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Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) scientific statement on the simplification of the drug regimen for secondary cardiovascular prevention

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The issue of suboptimal drug regimen adherence in secondary cardiovascular prevention presents a significant barrier to improving patient outcomes. To address this, the utilization of drug combinations, specifically single pill combinations (SPCs) and polypills, was proposed as a strategy to simplify treatment regimens. This approach aims to enhance treatment accessibility, affordability, and adherence, thereby reducing healthcare costs and improving patient health. The document is an Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) scientific statement on simplifying drug regimens for secondary cardiovascular prevention. It discusses the

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underuse of treatments despite available, effective, and accessible options, highlighting a significant gap in secondary prevention across different socio-economic statuses and countries. The statement explores barriers to implementing evidence-based treatments, including patient, healthcare provider, and system-related challenges. The paper also reviews international guidelines, the role of SPCs and polypills in clinical practice, and their economic impact, advocating for their use in secondary prevention to improve patient outcomes and adherence.

Introduction

Secondary prevention of cardiovascular diseases encompasses all the strategies aimed at improving prognosis and reducing the likelihood of cardiovascular events in patients with a previous cardiovascular event. These strategies include lifestyle modifications and pharmacological or non-pharmacological therapeutic interventions. With respect to pharmacological treatments, despite the availability of effective, safe, and, for the most part, easily accessible therapeutic agents, real-world data show an underuse of treatments even among patients at higher risk.[1] A survey conducted between 2003 and 2009 revealed that, in higher-income countries, only half of the patients with known cardiovascular disease take the recommended therapy for secondary prevention. In poorer social classes and countries, the use of pharmacological treatments for secondary prevention drops to 5% of eligible patients.[2] In a more recent international registry study, conducted between 2015 and 2018, the use of recommended treatments was reported in just over half of the patients with a previous coronary event [myocardial infarction (MI) or revascularization].[3]

In general, the possible barriers to the implementation of evidence-based treatments in secondary prevention can be divided into those related to the patient (including the difficulty to handle multiple drug therapies), to the doctor in charge, or to the healthcare system organization. These barriers have a negative impact on the adherence to treatment, defined as 'the degree to which a person's behaviour—taking a medication, following a diet and/or changing one's lifestyle—corresponds to what was agreed with the healthcare provider'. The World Health Organization (WHO) has identified adherence as a crucial element to reduce the global impact of chronic diseases, improve prognosis, and reduce healthcare costs.[4] Based on these premises, over 20 years ago, the WHO launched a project aimed specifically at simplifying the therapeutic regimen with the goal of improving therapeutic adherence. This project recognized combination therapies as one of the main tools to improve clinical outcomes.[4]

The combination of multiple drugs into a single pill has been proposed as a possible strategy to make therapeutic interventions more easily accessible and affordable, thereby allowing a larger number of patients to benefit from the therapies. According to the terminology commonly used in scientific literature, each formulation combining multiple therapeutic agents for one or more pathological conditions (e.g. multiple lipid-lowering or antihypertensive agents in a single pill) should be defined as 'single pill combination' (SPC), while the term 'polypill' should be used only for SPCs combining drugs for different conditions (e.g. antihypertensives, lipid-lowering agents, and antiplatelets).

In the last decade, numerous studies have demonstrated the efficacy and safety of a combination of multiple therapeutic agents in a single pill for both primary and secondary cardiovascular prevention. Simultaneously, numerous formulations with multiple combined agents in a single pill have been introduced to the market. The aim of this Position Paper by the National Association of Hospital Cardiologists (*Associazione Nazionale Medici Cardiologi Ospedalieri*, ANMCO) is to define the role of SPCs and polypills in secondary prevention. We will discuss the impact of poor therapeutic adherence on the prognosis of patients with cardiovascular disease and the evidence supporting the use of SPCs and polypills. Moreover, we will examine the advantages and possible limitations of SPCs and polypills and provide the recommendations proposed by the most recent international guidelines. Finally, we will list the therapeutic options actually available on the market in Italy and the position of the ANMCO about their use in clinical practice.

