WORLD HEART FEDERATION

WORLD HEART FEDERATION ROADMAP ON SINGLE PILL COMBINATION THERAPIES ROADMAP SUMMARY

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Cardiovascular disease (CVD) is the leading cause of death globally, with more than 20 million people dying each year and millions more suffering from a cardiovascular condition.[1] Around 75% of all CVD deaths occur in low- and middle-income countries (LMICs).

Multiple therapeutics play an important role in reducing morbidity and mortality from CVDs, particularly as they can address CVD risk factors, such as raised blood pressure, platelet activation and raised cholesterol levels. However, the resulting number of pills that patients may need to successfully prevent or treat CVDs can hinder adherence to treatment schedules and therefore health outcomes.

Single pill combination therapies (SPCs) are a vital tool to improve patient adherence to treatment schedules for CVDs, as they include more than one active pharmaceutical ingredient in a single pill, therefore reducing the pill burden on patients.[2] SPCs have been successfully utilized to treat certain CVD conditions yet remain underutilized globally in primary and secondary prevention* of CVDs – particularly in LMICs where the need is greatest – despite a growing evidence base from the last two decades that underscores their promise in improving health outcomes.

Defining single pill combination therapies

This document only uses the term SPC to reflect the fact that SPC, fixed-dose combination (FDC) and 'polypill' therapies are often used interchangeably as terms and that they have shared potential to improve cardiovascular health.

SPC is now often used as an alternative to fixed-dose combination (FDC) as the SPC platform is designed to alter the dose of different pharmaceutical components of a pill therapy – i.e. it is no longer 'fixed.'

The term 'polypill' is used to describe the combination of multiple drugs in one single pill to target more than one condition.

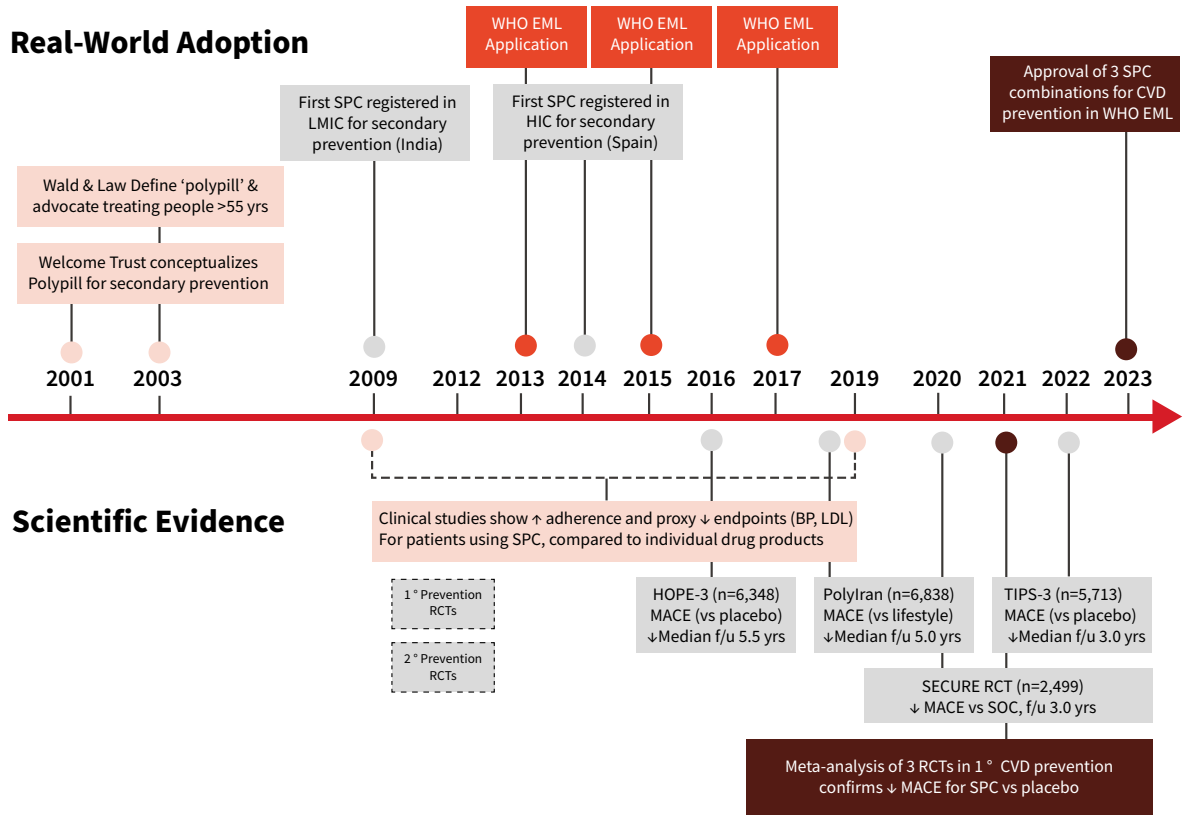
The inclusion of cardiovascular SPCs in the World Health Organization's 2023 List of Essential Medicines (EML) is a major milestone that can spur the further availability, accessibility and affordability of these therapeutics to combat CVDs. Inclusion in the WHO EML has the potential to positively influence government procurement efforts, professional guideline recommendations, and clinician adoption.

