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Why phenotypes and endophenotypes matter

Individualizing hypertension care



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Conflict of Interest Disclosure



In accordance with Resolution No. 1,595/2000 of the Federal Council of Medicine and RDC Resolution No. 96/2008 of the Brazilian Health Regulatory Agency – Anvisa, I declare that, during the past 12 months, I have had the following financial interests, arrangements, or affiliations with the organizations listed below:

Relationship	Companies / statement
Congress travel or accommodation	Servier, FQM, Novo Nordisk, Sanofi
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Scientific advisory committees	None declared
Institutional support from industry	None declared
Writing for industry-sponsored journals	None declared
Industry share ownership	None declared



The same office BP, different exposure





The same office BP, different exposure



Untreated adults	Patient A	Patient B
Office BP	152/94 mmHg	152/94 mmHg
Home BP	124/76 mmHg	148/92 mmHg
Suggested phenotype	White-coat hypertension	Sustained hypertension

Out-of-office measurement changes the clinical interpretation.



Phenotype, endophenotype and endotype

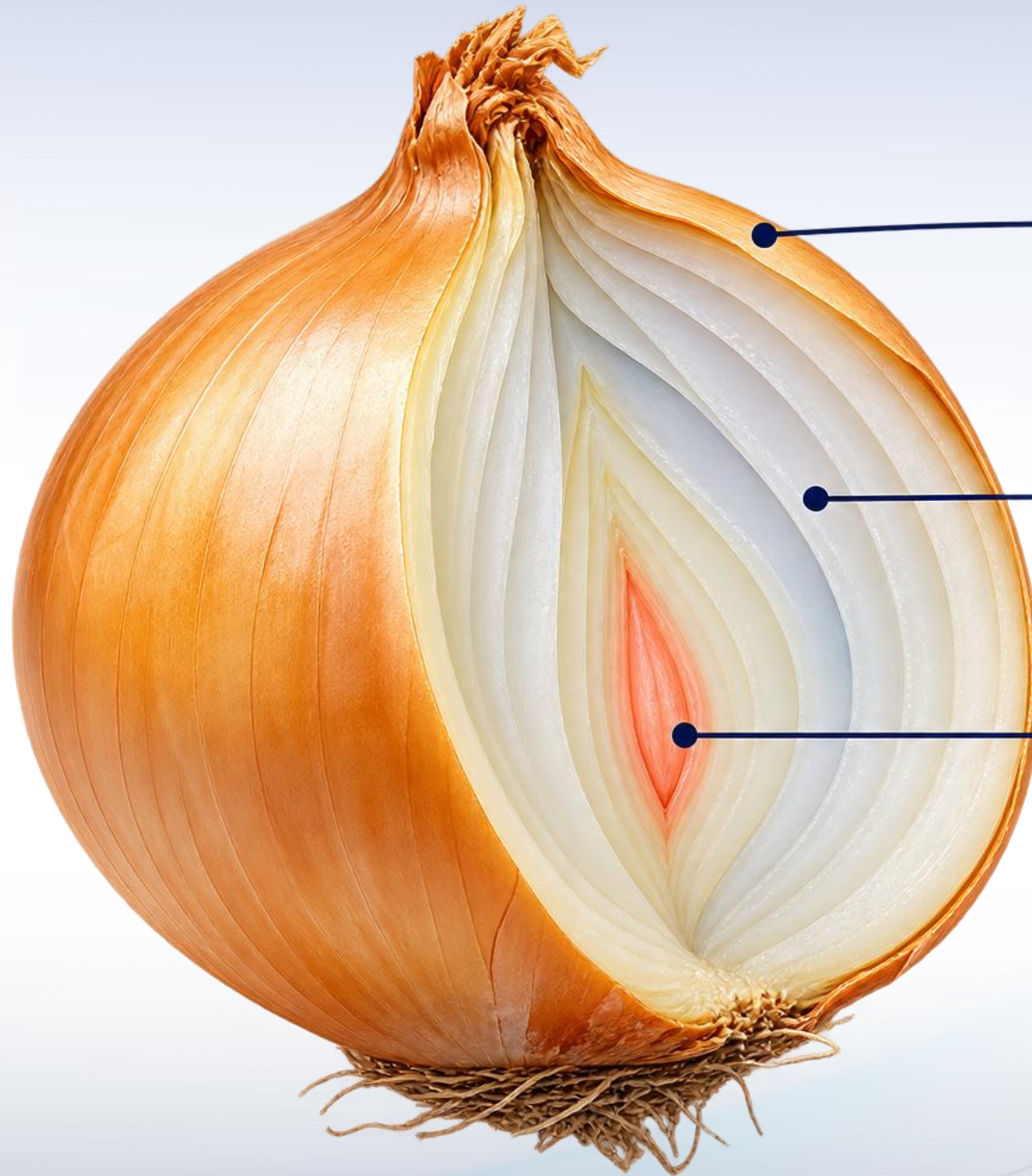


One patient, three levels of characterization

Phenotype	Endophenotype*	Endotype
Observable clinical pattern	Intermediate biological trait	Mechanistically defined subtype
Confirmed uncontrolled resistant hypertension	Suppressed renin + inappropriately high aldosterone	Primary aldosteronism: renin-independent aldosterone excess

A biological clue guides investigation.
A confirmed mechanism can guide treatment.

*Physiological usage in this example. A genetic endophenotype requires additional validation.



Phenotype

Clinical pattern

Endophenotype*

Biological profile

Endotype

Disease mechanism

*Physiological usage here; not a validated genetic endophenotype.



Office + home BP define four phenotypes



Brazilian 2025 diagnostic thresholds

Office BP	Home BP <130 AND <80	Home BP ≥ 130 OR ≥ 80
<140 AND <90	Normotension	Masked hypertension
≥ 140 OR ≥ 90	White-coat hypertension	Sustained hypertension

Treated patients: describe control status with the corresponding phenotype.

ESC 2024: home threshold $\geq 135/85$ mmHg.

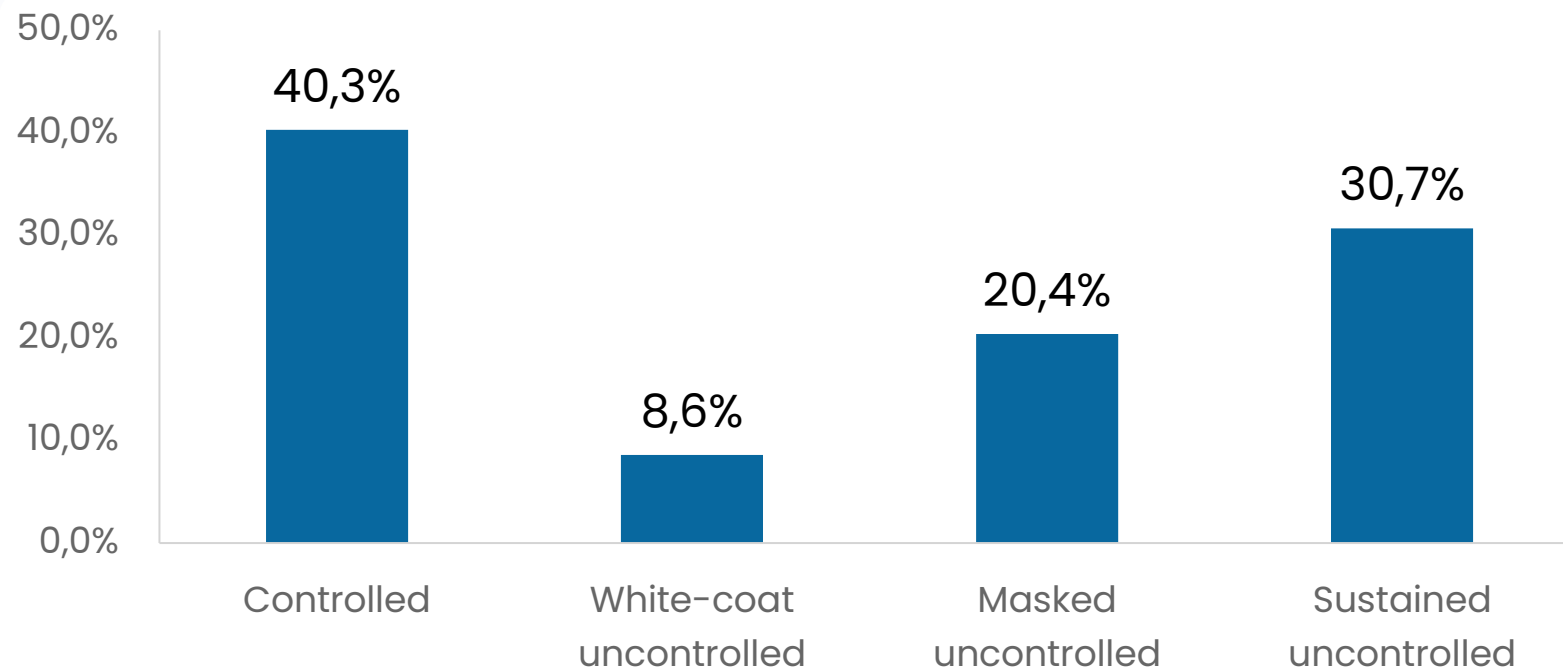
ABPM: 24 h $\geq 130/80$, daytime $\geq 135/85$, asleep $\geq 120/70$ mmHg.