Poor adherence to treatment as a cardiovascular risk factor

There is an increasing awareness that cardiovascular risk may be reduced by simplifying the therapeutic regimen and that poor therapeutic adherence is another, less apparent, cardiovascular risk factor.[5] Poor adherence is particularly critical in the setting of secondary cardiovascular prevention, as patients must take most drugs for their whole life to reduce their risk of disease progression and recurrent cardiovascular events. A meta-analysis on the setting of secondary prevention including data from nearly 2 million patients reported poor adherence in 40% of cases, with a similar proportion of poorly adherent patients across various types of cardiovascular treatments. There was a significant association between poor adherence and increased risk of cardiovascular diseases and death. This study estimated that a considerable portion (about 9%) of cardiovascular events could be attributed to poor adherence to cardiological drug treatments, highlighting the need to implement measures to improve therapeutic adherence.[6] In a more recent study, a 20% improvement in adherence to cardiovascular treatments was associated with an 8% reduction in the risk of cardiovascular events.[7] In a Canadian observational study investigating the prevalence of therapeutic adherence after 120 days from hospitalization for a MI, adherence to treatments prescribed at discharge was observed in 74% of patients,

and 1-year mortality was higher among those with lower adherence compared with those who were fully adherent.[8] In a more recent observational study enrolling 4349 patients with MI, a poor adherence (defined as a percentage of days of drug possession per year <80%) was reported for most drug classes (47.6% for dual antiplatelet therapy, 23.5% for lipid-lowering therapy, 47.3% for angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, and 88.1% for beta-blockers). On the other hand, patients with higher adherence for all these drug classes had a lower mortality and a lower incidence of major adverse events.[9] A clinical study assessing the impact of therapeutic adherence to clopidogrel, after percutaneous revascularization with the implantation of a drug-eluting stent, demonstrated that non-adherent patients, i.e. those who discontinued clopidogrel within 30 days of the procedure, had a 10-fold higher mortality rate and a risk of hospitalization for cardiovascular causes increased by about 50% compared with adherent patients.[10] Poor adherence is a complex phenomenon attributable to factors related to the patient (e.g. socio-economic status, literacy level, comorbidities, age, and chronicity of the disease) and others dependent on the therapy (e.g. adverse effects, complex treatment regimen, and polypharmacy). The use of formulations combining multiple therapeutic agents, therefore, is one of the possible strategies to simplify therapeutic schemes and improve adherence to treatments,[11] favouring the achievement of therapeutic targets and improving outcomes.[12]

Evidence on polypills and single pill combinations in secondary prevention

A 'polypill' strategy for the prevention of cardiovascular diseases was first proposed in 2003 by Wald and Law, who hypothesized that the use of multiple drugs active against various risk factors (including lipid-lowering agents, antihypertensives, antiplatelets, and folic acid) in a single formulation could reduce the risk of MI and stroke by over 80% in individuals aged ≥55 years, with an acceptable safety profile.[13] In the following decades, the polypill strategy has been widely debated in the scientific community. Numerous clinical studies conducted in the setting of primary or secondary prevention have found that a polypill strategy improves significantly the adherence to cardiovascular pharmacological treatments. For example, the randomized clinical trial UMPIRE found that a combination of an antihypertensive, lipid-lowering, and antiplatelet agent in a single tablet resulted in a significant improvement in adherence and a reduction in systolic blood pressure values (−4.9 mmHg) and low-density lipoprotein cholesterol (LDL-C) levels (−6.7 mg/dL) compared with standard therapy.[14] Additionally, randomized clinical trials have demonstrated a significant impact of a polypill strategy on clinical outcomes such as major adverse cardiovascular events (MACE).[15,16] The most recent is the Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) study, which evaluated the impact of a polypill-based strategy on clinical events in elderly patients with recent MI. A polypill containing aspirin, ramipril, and atorvastatin reduced the incidence of MACE in patients with MI compared with the same therapies given separately.[16] In both patient groups, risk factor management was optimal as LDL-C values 24 months after randomization were within the target recommended by the contemporary European guidelines.[16] The clinical benefit of a simpler therapeutic scheme could then be attributed to a greater adherence to treatment in the group taking the polypill.[17,18] The results of SECURE are consistent with those of the observational NEPTUNO study, which included patients with known cardiovascular disease, where the same polypill reduced MACE compared with three different standard therapeutic formulations.[19]

