Tiếp Cận Điều Trị THA Tối Ưu Theo Các Khuyến Cáo Mới Góc Nhìn Từ Các Chứng Cứ Mới

Approaching Optimal Management in Hypertension From Updated Guidelines And New Evidences

PGS. TS. BS. TRẦN VĂN HUY FACC FESC

Phó Chủ Tịch Phân Hội Tăng Huyết Áp Việt Nam

Những yếu tố quyết định chọn lựa thuốc trong điều trị BTM. Mục tiêu tiếp cận tối ưu

- Giảm tối đa nguy cơ về sinh bệnh và tử vong:
  - Hiệu qủa:
    - **Giảm tử vong chung,**
    - ***Giảm tử vong tim mạch và bệnh thận***
    - **Giảm các biến cố tim mạch và can thiệp**
    - **Bảo vệ các cơ quan đích**
    - **Cải thiện và tăng cường chất lượng cuộc sống**
  - An toàn: **Không có nguy cơ gây ung thư, ít tác dụng phụ…**
  - Kinh tế & Hiệu qủa: **Lợi ích chi phí giá / hiệu qủa**
  - Tuân thủ điều trị. Cao

Chẩn đoán THA Qua Các Khuyến Cáo

mmHg	ACC/AHA 2017*	ESH/ESC 2018**	VSH/VNHA 2018***	CHEP 2019****	NICE 2019*****
HAPK	130/80	140/90	140/90	140/90 +	140/90+
HA ngày	130/80	135/85	135/85	135/85	135/85
HA 24 giờ HA TN	125/75 130/80	130/80 135/85	130/80 135/85	130/80	 135/85

+HA PK : HATT/HATTr >180/110-120mmHg: THA và điều trị nggay

+HAPK: huyết áp phòng khám; HATN: huyết áp tại nhà

* Whelton PK, et al JACC 2017**.** **ESC/ESC guideline EH Journal (2018) 00, 1–98 ;
VSH/VNHA 2018; * Canada 2019. ***** NICE guideline Published: 28 August 2019

Đích HA Trong Điều Trị THA Qua Các Khuyến Cáo

	ACC/AHA 2017*	ESH/ESC 2018**	VSH/VNHA 2018***	CHEP 2019***	NICE 2019*****
HATT/HATTr mmHg	**<130/80**	<140/90 ⬇ **<130/80** Không dưới 120/70	<140/90 ⬇ **<130/80** Không dưới 120/70	<140/90 ĐTĐ **<130/80** Nguy cơ cao <120/70	<140/90 >80t <150/90 HA ngày <135/85

*Whelton PK, et al JACC 2017**.** ** ESC/ESC guideline EHJ (2018) 00, 1–98 ; *** VSH/VNHA 2018; **** Canada 2019. ***** NICE guideline Published: 28 August 2019

Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis

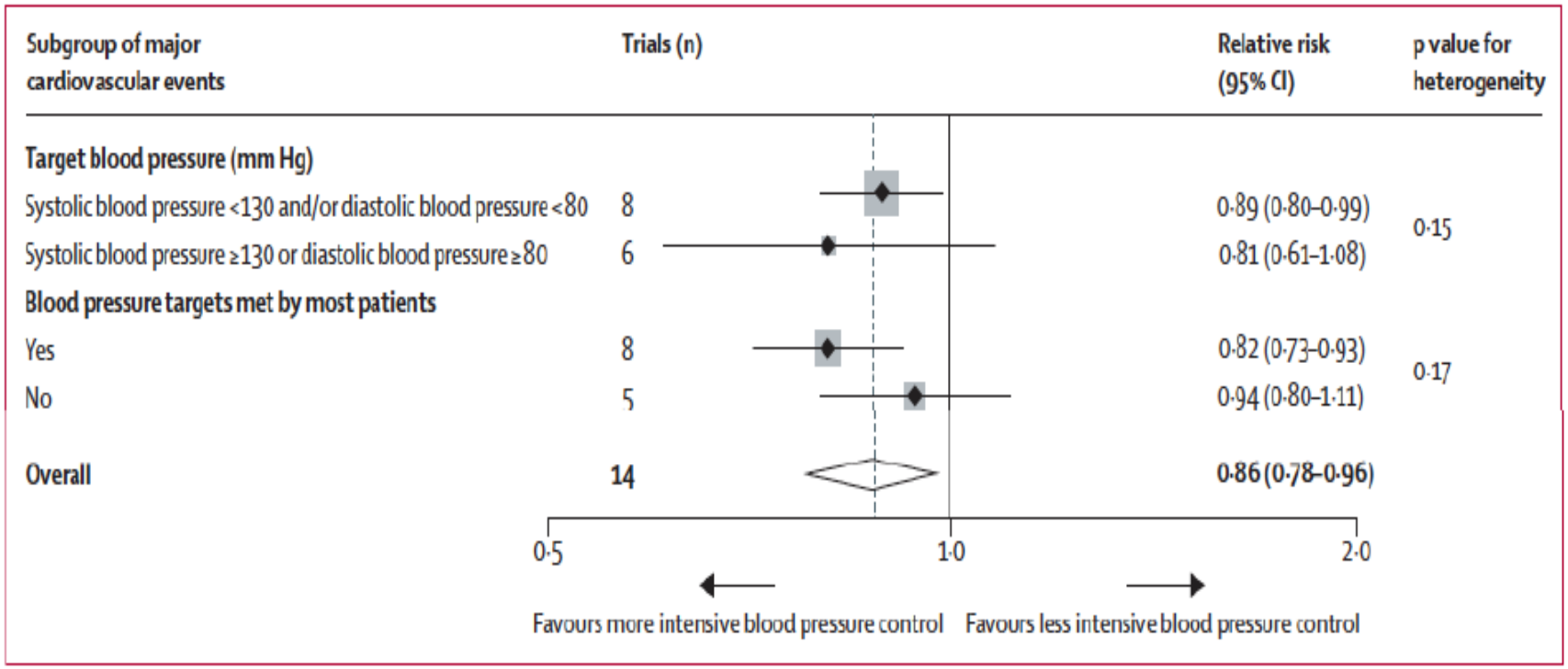
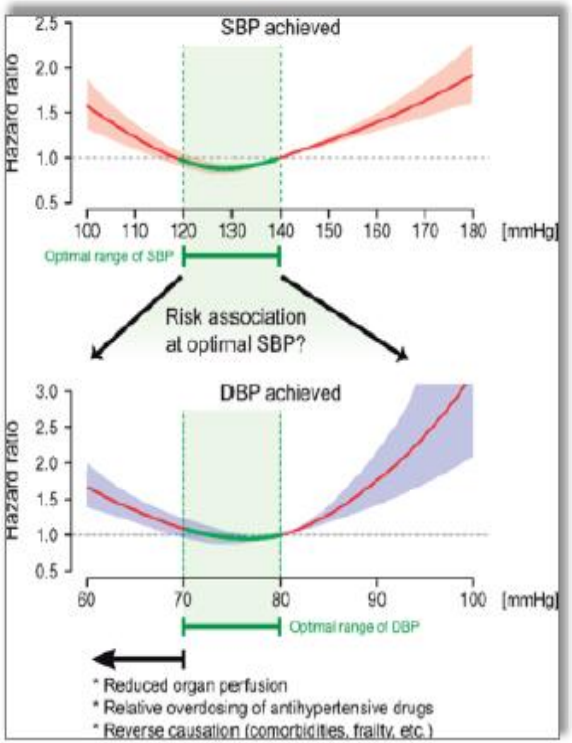


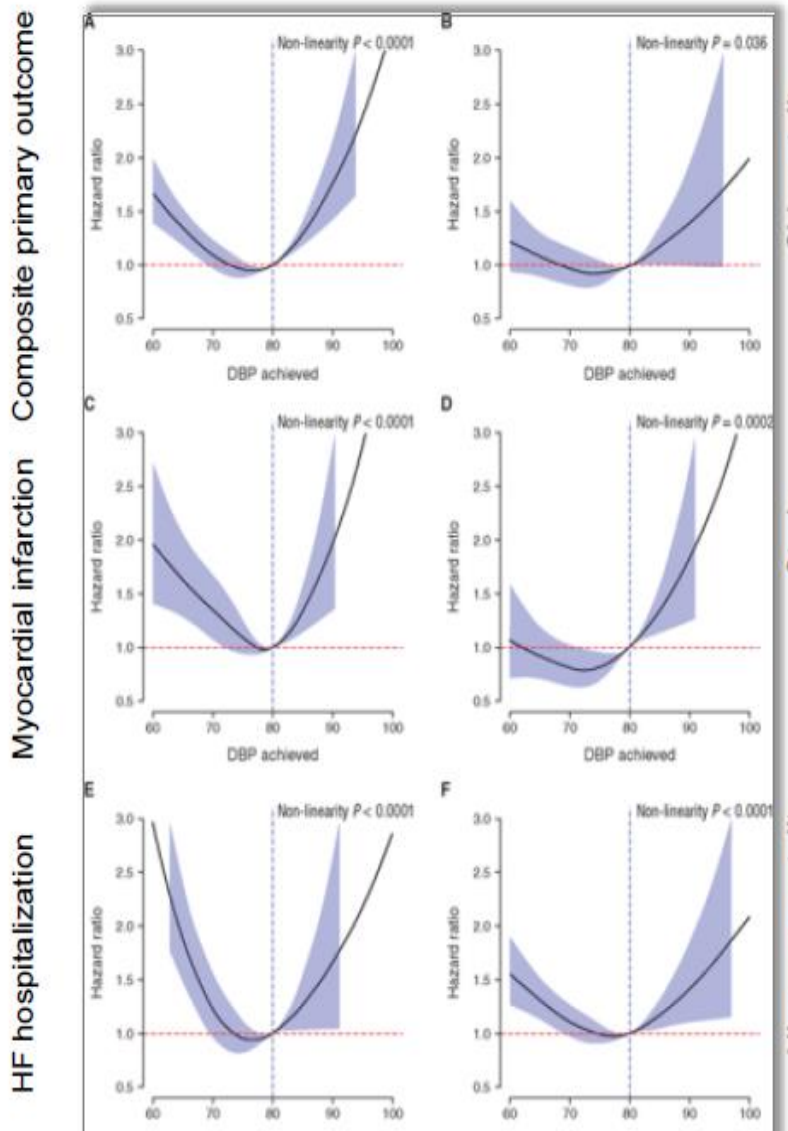
Figure 4: Effects of intensive blood pressure lowering on the risk of major cardiovascular events in subgroups of trials

Xie et al Lancet 2016. 387; 435

Target DBP in Patients Achieving 130-139 mm Hg SBP



ONTARGET and TRANSCEND: Patients >55 ys with CV disease randomized to ramipril, telmisartan, or the combination 16099 of 31546 patients achieved 120-139 mm Hg SBP. Adjusted for all available potential confounding factors.



