Fixed dose combination antihypertensive medications

Clinical evidence of their efficacy

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Resolve to Save Lives

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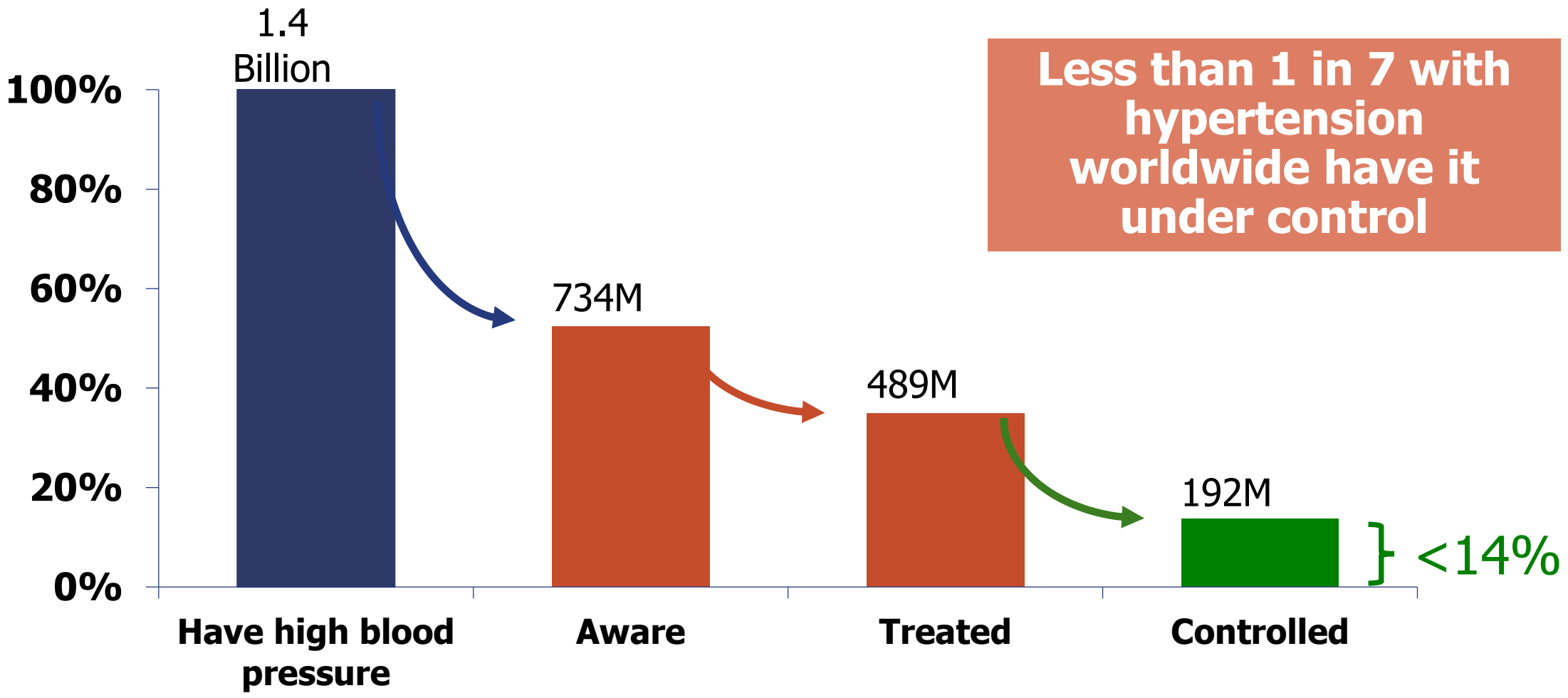
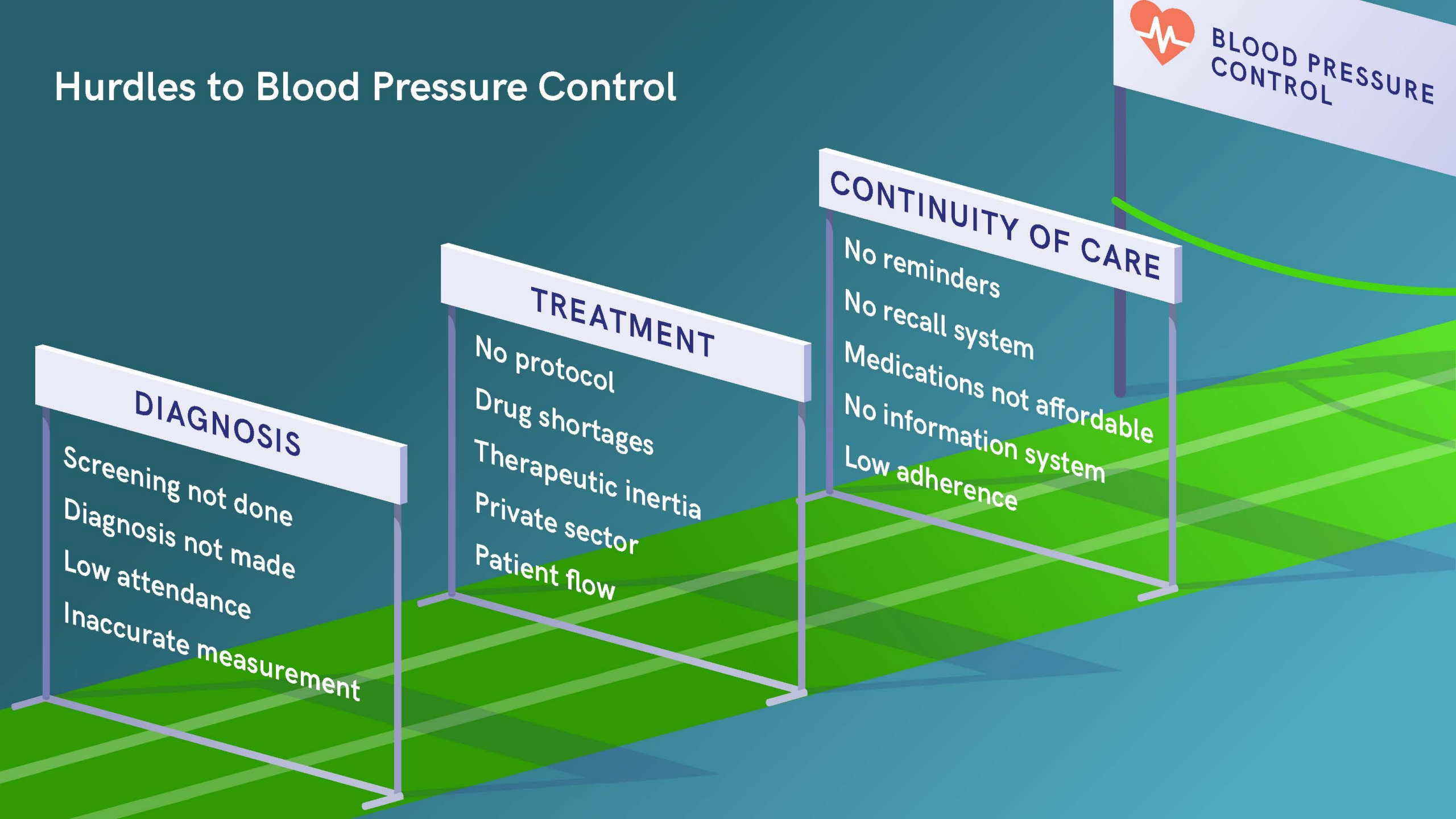
Most People With Hypertension Globally Do Not Have It Under Control