With respect to the administration of multiple antihypertensive agents into SPCs, many clinical studies have demonstrated that reducing the number of daily pills increases both treatment adherence and the rate of blood pressure control.[20] A meta-analysis of 33 randomized studies showed that a starting approach with a combination of two low-dose antihypertensive agents in a single pill is more effective for blood pressure control than monotherapy.[21] In two prospective observational studies, the bisoprolol/perindopril SPC in patients with hypertension, stable angina, and/or previous MI was associated with a significant reduction in blood pressure and an improved angina threshold.[22,23] An Italian study including over 18 800 patients with newly diagnosed hypertension and on antihypertensive drugs found that combination therapy was associated with greater therapeutic adherence, and a high adherence (defined again as >80% of days on treatment) reduced the risk of cardiovascular events during a mean follow-up of 4.6 years.[24] In the recent START study, an SPC strategy with four drugs increased therapeutic adherence and reduced MACE and all-cause mortality compared with the same drugs given separately.[25] An effective therapeutic approach in increasing blood pressure control while simultaneously improving tolerability consists of using combinations of three or even four antihypertensive drugs at low or very low doses. With this approach, the ability to effectively reduce high blood pressure seems to be maintained while most adverse effects are avoided.[26]

Several studies have found that the statin/ezetimibe combination in a single tablet is effective and safe for the treatment of hypercholesterolaemia. In the IMPROVE-IT study, an ezetimibe/statin combination therapy within 10 days of an acute coronary syndrome (ACS) significantly reduced the rates of ischaemic events compared with a statin-only therapy.[27] In a RACING study, conducted on patients with known atherosclerotic disease, moderate efficacy statin therapy (rosuvastatin 10 mg) combined with ezetimibe increased the percentage of patients achieving LDL-C targets compared with high-efficacy statin alone (rosuvastatin 20 mg), reduced the risk of statin dose suspension/reduction due to drug intolerance, and was non-inferior in terms of incidence of MACE at 3 years.[28] These results suggest that early initiation of a moderate efficacy statin/ezetimibe combination should be preferred to a high-efficacy statin monotherapy in patients with a very high cardiovascular risk.[29] Ezetimibe has also been tested in fixed combination with bempedoic acid, showing good efficacy in terms of LDL-C reduction with a favourable safety profile when added to maximally tolerated statin therapy in patients with hypercholesterolaemia and a high cardiovascular risk.[30] The available evidence thus supports