The WHF Roadmap on SPCs aims to capitalize on this momentum through outlining the well-established safety and efficacy SPCs for primary and secondary prevention of CVDs, along with the barriers that are hindering their implementation and proposed solutions to overcome them.

*Primary prevention = treatment of those considered at sufficiently high risk of developing clinically significant atherosclerotic CVD (ASCVD). Secondary prevention = preventing a recurrent event among people who already have established ASCVD or have experienced a major adverse cardiovascular event (MACE), such as myocardial infarction or stroke.

[1] Di Cesare M, Perel P, Taylor S, Kabudula C, Bixby H, Gaziano TA, et al. The Heart of the World. Glob Heart. 2024;19(1):11.
[2] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. Bmj. 2003;326(7404):1419.

Development and Implementation of Single Pill Combinations for Cardiovascular Disease[3]



EVIDENCE IN SUPPORT OF SPCS

Clinical studies of SPCs for primary and secondary CVD prevention indicate positive outcomes in reducing the incidence of major adverse cardiovascular events (MACE) and controlling CVD risk factors (e.g. blood pressure, cholesterol levels).

Importantly, analysis of trial data shows that patient adherence to SPCs across primary and secondary CVD prevention is notably higher compared to patients using individual drugs, while available data suggest that SPCs can be a cost-effective strategy for CVD prevention and control across countries at different income levels.[4]

Intermediate or clinical outcome	Findings
Major adverse cardiovascular events (MACE)	**Primary prevention** • SPCs can lead to rapid, large, and consistent reductions in fatal and non-fatal MACE among a wide spectrum of people *without* prior CVD. • Compared with usual care or placebo, an SPC strategy led to: – **38%** reduction in cardiovascular death, myocardial infarction, stroke, or arterial revascularization. – **11%** reduction in all-cause mortality – **29%** reduction in non-fatal ASCVD. **Secondary prevention** • Compared with treatment using individual drugs, and SPC strategy led to: – **24%** reduction in the primary composite MACE outcome of CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, or urgent revascularization.
CVD risk factors (e.g. blood pressure or cholesterol levels)	• Compared with control group, SPC interventions found to reduce mean systolic blood pressure and low-density lipoprotein-cholesterol in both primary and secondary prevention.

[3] Ferro EG, Satheesh G, Castellano J, Damasceno A, Erojikwe O, Huffman M, Irazola V, Joseph P, Lanas F, Ogola E, Ordunez P, Perel P, Pineiro D, Uchmanowicz I, Vardeny O, Webster R, Gamra H, Gaziano T, Murphy A. WHF Roadmap on Single Pill Combination Therapies. Global Heart. 2025; X(X): X. DOI: https://doi.org/10.5334/gh.145

[4] Lamy A, Tong W, Joseph P, Gao P, Huffman MD, Roshandel G, et al. Cost effectiveness analysis of a fixed dose combination pill for primary prevention of cardiovascular disease from an individual participant data meta-analysis. EClinicalMedicine. 2024;73:102651.

