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Can the new guidelines of hypertension affect the choice and combination of antihypertensive medications?

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Decleration of Interest

Research contracts from AMGEN, Medtronic, ReCor, and Regeneron, all outside the presented work

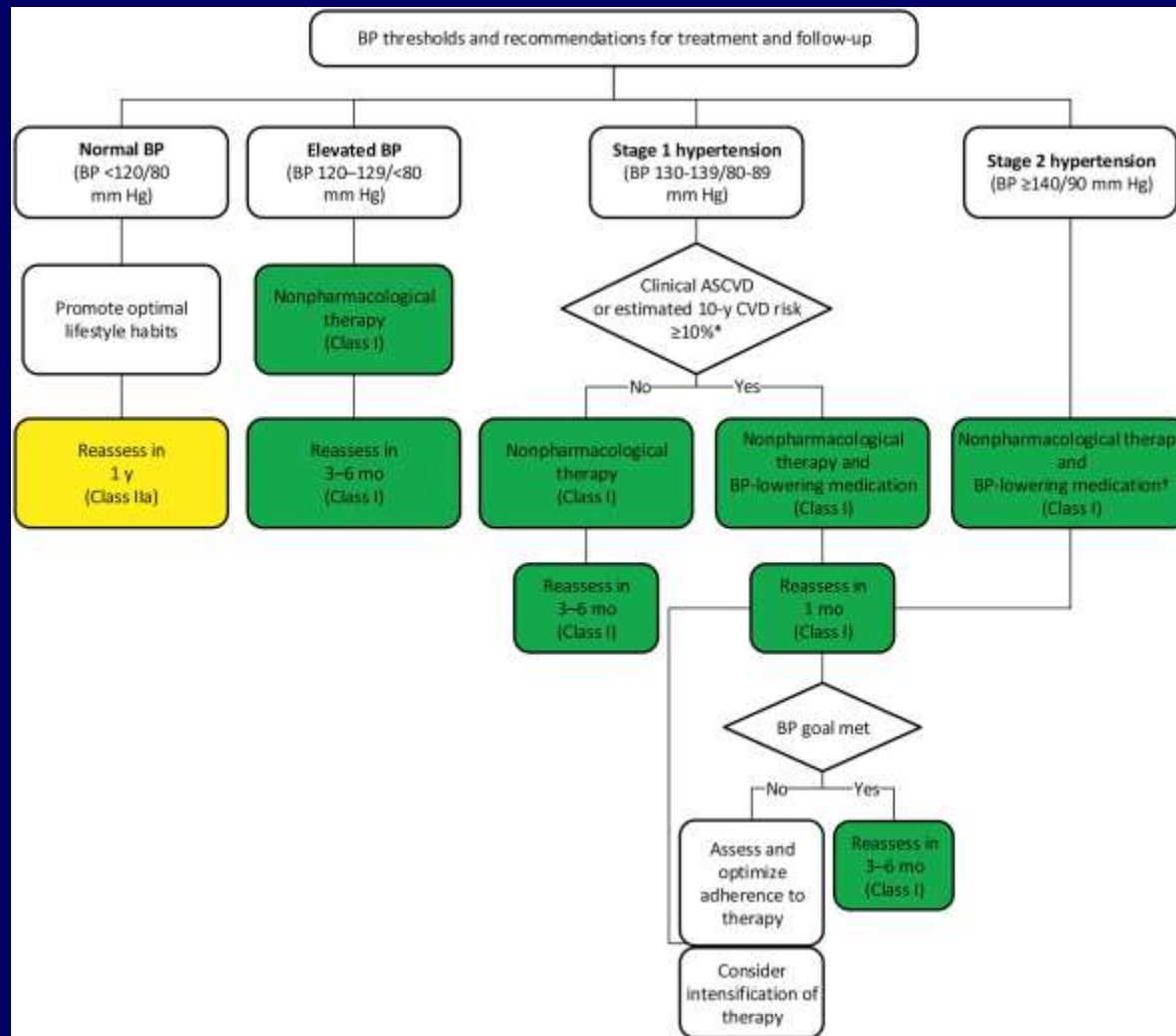
How the New Guidelines may Affect the Choice and Combination of Antihypertensive Medications

1. New lower target blood pressure values
2. Adherence to therapy a major problem
3. Proactive initiation of drug treatment
4. Single pill combinations recommended
5. Treatment of true resistant hypertension

Target Office Blood Pressure Ranges *ESC/ESH 2018 Guidelines*

| Age group | Office SBP treatment target ranges (mmHg) | | | | | DBP treatment target range (mmHg) |
|-----------------------------------|---|---|--|---|---|-----------------------------------|
| | Hypertension | + Diabetes | + CKD | + CAD | + Stroke/TIA | |
| 18–65 years | Target to 130 <i>or lower if tolerated</i> Not <120 | Target to 130 <i>or lower if tolerated</i> Not <120 | Target to <140 to 130 <i>if tolerated</i> | Target to 130 <i>or lower if tolerated</i> Not <120 | Target to 130 <i>or lower if tolerated</i> Not <120 | <80 to 70 |
| 65–79 years | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | <80 to 70 |
| ≥ 80 years | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | Target to <140 to 130 <i>if tolerated</i> | <80 to 70 |
| DBP treatment target range (mmHg) | < 80 to 70 | < 80 to 70 | < 80 to 70 | < 80 to 70 | < 80 to 70 | |

Initiation of Antihypertensive Treatment and Target Blood Pressures: ACC/AHA 2018 Guidelines



Associations with Discontinuation 2 years After Initiation: *Adjusted Hazard Ratios*