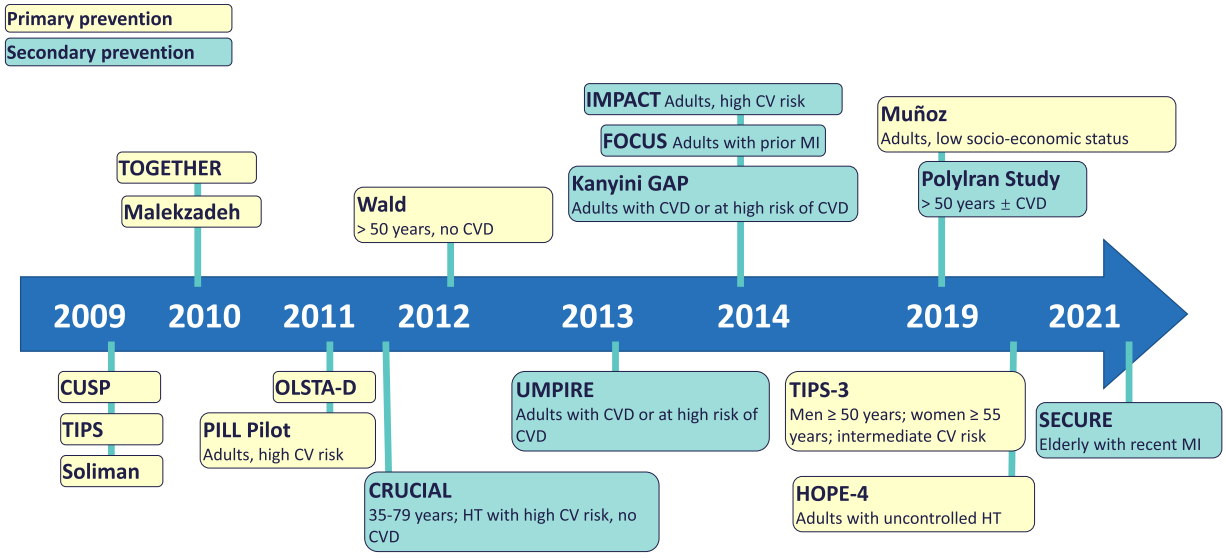

Figure 1 Main studies on polypills for primary or secondary cardiovascular prevention. See text for details and references. CV(D), cardiovascular (disease); HT, hypertension; MI, myocardial infarction.

the use of fixed combinations even in the management of hypercholesterolaemia.

Some clinical studies have compared treatment with aspirin and clopidogrel with a combined formulation of the two drugs. The strategy of dual antiplatelet therapy with a single pill proved superior to the individual drugs taken separately in terms of adherence[31] and comparable in terms of pharmacodynamic efficacy, evaluated through the analysis of platelet reactivity (*Figure 1*).[32,33]

The results of the main studies testing different formulations of polypills and SPCs are reported in *Table 1*.

Advantages, limitations, and precautions

Understanding the benefits, limitations, and potential risks of drug combinations (*Table 2*) is crucial for the optimal selection of SPCs and polypills. It is also vital to be familiar with strategies to minimize possible adverse effects. Beyond the clinical efficacy on cardiovascular outcomes,[16] the primary benefit of SPCs and polypills lies in the simplification of the medication regimen. A simpler regimen is often preferred by patients, leading to improved adherence (as shown by many studies) and a greater likelihood of meeting therapeutic targets (such as achieving recommended LDL-C levels or blood pressure values).[41] Additionally, the strategy of employing SPCs or polypills in secondary cardiovascular disease prevention offers the advantage of reducing healthcare costs, benefiting both the overall healthcare system and individual patients.[42]

A recent pharmacoeconomic evaluation study in Italy developed a budget impact model to compare the economic impact of a fixed-dose combination (single-pill) of aspirin 100 mg and rosuvastatin (5, 10, or 20 mg) against a multi-pill approach on the national health service's expenditure. The findings suggest significant savings with the single-pill usage, ranging from € 951 201 with a 50% adoption rate to € 1 902 402 with full (100%) adoption.[43]

One limitation of SPCs and polypills is the restricted ability to adjust individual component doses, potentially leading to under-treatment of higher-risk patients.[12] However, the market availability of SPCs and polypills in various dose combinations mitigates this issue, emphasizing the importance of selecting the appropriate dosage for each patient. Additionally, in clinical practice, it may be necessary to supplement the SPC with a separate single-component drug to achieve the desired dosage. Another concern is the risk associated with missing or voluntarily discontinuing the SPC or polypill, which would result in the interruption of multiple treatments. Despite this, clinical studies have consistently shown the safety of these approaches compared with standard treatments, suggesting that the overall clinical risk is minimal.

Managing adverse events or intolerance to SPCs or polypills, with the potential for treatment discontinuation, requires careful assessment and prompt treatment adjustment. The risk of therapeutic duplication is also notable, particularly if additional prescribers are unaware of the SPC or polypill components and prescribe overlapping medications, a situation not uncommon in the management of hypertensive patients.[44]

Finally, both patients and healthcare providers might neglect lifestyle modifications in favour of pharmacological therapy with SPCs or polypills. The clinical should emphasize that these pharmacological interventions should complement lifestyle changes in managing conditions and not replace them.

