

***Making the List: Why Now is  
the Time to Declare That  
Antihypertensive Combination  
Therapies are Essential***

# Outline

- WHO Essential Medicines List & Why It Matters
- Global Burden of Hypertension & Key Gaps
- Rationale for Fixed Dose Combinations (FDC) for Hypertension as an Essential Medicine
  - Guidelines
  - Efficacy
  - Cost
- Resources

# WHO Essential Medicines List (EML)

- Initiated in 1977: 204 products; 2017: 433 products
- Definition: Essential medicines are those that satisfy the priority healthcare needs of the population
- Criteria:
  - Disease prevalence,
  - Public health relevance,
  - Clinical efficacy and safety
  - Comparative cost/cost-effectiveness within class
- Informs national-level priorities (National EML)
- Guides drug donations/priorities by United Nations agencies

## Media centre

# WHO takes major steps to make HIV treatment accessible

22 APRIL 2002 - Treatment Guidelines and AIDS Medicines List Announced by WHO

In a decisive move to strengthen action against AIDS in developing countries, the World Health Organization (WHO) has today announced the first treatment guidelines for HIV/AIDS in poor settings. Parallel to that, WHO has endorsed the inclusion of AIDS medicines in its Essential Medicines List. The action is a breakthrough in a comprehensive "prevention through care" package that could contribute to dramatically wider access to treatment over the coming years.



# WHO EML: Cardiovascular Disease

Year	Medication	Square Box	Indication	Rationale and Summary
<b>Additions</b>				
2007	Simvastatin	Yes	Lipid-lowering agents	Reduce atherosclerotic burden; generic production reduced costs significantly <ul style="list-style-type: none"> <li>• Cost</li> <li>• Clinical practice guidelines</li> </ul>
2011	Bisoprolol	Yes	Antihypertensive Medicines used in heart failure	Remove substandard medication (atenolol) <ul style="list-style-type: none"> <li>• Clinical practice guidelines</li> <li>• Feedback loops and continual improvement</li> </ul>
2013	Spironolactone	No	Medicines used in heart failure	Add new indication—heart failure <ul style="list-style-type: none"> <li>• Clinical practice guidelines</li> </ul>
2015	Clopidogrel	No	Antithrombotic	Address rise in percutaneous coronary interventions worldwide <ul style="list-style-type: none"> <li>• Clinical practice guidelines</li> </ul>
2017	Losartan	Yes	Antihypertensive	Alternative to ACE inhibitors, overcoming side effects <ul style="list-style-type: none"> <li>• Clinical practice guidelines</li> </ul>
<b>Rejections</b>				
2013	Fixed-dose combination	Yes	N/A	Secondary prevention of atherosclerotic disease, improved “polypill” adherence <ul style="list-style-type: none"> <li>• Clinical practice guidelines</li> </ul>
2015	Direct oral anticoagulants	Yes	Antithrombotic	Prevention of stroke in patients with nonvalvular atrial fibrillation; clinically superior to warfarin and cost-effective given less monitoring <ul style="list-style-type: none"> <li>• Cost</li> <li>• Clinical practice guidelines</li> </ul>
2017	Lisinopril-hydrochlorothiazide	Yes	Antihypertensive	Dual-agent blood pressure regimen superior to single agent <ul style="list-style-type: none"> <li>• Clinical practice guidelines</li> </ul>

Kishore SP, Blank E, Heller DJ, Patel A, Peters A, Price M, et al. Modernizing the World Health Organization List of Essential Medicines for Preventing and Controlling Cardiovascular Diseases. *J Am Coll Cardiol.* 2018;71(5):564-74.

# WHO EML: Hypertension

<b>12.3 Antihypertensive medicines</b>	
<input type="checkbox"/> amlodipine	<b>Tablet:</b> 5 mg (as maleate, mesylate <b>or</b> besylate).
<input type="checkbox"/> bisoprolol*	<b>Tablet:</b> 1.25 mg; 5 mg. * includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years
<input type="checkbox"/> enalapril	<b>Tablet:</b> 2.5 mg; 5 mg (as hydrogen maleate).
hydralazine*	<b>Powder for injection:</b> 20 mg (hydrochloride) in ampoule. <b>Tablet:</b> 25 mg; 50 mg (hydrochloride). * Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
<input type="checkbox"/> hydrochlorothiazide	<b>Oral liquid:</b> 50 mg/5 mL. <b>Solid oral dosage form:</b> 12.5 mg; 25 mg.
methyldopa*	<b>Tablet:</b> 250 mg. * Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.
<input type="checkbox"/> losartan	<b>Tablet:</b> 25 mg; 50 mg; 100 mg.