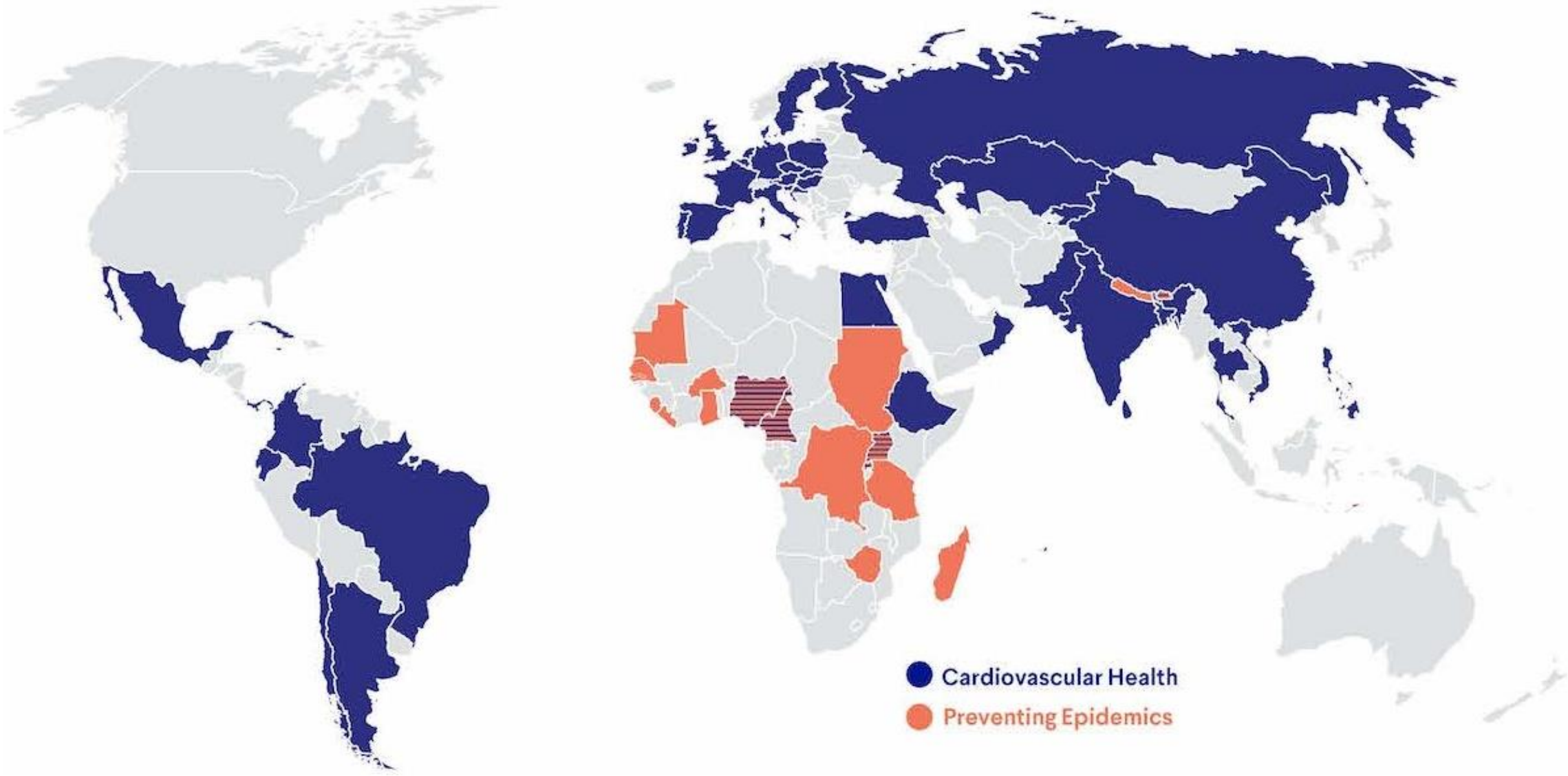


Mills KT et al. Circulation. 2016 Aug 9;134(6):441-450.