Guidelines and consensus documents

In the field of cardiovascular prevention, the European Society of Cardiology (ESC) 2012 guidelines mentioned for the first time fixed-dose combination drugs. These guidelines highlighted the treatment simplification offered by SPCs and the potential prognostic benefit linked to their use. The guidelines also noted the need

Table 1 Randomized clinical trials and observational studies on the use of the polypill or combination therapies in secondary prevention

First author (year)	Study design	Study population (patient, *n*)	Comparison	Primary endpoint	Primary endpoint: results	Interpretation
Polypill						
Castellano *et al.* (2022)[16]	RCT	Patients with MI in the previous 6 months (2499)	Polypill containing aspirin 100 mg, ramipril 2.5/5/10 mg, atorvastatin 20/40 mg vs. standard therapy	Composite of CV death, non-fatal MI, non-fatal ischaemic stroke, or urgent coronary revascularization	HR 0.76; 95% CI 0.60–0.96; $P < 0.001$ for non-inferiority, $P = 0.02$ for superiority	Treatment with the polypill resulted in a significantly lower risk of MACE compared with standard therapy
González-Juanatey *et al.* (2022)[19]	Observational study	Patients with known CV disease (6456)	Polypill containing aspirin 100 mg, ramipril 2.5/5/10 mg, atorvastatin 20/40 mg vs. standard therapy with 3 different formulations (single-component, equipotent, other therapies)	MACE	Single-component: HR 1.22; 95% CI 1.06–1.45; $P = 0.017$. Equipotent: HR 1.25; 95% CI 1.08–1.43; $P = 0.002$. Other therapies: HR 1.27; 95% CI 1.10–1.41; $P = 0.001$	Treatment with the polypill (with 3 different formulations) resulted in a significantly lower risk of recurrent MACE compared with standard therapy
Patel *et al.* (2015)[34]	RCT	Patients with known CV disease (623)	Polypill containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg or HCT 12.5 mg vs. standard therapy	Adherence to treatment, changes in SBP and total cholesterol	Adherence to treatment with polypill vs. standard therapy: 70% vs. 47%; RR 1.49, 95% CI 1.30–1.72; $P < 0.0001$. Changes in SBP: −1.5 mmHg; 95% CI −4.0 to 1.0; $P = 0.24$. Changes in total cholesterol: 0.08 mmol/L; 95% CI −0.06 to 0.22); $P = 0.26$	The use of a polypill led to a significant improvement in medication adherence without significant changes in blood pressure and total cholesterol levels
Castellano *et al.* (2014)[35]	RCT	Patients with MI (695)	Polypill containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5, or 10 mg vs. standard therapy	Adherence to treatment	Adherence to treatment with polypill vs. standard therapy: 50.8% vs. 41% ($P = 0.019$)	The use of a polypill led to a significant improvement in the adherence to treatment
Thom *et al.* (2013)[14]	RCT	Patients with known CV disease (2004)	Polypill containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg vs. polypill (aspirin 75 mg	Adherence to treatment, changes in SBP and LDL-C	Adherence to therapy with the polypill vs. standard therapy: 86% vs. 65%; RR 1.33; 95% CI 1.26–1.41; $P < 0.001$	The use of a polypill resulted in a significant improvement in medication adherence and statistically