HURDLES AND POTENTIAL SOLUTIONS TO IMPLEMENTATION OF SPCS FOR CARDIOVASCULAR DISEASE

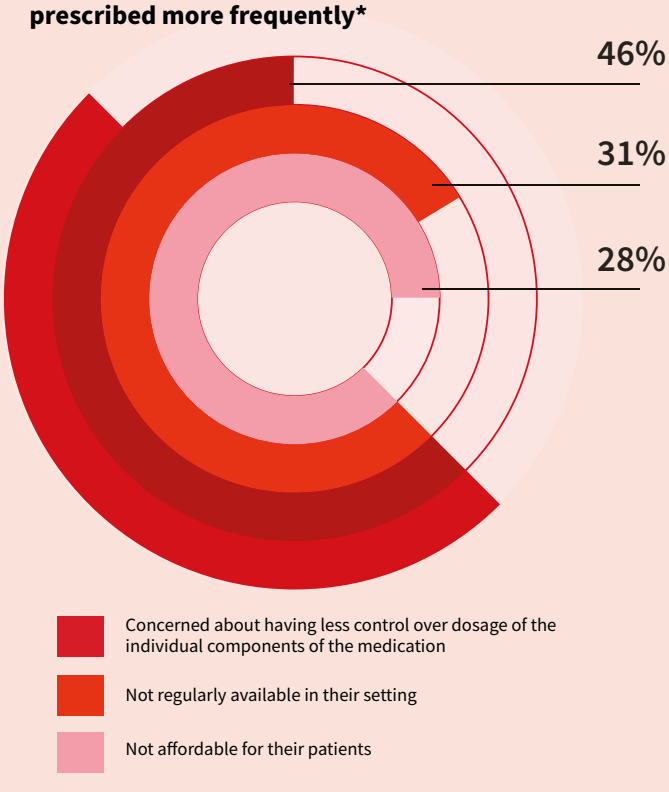
	HURDLES	POTENTIAL SOLUTIONS
AVAILABILITY	• Limited manufacturing capacity • Reliance on importation increased costs • Complex, costly regulatory approval	• Financial incentives for manufacturers • Technology transfers to LMICs • Grants for local manufacturing • Regulatory harmonisation & support
AFFORDABILITY	• Higher cost vs. individual meds • Low procurement volume • Exclusions from essential medicine lists	• Pooled procurement mechanisms • Inclusion in national EMLs & insurance schemes
ADOPTION	• Inconsistent guideline inclusion • Prescriber hesitation • Low patient awareness	• Update national guidelines • Provider education & mentoring • Awareness campaigns • Co-designed implementation strategies

ROADBLOCKS AND POTENTIAL SOLUTIONS TO SPC ACCESS

Several factors hinder the global uptake of SPCs. Guided by access to medicines frameworks and a focus primarily on the public sector, the Roadmap identifies four key hurdles to successful implementation of SPCs:

1. Limited manufacturing of SPCs
2. Higher cost of SPCs
3. Inconsistent recommendations of SPCs in international and national guidelines and treatment protocols
4. Prescriber inertia

Main reasons cardiovascular polypills not prescribed more frequently*



* WHF Member Survey of responses from 105 healthcare professionals, including cardiologists, endocrinologists, general practitioners, and nurses from 27 Countries.

Solutions to overcome the hurdles should be approached as a coordinated set of strategies, as the challenges are often intersecting and inter-dependent.

Other considerations for SPC implementation – e.g. related to supply chain forecasting, distribution, and delivery – are important, though fall outside the scope of this Roadmap. Strategies and policies to address these challenges should draw on documented lessons from across LMIC settings and various disease areas.

Despite the benefits of SPCs, global adoption and implementation remain limited, particularly in LMICs where the need is greatest. Stronger advocacy by international and national cardiac societies for inclusion of SPCs in national guidelines, and targeted education for healthcare providers and patients. Expanding access to SPC therapy and supporting efforts is critical to reduce the global mortality and morbidity burden of CVDs.

> If implemented, WHF roadmap on SPC will impact the outcome of millions of people leaving with CVD and/or cardiovascular risk factors by enhancing medication adherence and reducing major adverse cardiovascular events, especially in low and middle income countries where SPC is mostly needed."

PROFESSOR HABIB GAMRA
Co-Chair of WHF Roadmap on Single Pill Combination (SPC) therapies

> The WHF Roadmap on Single Pill Combination (SPC) therapies provide a significant contribution to the field of cardiovascular disease prevention. The trials of SPCs that show important reductions in morbidity and mortality have been done. The WHO has added them the Essential Medicine List. Now governments, private individuals, providers, and industry need to advocate to make them available throughout the world so that nobody is left behind. The Roadmap will guide them on this journey to better CVD health for all."

DR THOMAS GAZIANO
Co-Chair of WHF Roadmap on Single Pill Combination (SPC) therapies

> The WHF Roadmap on Single Pill Combination (SPC) therapies identifies key hurdles to implementation of SPCs around the world and offers potential solutions to address these. The task now is to adapt these solutions to local health systems and to ensure they are feasible, effective, and sustainable. Acting on the Roadmap's recommendations is crucial for improving universal access to this essential medication."

DR ADRIANNA MURPHY
Co-Chair of WHF Roadmap on Single Pill Combination (SPC) therapies

CASE STUDY

HEARTS IN THE AMERICAS – A SCALABLE APPROACH TO CVD PREVENTION IN PRIMARY CARE SETTINGS

HEARTS in the Americas is the regional adaptation of the WHO's Global HEARTS initiative, aiming to improve hypertension control and the secondary prevention of cardiovascular disease (CVD) through stronger primary care.