Hurdles to Blood Pressure Control



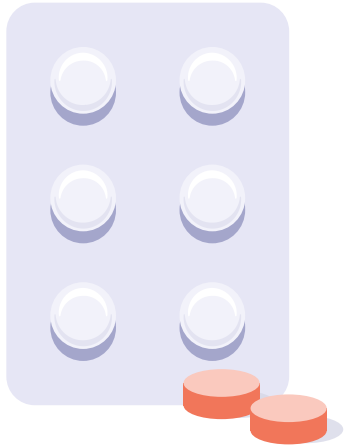
Resolve to Save Lives' Global Activities



Effective Hypertension Care As Pathfinder for PHC

Simple, Practical Protocol

Manage other chronic conditions; improve evidence-based care; reduce costs



Medication and Equipment Supply

Improve purchasing and supply chain management

Team-Based Care

Applicable to wide range of chronic health conditions

Patient-Centered Services

Improve patient support; access to and confidence in primary care; reduce reliance on hospital care; reduce financial and other barriers

Information Systems

Create feedback loops applicable to other conditions; strengthen data-driven culture of accountability and quality improvement

Advantages of single pill FDC antihypertensive medications

Single pill FDCs simplify the treatment regimen by:

1. Decreasing daily pill burden
2. Improved medication adherence (in terms of execution and persistence)
3. Faster BP control
4. Less time exposed to CVD-risk

Fixed-dose combinations for hypertension control

- **Potential Advantages**
  - Combination more effective than increased monotherapy doses (5x)
  - Simplified logistics for supply chain management
  - Greater ability to train and task-share
  - Fewer steps in protocol-based treatment
  - Improved treatment adherence: simpler dosing and reduced pill burden
  - Reduced aggregate costs
- **Potential Disadvantages**
  - Patients must not have contraindications for either component
  - If adverse events occur, may not be clear which medication caused
  - Challenge in individualizing drug titration

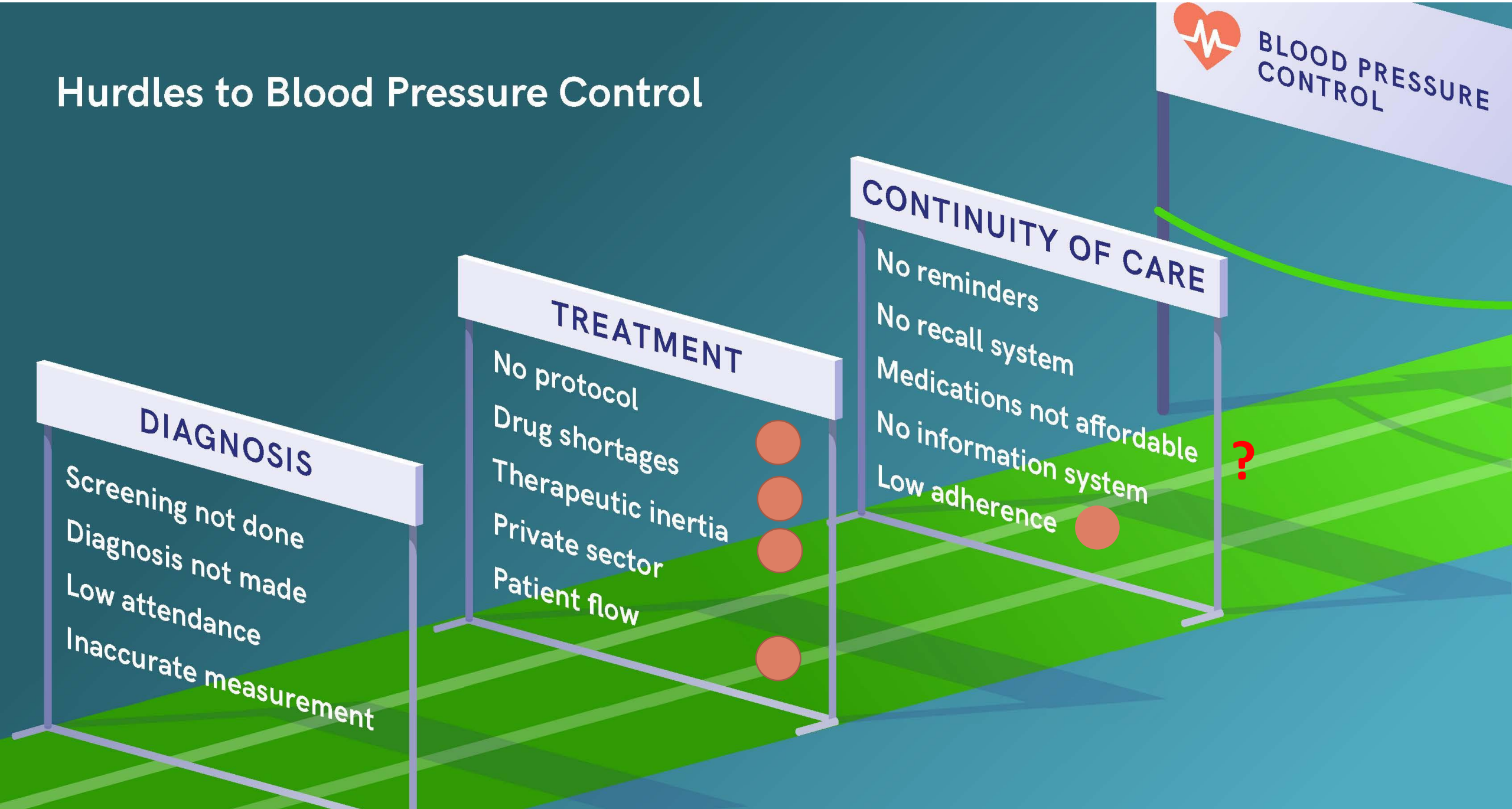
Chobanian AV, Bakris GL, Black HR, et al. Hypertension 2003;42:1206–52.
Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. BMJ (Clinical research ed.) 2011;343:d4891..
Indian guidelines on hypertension (I.G.H.) - III. 2013. The Journal of the Association of Physicians of India 2013;61: 6–36.
Seedat YK, Rayner BL, Veriava Y. Cardiovascular journal of Africa 2014;25:288–94..
Hackam DG, Khan NA, Hemmelgarn BR, et al. Canadian Journal of Cardiology 2010;26:249–58.