Office BP can miss uncontrolled hypertension



7,852 treated patients in a Brazilian real-world study



20.4%

Masked uncontrolled hypertension

Observed in this sample. Generalizability and causality are limited.



Night-time BP and dipping answer different questions



Nocturnal hypertension

Mean asleep BP ≥ 120 systolic and/or ≥ 70 diastolic mmHg

Non-dipping pattern

Less than 10% fall in BP during sleep
Reproducibility is limited

BedMed: routine bedtime dosing did not improve clinical outcomes.

3,357 participants. Adjusted HR 0.96 (95% CI 0.77–1.19).



Resistance requires confirmation



Apparent resistance

Check technique, adherence, doses and substances that raise BP

Confirmed resistance

Uncontrolled out-of-office BP despite three appropriate drugs, including a diuretic

The phenotype identifies a need to investigate mechanisms.



One patient, three levels of characterization



Clinical phenotype

Confirmed uncontrolled resistant hypertension

Biochemical profile*

Suppressed renin + inappropriately high aldosterone

Mechanistic endotype

Renin-independent aldosterone excess
Primary aldosteronism after evaluation

Treatment: mineralocorticoid receptor antagonist or adrenalectomy, according to lateralization, eligibility and patient preference.

*Broad physiological use of “endophenotype”. Low renin alone is insufficient.



PATHWAY-2 supports a salt-retaining mechanism



-8.70 mmHg

Home systolic BP difference vs placebo

95% CI -9.72 to -7.69

Lower renin predicted greater response.
Renin explained about 11% of response variability.

BP lowering does not establish a diagnosis or prove an event benefit.