Continued

Table 1 Continued

First author (year)	Study design	Study population (patient, *n*)	Comparison	Primary endpoint	Primary endpoint: results	Interpretation
			and simvastatin 40 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5 mg) vs. standard therapy		Differences in systolic BP: −2.6 mmHg; 95% CI −4.0 to −1.1 mmHg; $P < 0.001$ Differences in LDL cholesterol: −4.2 mg/dL; 95% CI −6.6 to −1.9 mg/dL; $P < 0.001$	significant improvements in SBP and LDL-C
Combination antihypertensive therapies						
Schmieder *et al.* (2023)[25]	Observational study	Hypertensive patients, primary or secondary prevention (57 998)	SPC (Val/Amlo; Can/Amlo; Rami/Amlo;Val/Amlo/HCT) vs. MPC	All-cause death	Val/Amlo: IRR 0.761; 95% CI 0.68–0.84; $P < 0.001$. Can/Amlo: IRR 0.538; 95% CI, 0.28–0.98; $P = 0.031$; Rami/Amlo: IRR 0.526; 95% CI, 0.46–0.59; $P < 0.001$ Val/Amlo/HCT: IRR 0.515; 95% CI 0.37–0.70; $P < 0.001$	Combination antihypertensive therapy reduces all-cause mortality when administered as a single pill compared with multiple-pill administration
Kobalava *et al.* (2023)[23]	Observational study	Hypertensive patients with previous MI (504)	SPC (Bis/Peri) vs. MPC	Changes in mean SBP and DBP	SPC is associated to a reduction in systolic/diastolic BP of 24.9/12.2 mmHg ($P = 0.001$).	Treatment with Bis/Peri is associated to significant decreases in systolic/diastolic BP
Chow *et al.* (2021)[36]	RCT	Hypertensive patients, primary or secondary prevention (591)	SPC (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg) vs. irbesartan 150 mg/die	Changes in SBP	Significant reduction in SBP (6.9 mmHg ($P < 0.0001$) with SPC compared with irbesartan 150 mg/day	An early treatment strategy with a fixed-dose quadruple combination achieved and maintained a greater lowering of blood pressure compared with monotherapy
Boytsov *et al.* (2021)[22]	Observational study	Patients with hypertension and stable angina (1892)	SPC (Bis/Peri) vs. MPC	Changes in SBP and DBP; number of angina attacks	SPC resulted in a reduction in systolic/diastolic BP of 22.3/11 mmHg and 31.5/15.9 mmHg at 1 and 3 months ($P < 0.001$). SPC resulted in a reduction in the number of angina attacks ($n = -4.1$; $P < 0.001$)	Treatment with Bis/Per SPC for 3 months was associated with significant reductions in SBP/DBP and was accompanied by an improvement in angina symptoms
Rea *et al.* (2018)[37]	Observational study	Hypertensive patients, primary or secondary prevention (44 534)	SPC vs. monotherapy	MACE	HR 0.85; 95% CI 0.74–0.97; $P = 0.02$	The antihypertensive SPC results in a significant reduction in major cardiovascular events

Continued

Table 1 Continued

First author (year)	Study design	Study population (patient, *n*)	Comparison	Primary endpoint	Primary endpoint: results	Interpretation
Giles *et al.* (2014)[20]	RCT	Hypertensive patients, primary or secondary prevention (4161)	SPC (Nebi/ vals) vs. MPC	Changes in SBP and DBP	Significant reduction in SBP ($P < 0.001$) and DBP ($P < 0.001$) in the SPC compared with the MPC	The fixed-dose combination of nebivolol and valsartan was associated with significant reductions in blood pressure compared with multi-pill administration
Gradman *et al.* (2013)[38]	Observational study	Hypertensive patients, primary or secondary prevention (1762) 0.84; $P = 0.0008$	Early vs. late SPC/MPC	MACE/all-cause death, achievement of target BP	MACE/all-cause death: IRR, 0.66; 95% CI 0.52–0.84; $P = 0.0008$ Target BP reached: 9.7 months (early SPC/MPC) vs. 11.9 months (late SPC/MPC); log-rank $P = 0.0040$	Early combination antihypertensive therapy was associated with a significant reduction in the risk of CV events and better BP control compared with a later start of the same therapy
Lipid-lowering combination therapies						
Lewek *et al.* (2023)[39]	Observational study	Patient with recent ACS (38 023)	Statin (rosuvastatin/ atorvastatin)/ezetimibe vs. statin (rosuvastatin/ atorvastatin)	All-cause death	OR 0.53; 95% CI 0.38–0.73; $P < 0.001$	Early initiation of combined lipid-lowering therapy is superior to statin monotherapy for all-cause mortality
Kim *et al.* (2022)[28]	RCT	Patients with known CV disease (3780)	Rosuvastatin 10 mg/ ezetimibe 10 mg vs. rosuvastatin 20 mg	Combination of CV death, MACE or non-fatal stroke	HR 0.92; 95% CI 0.75–1.13; $P = 0.43$	The combination therapy with moderate-intensity statins plus ezetimibe was not inferior to high-intensity statin monotherapy for composite outcomes at 3 years
Ballantyne *et al.* (2019)[30]	RCT	Patient with hypercholesterolaemia and high CV risk (301)	Bempedoic acid 180 mg/ ezetimibe 10 mg vs. bempedoic acid 180 mg vs. ezetimibe 10 mg vs. placebo	Change in LDL-C	LDL-C change with bempedoic acid/ezetimibe: −36.2% vs. ezetimibe −23.2% ($P < 0.001$) bempedoic acid −17.2% ($P < 0.001$) placebo 1.8% ($P < 0.001$)	The fixed-dose combination of bempedoic acid and ezetimibe significantly reduced LDL-C compared with placebo or other oral monotherapies