FDCs Definitely Indicated for Patients on Multiple Medications and Recommended as 1st Line Treatment for All Patients

- Simplifies protocol
- Recently endorsed in 2018 European Society of Cardiology/ European Society of Hypertension guidelines*
- Kaiser Permanente Northern California does this, and has achieved very high control rates (85-90%)
- FDC Contraindications
  - Renovascular HTN
  - Severe renal impairment
  - Pediatric HTN

**ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018;39:3021–3104.*

Hurdles to Blood Pressure Control



Guidelines: International Support for FDCs

	ACC/AHA 2017	ESC/ESH 2013/2018	India 2013	China 2010	Thailand 2015	WHO HEARTS
Recommendations when to use two BP lowering drugs						
Not controlled on monotherapy	Yes	Yes	Yes	Yes	Yes	Yes
Initial treatment for selected patients e.g. >20/10mmHg from goal* and/or high CV risk	Yes	Yes	Yes	Yes	Yes	Yes
Recommendations when to use single pill combinations						
Recommended to substitute for separate pills to improve adherence	Yes	Yes	Yes	Yes	NR	NR

* Some referred to this as stage II HTN or marked BP elevation, NR=Not reported

Indian guidelines on hypertension (I.G.H.) - III. 2013. Journal of the Association of Physicians of India 2013;61:6–36.
Mancia G, Fagard R, Narkiewicz K, et al. Journal of hypertension 2013;31:1281–35.
Whelton PK, Carey RM, Aronow WS, et al. Journal of the American College of Cardiology 2017:24430.
Jaffe MG, Frieden TR, Campbell NRC, et al. J Clin Hypertens (Greenwich) 2018;20:829–36.

Efficacy: FDC for Hypertension Control

- **14 randomized controlled trials** (5,120 participants) for initial dual vs monotherapy (at least 4 weeks) indicates a **27% (95% CI 15–41%) improvement in blood pressure control** without an increase in withdrawals due to adverse events[1]

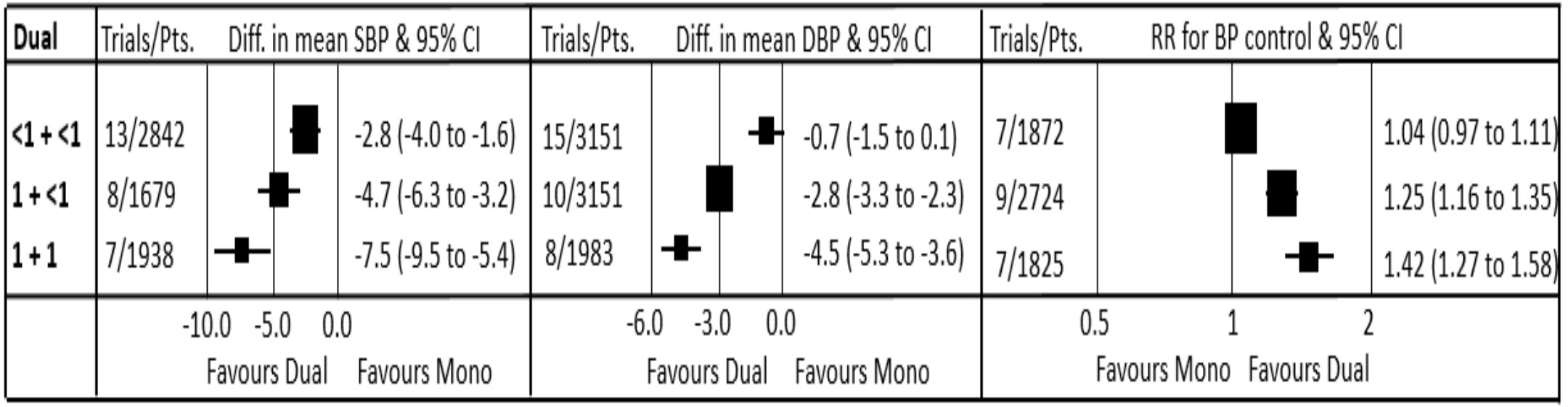
- **42 trials (10,968 participants) showed that combining drugs from four classes produced additive BP lowering effects[2]**
  - Effect was approximately five times greater compared to doubling the dose of monotherapy[2]

- **Improving global rates by just 25% with dual therapy would increase the number of patients with controlled HTN by *80 million*,[1]** preventing two million strokes and heart attacks and more than 600,000 cardiovascular deaths over 5 years

1 *Salam A, Kanukula R, Esam H, et al. An application to include blood pressure lowering drug fixed dose combinations to the model essential medicines list for the treatment of essential hypertension in adults.*
2 *Magrini N, Robertson J, Forte G, et al. Tough decisions on essential medicines in 2015. Bulletin of the World Health Organization 2015;93:283–84.*

Efficacy: FDC for Hypertension Control

Figure 2: Dual therapy vs standard-dose monotherapy – effects on mean BP reduction and hypertension control rates



- <1+<1 = dual low dose;
- 1+<1 = standard and low dose;
- 1+1 = dual standard dose
- WDAE = withdrawal due to adverse event

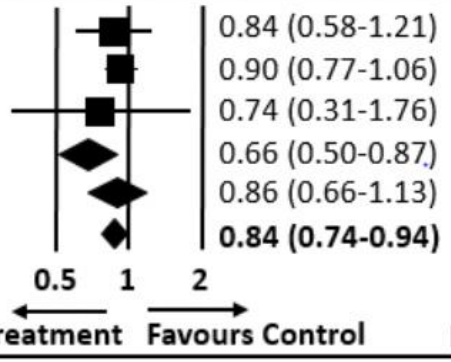
Efficacy: FDC for Hypertension (Cardiovascular Outcomes)

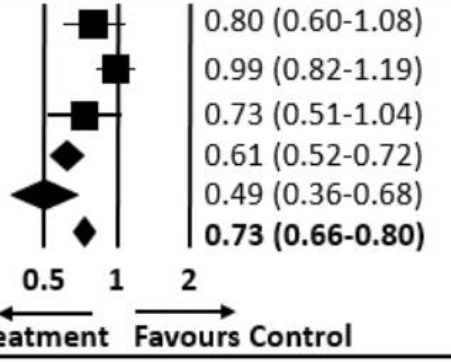
Effects of combination therapy vs. placebo on CHD, stroke, heart failure and death				
	Studies	Intervention	Control	RR (95% CI)
		events/participants	**events/participants**	
Studies with >6 mm Hg reduction in SBP				
CHD	11	175/5585	240/5694	0.75 (0.62-0.91)
Stroke	11	310/5669	518/5694	0.61 (0.53-0.69)
Heart failure	8	66/3172	157/3879	0.48 (0.36-0.63)
Death	11	499/5596	627/5694	0.81 (0.72-0.90)
Studies with ≤6 mm Hg reduction in SBP				
CHD	2	317/11925	356/11920	0.90 (0.77-1.03)
Stroke	2	290/11925	312/11920	0.93 (0.80-1.10)
Heart failure	1	21/6356	29 / 6349	0.72 (0.41-1.27)
Death	2	750/11925	820/11920	0.91 (0.83-1.00)
All studies				
CHD	13	492/17510	596/17614	0.84 (0.74-0.94)
Stroke	13	600/17594	830/17614	0.73 (0.66-0.80)
Heart failure	9	87/9528	186/10228	0.52 (0.40-0.67)
Death	13	1249/17521	1447/17614	0.87 (0.80-0.93)