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

Các Nhóm Thuốc Chính Trong Điều Trị THA Qua Các Khuyến Cáo

	ACC/AHA 2017*	ESH/ESC 2018**	VSH/VNHA 2018***	CHEP 2019****	NICE 2019*****
	ƯCMC, CTTAII CKCa LT	ƯCMC, CTTAII CKCa LT CB	ƯCMC, CTTAII CKCa LT *CB*	ƯCMC, CTTAII CKCa LT CB	ƯCMC, CTTAII CKCa LT

*Whelton PK, et al JACC 2017.** ESC/ESC guideline European Heart Journal (2018) 00, 1–98
VSH/VNHA 2018; * Canada 2019.***** NICE guideline Published: 28 August 2019

Reboussin DM, et al.
2017 High Blood Pressure Systematic Review

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

- No class of medications (i.e.,angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, or beta blockers) was significantly better than thiazides and thiazide-like diuretics as a first-line therapy for any outcome
- The RRs of cardiovascular mortality were 1.1 (95% CrI: 0.92–1.3) for ACEIs; 1.1 (95% CrI: 0.87–1.5) for ARBs; **1.2 (95% CrI: 0.98–1.4) for beta blockers**; and 1.0 (95% CrI: 0.86–1.2) for CCBs, compared with THZ
- There were no significant risks of all-cause mortality, MI, or renal outcomes for any of the antihypertensive medication class to class comparisons

Chiến Lược Phối Hợp Thuốc Sớm Với Viên Cố Định Liều Ngay Từ Đầu. Chứng Cứ?

Hầu hết các khuyến cáo điều thống nhất nên kết hợp thuốc ngay từ đầu: ACC/AHA, CHEP, ESH/ESC, VSH/VNHA

Riêng NICE 2019 không ủng hộ mà qua 4 bước đơn, phối hợp 2,3,4 thuốc

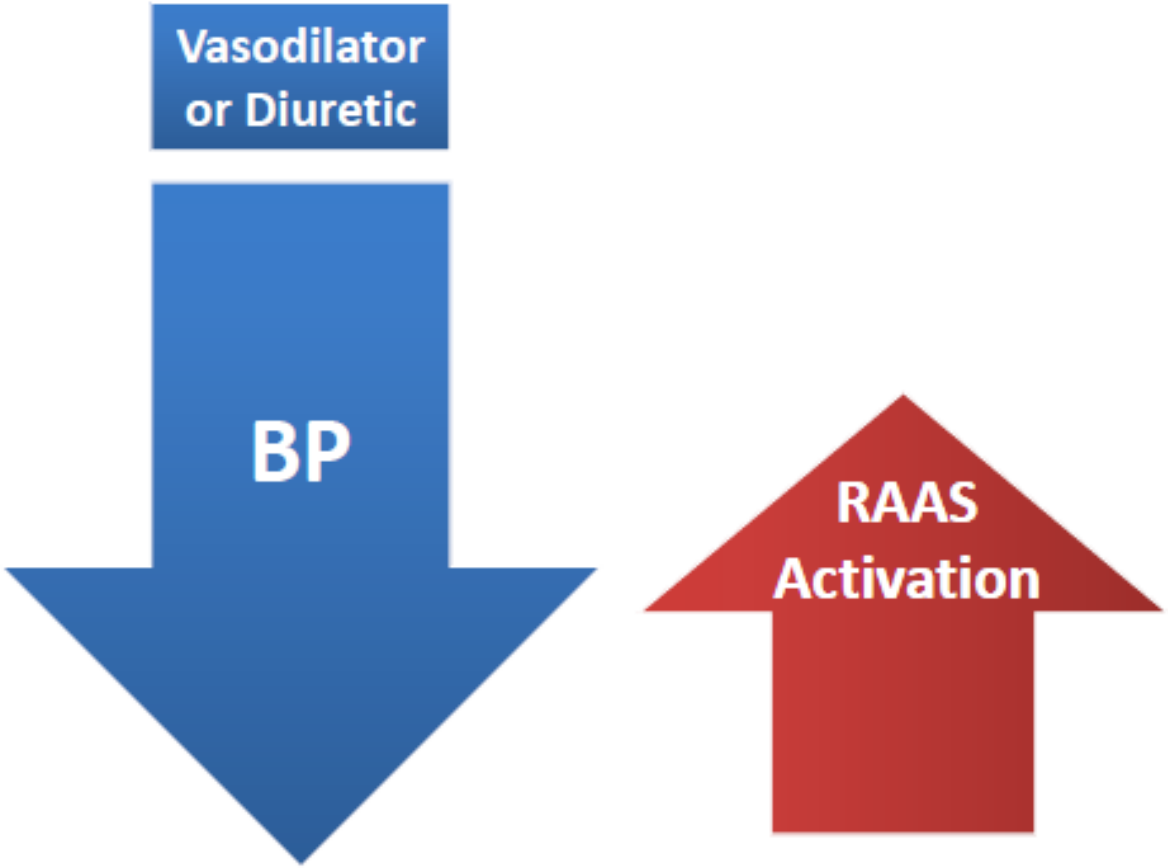
Whelton PK, et al JACC 2017. ESC/ESC guideline European Heart Journal (2018) 00, 1–98 ; VSH/VNHA 2018; Canada 2019. NICE guideline Published: 28 August 2019

4 lý do nên phối hợp thuốc ngay từ đầu đối với BN THA

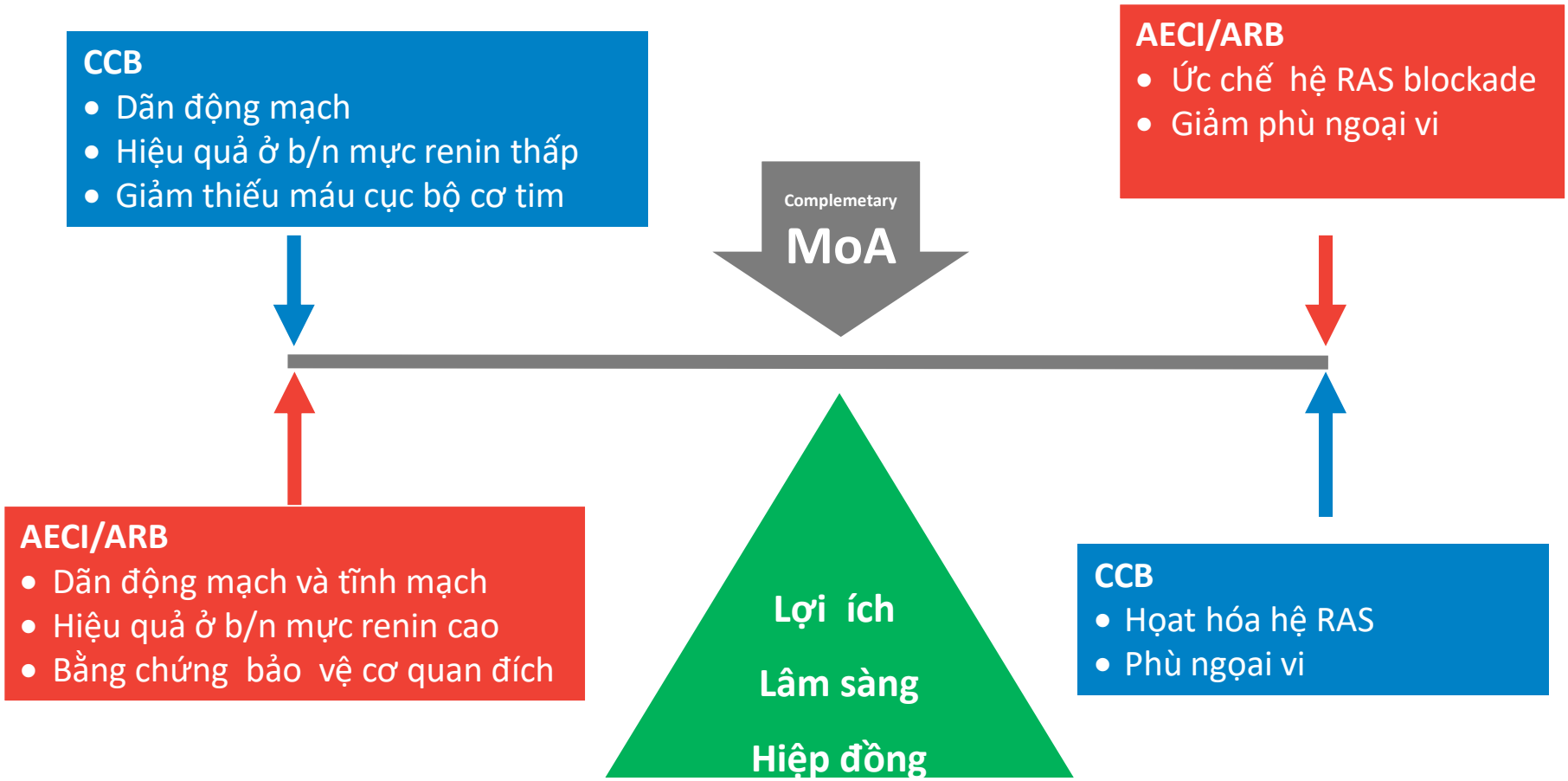
1. Phối hợp thuốc giúp giảm HA mạnh hơn và nhanh hơn về mức mong muốn
2. Khi BN có nguy cơ cao, các biến cố có thể xảy ra trong thời gian ngắn → hạ HA phải được thực hiện nhanh chóng
3. Trong một số NC, hiệu quả bảo vệ cơ quan đích của điều trị THA có thể xuất hiện nhanh sau khi đạt mức HA mục tiêu
4. Việc phối hợp thuốc từ đầu làm tăng độ tuân trị

Mancia G, et al. *J Hypertens.* 2009;27:2121-2158.

