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From Recent Trials and Real-World Evidence to Guidelines

The Impact of Single-Pill Combinations on Prognosis, Adherence, and Guideline Updates

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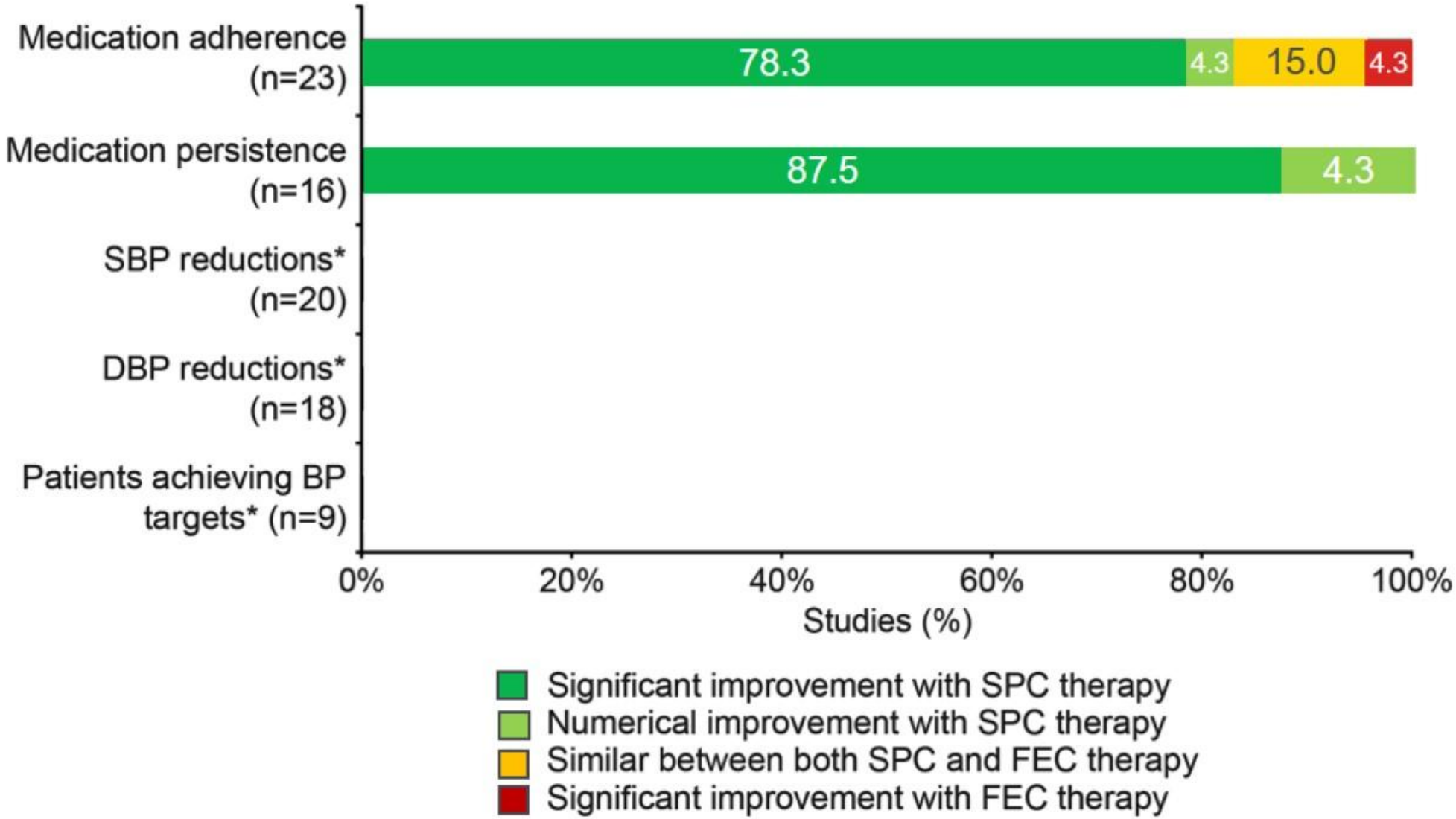
Single Pill Combination vs Free Equivalent Combination
Meta-Analysis

Does an SPC-based regimen lead to improved adherence, persistence, and better BP control compared with FEC therapy in patients with hypertension?

- 44 studies
- 2 pills vs 1, or 3 pills vs 1 (free equivalent vs SPC)

Parati G, et al. Hypertension. 2021;77:692-705.