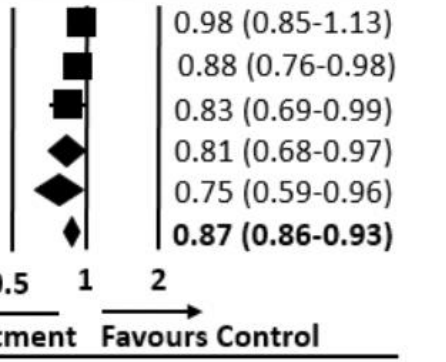
Salam A, Kanukula R, Esam H, et al. An application to include blood pressure lowering drug fixed dose combinations to the model essential medicines list for the treatment of essential hypertension in adults.

Efficacy: FDC for Hypertension (Sub-populations)

Patient Group	Trial(s)	Mean SBP/DBP Reduction, mmHg	CHD Events	Stroke Events	Death
Intermediate CV risk	HOPE 3	6.0/3.0	0.84 (0.58-1.21)	0.80 (0.60-1.08)	0.98 (0.85-1.13)
Diabetes	ADVANCE	5.6/2.2	0.90 (0.77-1.06)	0.99 (0.82-1.19)	0.88 (0.76-0.98)
Elderly	HYVET	13.9/5.9	0.74 (0.31-1.76)	0.73 (0.51-1.04)	0.83 (0.69-0.99)
Stroke/TIA	5 trials	15.0/6.1	0.66 (0.50-0.87)	0.61 (0.52-0.72)	0.81 (0.68-0.97)
Hypertension	5 trials	21.1/11.1	0.86 (0.66-1.13)	0.49 (0.36-0.68)	0.75 (0.59-0.96)
Overall		**9.2/4.2**	**0.84 (0.74-0.94)**	**0.73 (0.66-0.80)**	**0.87 (0.86-0.93)**







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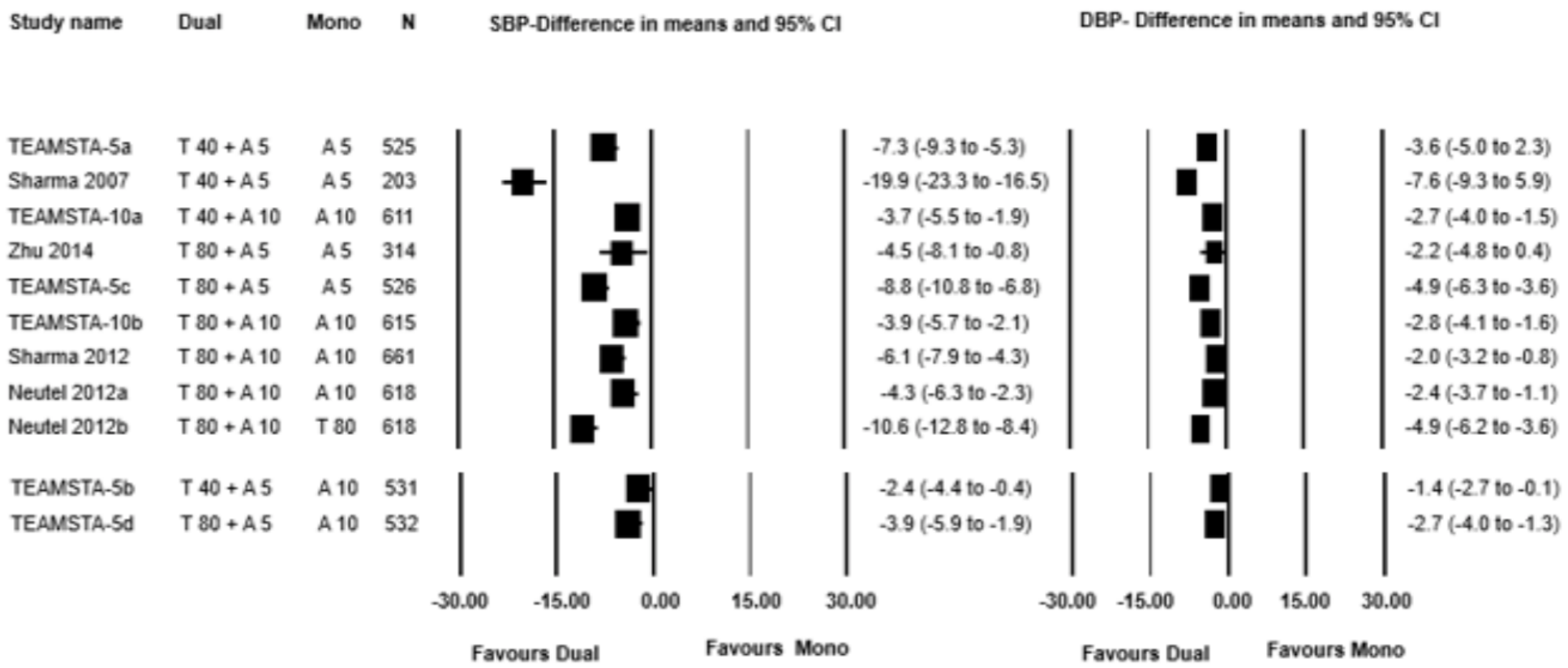
Example: Telmisartan + Amlodipine FDC

versus initial monotherapy:



Example: Telmisartan + Amlodipine FDC

- **Telmisartan**
  - Long-acting angiotensin receptor blocker (ARB)
  - Available as a generic
- **Amlodipine**
  - Calcium channel blocker (CCB)
  - Available as generic
  - Widely available in LMICs
- **Combination reduces incidence of pedal edema**
  - Most common amlodipine associated adverse event

Salam A, Kanukula R, Esam H, et al. An application to include blood pressure lowering drug fixed dose combinations to the model essential medicines list for the treatment of essential hypertension in adults.