MORE THAN 7,000 PHC FACILITIES ARE CURRENTLY IMPLEMENTING THE MODEL, COVERING A POPULATION OF OVER 35 MILLION PEOPLE, WITH NEARLY 6 MILLION INDIVIDUALS RECEIVING TREATMENT – 62% OF WHOM HAVE CONTROLLED BLOOD PRESSURE.

To date, 33 countries in Latin America and the Caribbean are committed to implementing the program and scaling it up across their entire primary health care (PHC) networks. As of now, 12 countries have scaled up the program to cover more than 80% of their PHC facilities. More than 7,000 PHC facilities are currently implementing the model, covering a population of over 35 million people, with nearly 6 million individuals receiving treatment – 62% of whom have controlled blood pressure.

At the center of HEARTS is a standardized, high-quality clinical pathway, whose core is a standardized treatment protocol – a simple, step-by-step approach using specific medications at set doses. It starts with two complementary blood pressure medicines at half doses, followed by full doses, and then adds a third drug if needed. For people with CVD, high-intensity statins and low-dose aspirin are included. For those at high risk (but without CVD), moderate-intensity statins are recommended, without aspirin.

To support this, the PAHO Strategic Fund has created a preferred list of medicines and assists countries in updating their essential medicines lists, aligned with the WHO's latest recommendations — including SPCs for hypertension and CVD prevention. A key goal of the program is to make Single Pill Combinations (SPCs) more accessible and affordable, using formulations that are easy for primary healthcare professionals to use and titrate. HEARTS encourages the use of a small set of long-acting medications to simplify treatment, reduce costs, and streamline supply chains. This strategy helps countries better predict medicine needs and negotiate lower prices.

HEARTS in the Americas follows the 2021 WHO hypertension guidelines and has already influenced prescribing practices across the region:

- **26** countries have approved national clinical pathways for hypertension and CVD primary and secondary prevention
- **17** of those **26** include SPCs in their national medical formularies
- **24** countries recommend initiating treatment with two medications
- **26** countries recommend statins for CVD prevention; **23** of them use high-intensity statins

This approach shows that by combining evidence-based clinical pathways with better access to essential medicines, strong political will, and a clear focus on public health and primary health services, countries – especially low- and middle-income countries (LMICs) – can greatly expand CVD prevention and treatment within primary care settings.

WORLD HEART FEDERATION ROADMAPS

CVDs and related conditions can often be prevented, or, through early detection, can be treated cost-effectively to prevent hospitalizations and death.

Successfully tackling CVDs requires coordinated national policy and health systems responses built around evidence-based strategies. Health resources are limited meaning cost-effective interventions for the prevention, detection and management of CVD must be prioritized to plan effective health systems responses.

WHAT ARE ROADMAPS?

WHF Roadmaps are a global framework that can be adapted and used at national or regional level. Their goal is to trigger effective action that can measurably reduce premature deaths and the associated global economic burden caused by CVD.

WHF ROADMAPS AIM TO SPUR ACTION THROUGH:

1. **Summarizing current recommendations that are proven, practical and cost effective to reduce the burden of CVD.**
2. **Highlighting obstacles to implementing these recommendations.**
3. **Proposing potential solutions for overcoming these obstacles.**
4. **Providing tools and strategies to adapt solutions to local needs.**

HOW DO THEY WORK?

WHF Roadmaps offer a global framework, tools and solutions that can then be used and adapted, through stakeholder collaboration, to meet the specific needs of individual regions and nations. *This requires:*

- A situation analysis of the current health system based on tools such as WHF CVD Scorecards
- Roundtables with multiple stakeholders to discuss obstacles, solutions and appropriate strategies
- A plan to implement and evaluate the proposed strategies

WHO ARE THEY FOR?

Roadmaps empower WHF Members, including CVD foundations, societies and patient associations, to lead country-specific, action-oriented initiatives, including Roundtables.

These involve diverse stakeholders, such as:

- Governments and policy makers
- NGOs, health activists and advocates
- Healthcare professionals
- Corporate entities
- Academic and research institutions
- Patients and patient groups

TO DOWNLOAD THE FULL ROADMAP PLEASE VISIT – WORLD-HEART-FEDERATION.ORG/CVD-ROADMAPS

We recognise Ferrer and Servier for their support of the WHF Roadmap on Single Pill Combination Therapies. The content is the sole remit of the co-authors.

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