Những hạn chế của điều trị đơn trị liệu: sự kích thích chống lại do cơ chế điều chỉnh



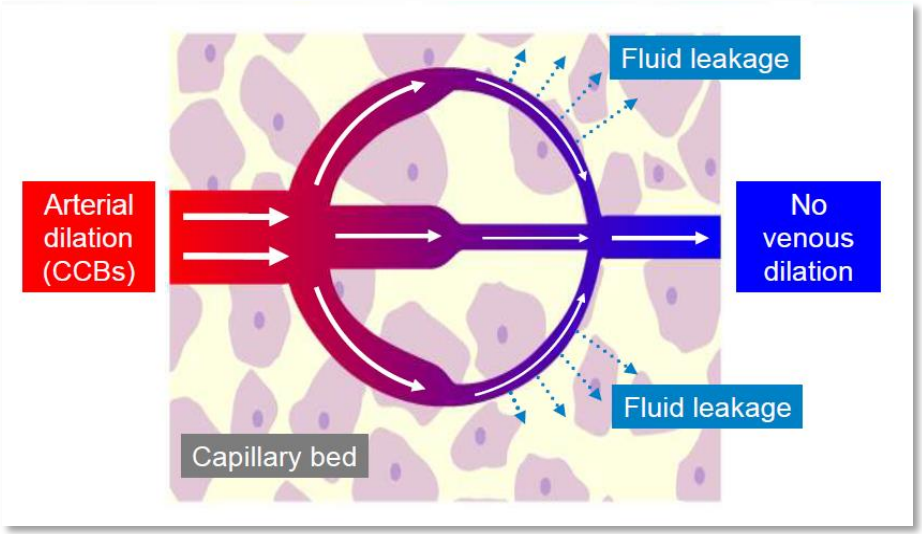
Phối Hợp AECIs + Chẹn Kênh Canxi
Hiệu ứng hiệp đồng

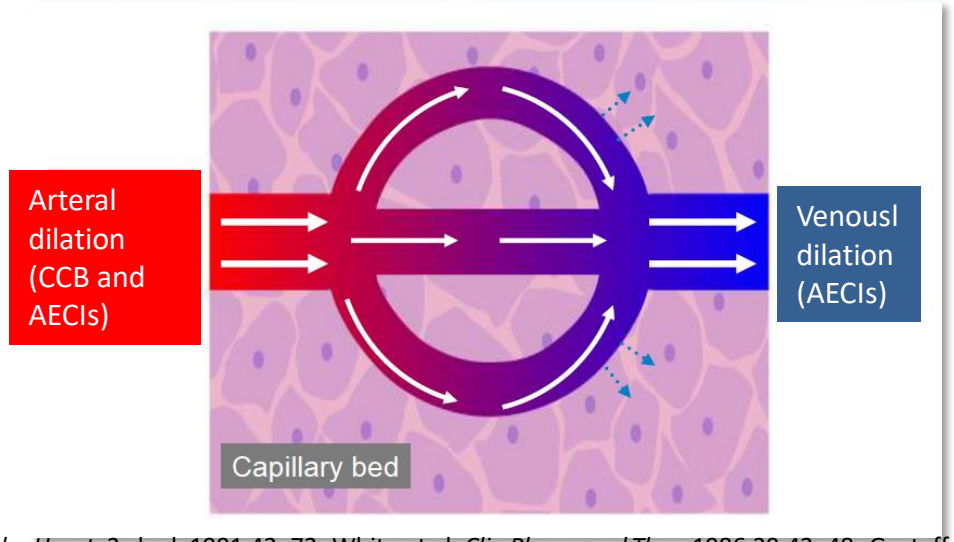


Mistry et al. *Expert Opin Pharmacother.* 2006;7:575–581; Sica. *Drugs.* 2002;62:443–462;
Quan et al. *Am J Cardiovasc Drugs.* 2006;6:103–113.

Thuốc ƯCMC giảm hiện tượng phù ngoại vi do thuốc chẹn kênh Ca

CCB



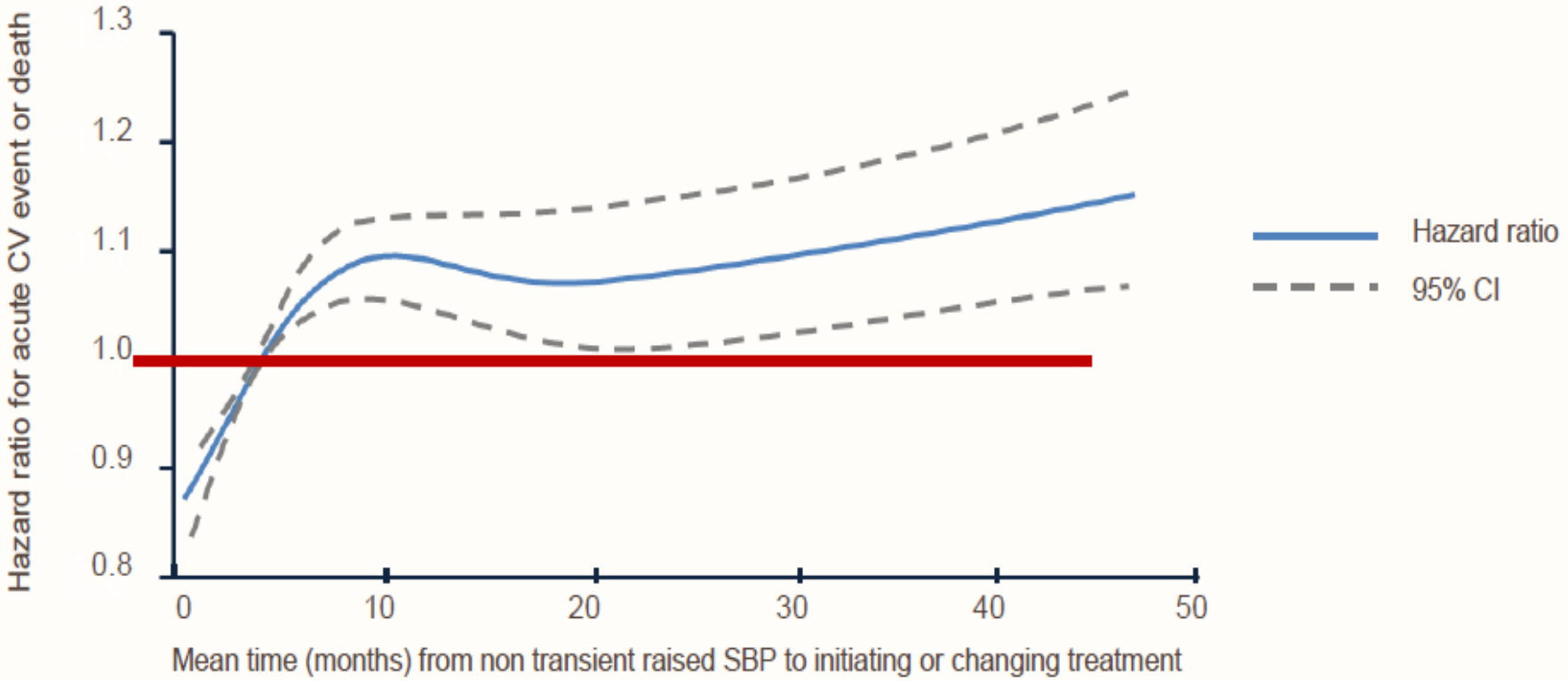


+ AECIs

Opie et al. In: Opie LH, editor. *Drugs for the Heart*. 3rd ed. 1991:42–73; White et al. *Clin Pharmacol Ther.* 1986;39:43–48; Gustaffson. *J Cardiovasc Pharmacol.* 1987;10:S121–S131; Messerli et al. *Am J Cardiol.* 2000;86:1182–1187.
Makani H, Bangalore S, Romero J, et al. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. Am J Med. 2011;124:128–135.

Delaying BP control increases CV risk

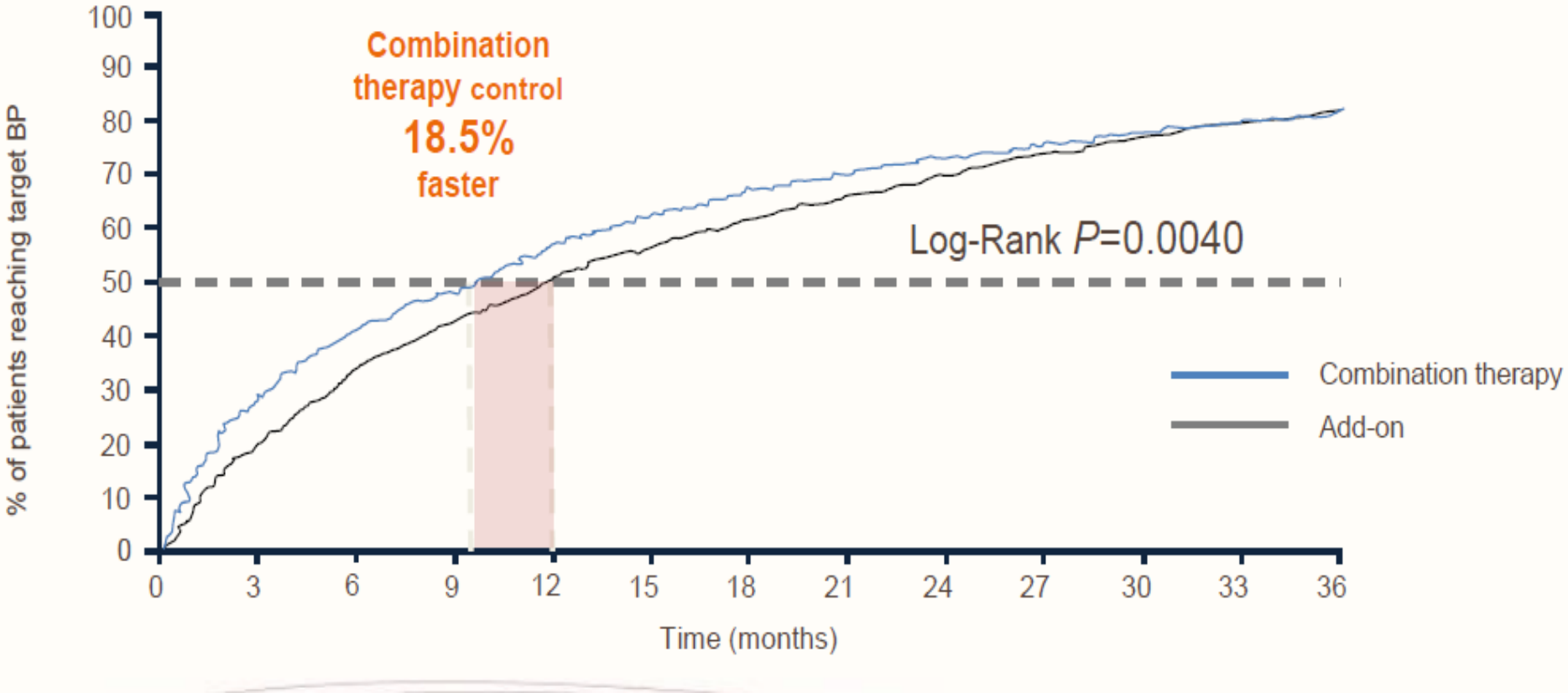
•**Delays of greater than 6 weeks,** after SBP elevation, before initiating or increasing treatment **significantly increase risk** of an acute CV event or death.