# WHO EML: Square Box Notations

*The square box symbol is primarily intended to indicate similar clinical performance within a pharmacological class.*

*The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety.*

*In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective.*

*Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.*

# Translation of WHO EML to National EML<sup>1</sup>

- NEML increases availability but still imperfectly
- Availability poor in public sector

	Listed on NEML	Not Listed on NEML
Availability <sup>2</sup>	<b>62%</b> (40% in public sector)	<b>27%</b> (6% in public sector)

- Medicines on NEML have lower prices
  - Anti-hypertensives (hydrochlorothiazide, amlodipine and enalapril) are 1.3 – 3.7x less expensive
- Variation on composition of sub-national EMLs and procurement models (e.g. India: 153 to 1390 medicines)

1 Wirtz VJ, Kaplan WA, Kwan GF, Laing RO. Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries. *Circulation*. 2016;133(21):2076-85.

2 Bazargani YT, Ewen M, de Boer A, Leufkens HG, Mantel-Teeuwisse AK. Essential medicines are more available than other medicines around the globe. *PLoS One*. 2014;9(2):e87576.

# Global Burden of Hypertension

- Leading cause of cardiovascular disease: 10 million deaths annually
  - Systolic Blood Pressure (SBP) > 140 mmHg OR
  - Diastolic BP (DBP) > 90 mmHg
  - Reducing BP reduces CV events<sup>1,2,3</sup>
- 1.4 B with HTN Globally. < 15% of these are controlled (<8% in LMIC)<sup>4</sup>
  - 510 M individuals treated for HTN (37% of need)
    - In LMIC, 70% of patients on treatment are **not** controlled<sup>5</sup>
      - » 6/10 treated receive monotherapy<sup>5</sup>
      - » **~75% of individuals on treatment require ≥ 2 HTN drugs<sup>2,6</sup>**

1 Ettehad D, Emdin CA, Kiran A, et al. *Lancet* 2016;387:957–67.

2 Law MR, Morris JK, Wald NJ. *BMJ (Clinical research ed.)* 2009;338:b1665.

3 Xie X, Atkins E, Lv J, et al. *Lancet* 2016;387:435–43.

4 Mills KT, Bundy JD, Kelly TN, et al. *Circulation* 2016;134:441–50.

5 Chow CK, Teo KK, Rangarajan S, et al. *JAMA* 2013;310:959–68.

6 Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. *American Journal of Medicine* 2009; 122: 290–300.

# Fixed-dose combinations (FDC) for Hypertension

- Potential Advantages
  - Combination more effective than increased monotherapy doses (5x)
  - Reduced variation in treatment response
  - 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 1<sup>st</sup> Line Treatment for All Patients**

- Simplifies protocol
- Recently endorsed in 2018 European Society of Cardiology/  
European Society of Hypertension guidelines
  - 7.5.2.4 Rationale for single-pill combination therapy as usual therapy for hypertension
- Kaiser Permanente Northern California does this, and has achieved very high control rates (85-90%)
- FDC Contraindications
  - Renovascular HTN
  - Severe renal impairment
  - Pediatric HTN

# **Making the List: FDC for Hypertension as WHO Essential Medicines**

- Guidelines
- Efficacy
- Cost



# Guidelines: International Support for FDC

	ACC/AHA 2017	ESC/ESH 2013/2018	India 2013	China 2010	Thailand 2015	WHO HEARTS
<b><i>Recommendations when to use two BP lowering drugs</i></b>						
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
<b><i>Recommendations when to use single pill combinations</i></b>						
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

- For patients needing >1 BP lowering drug, fixed dose combination (FDC) is recommended <sup>14,17-19</sup>
- ACC/AHA 2017 – [ARB or ACEI] [Thiazide/Thiazide Like] [CCB]

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.