SPC vs FEC on Adherence, Persistence, and Outcomes
Meta-Analysis



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SPC vs FEC on Adherence, Persistence, and Outcomes
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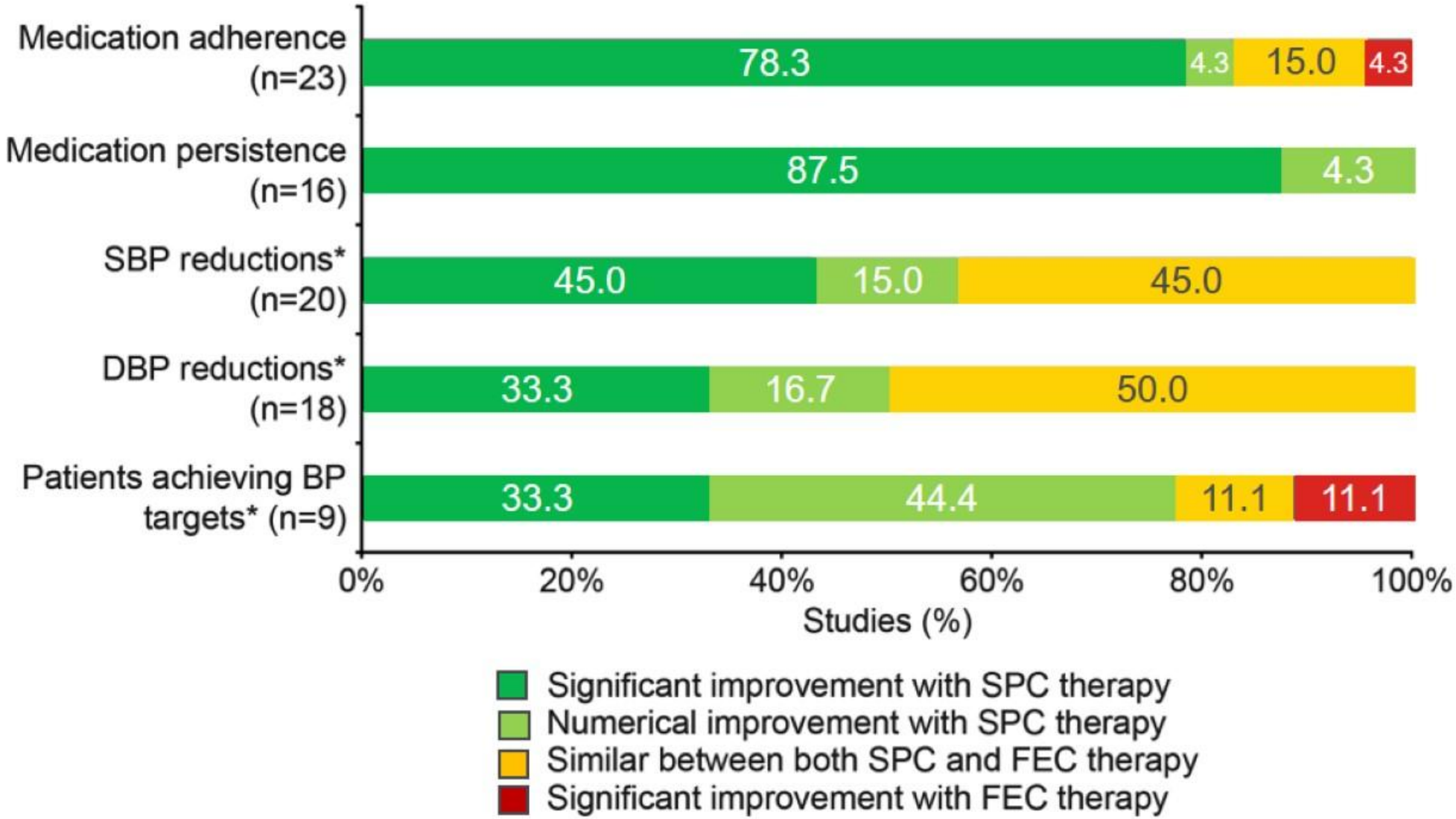

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Single Pill Combination vs Free Equivalent Combination

Comparing the equivalent doses of two drugs in a single pill with equivalent doses with two pills, the better reduction of blood pressure may only be due to better adherence;