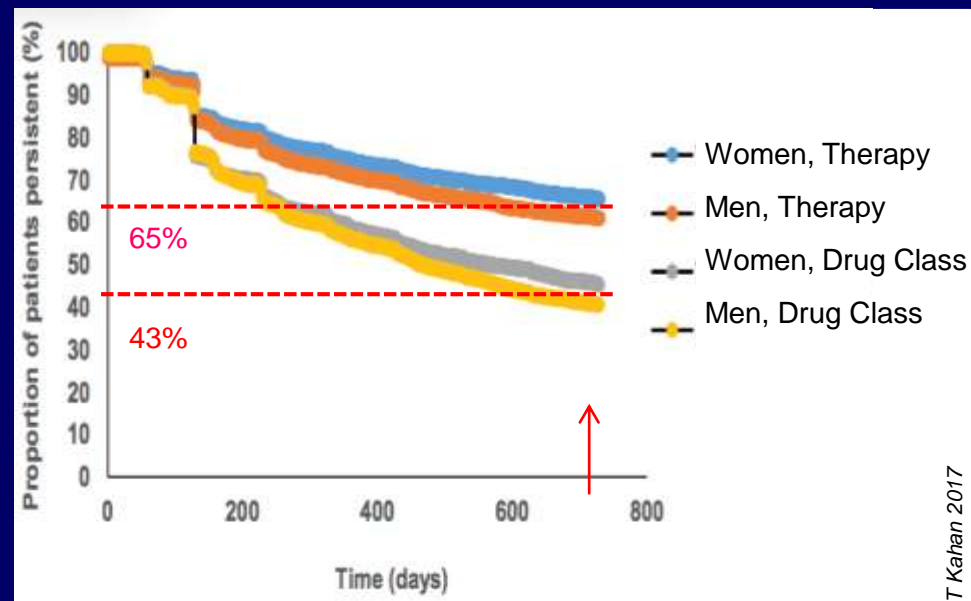
Significant association

| | Hazard ratio [95% CI] | P (trend) |
|---|-----------------------|-----------|
| Male gender | 1.19 [1.07–1.32] | 0.002 |
| Young age (eg 30-49 vs 50-59 ys) | 1.37 [1.20–1.59] | <0.001 |
| Diabetes | 0.77 [0.60–0.99] | 0.040 |
| Low SBP (eg <140 vs 160-179 mm Hg) | 1.39 [1.11–1.75] | <0.001 |
| Country of birth (outside Nordic countries) | 2.11 [1.79–2.48] | <0.001 |
| Low income (eg Q1 vs Q4) | 1.24 [0.96–1.32] | <0.001 |

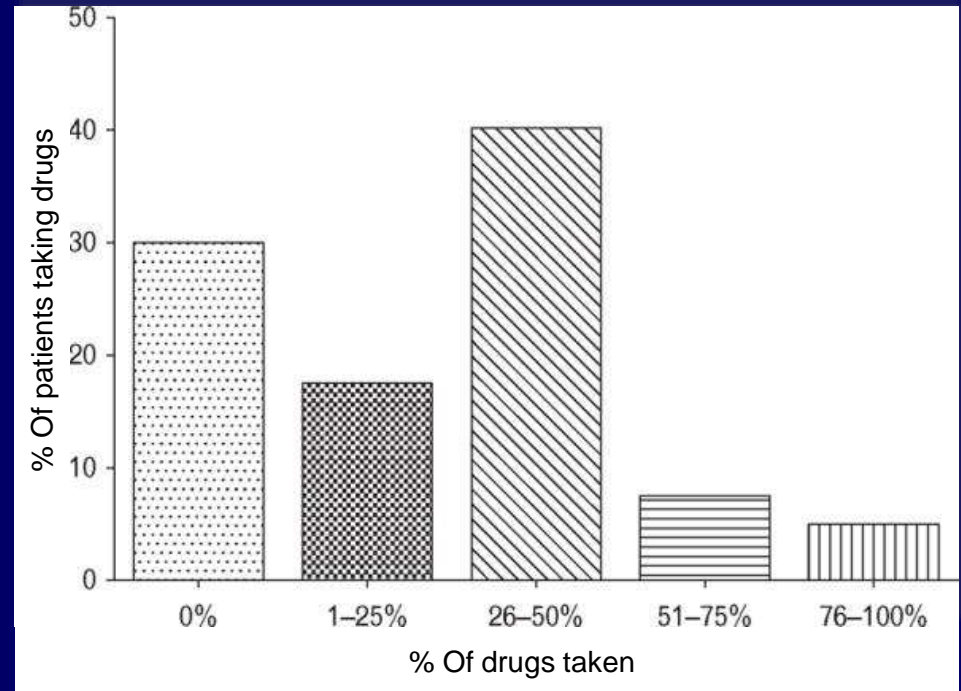
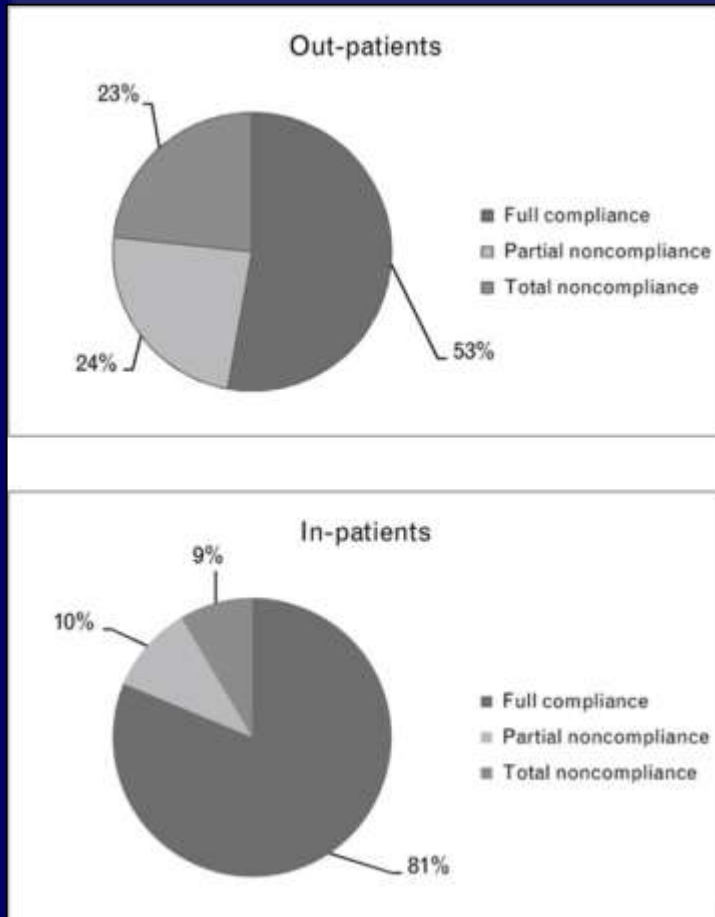
No association to CV comorbidity, number of other drugs, DBP, educational level