Outcome risk increased progressively from the lowest (0–1.4 months) to the highest fifth of time to medication intensification (hazard ratio 1.12, 1.05 to 1.20; P = 0.009 for intensification between 1.4 and 4.7 months after detection of elevated blood pressure)

Xu W et al. *BMJ. 2015;350:h158*

Initial combination therapy controls BP faster than monotherapy…



Gradman AH et al. *Hypertension. 2013;61:309-318.*

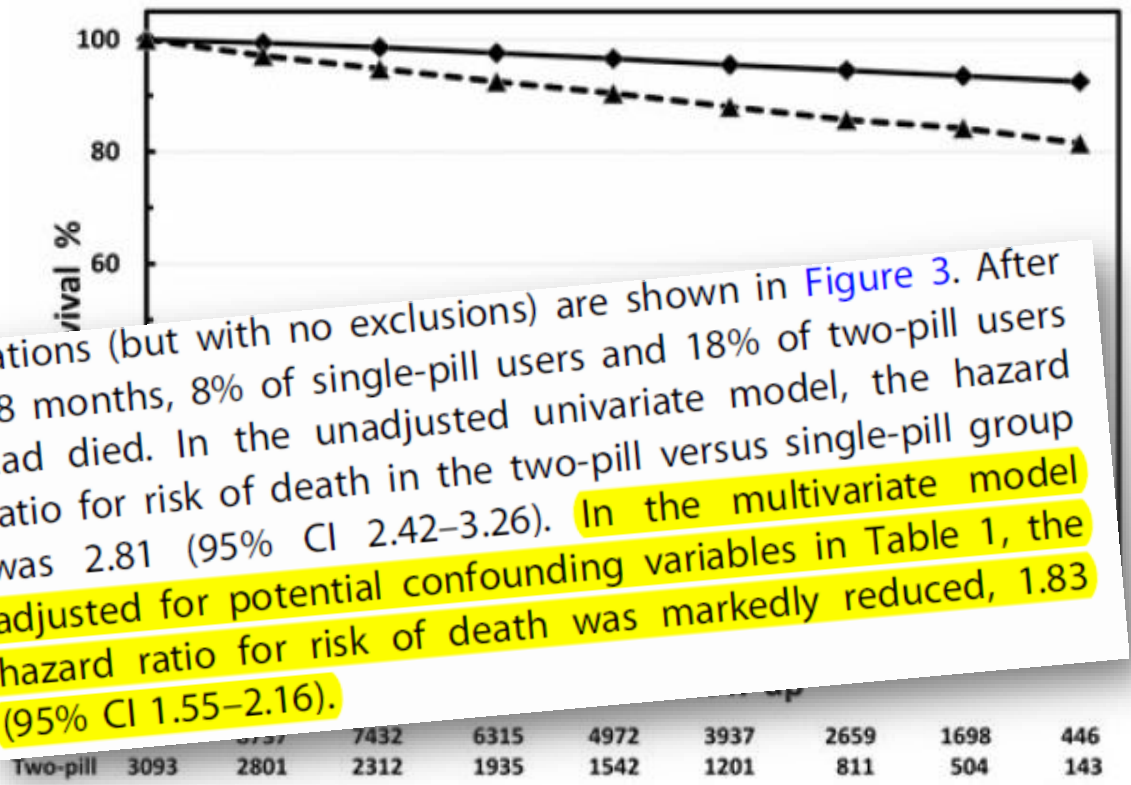
Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

SINGLE-PILL COMBINATION
REDUCE THE RISK OF DEATH

Long-term persistence with single-pill, fixed-dose combination therapy versus two pills of amlodipine and perindopril for hypertension: Australian experience

The FIRST TIME

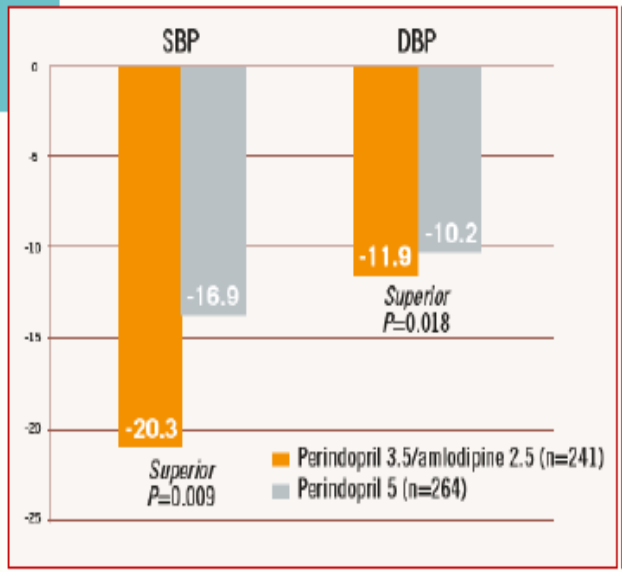


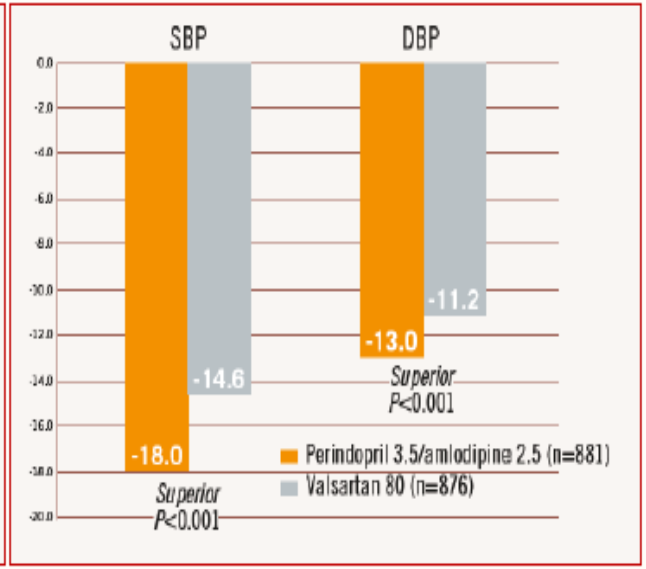
cations (but with no exclusions) are shown in Figure 3. After 48 months, 8% of single-pill users and 18% of two-pill users had died. In the unadjusted univariate model, the hazard ratio for risk of death in the two-pill versus single-pill group was 2.81 (95% CI 2.42–3.26). In the multivariate model adjusted for potential confounding variables in Table 1, the hazard ratio for risk of death was markedly reduced, 1.83 (95% CI 1.55–2.16).

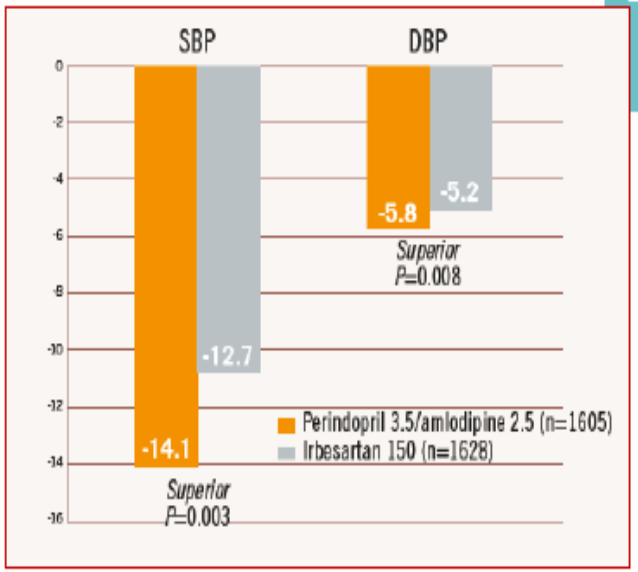
x2

Leon A. Simons et al *Current Medical Research and Opinion,* 2017 Oct;33(10):1783-1787

Better blood pressure-lowering efficacy and similar tolerability compared with RAAS monotherapies





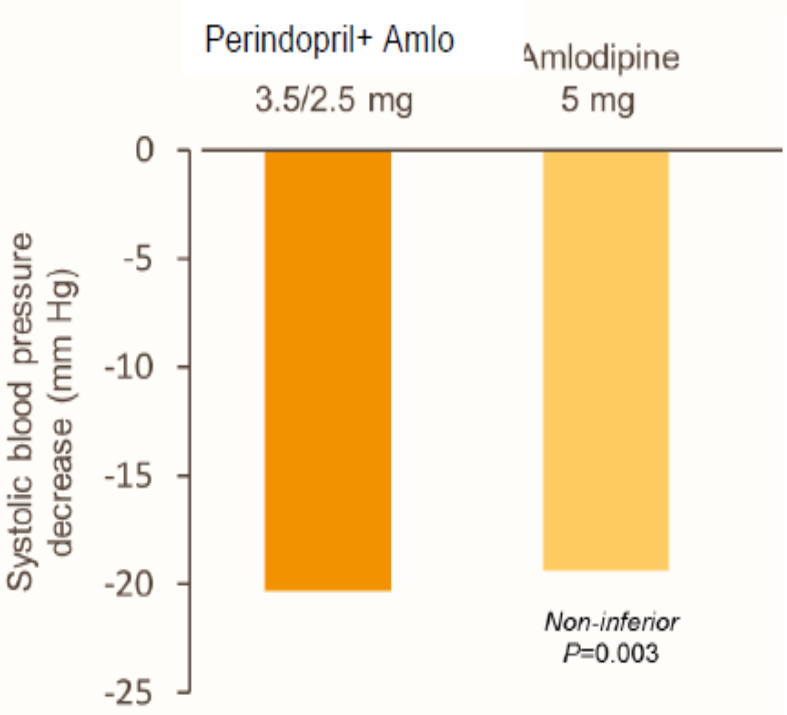


	Peri + Amlo 3.5 mg/2.5 mg n=2753	Comparator n=3072	*P*-value
EAE*	28.4%	27.2%	0.319
Severe EAE	0.8%	1.2%	0.112
Peripheral edema	2.1%	1.6%	0.165
Hypotension	-	0.1%	0.625
Headache	2.1%	3.0%	0.040
Cough	4.5%	1.0%	<0.001

Laurent S. *J Hypertens. Vol 34, e-supplement 2, September 2016 – PP.26.16*

Similar blood pressure-lowering efficacy with better tolerability compared to CCB

▪1. Laurent S et al. *J Hypertens*. 2015;33(3):653-662.