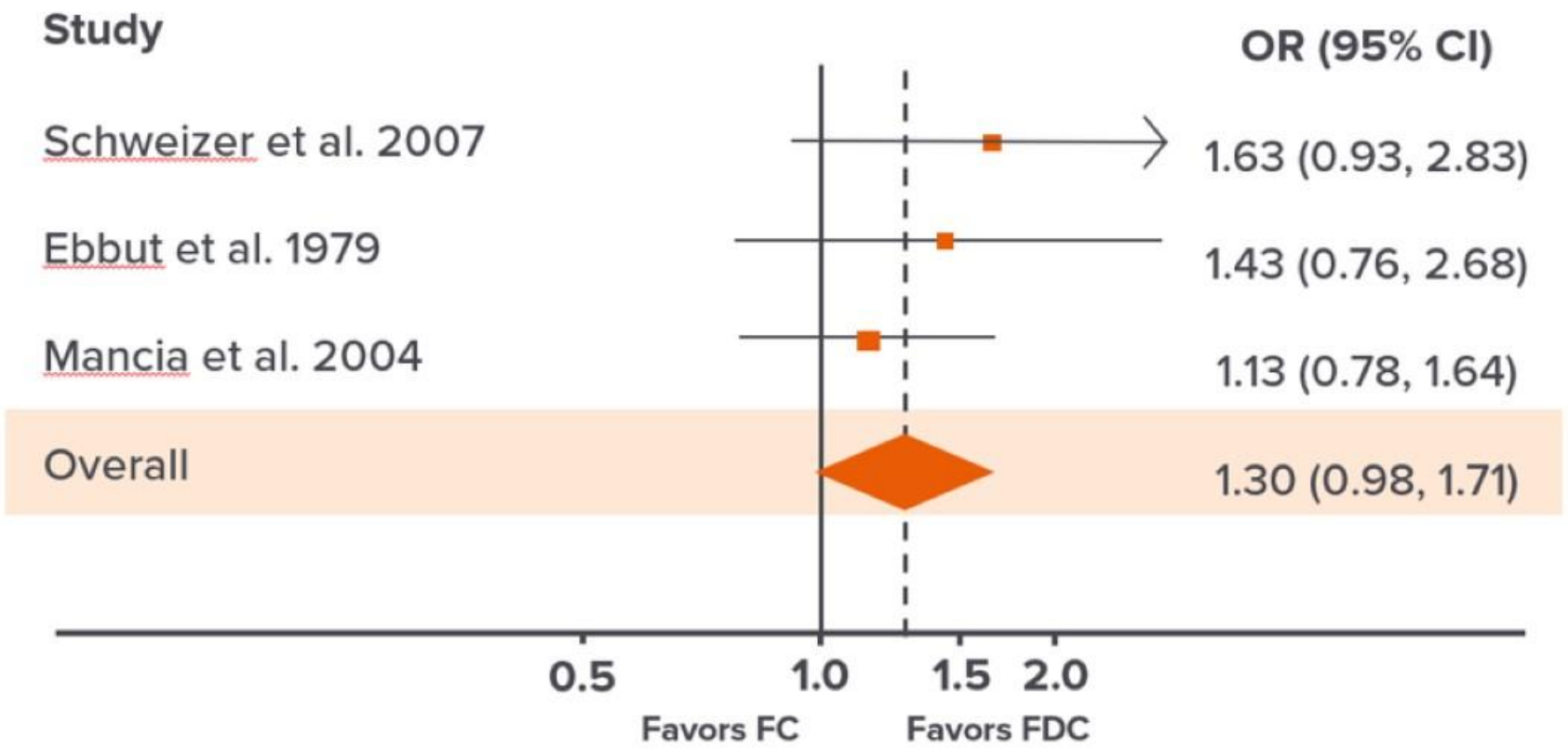
there is no other reason than better adherence.

Expert opinion.

Initial SPC Reduces CV Events in Hypertension
Meta-Analysis

SBP and DBP Normalization Ratios

Three studies including 653 patients



FC, free combination; FDC, fixed-dose combination.
Gupta AK, et al. Hypertension. 2010;55:399-407.