# Guidelines: Focus on 4 Combinations

	Example combinations*	Dose options (mg)
ACEI and thiazide or thiazide-like diuretics	Lisinopril and hydrochlorothiazide	10 mg and 12.5 mg; 20 mg and 12.5 mg; 20 mg and 25 mg
ARB and CCB	Telmisartan and amlodipine	40 mg and 5 mg; 80 mg and 5 mg; 80 mg and 10 mg
ACEI and CCB	Lisinopril and amlodipine	10 mg and 5 mg; 20 mg and 5 mg; 20 mg and 10 mg
ARB and thiazide or thiazide-like diuretics	Telmisartan and hydrochlorothiazide	40 mg and 12.5 mg; 80 mg and 12.5 mg; 80 mg and 25 mg

\*Indicative components—similar clinical performance can be expected with other once-daily drugs from the same class (a “square box” application) to optimise choice. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. CCB=calcium channel blocker.

**Table: Two-drug fixed-dose combinations of antihypertensive drugs proposed for inclusion in WHO’s essential medicines list**

- Each qualified with a **square box**
- Ensures pharmacological class therapeutic equivalence; provides choice to nations while focusing options

Kishore SP, Salam A, Rodgers A, Jaffe MG, Frieden T. Lancet 2018;392:1072–1088.

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 (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<sup>1</sup>
- 42 trials (10,968 participants) showed that combining drugs from four classes produced additive BP lowering effects<sup>2</sup>
  - Effect was approximately five times greater compared to doubling the dose of monotherapy<sup>2</sup>
- Improving global rates by **just 25% with dual therapy would increase the number of patients with controlled HTN by 80 million,<sup>1</sup> 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.

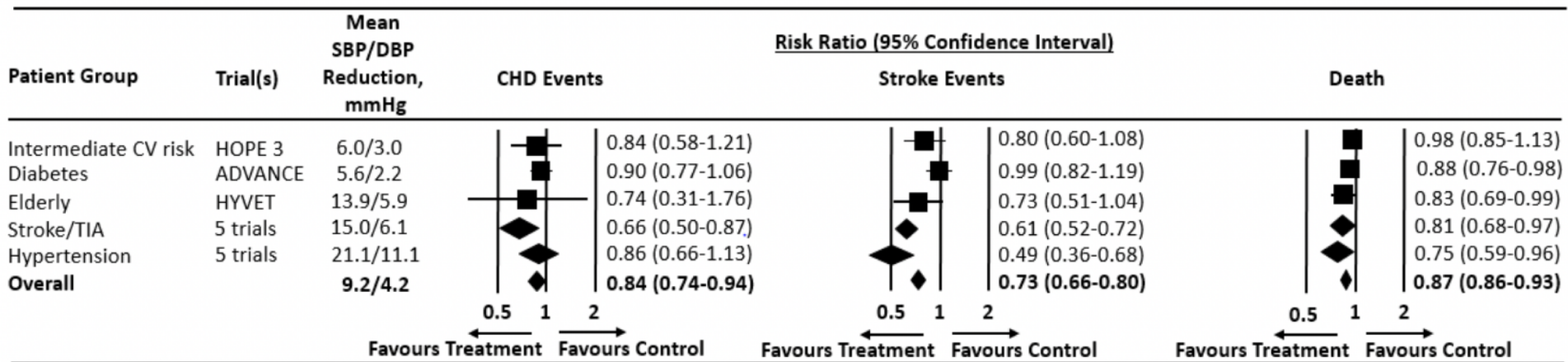
2 Magrini N, Robertson J, Forte G, et al. Tough decisions on essential medicines in 2015. *Bulletin of the World Health Organization* 2015;93:283–84.

# Efficacy: FDC for Hypertension (Cardiovascular Outcomes)

<b>Effects of combination therapy vs. placebo on CHD, stroke, heart failure and death</b>				
Studies		Intervention	Control	RR (95% CI)
		events/participants	events/participants	
<i>Studies with &gt;6 mm Hg reduction in SBP</i>				
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)
<i>Studies with ≤6 mm Hg reduction in SBP</i>				
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)
<i>All studies</i>				
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)



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.