Switching estimated to 19-25%

5225 hypertensive patients with newly started therapy, mean age 61 ys, mean BP 166/95 mm Hg. First prescription never purchased by 1%, 14% discontinued after first prescription.



Assessment of Non-Adherence in Resistant Hypertension Using Toxicological Analysis



Unanticipated blood sampling for serum LC/MS in 176 hospitalized patients and 163 out-patients referred for resistant hypertension.

375 patients referred for apparent resistant HTN; 76 remained uncontrolled on ≥ 4 drugs after drug optimization and exclusion of secondary causes including white coat effect. Percentage of drugs taken by 76 patients; according to urine LC/MS.

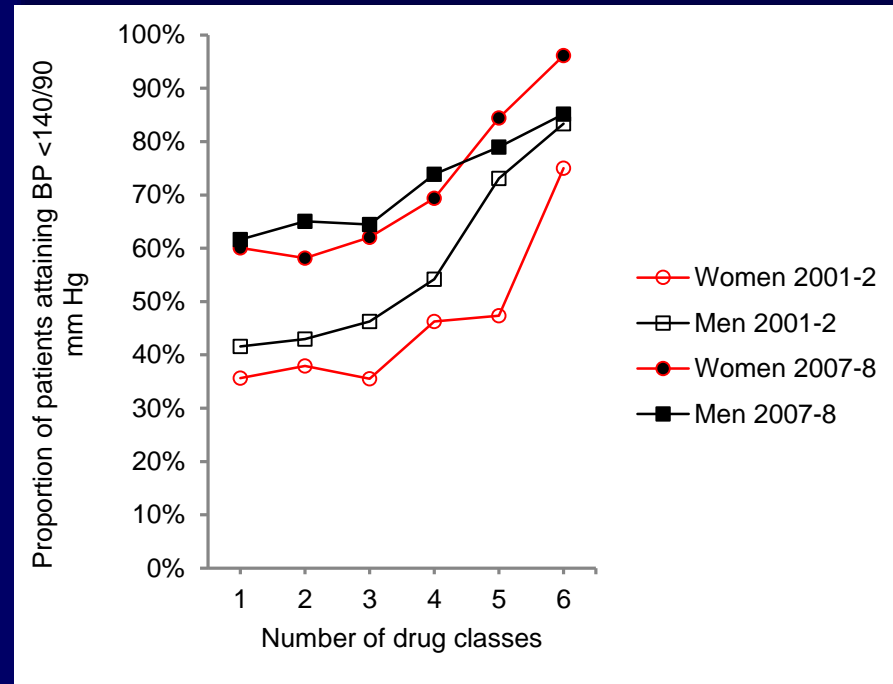
Jung et al. *J Hypertens* 2013;31:766-74

Strauch B et al. *J Hypertens* 2013;31:2455-61

Number of Antihypertensive Drugs in Relation to Target Blood Pressure: Care Provider Inertia