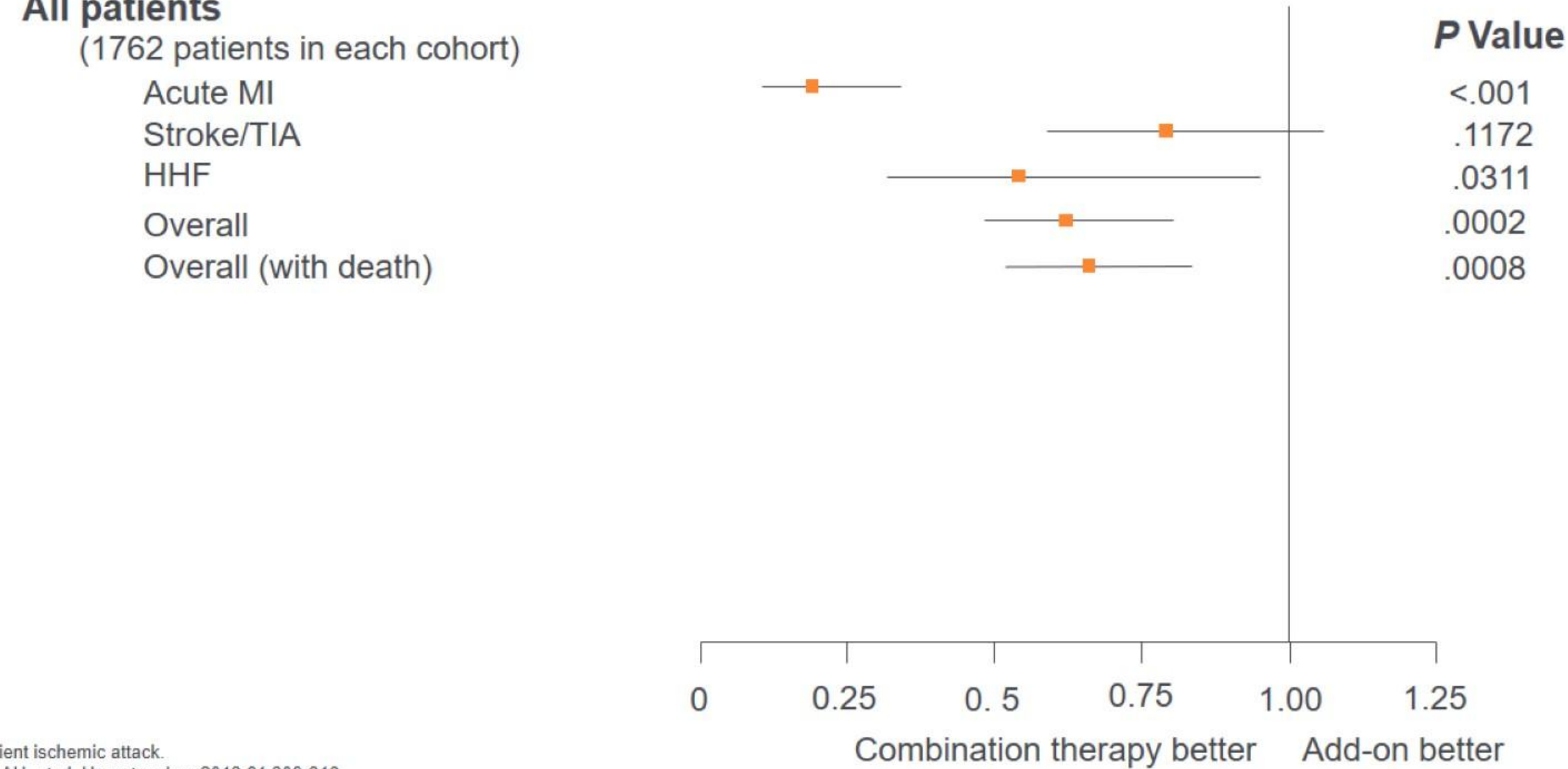
Single Pill Combination vs Free Equivalent Combination
The Evidence

Expert opinion.

- Better adherence
- Better persistence with therapy
- Better BP control
- Better target achievement
- Patients' preference

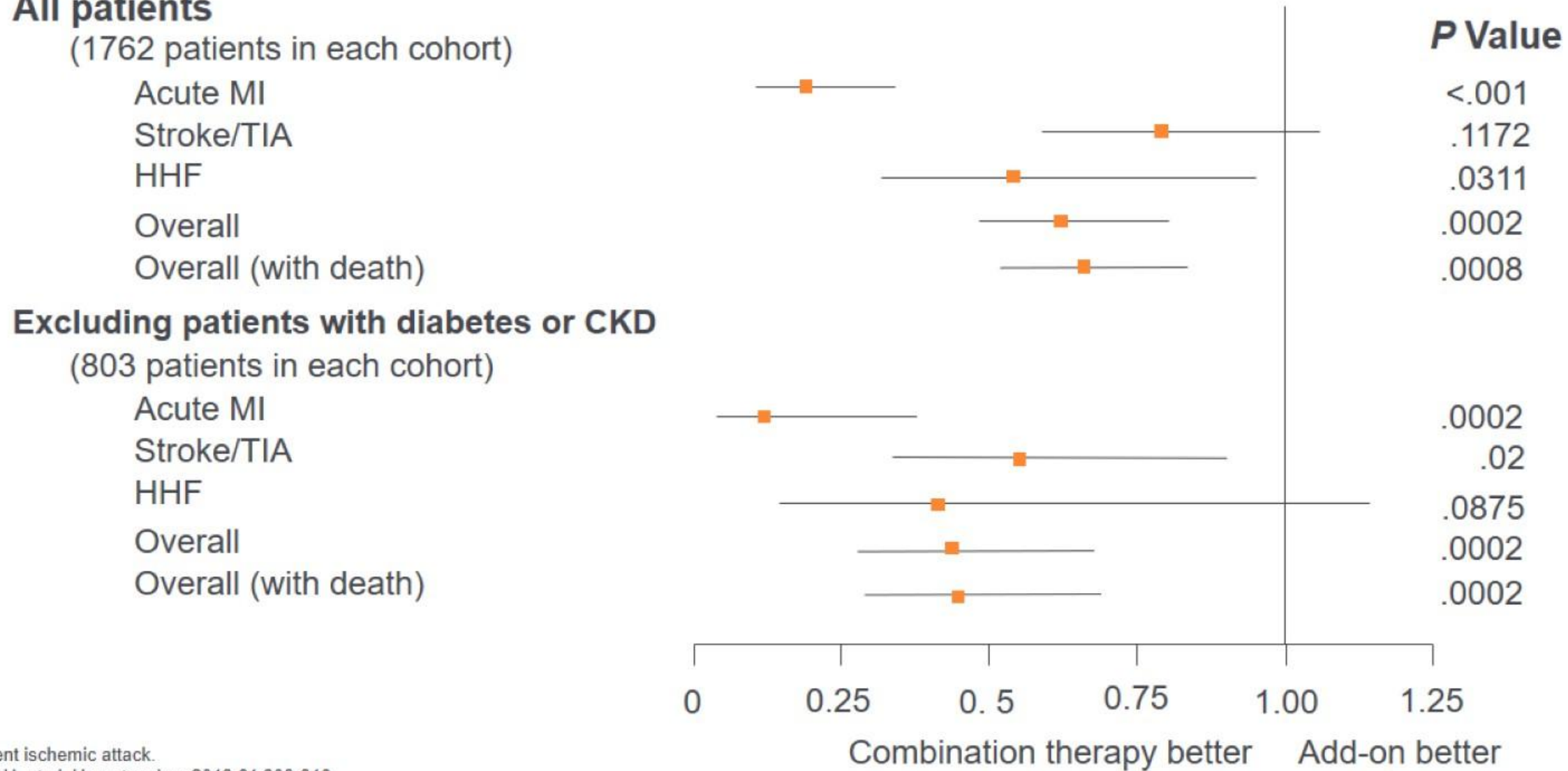
Initial SPC Reduces CV Events in Hypertension
Matched Cohorts in US Registry Data