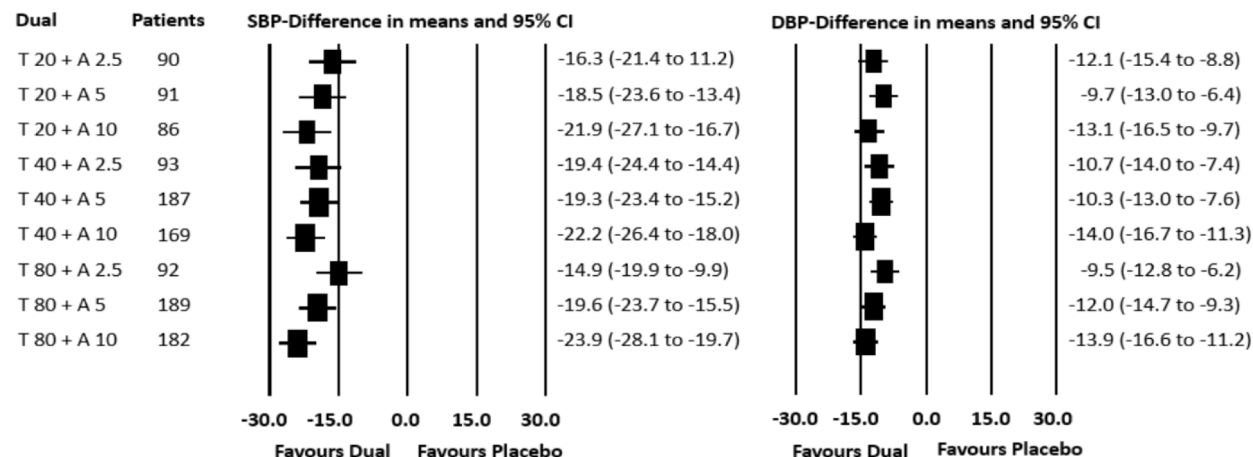
# Example:

## 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

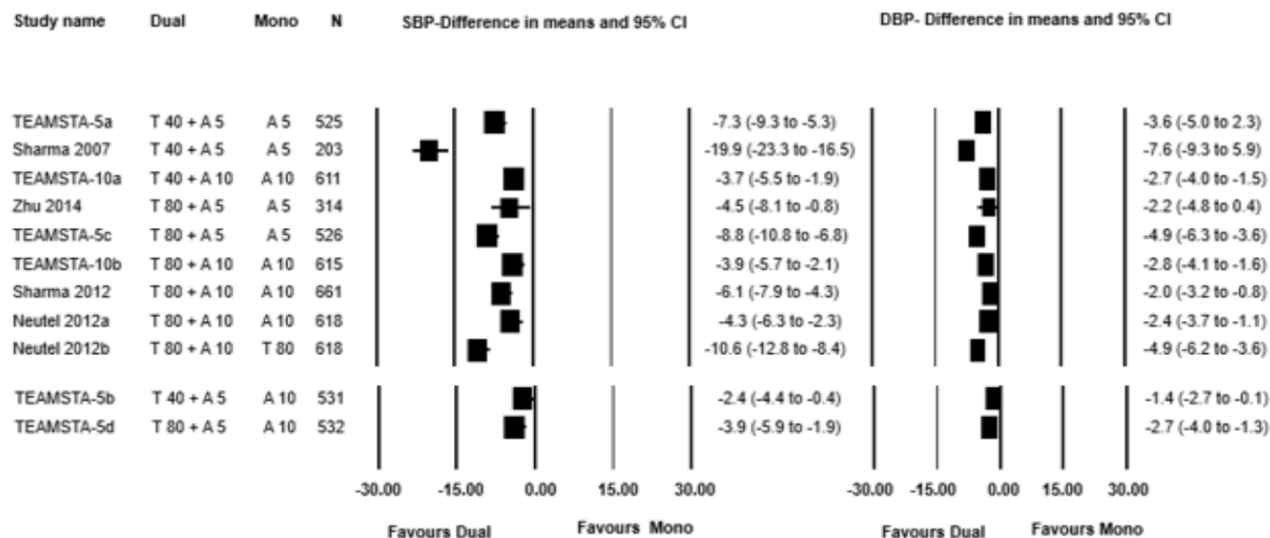
# Telmisartan + Amlodipine FDC

Vs Placebo:



T= Telmisartan; A = Amlodipine

Vs Mono:



# Cost: Global Analysis – ARB + CCB FDC (Quintiles IMS)

	2013		2014	
	Medicine units (pills) sold (in Millions)	Average Median price per pill (Euro)	Medicine units (pills) sold (in Millions)	Average price per pill (Euro)
<b>Australia</b>	1,245,306	0.12	1,557,842	0.11
<b>Brazil</b>	4,214,477	0.16	4,570,294	0.15
<b>China</b>	6,413,435	0.06	9,577,657	0.06
<b>France</b>	3,730,504	0.26	3,844,684	0.27
<b>Germany</b>	2,339,436	0.52	2,484,979	0.51
<b>India</b>	61,204,872	0.01	69,116,835	0.01
<b>Italy</b>	1,820,286	0.19	2,311,639	0.17
<b>Mexico</b>	908,476	0.29	1,029,660	0.31
<b>Turkey</b>	2,853,299	0.04	3,244,745	0.04
<b>UK</b>	77,594	0.26	79,040	0.26
<b>USA</b>	4,540,755	1.50	4,169,954	1.73
<b>Median of average price per pill</b>		0.19		0.17

*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.*



# Cost of FDC Is Similar to or Lower than Cost of Monotherapy with Constituent Pills (India)

	Median (range) unit price per pill (2018, Euros)
<b>Fixed dose combination</b>	
Lisinopril 5 mg + Hydrochlorothiazide 12.5 mg	<b>0.060</b> (0.013 – 0.087)
<b>Constituent monotherapy pills</b>	
Lisinopril 5 mg	0.045 (0.031-0.130)
Hydrochlorothiazide 12.5 mg	0.013 (0.008-0.026)
Sum of median prices of two monotherapy pills	<b>0.059</b>
<b>Fixed dose combination</b>	
Telmisartan 40mg + Amlodipine 5 mg	<b>0.090</b> (0.004-0.120)
<b>Constituent monotherapy pills</b>	
Telmisartan 40mg	0.079 (0.038-0.100)
Amlodipine 5 mg	0.026 (0.013-0.053)
Sum of median prices of two monotherapy pills	<b>0.11</b>
<b>Fixed dose combination</b>	
Telmisartan 40 mg + Hydrochlorothiazide 12.5 mg	<b>0.09</b> (0.004-0.190)
<b>Constituent monotherapy pills</b>	
Telmisartan 40 mg	0.088 (0.038-0.100)
Hydrochlorothiazide 12.5 mg	0.013 (0.008-0.026)
Sum of median prices of two monotherapy pills	<b>0.093</b>
Note: A full listing of retail and procurement prices is provided (Exhibit A) and manufacturers (Exhibit B) for one country (India)	

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.

# **Additional Cost Considerations for FDC**

- FDCs have been used as evergreening strategies in efforts by originator companies to reduce price erosion once a molecule comes off patent
- When combinations first hit the market or are scarce, they attract a price premium
- Retail drug prices need to be contextualized within the potential cost savings from improved hypertension control

# FDCs Improve Every Key Component of Hypertension Control

## Protocol



**Simpler  
treatment  
algorithm**

## Medication Supply



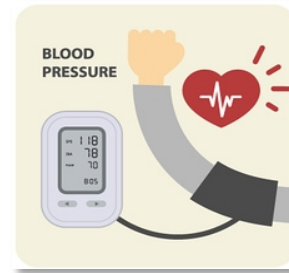
**Fewer  
stockouts**

## Community- Based Treatment



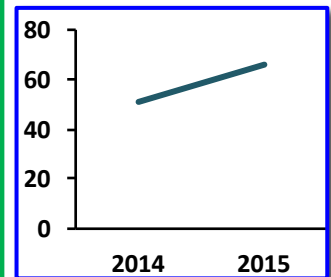
**Enhanced  
task sharing**

## 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/](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](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31814-2/fulltext)

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