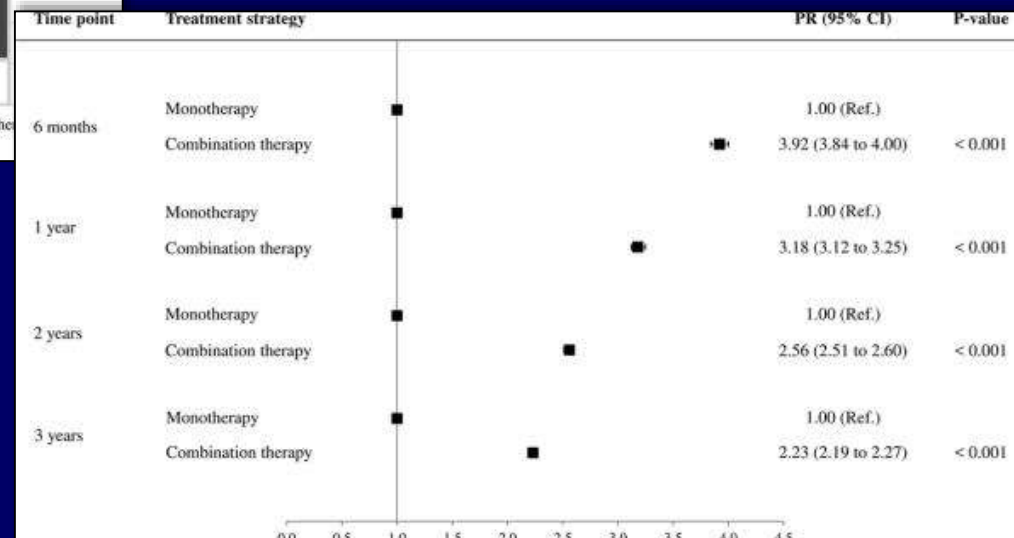
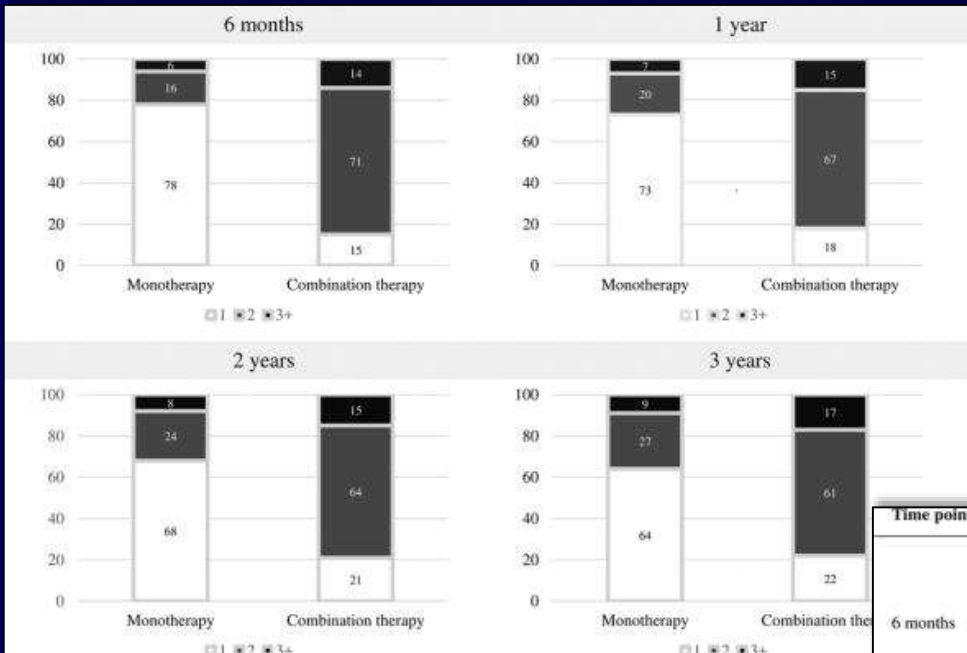
| Proportion of patients, % | Number of drugs | Proportion on target, % |
|---------------------------|-----------------|-------------------------|
| 8 | 0 | 23 |
| 31 | 1 | 29 |
| 36 | 2 | 30 |
| 20 | 3 | 30 |
| 5 | ≥4 | 25 |

Patients with diagnosed hypertension attending primary health care in Denmark. Target BP <140/90 mm Hg; <130/80 mm Hg in patients with diabetes; n=5260 at 183 general practices.



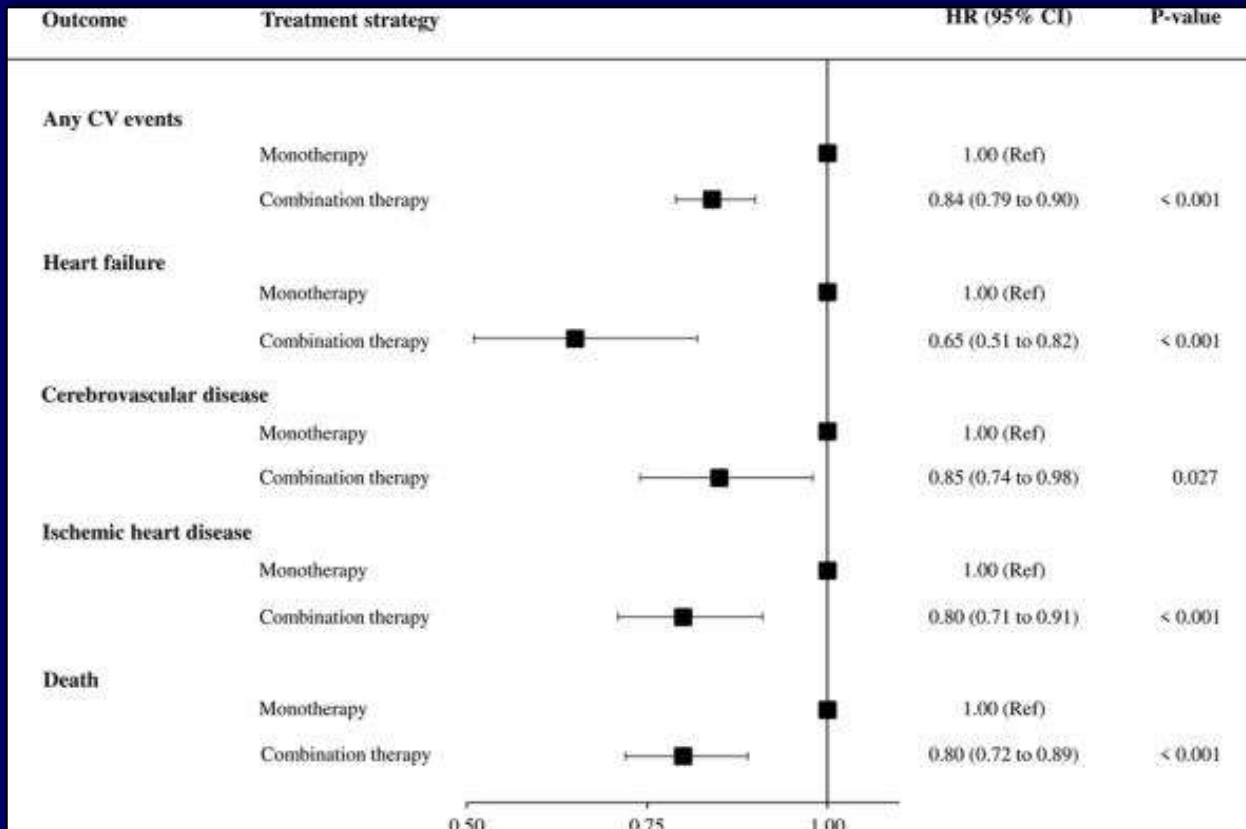
Patients with diagnosed hypertension attending Swedish primary health care. Target BP <140/90 mm Hg; n=43 239 (2001-2) and 42 407 (2007-8) at 48 general practices.