All patients
(1762 patients in each cohort)



TIA, transient ischemic attack.
Gradman AH, et al. Hypertension. 2013;61:309-318.

Initial SPC Reduces CV Events in Hypertension
Matched Cohorts in US Registry Data



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Initial SPC Reduces CV Events in Hypertension
Real World Data from Lombardy in Italy

Healthcare utilization database

- 44,534 residents of the region (aged 40-80 y) who started treatment with **1 antihypertensive** drug (n = 37,078) **or a 2-drug FDC** (n = 7456) in 2010
- Followed for 1 year after treatment initiation to compare the **risk for hospitalization for CVD** associated with the 2 treatment strategies

FDC, fixed dose combination.

Rea F, et al. Eur Heart J. 2018;39:3654-3661.

Initial SPC Reduces CV Events in Hypertension
Real World Data

Effect of Starting Antihypertensive Treatment With FDCs vs Monotherapy on the 1-y Risk for CV Outcomes

Outcome	HR (95% CI)	*P* Value
Any CV event	0.85 (0.74, 0.97)	.02
Ischemic heart disease	0.73 (0.56, 0.95)	.02
Cerebrovascular disease	0.83 (0.61, 1.14)	.26
Heart failure	0.9 (0.54, 1.51)	.69
Atrial fibrillation	0.63 (0.42, 0.94)	.02

Database of the Lombardy Region (Italy)

- 44,534 residents
- Started on monotherapy (n = 37,078) or an FDC (n = 7456)
- Evaluation of the risk for CV events
- FDCs were associated with more effective CV protection

Rea F, et al. Eur Heart J. 2018;39:3654-3661.