Young isolated systolic hypertension



Overlapping physiological profiles

Hyperdynamic

Higher stroke volume
and/or cardiac output

Metabolic

Obesity and associated
metabolic abnormalities

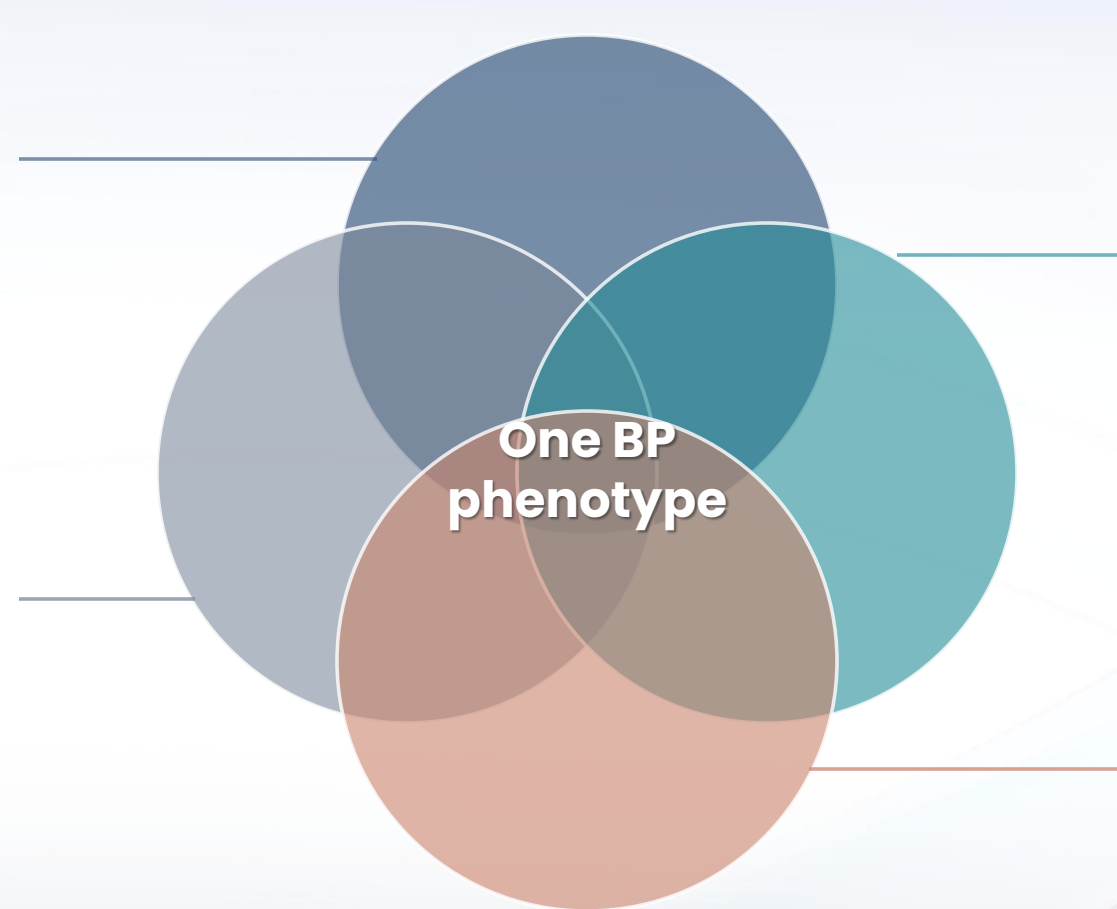
Sympathetic

Possible autonomic
contribution

Heart rate alone is nonspecific

Vascular

Greater aortic stiffness
or peripheral BP
amplification



Profiles can overlap. No validated four-group prescribing algorithm.

Conceptual schematic. Areas and overlaps do not represent measured proportions. BP: blood pressure.

Palatini et al. J Hypertens. 2018;36:1222–1236. McEvoy et al. Eur Heart J. 2024;45:3912–4018.



Individualizing hypertension treatment

Clinical clues guide evaluation. Treatment follows established indications.

Clinical clue	Possible mechanism	Treatment when indicated
 Low renin	 Sodium / volume retention	Thiazide-type diuretic when indicated. MRA for resistant hypertension or PA.
 Obesity + OSA	 Metabolic and sympathetic factors	Obesity treatment + OSA care, including PAP. Tirzepatide in eligible patients.*
 Tachycardia	 Possible sympathetic activation	Evaluate the cause. Beta-blocker for an appropriate clinical indication.
 Wide pulse pressure	 Possible arterial stiffness	DHP-CCB or thiazide-type diuretic for systolic hypertension, when indicated.

A clue alone does not establish an endotype or determine a prescription.

*Tirzepatide trial evidence: adults with obesity and moderate-to-severe OSA.

MRA: mineralocorticoid receptor antagonist. PA: primary aldosteronism. OSA: obstructive sleep apnea.