Initial Antihypertensive Treatment Strategies and Therapeutic Inertia



Data from health care utilization databases in Lombardy (Italy), where 100.962 patients (age 40-65 years) started antihypertensive treatment on 1 drug and 24.653 on ≥ 2 drugs (fixed dose or free combinations).

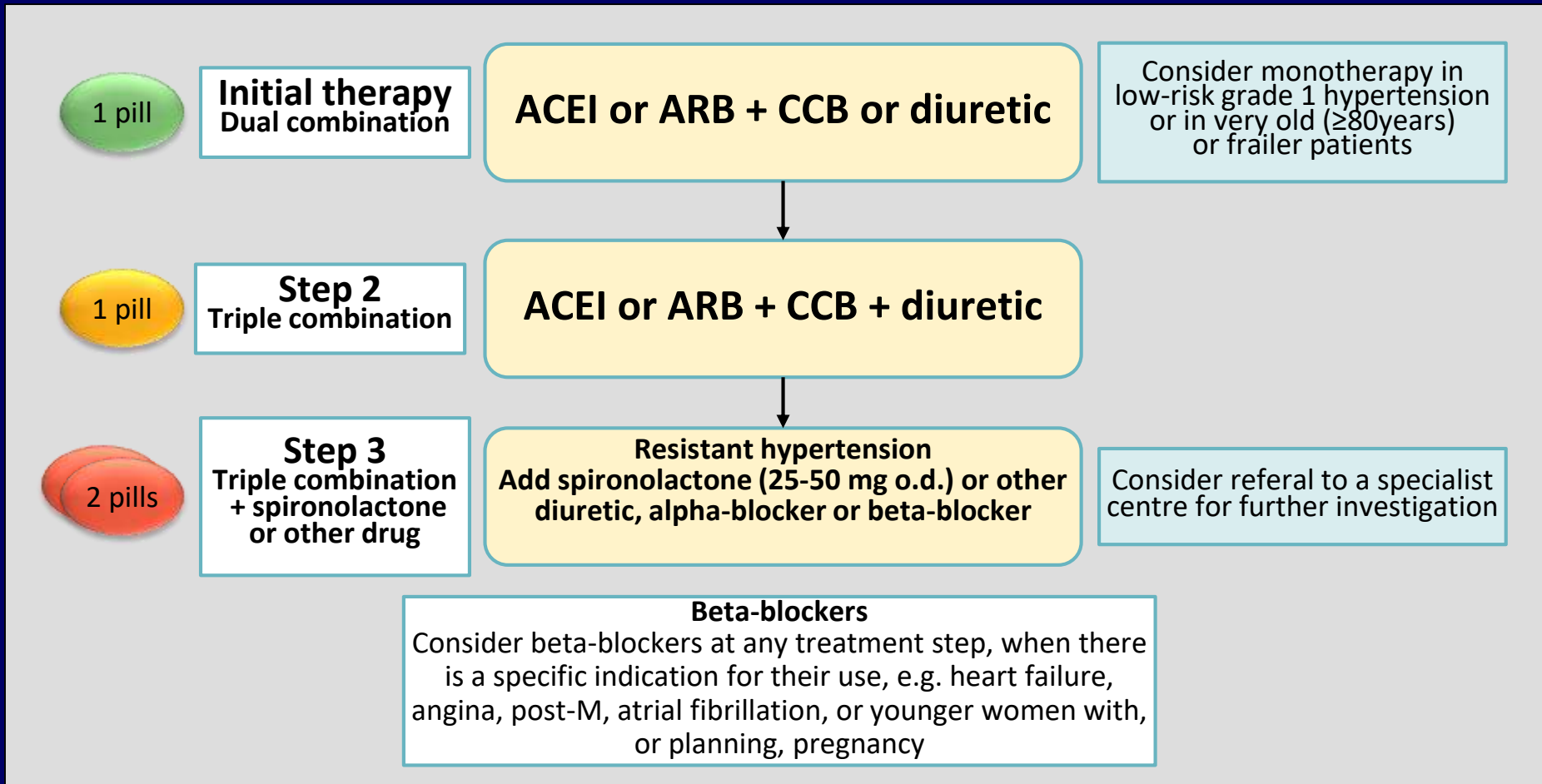
Initial Antihypertensive Treatment Strategies and Therapeutic Inertia



Data from health care utilization data-bases in Lombardy (Italy), where 100.962 patients (age 40-65 years) started treatment on 1 drug and 24.653 on ≥ 2 drugs. HR and 95% CI estimating the risk of CV outcomes and death during 3 years of follow-up. Patients were initially matched by high-dimensional propensity score.