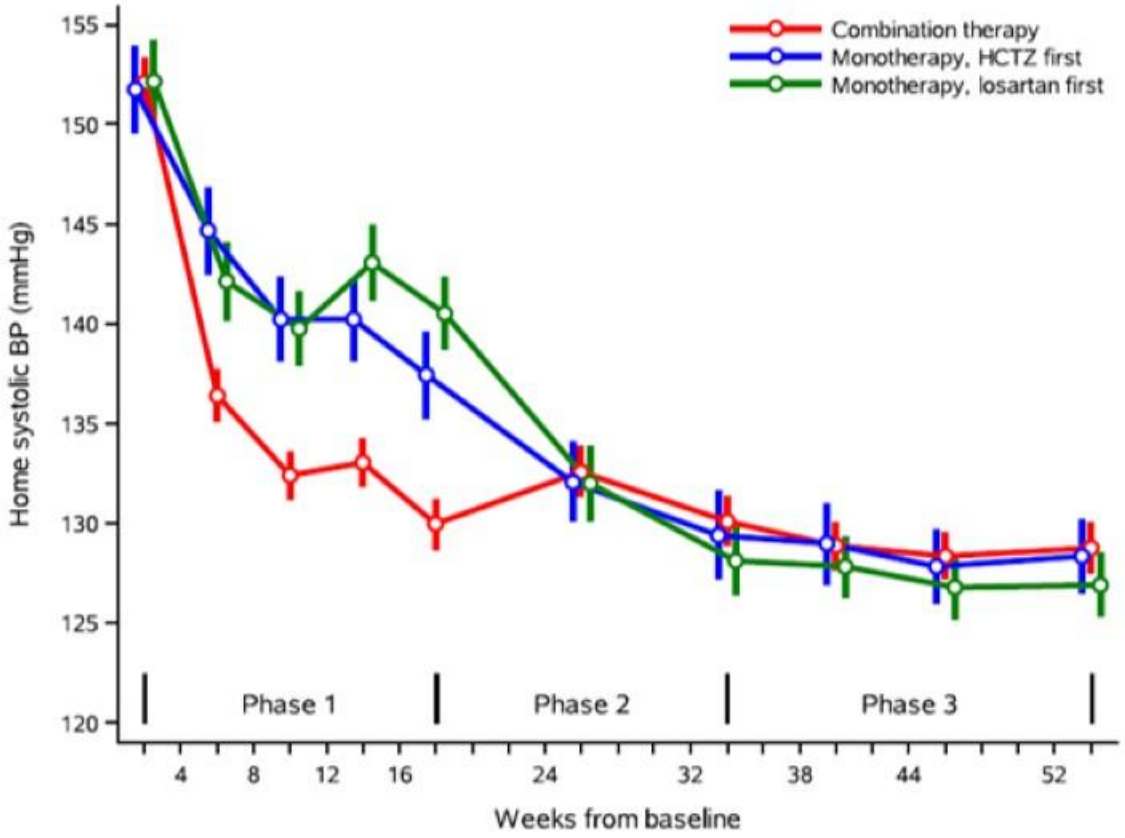
What Have We Learned From These Studies?

> **Efficacy** of pharmacological therapies is **not** the major limitation to achieving blood pressure control

Expert opinion.

Combination Therapy Superiority to Sequential Monotherapy
Initial Treatment of Hypertension

Means of Home SBP in the Monotherapy and Combination Therapy Arms



Days Since Randomization

- This **randomized double-blind trial** showed that initial combination therapy was associated with a better earlier response rate

MacDonald TM, et al. J Am Heart Assoc. 2017;6:e006986.

Therapeutic Inertia in Hypertension in Primary Care
A Dutch Cohort Study

Julius General Practitioners' Network (n = 530,564)

- Patients with a diagnosis of hypertension, SBP ≥ 140 mm Hg, and/or DBP ≥ 90 mm Hg, and 1 or 2 BP-lowering drug(s)
- **Therapeutic inertia** was defined as **not undertaking therapeutic action** in follow-up **despite uncontrolled BP**

- **10%** of all patients **with hypertension** had **uncontrolled BP** on 1 or 2 BP-lowering drugs
- **Therapeutic inertia was 87%**
- Older age, closer to target BP, and concurrent diabetes were associated with therapeutic inertia

Ali DH, et al. J Hypertens. 2021;39:1238-1245.

Why SPCs?

Need to move to more common use of 2-drug combination therapy as initial treatment

- To improve BP-lowering efficacy for achieving BP goals
- To increase the speed to achieve BP goal
- To overcome therapeutic inertia
- To reduce variability in BP response

Slide courtesy of Williams B, MD, FRCP. Williams B, et al. Eur Heart J. 2018;39:3021-3104.

Long-Term Event Rates, Risk Factors, and Treatment Patterns in Patients Qualifying for Dual BP-Lowering Therapy