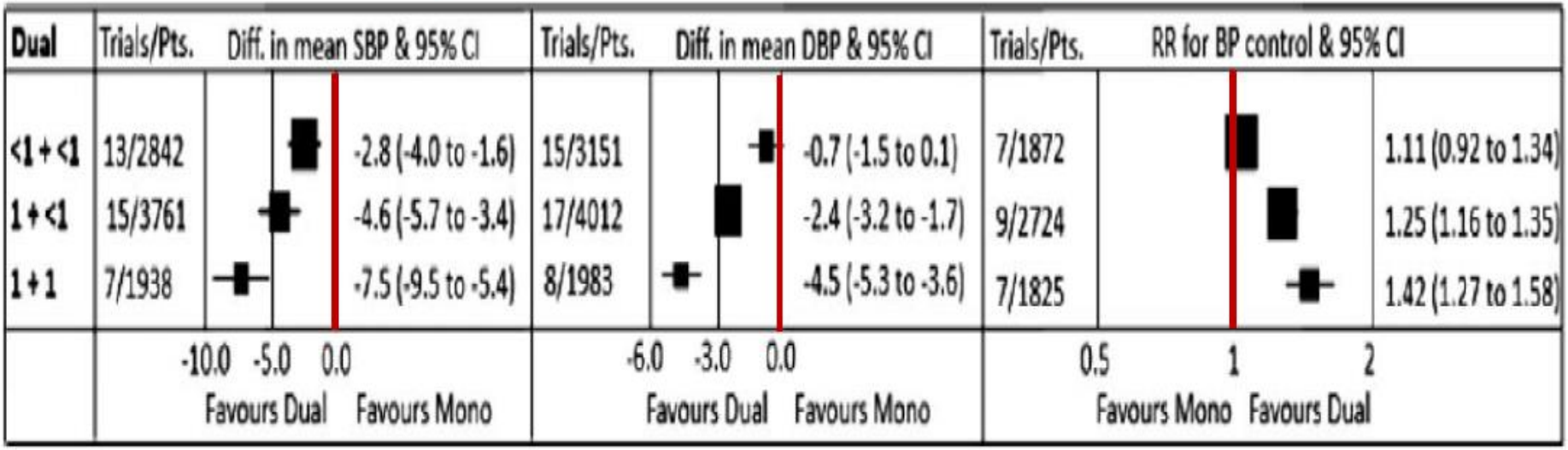
	Peri + Amlo 3.5 mg/2.5 mg n=249	Amlodipine 5 mg n=264
Any emergent adverse event n(%)	18.9%	21.6%
Edema n(%)	1.6%	4.9%*
Cough n(%)	0.8%	0.4%
Flushing n(%)	0.4%	1.9%
Hypotension n(%)	0	0

* Significant, $P<0.05$

Efficacy and Safety of Dual Combination Therapy as Initial Treatment for Hypertension - A Systematic Review and Meta-Analysis

33 trials, 13,095 participants, mean baseline mean BP 155/100mmHg
Compared low-standard dose dual combinations <1 + <1, 1 + <1, 1+1

Blood Pressure Lowering - Initial Dual versus Mono therapy

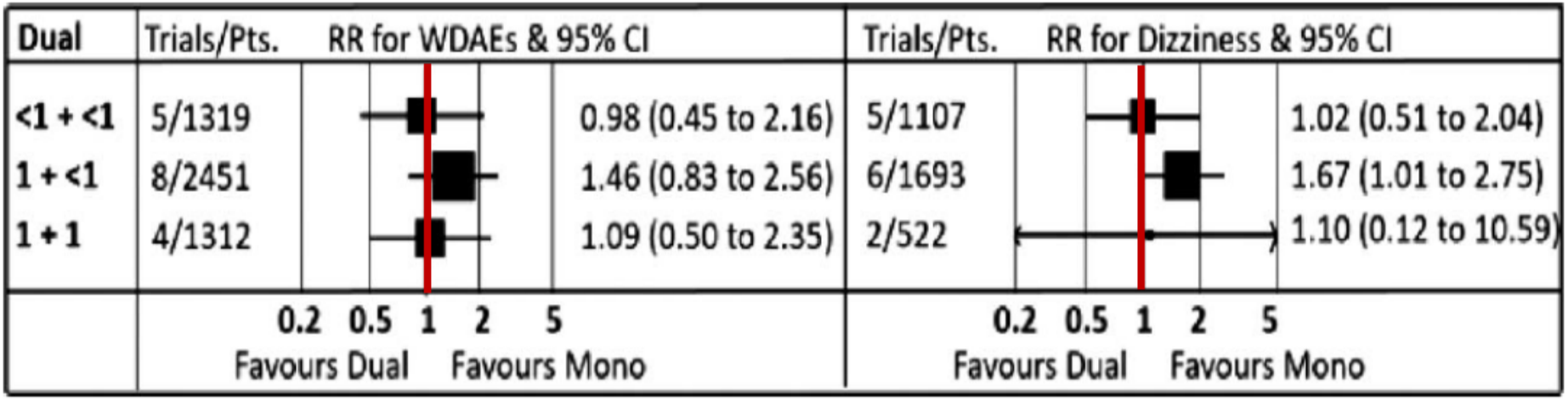


Salam A, et al. J Hypertens 2019

Efficacy and Safety of Dual Combination Therapy as Initial Treatment for Hypertension - A Systematic Review and Meta-Analysis

33 trials, 13,095 participants, mean baseline mean BP 155/100mmHg
Compared low-top standard dose dual combinations <1 + <1, 1 + <1, 1+1

Withdrawals for Adverse Events (WDAE) - Dual vs. Mono therapy



Conclusion: Compared with standard-dose monotherapy, initiating treatment with low-standard-dose dual combination therapy is more efficacious without increasing withdrawals for adverse events…..these data support the ESC-ESH and US Hypertension guideline recommendations…..

Salam A, et al. J Hypertens 2019

Clinical outcomes among individuals treated with multipill or FDC antihypertensive regimens, primary intention-to-treat analysis

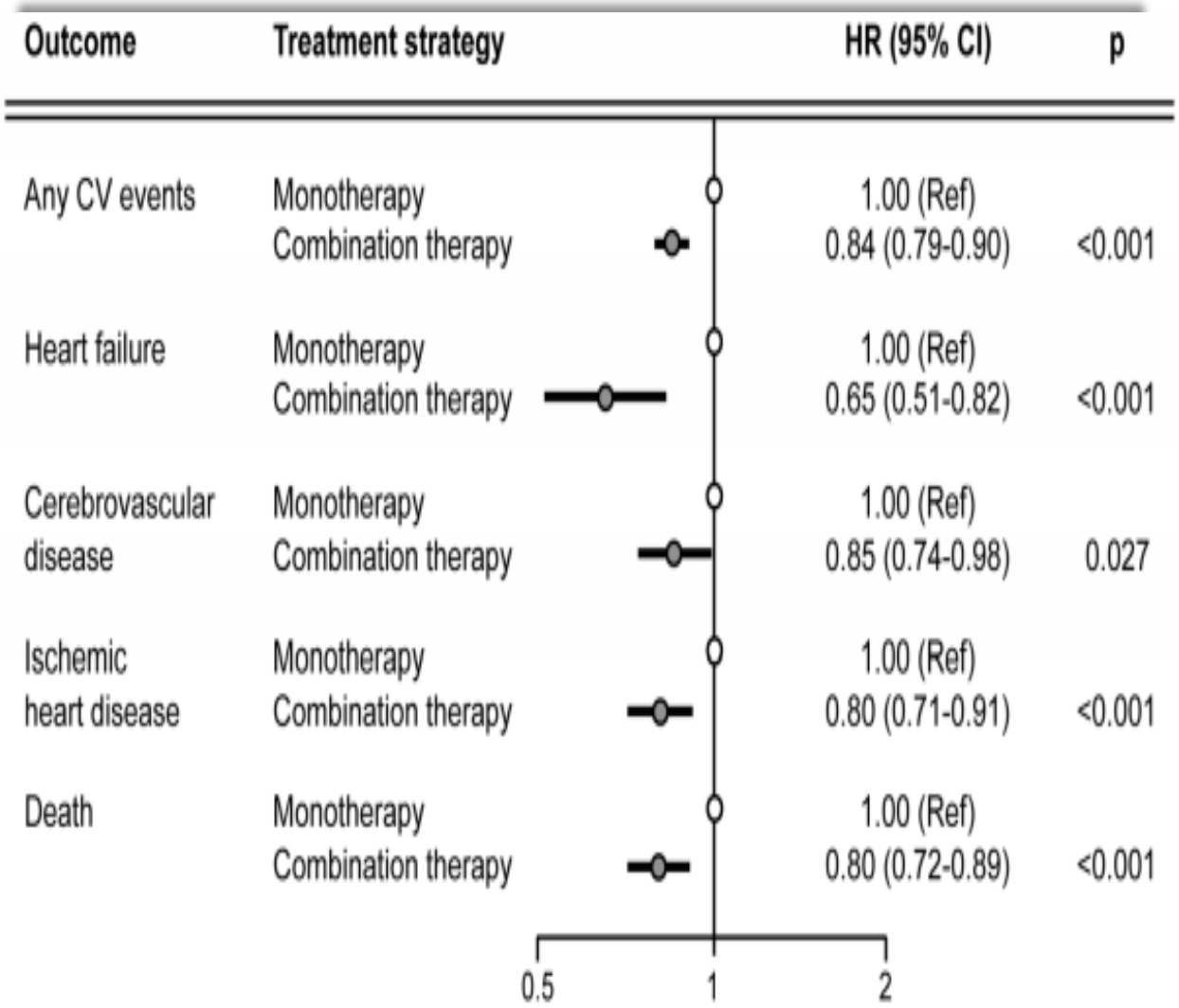
Outcome	Multipill	FDC	HR† (95% CI)	*P* value
	N = 6,675	*N* = 6,675		
	Event Rate* (Events/Years of Follow-up)	Event Rate* (Events/Years of Follow-up)		
Primary Outcome	3.9 (1,008/25,967)	3.4 (904/26,226)	0.89 (0.81–0.97)	<0.01
Secondary Outcomes				
AMI	0.6 (158/26,376)	0.5 (142/26,569)	0.89 (0.71–1.12)	0.33
Heart failure	0.4 (97/26,526)	0.3 (91/26,605)	0.93 (0.70–1.24)	0.62
Stroke	0.5 (139/26,440)	0.6 (151/26,604)	1.08 (0.86–1.36)	0.51
Death	2.8 (755/26,699)	2.4 (646/26,854)	0.85 (0.77–0.94)	<0.01
Instance of drug discontinuation	93.4 (5,921/6,333)	67.0 (554/8,268)	0.80 (0.77–0.83)	<0.01
Safety Outcomes				
Hypokalemia	N/A††	N/A††	N/A††	N/A††