Continued

Table 1 Continued

First author (year)	Study design	Study population (patient, *n*)	Comparison	Primary endpoint	Primary endpoint: results	Interpretation
Cannon *et al.* (2015)[27]	RCT	Patients admitted for ACS (18 144)	Simvastatin 40 mg/ ezetimibe 10 mg vs. simvastatin 40 mg	Composite of CV death, non-fatal MI, unstable angina requiring rehospitalization, coronary revascularization, or non-fatal stroke	HR 0.94; 95% CI 0.89–0.99; $P = 0.016$	Added to statin therapy, ezetimibe resulted in an improvement in cardiovascular events compared with statin monotherapy
Antiplatelet combination therapies						
Lim *et al.* (2016)[40]	Observational study	Previous PCI (965)	Aspirin 100 mg/clopidogrel 75 mg vs. aspirin 100 mg + clopidogrel 75 mg	PRU	PRU >27 517.7% vs. 21.7%; $P = 0.129$.	DAPT with a single pill has shown similar efficacy to DAPT with two pills in terms of platelet reactivity in patients treated with DES
Koh *et al.* (2017)[32]	Randomized, cross-over study	Prior PCI (30)	Aspirin 100 mg/clopidogrel 75 mg vs. aspirin 100 mg + clopidogrel 75 mg	PRU	PRU 202 ± 52 vs. 207 ± 60; non-inferiority $P = 0.015$	The single-pill DAPT has shown similar efficacy to the same therapy with two separate pills in terms of platelet reactivity in patients treated with DES
Oh *et al.* (2016)[33]	Observational study	Prior PCI (648)	Aspirin 100 mg/clopidogrel 75 mg vs. aspirin 100 mg + clopidogrel 75 mg	ARU and PRU	ARU: 445.1 ± 69.2 to 446.2 ± 63.0, $P = 0.799$) PRU: $29.2 \pm 20.0\%$ to $29.0 \pm 19.9\%$, $P = 0.708$	The single-pill DAPT has shown similar efficacy to the same therapy with two separate pills in terms of platelet reactivity in patients treated with DES

ACS, acute coronary syndrome; ARU, aspirin reaction unit; BP, blood pressure; Can/Amlo, candesartan/amlodipine; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; DES, drug-eluting stent; HR, hazard ratio; IRR, incidence rate ratio; LDL-C, low-density lipoprotein cholesterol; MPC, multiple pill combination; Nebi/Vals, nebivolol/valsartan; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction unit; Rami/Amlo, ramipril/amlodipine; RR, relative risk; SBP, systolic blood pressure; SPC, single pill combination; Val/Amlo, valsartan/amlodipine,; Val/Amlo/HCT, valsartan/amlodipine/hydrochlorothiazide.

Table 2 Limitations associated with the use of fixed-dose combinations and polypills and possible solutions

Limits	Solutions
Challenges in determining the optimal dosage for each component	It is essential to be aware of the available dose combinations. If necessary, add an individual component of the SPC to achieve the desired dosage.
When a patient either forgets or decides to stop taking the medication, it results in the cessation of intake for many active ingredients, along with associated risks.	Provide detailed information to both the patient and caregiver about the dangers of discontinuing the medication.
Adverse reactions or intolerances to medications require careful and immediate assessment, followed by swift substitution of the medication if necessary due to the adverse event.	Ensure prompt and thorough evaluation of any adverse events and consider replacing the medication quickly if discontinued because of an adverse reaction.
Special attention is needed for the individual components contained within the SPC to avoid duplication of therapy.	Carefully review the components of the SPC to prevent therapeutic duplication.

