Fixed-dose combination antihypertensive medications

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Mariam Chekhchar and colleagues[1] discuss branch retinal artery occlusion in a young woman, probably due to occult cardioembolus from rheumatic mitral stenosis. Despite decreasing incidence in developed nations, rheumatic heart disease remains a major source of preventable morbidity and mortality worldwide[2] and we commend the authors for bringing attention to this important clinical entity. However, given this valvulopathy's highly thrombogenic nature, therapeutic anticoagulation should be considered.

Echocardiography in mitral stenosis typically shows the leaflets to appear thickened, calcified, tethered, and poorly mobile with commissural fusion; this promotes stagnation of blood flow between the left atrium and ventricle, with consequent left atrial dilatation.[3] Transient subclinical atrial fibrillation thus occurs frequently with mitral stenosis and is an important risk factor for stroke and systemic embolus.[3–6] Before the widespread use of anticoagulation, over 25% of patients with mitral stenosis suffered an embolic event during the course of their disease.[4] Both US and European guidelines therefore recommend initiating therapeutic anticoagulation after an occult embolic event in the setting of mitral stenosis, irrespective of identification of atrial fibrillation (class I recommendation).[5,6] Despite the frequent coexistence of mitral stenosis and atrial fibrillation, trials assessing direct oral anticoagulation have consistently excluded patients with mitral stenosis, leaving warfarin as their primary option for oral anticoagulation.[5,6]

Although the patient in this scenario was initiated on low-dose acetylsalicylic acid, this treatment might be inadequate in the setting of concomitant rheumatic mitral stenosis; indefinite therapeutic anticoagulation with warfarin, targeting an international normalised ratio of 2·5, is therefore recommended as the risk of recurrence remains high.[5,6]

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On July 9, 2019, WHO added fixed-dose combination antihypertensive medications to the WHO Essential Medicines List. Treatment with fixed-dose combination medicines, also known as single-pill combinations, is the emerging best practice for safe, effective, rapid, and convenient hypertension control. But for these essential medicines to improve care and save lives, countries and health systems must ensure that everyone who needs treatment for hypertension can access them.

Of the roughly 1·4 billion people with hypertension worldwide, only about one in seven has their blood pressure successfully treated and adequately controlled.[1] For most patients, successful treatment requires two or more medications. Effective, safe medications of all major classes are available in generic form. Combining two medicines in a single pill can be cost-neutral and has important benefits for patients and for health systems, including improved patient adherence to daily medication regimens, which may improve clinical outcomes;[2] improved blood pressure control rates and shortened time to blood pressure control;[3] and more efficient hypertension management for health systems by simplifying drug supply and procurement logistics.

Some clinicians are concerned about initiating two or more drugs simultaneously, but the safety of single-pill combinations has been established in multiple clinical trials. In an analysis of more than 30 initial dual versus initial monotherapy trials, withdrawals due to adverse events were uncommon with two-drug combinations of a low-to-standard dose, with no significant difference in adverse events compared with those associated with standard-dose monotherapy.[3]

	ACC/AHA 2017	ESC/ESH 2018	India 2013	China 2010	Thailand 2015	LASH 2017	WHO HEARTS
When to use two blood pressure lowering drugs							
Not controlled on monotherapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Initial treatment for all individuals	No	Yes*	No	No	No	Yes	No
Initial treatment for selected individuals, eg, those who are >20/10 mm Hg from goal† or at high cardiovascular risk	Yes	Yes	Yes	Yes	Yes	Yes*	Yes
When to use single-pill combinations							
Recommended to substitute for separate pills to improve adherence	Yes	Yes	Yes	Yes	NR	Yes	NR

ACC=American College of Cardiology. AHA=American Heart Association. ESC=European Society of Cardiology. ESH=European Society of Hypertension. LASH=Latin American Society of Hypertension. NR=not reported. *Consider monotherapy in patients with low-risk grade 1 hypertension (systolic blood pressure <150 mm Hg), or patients who are frail or aged >80 years. †Some referred to this as stage II hypertension or marked increased blood pressure. Adapted from Salam et al.[4]

Table: **Selected hypertension guidelines' recommendations for dual combination and fixed-dose combinations**

As organisations with a shared goal of improving hypertension control worldwide, the American Heart Association, European Society of Hypertension, International Society of Hypertension, *Lancet* Commission on Hypertension Group, Latin American Society of Hypertension, Resolve to Save Lives, World Heart Federation, World Hypertension League, and World Stroke Organization commend WHO for making single-pill combination antihypertensive medications more widely available by including them in the WHO Essential Medicines List. This inclusion aligns with the recommendations for single-pill combinations in multiple national and international hypertension treatment guidelines (table).

Countries must now implement policies that put single-pill combinations in the hands of the patients who need them. Countries should follow WHO's lead and include affordable single-pill combinations in their own essential medicines lists, procure and promote sufficient supplies of quality assured low-cost single-pill combinations, and create and implement simple, practical, hypertension treatment protocols incorporating single-pill combinations as a core medication.[5] These actions can be especially effective and resource-efficient in low-income and middle-income countries, where the burden of hypertension is rising and control rates are very low.

IJB is President of the American Heart Association. RK is Secretary of the European Society of Hypertension. MHO is a member of the *Lancet* Commission on hypertension. AES is President of the International Society of Hypertension. PL-J is President of the Latin American Society of Hypertension. TRF is President and CEO of Resolve to Save Lives, an initiative of Vital Strategies. KS is President of the World Heart Federation. DTL is President of the World Hypertension League. MB is President of the World Stroke Organization. AES has received speaker honoraria from Novartis, Omron, and Servier on presentations to raise awareness of elevated blood pressure and risk stratification. She has also provided paid consultative advice to Abbott Pharmaceuticals on a project to investigate the use of selective imazidoline receptor antagonists in low-income and middle-income countries. RK has received honoraria for consultancy, lectures, and support for research from Bayer AG, Berlin-Chemie Menarini, Daiichi Sankyo, and Servier. MHO has received a part-time research grant from the Novo Nordic Foundation. PL-J has received honoraria for lectures from Menarini, Abbott, Merck, Servier, Boehringer Ingelheim and Sanofi. All other authors declare no competing interests. Resolve to Save Lives, including support for development of this paper, is funded in part by grants from Bloomberg Philanthropies; the Bill & Melinda Gates Foundation; and the Chan Zuckerberg Initiative DAF, an advised fund of Silicon Valley Community Foundation.

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