Vermaa et al PLOS Medicine June 11, 2018

Initial Antihypertensive Treatment Strategies and Therapeutic Inertia: 3 Year Outcomes

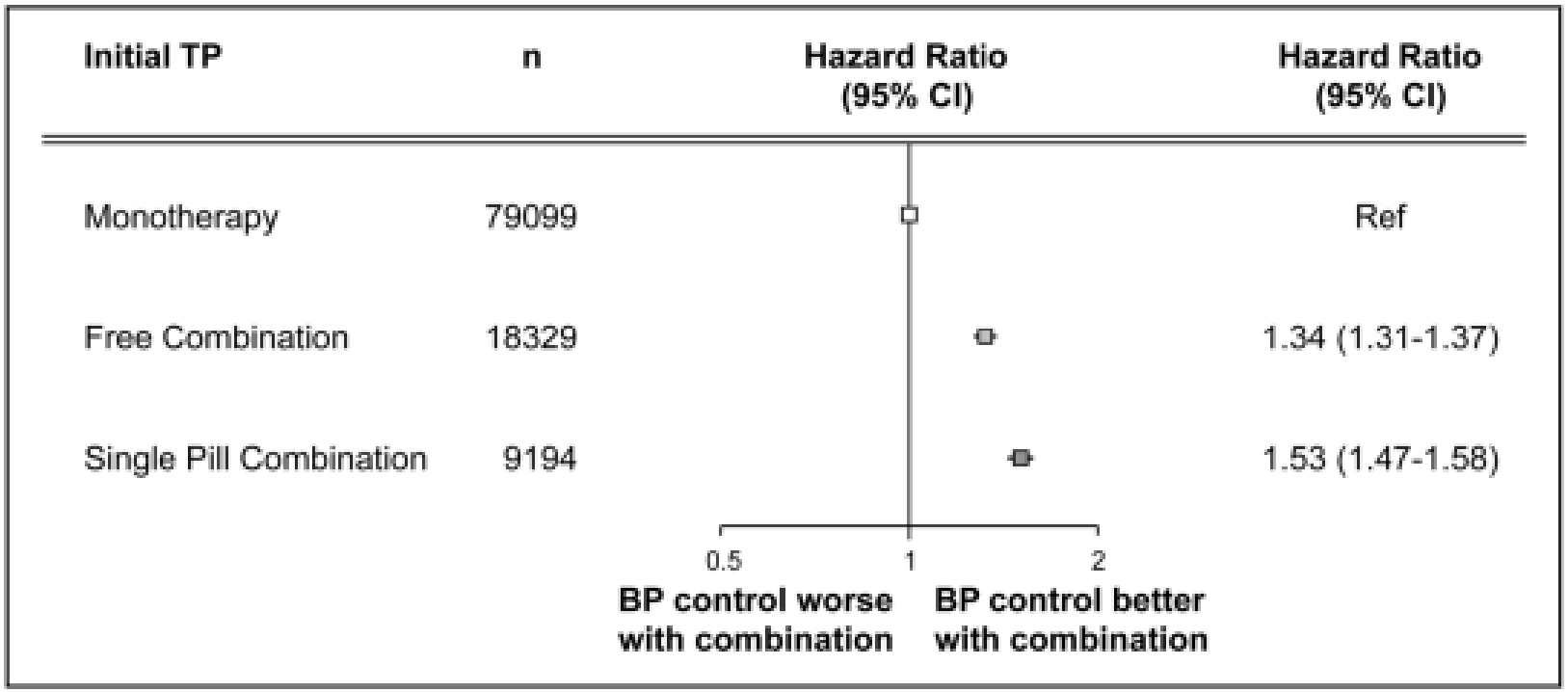
Data from health care utilization data-bases in Lombardy (Italy), where 100.962 patients (age 40-65 years) started tretament on 1 drug and 24.653 on >2 drugs.

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.



Mancia , Rea et al Circ Res. 2019;124:1113- 1123

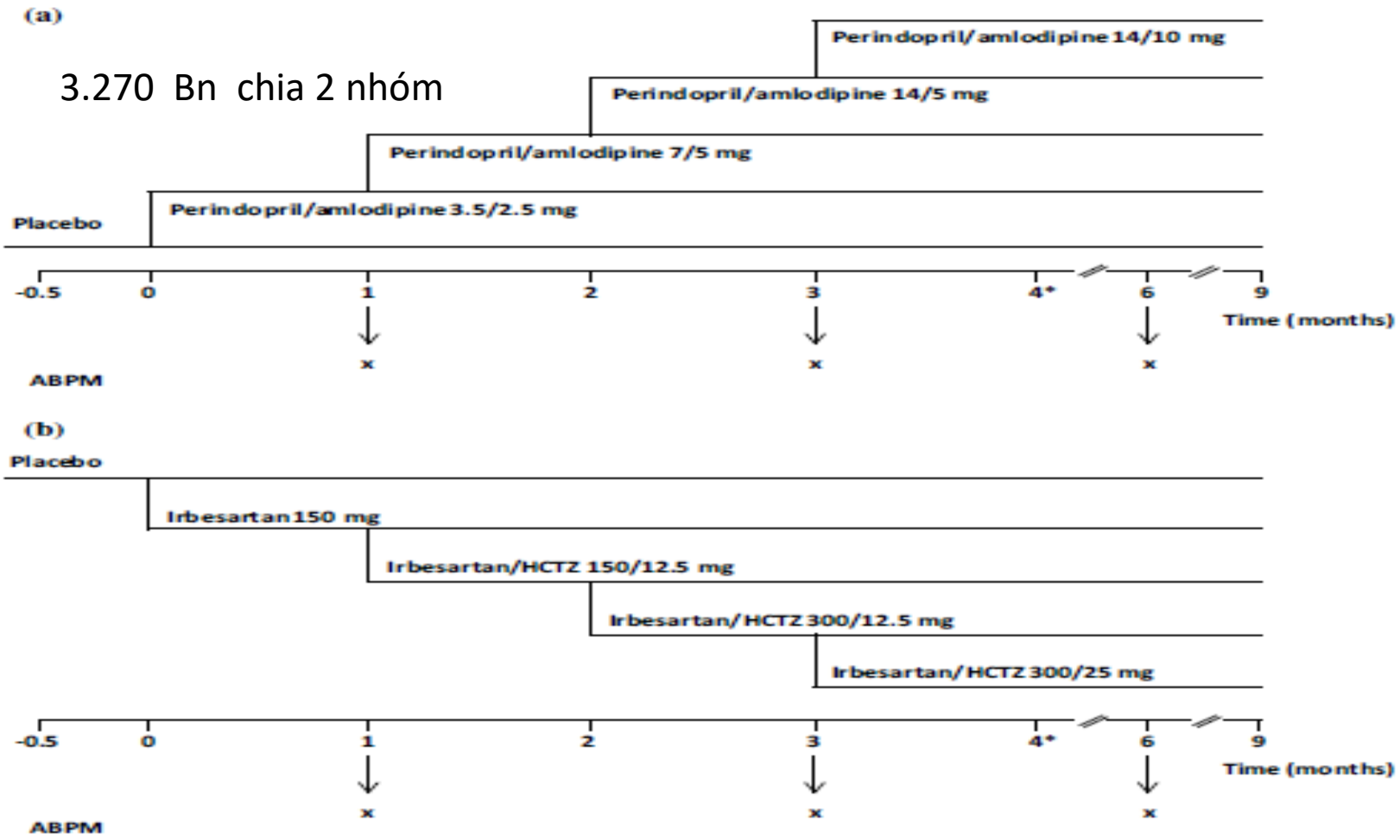
Kiểm Soát HA Tốt Hơn Với Phối Hợp Thuốc Cố Định Liều



Mancia , Rea et al Circ Res. 2019;124:1113- 1123

Hiệu qủa phối hợp cố định liều của perindopril/amlodipine vs. irbesartan/HCTZ

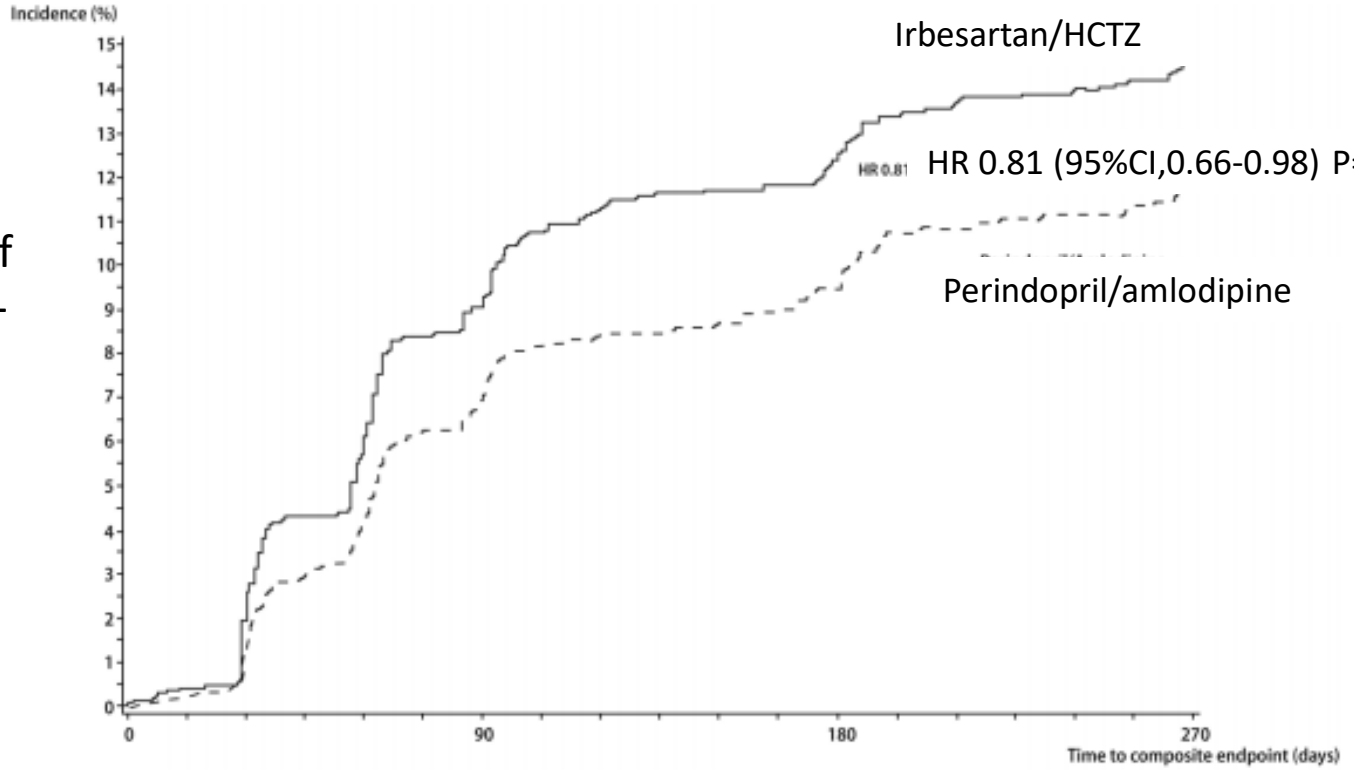
3.270 Bn chia 2 nhóm



N Poulter et al. American Journal of Cardiovascular Drugs June 2019, V9, Issue 3, pp 313–323

Hiệu qủa phối hợp cố định liều của perindopril/amlodipine vs. irbesartan/HCTZ

Emergent clinical events of special interest (composite of cardiovascular+renal+ glucometabolic endpoints) .