PAP: positive airway pressure. DHP-CCB: dihydropyridine calcium-channel blocker.

Sources: ESC Hypertension Guidelines 2024; Endocrine Society PA Guideline 2025; Malhotra et al., NEJM 2024 (SURMOUNT-OSA).



PHYSIC: individual drug response



Randomized, double-blind, repeated crossover trial (Sweden)



280 randomized participants
270 contributed treatment data

Four drugs in random order*
Two treatments repeated
Daytime systolic BP by ABPM

Grade 1 hypertension
Low cardiovascular risk

4.4 mmHg

Estimated potential
additional systolic
BP reduction

Individualized drug selection
vs a fixed drug choice

Responses differ between patients.
The 4.4 mmHg gain is a model-based estimate.

Genotype-guided prescribing and cardiovascular outcomes were not tested.

*Drugs: lisinopril, candesartan, hydrochlorothiazide, amlodipine. ABPM: ambulatory blood pressure monitoring. Sundström et al. JAMA. 2023;329:1160–1169. doi:10.1001/jama.2023.3322.



Pharmacogenomics-guided therapy (2026)



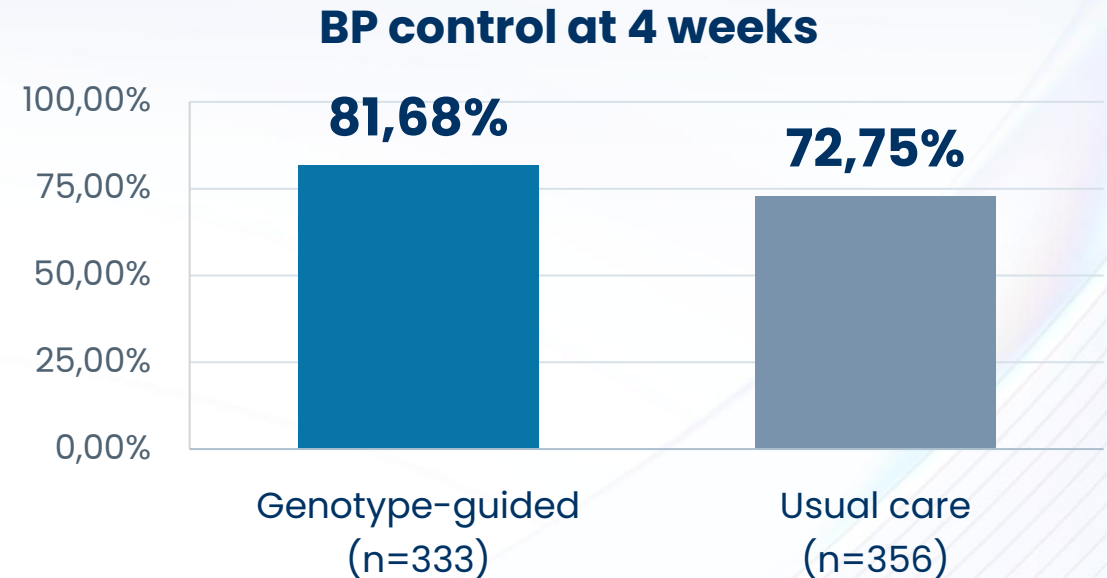
Randomized, single-blind trial in 776 patients at 8 Chinese hospitals



4 weeks of standardized care

Then 4 weeks of
treatment:
7-polymorphism-guided
therapy vs usual care

Office BP endpoint:
<140/90 mmHg



+8.93 percentage points

Per-protocol analysis: 689 patients

Short-term BP control improved. Long-term clinical benefit remains unproven.

Limits: 4-week intervention, unblinded clinicians, unquantified adherence. BP: blood pressure.

unadjusted P=0.005, Holm-Bonferroni adjusted P=0.015



What changes in practice



Out-of-office BP establishes the clinical phenotype.

A biological clue guides further investigation.

A confirmed mechanism can support targeted treatment.

Risk, organ damage and tolerability remain part of every decision.



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Thank you

Audes Feitosa
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