Real world effectiveness of single pill FDC*

- **Data source**
  - UK Clinical Practice Research Datalink (National Health Service primary care data), 2006-2014
- **Patient sample**
  - 54,523 eligible
  - 2,807 initial 2-drug FDC (10% single pill), matched to 5,614, initial monotherapy
  - 76.5% changed from their initial regimen by 12 months
- **Study design**
  - "New user" analysis (established hypertension diagnosis and no meds in prior 6 months)
  - FDC matched to mono using propensity scores including baseline age, DM and CKD status
  - Primary outcome: first hypertension control; secondary outcome: major CVD event
  - Mean follow up: 12.6 months

**Marineir K et al., Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension, Pharmacoepidemiology & Drug Safety, 2019*

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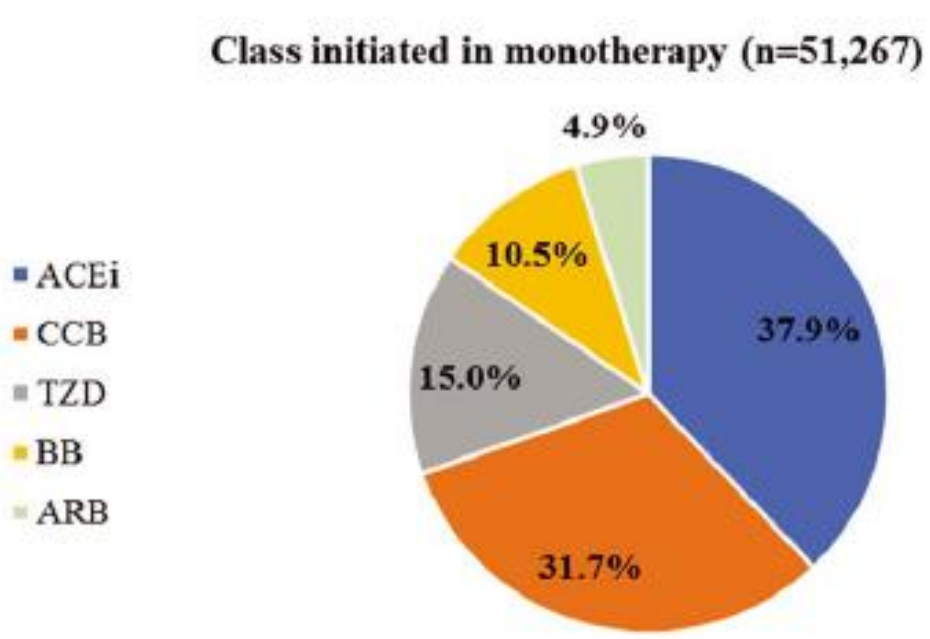
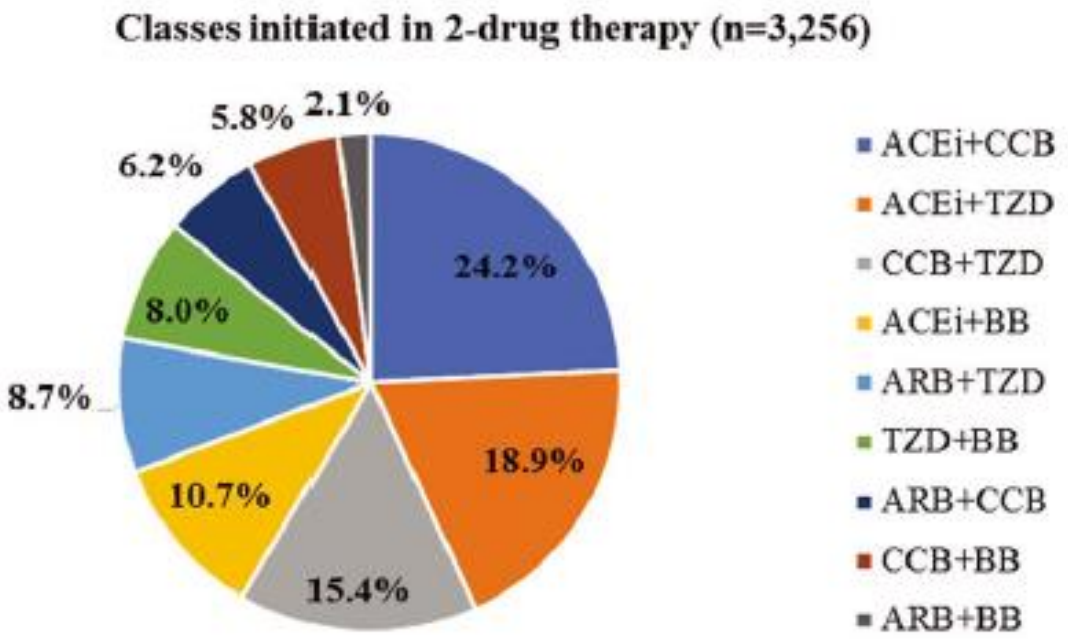
Distribution of initial monotherapy or FDC*