Core Drug Treatment Strategy in Hypertension

ESC/ESH 2018 Guidelines

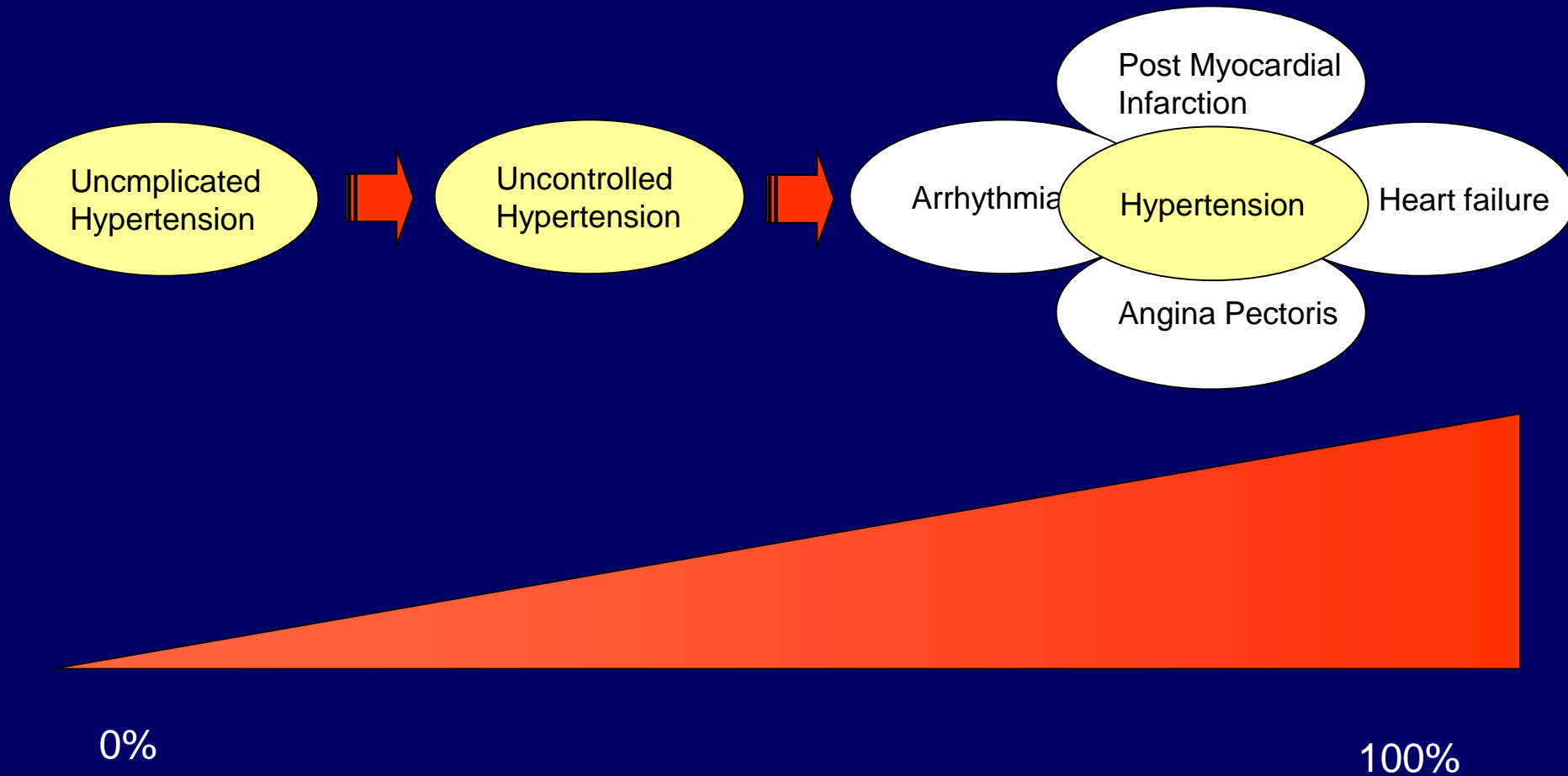


Evidence Based Treatment Strategy in Hypertension

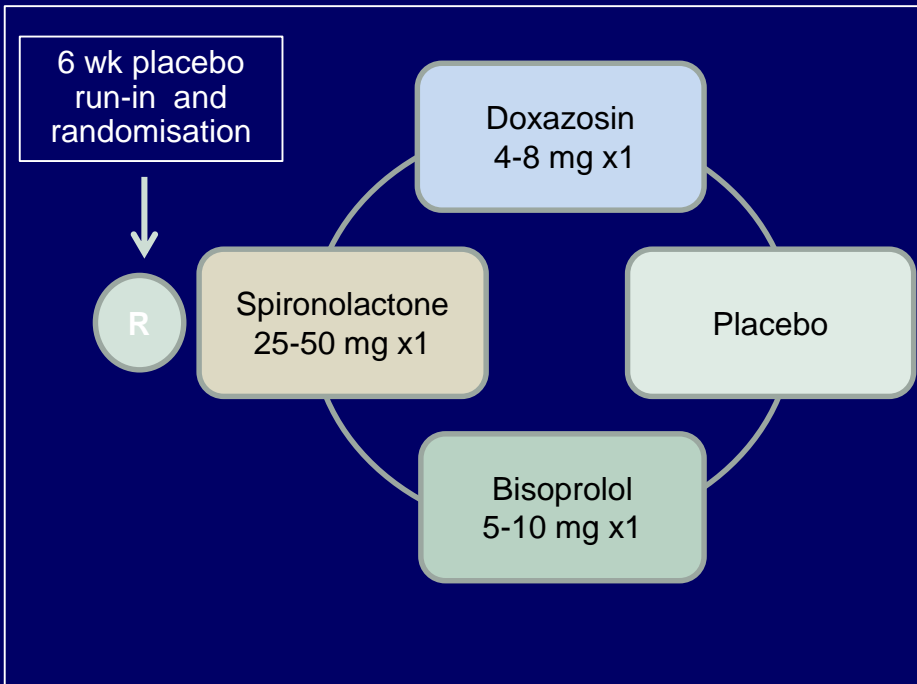
ESC/ESH 2018 Guidelines

| Recommendations | Class | Level |
|---|-------|-------|
| Among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies. | I | A |
| Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used. | I | A |
| It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control. | I | A |
| It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg). | I | B |
| It is recommended that if BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC. | I | A |
| It is recommended that if BP is not controlled with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alpha-blocker. | I | B |
| The combination of two RAS blockers is not recommended. | III | A |