Presented at ESH 2023

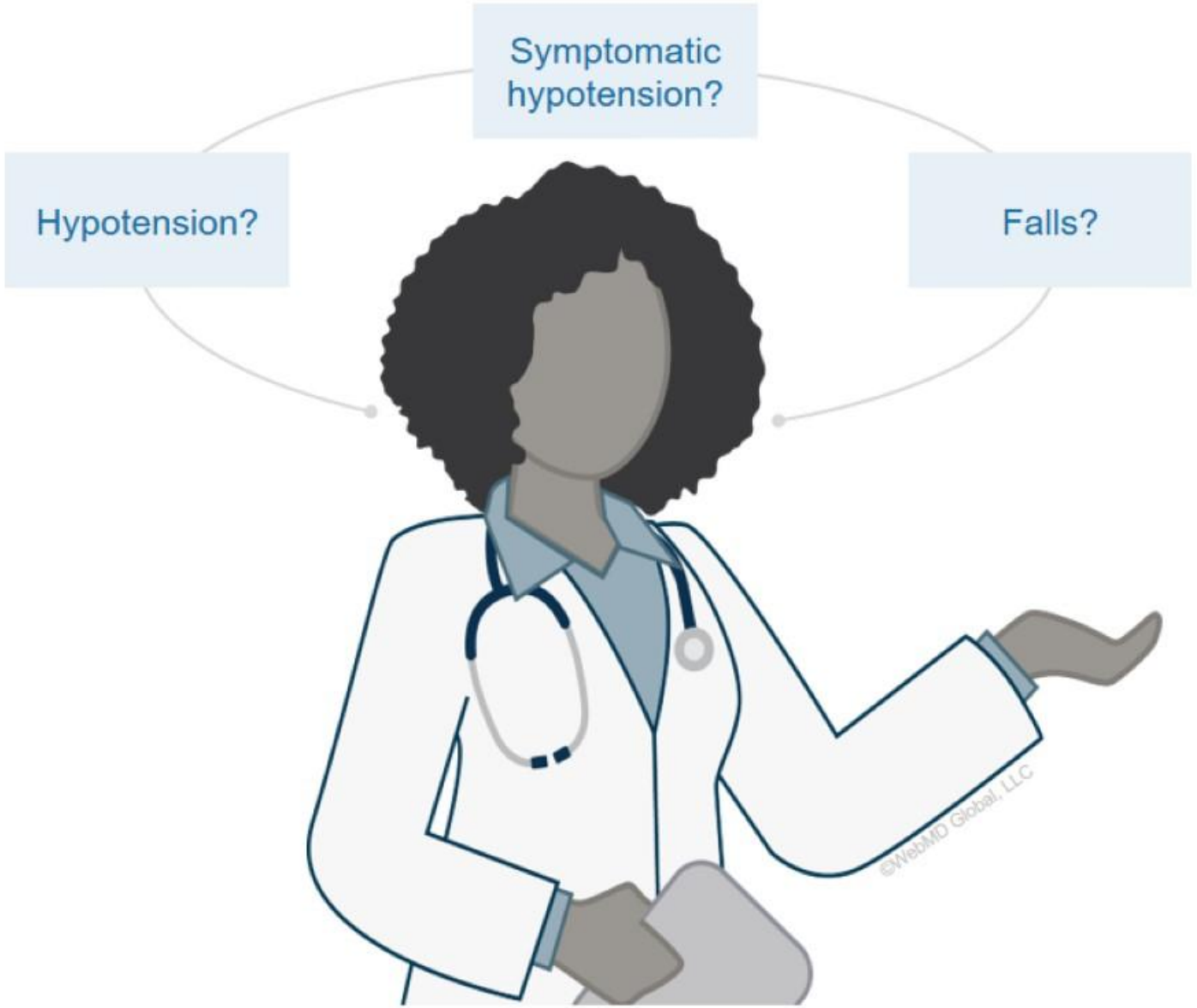
Database study

- CPRD, HES, and ONS databases in England 2005 to 2019
- 1,426,079 individuals aged ≥ 18 y with hypertension, qualifying for dual BP-lowering therapy per the ESC/ESH guidelines
- At variance with guidelines, **BP-lowering monotherapy** was the **most common treatment pattern** (42.6%-56.7% of patient-time) over a 5-y follow-up period

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics.

Coca A, et al. J Hypertens. 2023;41(suppl 3):e29-e30.

Clinicians' Worries About Starting 2 or More Antihypertensive Medications at Once



Faculty opinion.

Clinicians' Worries About Starting 2 Antihypertensives at Once

- Initiating therapy with 2 drugs in a single pill does not lead to high frequency of hypotension, symptomatic hypotension, or falls
- Most patients tolerate the treatment very well and have better BP control

Faculty opinion.

Studies Reporting Rates of Nonadherence in Patients With Treatment-Resistant Hypertension

Study	Adherence Assessment Method	% Non-Adherent
Daugherty, 2012	Prescription refill rate	12.4
Sim, 2013	Prescription refill rate	7
Burnier, 2001	MEMS	51.2
Grigoryan, 2013	MEMS	29
Brinker, 2014	Therapeutic drug monitoring	53.6
Ceral, 2011	Serum drug level	65.5
Ewen, 2015	Direct plasma and/or urine testing	48
Jung, 2013	Direct urine testing	52.6
Rosa, 2014	Direct blood testing	37.5
Strauch, 2013	Direct blood testing	32.4
Beaussier, 2015	Combination of plasma and urine tests, pill count, patient interview	18.3

MEMS, medication event monitoring system.
Hameed MA, et al. Drugs Context. 2019;8:212560.

Number of Antihypertensives and Adherence

Increased number of antihypertensive drugs prescribed associated with poor adherence

Chapman RH, et al. Drugs Aging. 2008;25:885-892; Gazmararian JA, et al. J Gen Intern Med. 2006;21:1215-1221; Ghembaza MA, et al. Curr Hypertens Rev. 2014;10:41-48; Holmes HM, et al. J Am Geriatr Soc. 2012;60:1298-1303.

What Have We Learned From These Studies?

> There's no reason to start monotherapy knowing that the **SPC is effective,** is **safe,** and in the long term **improves adherence and persistence**

Expert opinion.

