging supporting long-term cardiovascular benefits, **specifically HF, in patients with and without DM**
4. EMPA-REG, CANVAS and DECLARE-TIMI are the 3 major cardiovascular trials examining MACE as primary outcome with drugs of this class
5. Subgroup analysis showed that **HF benefits extended to patients with previous cardiovascular events**
6. DAPA-HF results indicate a possible expanding role of SGLT2 inhibitors in **nondiabetic patients with HFrEF**

Potential Mechanisms Involved in the Reduction of HF and Cardiovascular Events by SGLT2-Inhibitors



HF-patients with and without DM may profit from SGLT2-Inhibition

Take home messages

1. HTN is the major risk factor for HF and CVD
2. Lowering BP clearly confers clinical benefit (130/80)
3. Heart rate is a major therapeutic target in CAD and HF
4. Antihypertensive combination therapy including a diuretic is standard and reduces HF events
5. LVH, impaired LV relaxation, and fibrosis lead to HFpEF
6. In HF-patients with (and without?) DM, SGLT2 inhibitors should be considered
7. Optimal antihypertensive therapy is optimal HF therapy