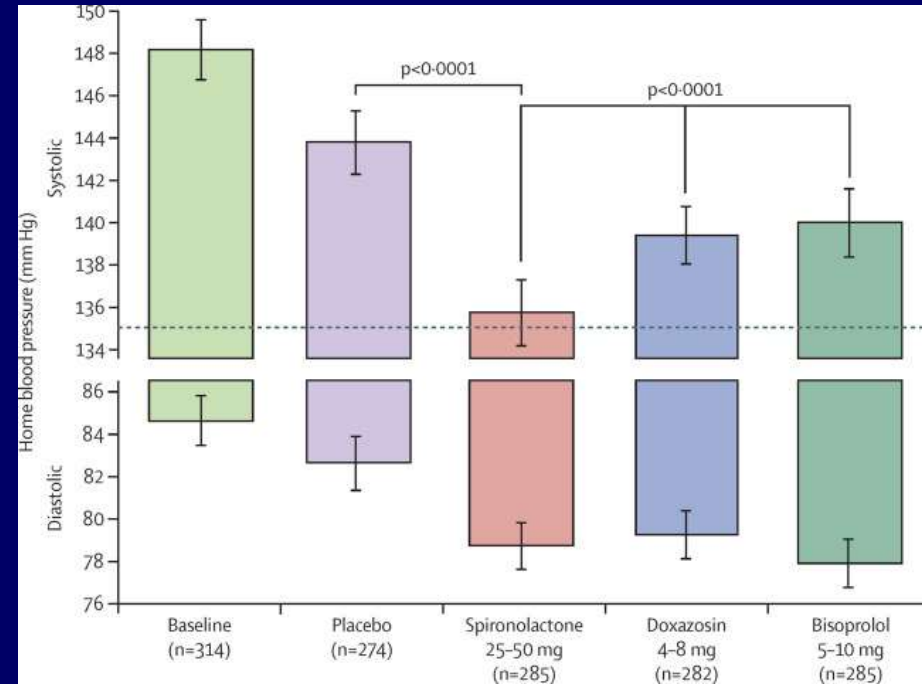
Proposed use of Beta-Blockers for Hypertension



Treatment in Resistant Hypertension : PATHWAY 2



314 Patients with resistant hypertension (157/90 mm Hg), treated with ACEI/ARB, CCB, and thiazide; 12 wk treatment periods



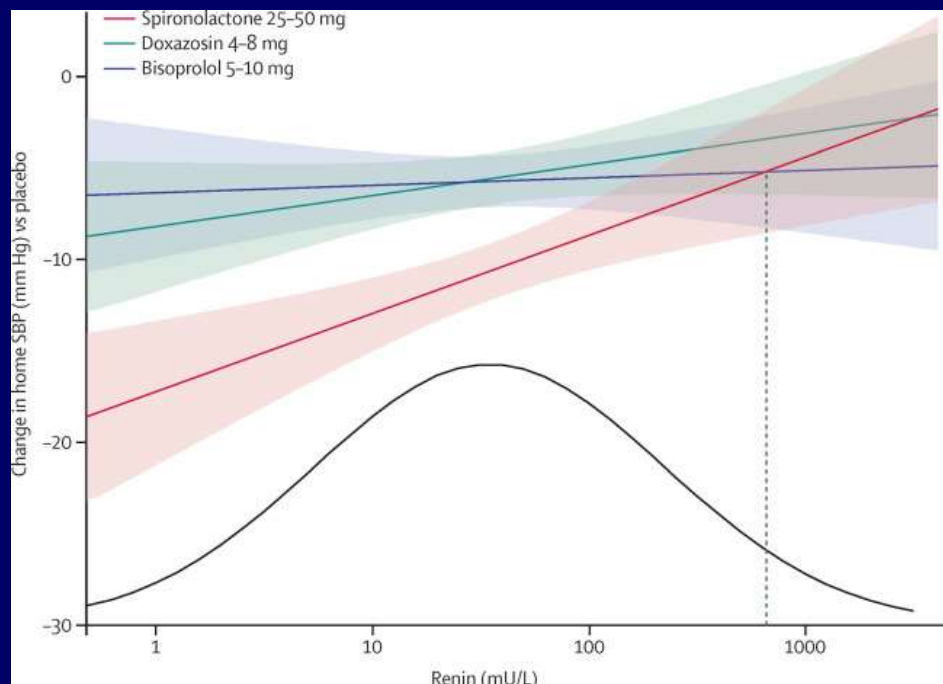
Spironolactone vs placebo
8.70 (-9.72 to -7.69); $p < 0.0001$

Spironolactone vs mean bisoprolol and doxazosin
-4.26 (-5.13 to -3.38); $p < 0.0001$