	Perindopril/Amlodipine N=1605		Irbesartan/HCTZ N=1628		Hazard ratio	P value
	Patients at risk (N)	Patients with event (N)[%]	Patients at risk (N)	Patients with event (N)[%]		
Composite endpoint	1605	179 (11.2)	1628	225 (13.8)	0.811	0.036
- CV endpoint	1605	42 (2.6)	1628	36 (2.2)	1.227	0.366
- Diabetes and glucometabolic impairment	1391	132 (9.5)	1397	160 (11.5)	0.826	0.103
- Renal impairment	1605	4 (0.2)	1628	35 (2.1)	0.118	<0.001

N Poulter et al. American Journal of Cardiovascular Drugs June 2019, V9, Issue 3, pp 313–323

Antihypertensive Medication Adherence Strategies

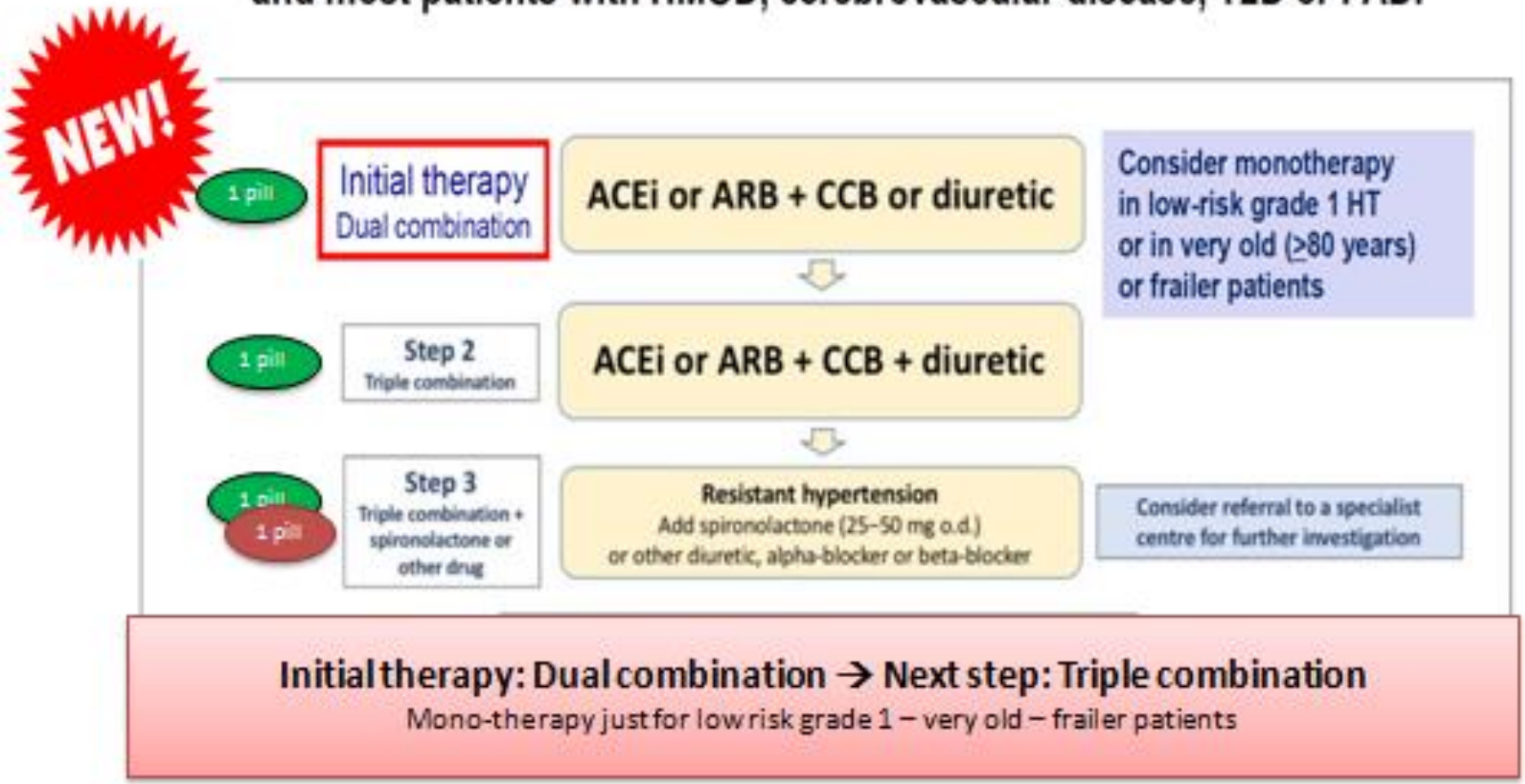
COR	LOE	Recommendations for Antihypertensive Medication Adherence Strategies
I	B-R	In adults with hypertension, dosing of antihypertensive medication once daily rather than multiple times daily is beneficial to improve adherence.
IIa	B-NR	Use of combination pills rather than free individual components can be useful to improve adherence to antihypertensive therapy.

ESC
European Society of Cardiology

2018 ESH-ESC Guidelines

Initial therapy with dual combination for uncomplicated HT,

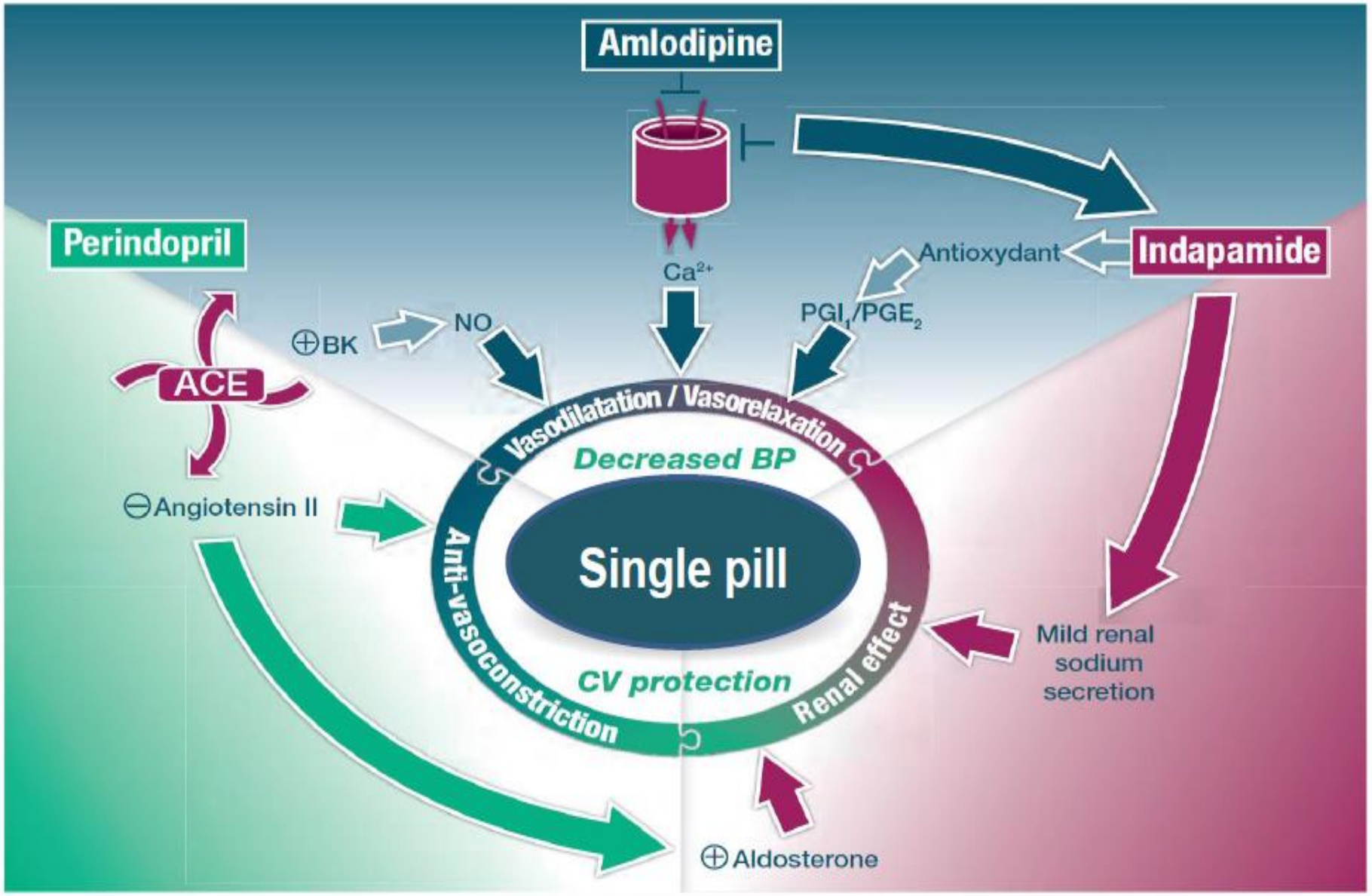
and most patients with HMOD, cerebrovascular disease, T2D or PAD.