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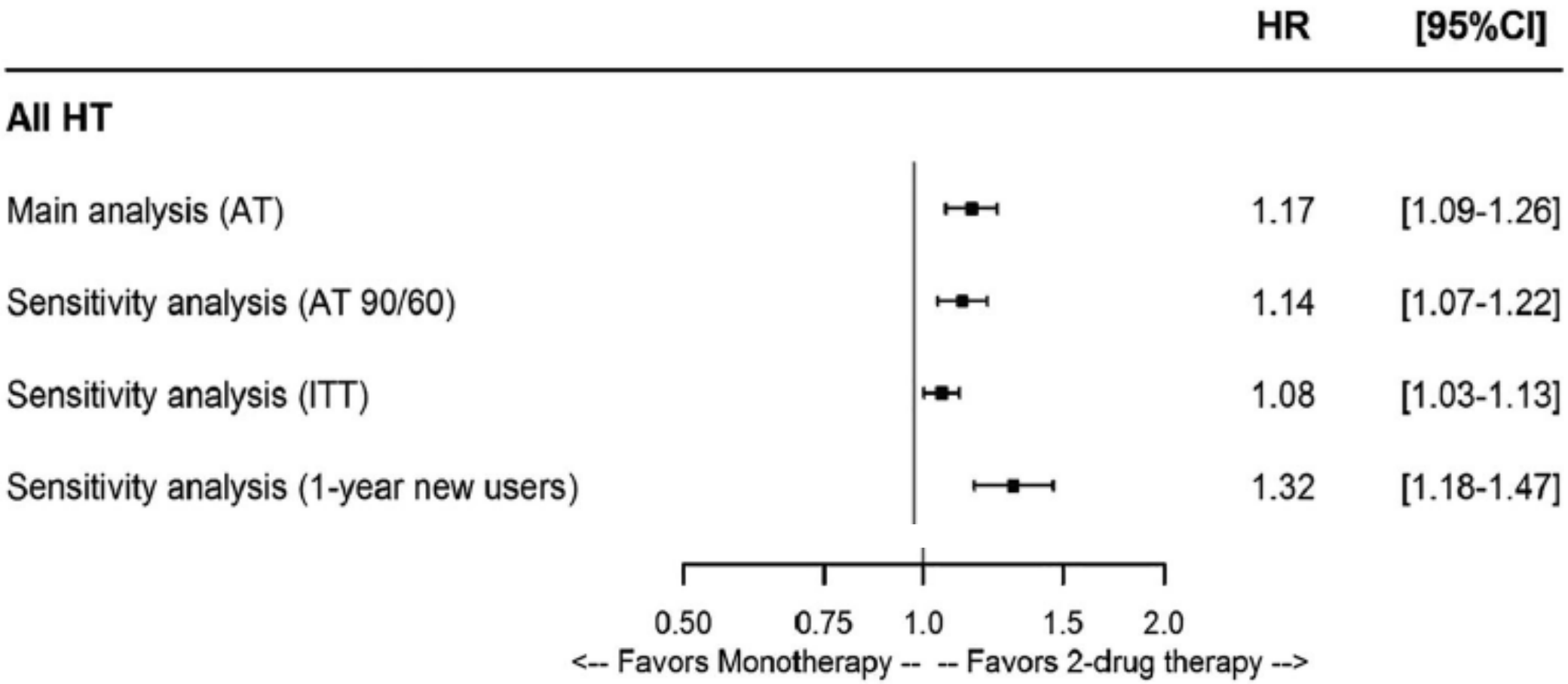
Higher rate of hypertension control with FDC*



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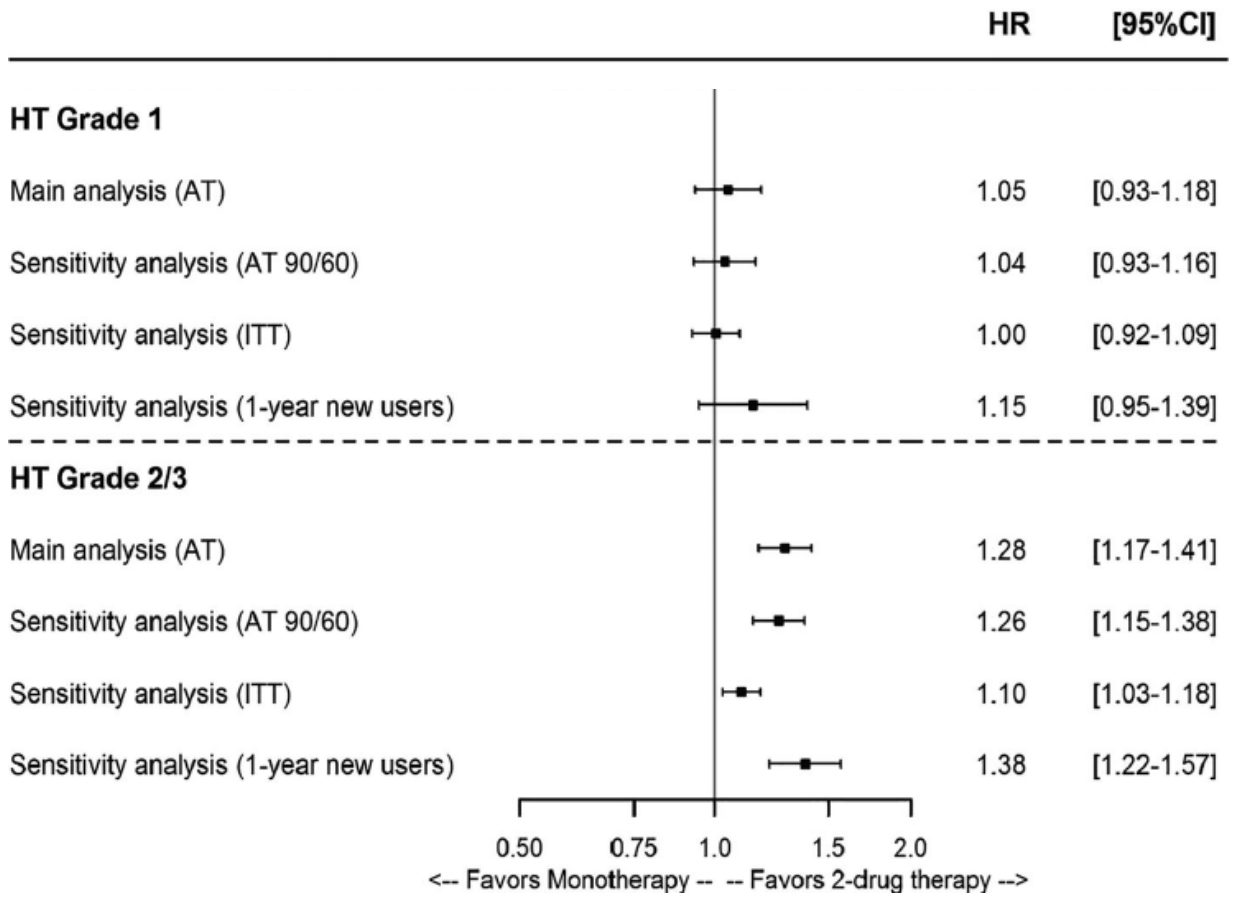