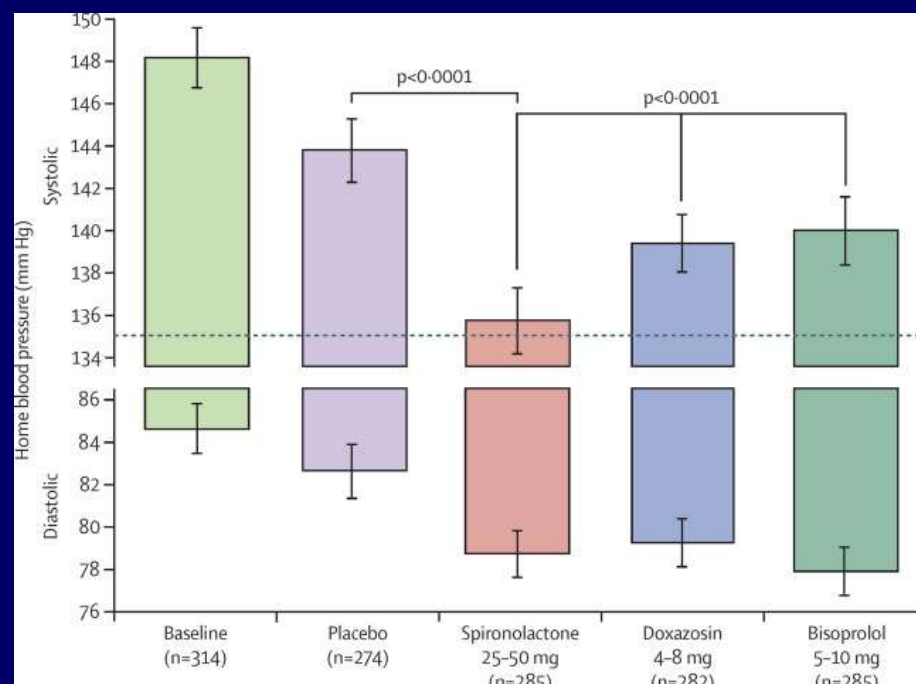
Spironolactone vs doxazosin
-4.03 (-5.04 to -3.02); $p < 0.0001$

Spironolactone vs bisoprolol
-4.48 (-5.50 to -3.46); $p < 0.0001$

Volume Overload in Resistant Hypertension: PATHWAY 2



Regression (90% CI) of placebo corrected change in home SBP vs renin for spironolactone ($r^2=0.037$, $p=0.003$), doxazosin ($r^2=0.007$, $p=0.183$), and bisoprolol ($r^2=0.0004$, $p=0.750$).



Spironolactone vs placebo

8.70 (-9.72 to -7.69); $p<0.0001$

Spironolactone vs mean bisoprolol and doxazosin

-4.26 (-5.13 to -3.38); $p<0.0001$

Spironolactone vs doxazosin

-4.03 (-5.04 to -3.02); $p<0.0001$

Spironolactone vs bisoprolol

-4.48 (-5.50 to -3.46); $p<0.0001$

Evidence Based Treatment Strategy in Resistant Hypertension

ESC/ESH 2018 Guidelines

Definition of treatment resistance:

- Optimal doses of an appropriate therapeutic strategy, which should include a diuretic, fails to lower clinic BP to < 140/90 mmHg; and
- the inadequate control confirmed by ABPM or HBPM; and
- exclusion of various causes of pseudo-resistant and secondary hypertension.

| Recommendations | Class | Level |
|--|-------|-------|
| <p>It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when:</p> <ul style="list-style-type: none"> • Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively; and • The inadequate control of BP has been confirmed by ABPM or HBPM; and • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension. | I | C |
| <p>Recommended treatment of resistant hypertension is:</p> <ul style="list-style-type: none"> • Reinforcement of lifestyle measures, especially sodium restriction. • Addition of low-dose spironolactone^c to existing treatment; • Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone,^c amiloride,^c a higher-dose thiazide/thiazide-like diuretic, or a loop diuretic, • Or the addition of bisoprolol or doxazosin. | I | B |

Therapeutic Strategies in Hypertensive Patients with Heart Failure or LV Hypertrophy

ESC/ESH 2018 Guidelines

Heart failure

HFrEF

HFpEF

LV hypertrophy

| Recommendations | Class | Level |
|--|-------|-------|
| In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is $\geq 140/90$ mmHg. | IIa | B |
| In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a beta-blocker and diuretic and/or MRA if required. | I | A |
| Dihydropyridine CCBs may be added if BP control is not achieved. | IIb | C |
| In patients with HFpEF, BP treatment threshold and target values should be the same as for HFrEF. | IIa | B |
| Because no specific drug has proven its superiority, all major agents can be used. | I | C |
| In all patients with LVH: <ul style="list-style-type: none"> ● It is recommended to treat with an RAS blocker in combination with a CCB or diuretic. ● SBP should be lowered to a range of 120–130 mmHg. | I | A |
| | IIa | B |

Williams B et al. *Eur Heart J* 2018;39:3021-3104; *J Hypertens* 2018;36:1953-2041

Therapeutic Strategies in Hypertensive Patients with Coronary Artery Disease

ESC/ESH 2018 Guidelines

| Recommendations | Class | Level |
|--|-------|-------|
| In patients with CAD receiving BP-lowering drugs, it is recommended: | | |
| ● To target SBP to ≤ 130 mmHg if tolerated, but not <120 mmHg. | I | A |
| ● In older patients (aged ≥ 65 years), to target to an SBP range of 130–140 mmHg. | I | A |
| ● To target DBP to <80 mmHg, but not <70 mmHg. | I | C |
| In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment. | I | A |
| In patients with symptomatic angina, beta-blockers and/or CCBs are recommended. | I | A |

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Summary and Conclusions

- ✓ New guidelines of hypertension will affect the choice and combination of antihypertensive medications
- ✓ Current lower target blood pressure values will require more drugs
- ✓ Adherence to therapy remains a major problem
- ✓ Proactive initiation of drug treatment is important
- ✓ Most patients require to start on two drugs
- ✓ Single pill combinations are recommended
- ✓ Treatment of true resistant hypertension will often benefit from the addition of a MRA (spironolactone)



**Preliminary
Programme**

Lugano

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International Society of Cardiovascular Pharmacotherapy

24th Scientific Meeting of the
**International Society of
Cardiovascular Pharmacotherapy
(ISCP)**

Palazzo dei Congressi, Lugano, Switzerland

**May 9th-10th
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