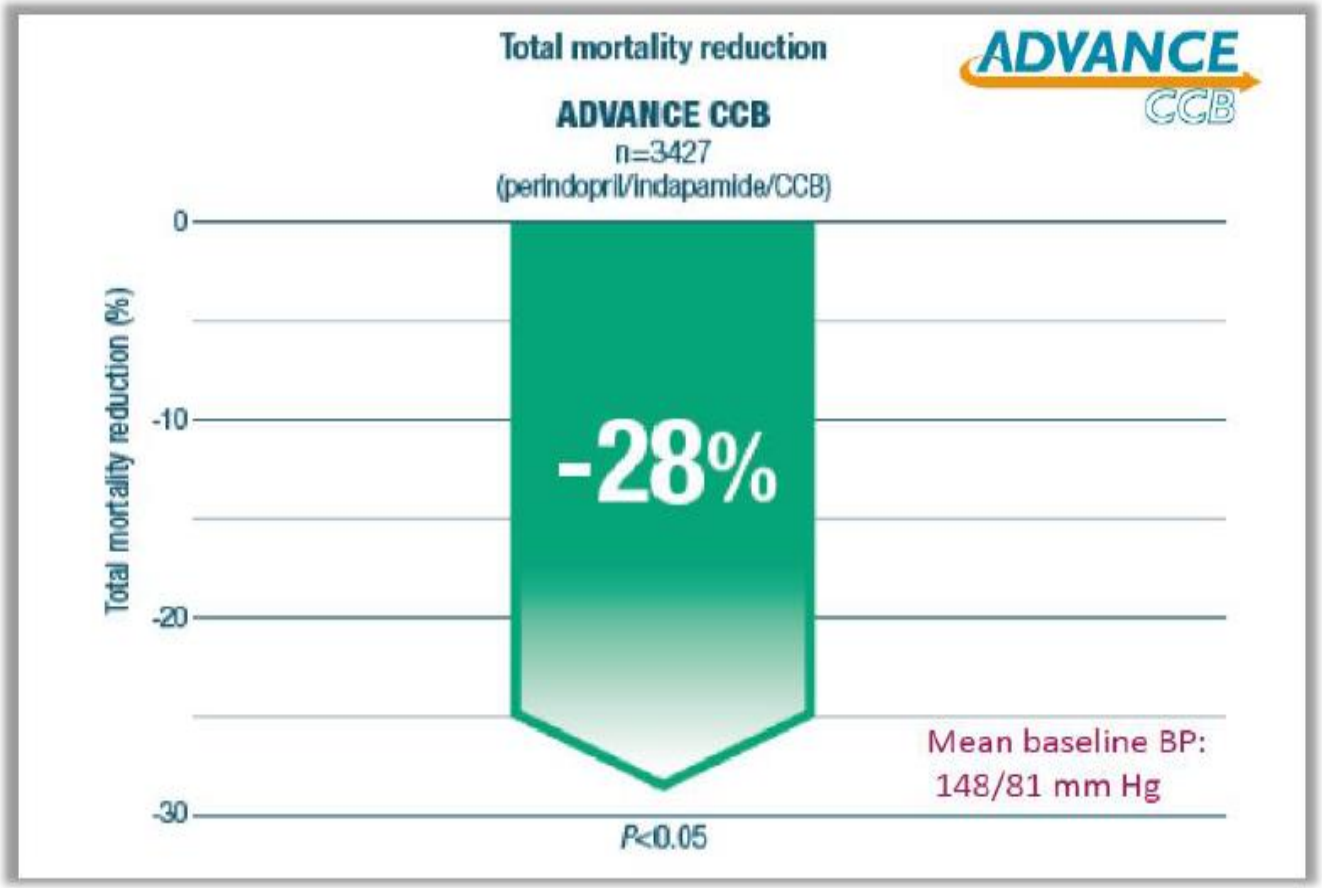
Initial therapy: Dual combination → Next step: Triple combination

Mono-therapy just for low risk grade 1 – very old – frailer patients

Three complementary modes of action



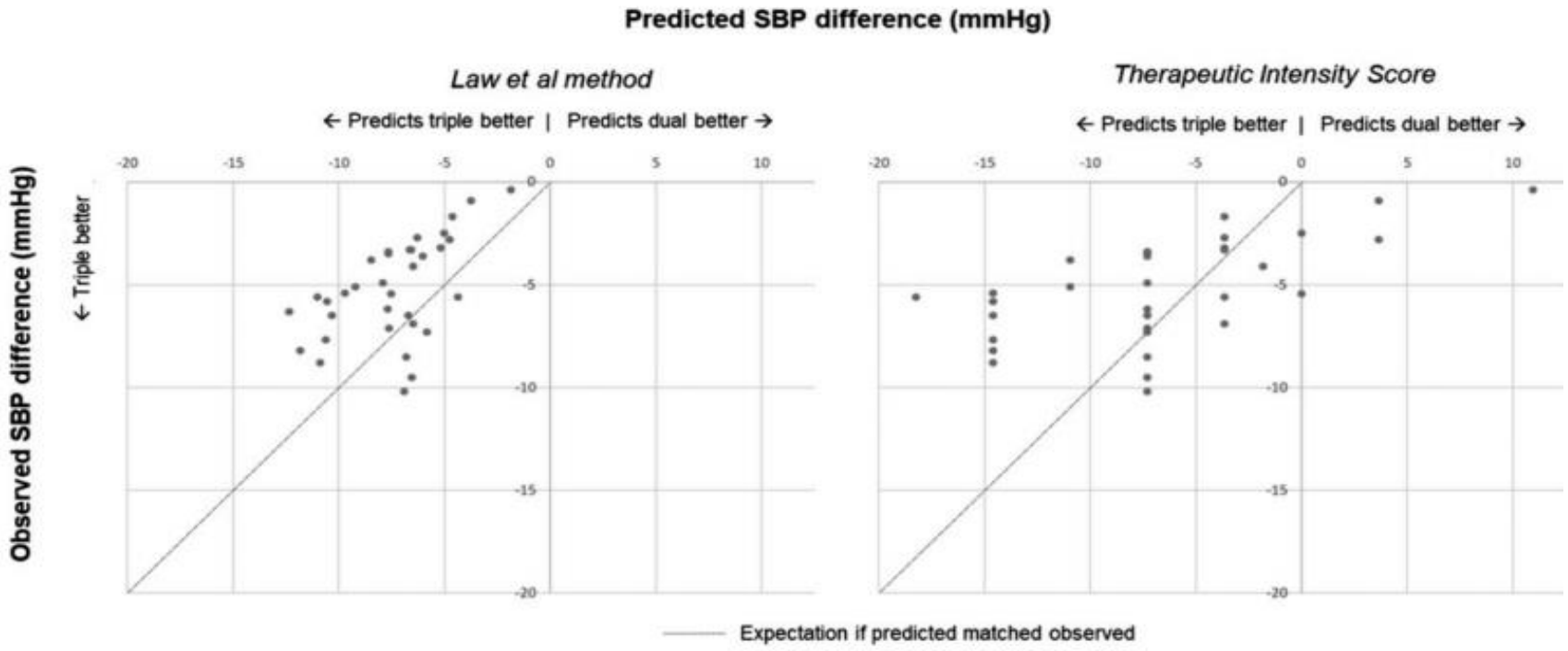
Significant lifesaving benefits with a perindopril-based triple combination



Hypertension 2014

Chalmers J et al. *Hypertension*. 2014;63:259-264.

Efficacy and safety of triple versus dual combination blood pressure-lowering drug therapy: a systematic review and meta-analysis of randomized controlled trials



Fourteen RCTs (11 457 participants) were included. Overall, triple compared with dual therapy reduced BP by 5.4/3.2 mmHg ($P < 0.001$), and improved BP control by 58 versus 45% [relative risk (RR) 1.33 (95% CI 1.25–1.41)], whereas incidence of withdrawals because of adverse events were 3.3 versus 3.4% [RR 1.24 (95% CI 1.00–1.54), P= 0.05].

Salm A. Journal of Hypertension 2019, 37:1567–1573

Khuyến Cáo Điều Trị THA VNHA/VSH 2018

HA ≥ 140/90 mmHg ở BN > 18 tuổi
(BN có Bệnh Tim Mạch đặc biệt Bệnh Mạch Vành HA ≥ 130/85 mmHg)

Thay đổi lối sống

Điều Trị Thuốc Theo Cá Nhân Hóa

THA độ I + Nguy cơ Thấp*

Lợi tiểu, ƯCMC, CTTA, CKCa, CB*

Tăng HA độ I + Nguy cơ TB, Cao, Rất Cao Hoặc THA độ II,III**

Phối hợp 2 thuốc **
ƯCMC/CTTA + CKCa hoặc lợi tiểu

Phối hợp 3 thuốc **
ƯCMC/CTTA + lợi tiểu + CKCa

THA Kháng Trị: Thêm kháng aldosterone hay lợi tiểu khác, chẹn alpha hoặc chẹn bêta

Tham khảo chuyên gia về THA

Tăng HA có chỉ định điều trị bắt buộc

- **Bệnh mạch vành: CB + ƯCMC/ CTTA, CKCa**
- **Suy tim: ƯCMC/CTTA + CB + kháng aldosterone, LT quai khi ứ dịch**
- **Đột quị: ƯCMC+ lợi tiểu**
- **Bệnh thận mạn: ƯCMC/CTTA+LT/CKCa**
- **ĐTĐ: ƯCMC/CTTA+CKCa/LT**

* Xem xét đơn trị liệu ở THA độ I nguy cơ thấp sau 3 tháng TĐLS không kiểm soát HA, hoặc bn ≥ 80 tuổi , hội chứng lão hóa.

* CB cho ở bất kỳ bước nào như suy tim, đau thắt ngực, sau NMCT, rung nhĩ, kiểm soát tần số nhịp hoặc phụ nữ có thai

- Lợi tiểu thiazide –like ưu tiên hơn lợi tiểu thiazide
- HA bình thường cao có bệnh tim mạch ,đặc biệt bệnh mạch vành có nguy cơ rất cao cần điều trị thuốc ngay. s

** **Điều trị thuốc ngay với ưu tiên một viên thuốc cố định liều**

ƯCMC: ức chế men chuyển - CTTA: chẹn thụ thể angiotensin II - CKCa: chẹn kênh canxi ; CB: chẹn beta ;YTNC: yếu tố nguy cơ; HATT: Huyết áp tâm thu - HATTr: Huyết áp tâm trương – ĐTĐ: đái tháo đường ; TB: trung bình; TTCQĐ: tổn thương cơ quan đích; TĐLS: thay đổi lối sống

KẾT LUẬN

- Mục đích điều trị THA tối ưu là giảm bệnh sinh và tử vong chung, tử vong tim mạch, bảo vệ cơ quan đích và cải thiện chất lượng cuộc sống.
- Đòi hỏi liệu trình điều trị phải ít tác dụng phụ và có sự tuân thủ cao
- Hướng tiếp cận mới tối ưu là kiểm soát HA đạt mục tiêu với khởi trị phối hợp thuốc sớm từ liều thấp
- Phối hợp thuốc sớm ngay từ đầu với hai loại thuốc trong một viên cố định liều nếu không đạt mục tiêu phối hợp 3 thứ thuốc nhằm tăng sự tuân thủ và giảm các biến cố tim mạch.