**Marineir K et al., Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension, Pharmacoepidemiology & Drug Safety, 2019*

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- Norm Campbell, University of Calgary

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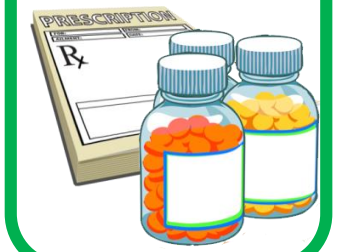
FDCs Improve Every Key Component of Hypertension Control

Protocol

Simpler treatment algorithm

Medication Supply



Fewer stockouts

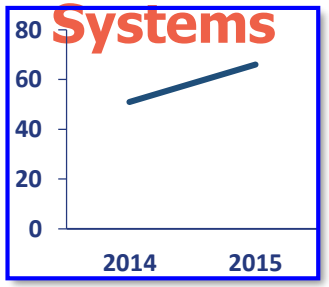
Community-Based Treatment

Enhanced task sharing

Patient-Centered Care

Lower pill burden

Information Systems



Better control rates

Resources

- **Expert Committee on the Selection and Use of Essential Medicines application:**
  - **http://www.who.int/selection_medicines/committees/expert/22/fixed-dose_combination_antihypertensives/en/**

- **Fixed dose combinations for hypertension (Lancet 2018)**
  - **https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31814-2/fulltext**

When does

50 + 30 + 0 = 100?

Globally, we can save 100 million lives over the next 30 years

Increase global control of blood pressure from 14% to 50%

Reduce global dietary sodium intake by 30%

Eliminate artificial trans fats 0%

Prevent Epidemics

MAKE WORLD SAFER FROM EPIDEMICS

DEVELOP TRACKING SYSTEMS

TRAIN "DISEASE DETECTIVES"

SUPPORT LABS

DEVELOP RAPID RESPONSE TEAMS

Resolve to Save Lives is a global partnership

Core organizations

World Health Organization

THE WORLD BANK
IBRD • IDA | WORLD BANK GROUP

CDC Foundation
Together our impact is greater

Global Health Advocacy Incubator

Vital Strategies

Donors

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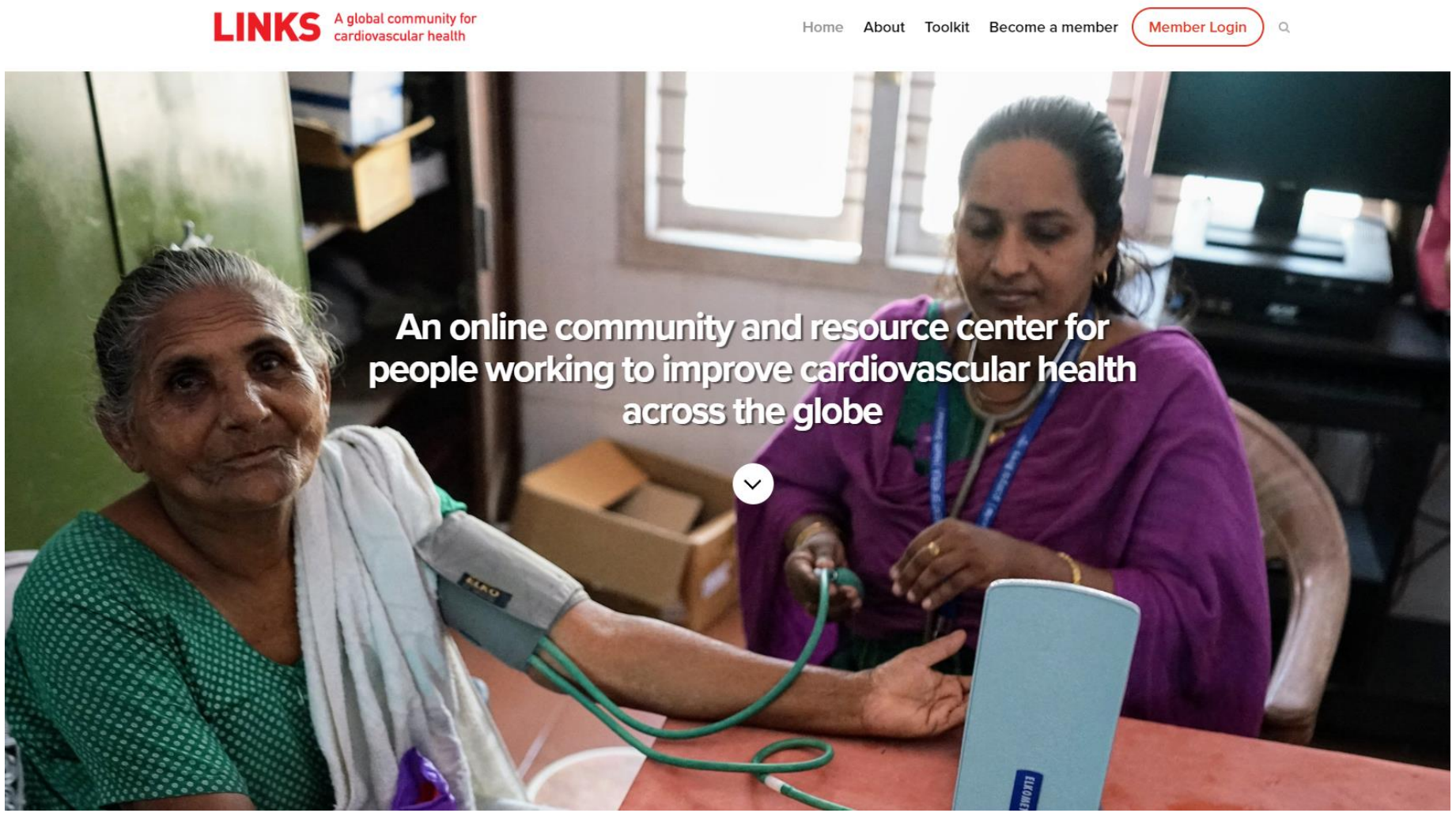

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