SPC Leads to Improved BP Control and Improved Persistence

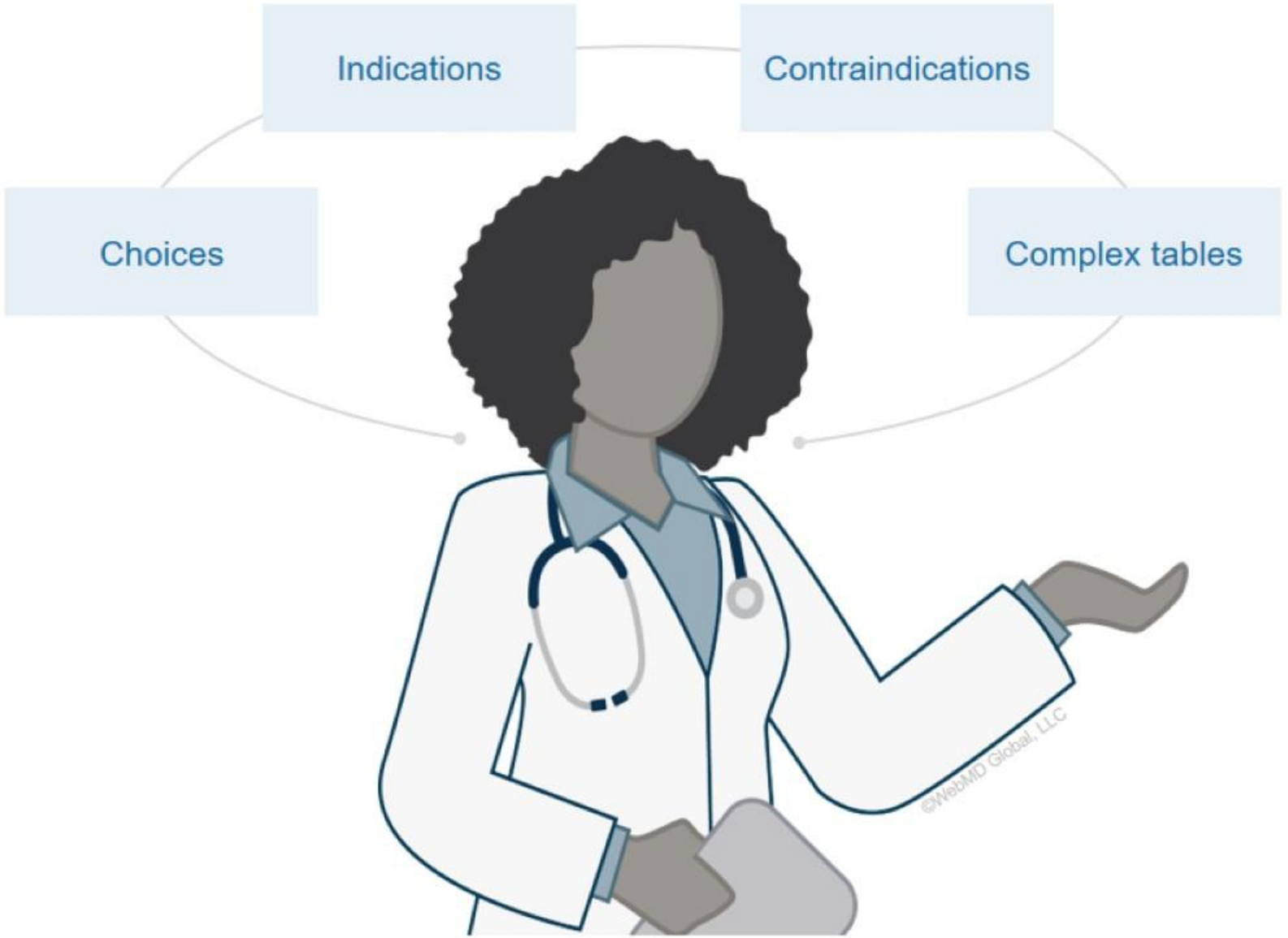
Starting with a single drug leads to **lower BP control rate** vs combination therapies

Starting with a single drug leads to **clinical inertia** lasting for years after treatment initiation

Rate of **treatment discontinuations is lower** in patients **starting treatment with combination therapy** than in patients starting a single-class antihypertensive regimen

Tocci G, et al. High Blood Press Cardiovasc Prev. 2020;27:587-596.

Complex Treatment Strategies in Previous Guidelines



Expert opinion

Combination Approach Simplifies Treatment Decisions

- Combination approach combining a RAS blocker with a CCB or a diuretic, for most patients, makes it much simpler to follow the guidelines
- Clear, simple algorithms in the latest guidelines
- Start with a single pill in most patients
  - Monotherapy for just a few patients

Faculty opinion.

Summary

Need to move to more common use of 2-drug combination therapy as initial treatment

- To improve BP-lowering efficacy for achieving BP goals
- To increase the speed to achieve BP goal
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- To reduce variability in BP response

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