SPC, single-pill combination.

for additional research before the polypill could be recommended for clinical use.[45] By 2016, the ESC guidelines, informed by available evidence, contemplated the use of polypills and fixed combinations for streamlining therapeutic regimens and boosting adherence, assigning a Class IIb recommendation with Level B evidence.[46] This cautious recommendation stemmed from the lack of evidence on clinical outcomes. The 2021 guidelines on cardiovascular prevention did not mention the polypill as a therapeutic option because of the lack of definite evidence of efficacy.[47] Nonetheless, the SECURE study later showcased a significant decrease in MACE and cardiovascular mortality using a polypill (comprising ramipril, atorvastatin, and aspirin) in secondary prevention after MI.[16] Consequently, the 2023 ESC guidelines for the management of ACS suggested considering a polypill, incorporating recommended agents for secondary prevention after an ACS, with a Class IIa recommendation and lLevel B evidence.[48] This position was echoed by the European Society of Hypertension guidelines for both primary prevention (polypill with two antihypertensive drugs and a statin) and secondary prevention (including also aspirin).[26] In contrast, the ESC guidelines on the management of cardiovascular risk in diabetic patients acknowledged the importance of addressing prevalent comorbidities like hypertension and hypercholesterolaemia but did not specifically endorse the polypill for secondary prevention, despite acknowledging its potential to reduce cardiovascular events.[49]

Unlike European guidelines, American guidelines have issued a recommendation for the polypill in cardiovascular care. Nevertheless, as of July 2023, the WHO included the cardiovascular polypill in a list of essential medicines, recognizing its superior therapeutic effect, enhanced adherence, economic advantages, and event reduction capabilities compared with individual drug therapies.[50] Most international guidelines now strongly advocate for combination therapy using ACE inhibitors or sartans with calcium antagonists and/or diuretics for hypertension treatment (Class I).[46,48,51,52] While European guidelines strongly support combination therapy from the first prescription, the American[52] and WHO guidelines[53] offer a more tepid endorsement, specifically recommending combination therapy when baseline systolic blood pressure exceeds the target by 20 mmHg or more.

To achieve LDL-C targets, currently available pre-constituted combinations include statin/ezetimibe and bempedoic acid/ezetimibe. Although the international guidelines for the treatment of hypercholesterolaemia,[54,55] as well as the recent ESC guidelines on diabetes[49] and the ESC guidelines on acute and chronic coronary syndromes,[48,56] have all assigned a Class I recommendation to the use of statin and ezetimibe therapy to achieve the LDL-C target and reduce cardiovascular events when statin alone is not sufficient, they do not explicitly refer to fixed combinations of these drugs. A recent ANMCO position paper has advocated for the pre-constituted statin/ezetimibe combination to simplify therapy and promote adherence.[57] The bempedoic acid/ezetimibe combination, while recognized for its LDL-C-lowering efficacy in dyslipidaemia[54] and cardiovascular prevention guidelines,[47] lacks specific usage recommendations due to the absence of outcome evidence at the time of guideline publication. Nevertheless, ANMCO's expert opinion on bempedoic acid, following the CLEAR Outcomes study, highlights the pre-constituted bempedoic acid/ezetimibe combination's role for patients who are intolerant to statins.[58]

Numerous pre-constituted oral combinations exist for the treatment of Type 2 diabetes, including metformin plus gliflozins, GLP1-RA, or DPP4 inhibitors (gliptins), and combinations of gliptins with gliflozins. The European Association for the Study of Diabetes endorses the consideration of pre-constituted combinations to reduce the number of prescribed medications.[59]

Dual antiplatelet therapy remains a cornerstone in managing ACS and post-revascularization care, yet international guidelines lack specific recommendations for the available clopidogrel and aspirin combination. *Table 3* consolidates the main recommendations on the polypill and fixed combinations in secondary prevention from international guidelines.

Therapeutic options in Italy, indications, and reimbursability

Polypills, like combinations of single drugs, are indicated in patients with dyslipidaemia and hypertension not

Table 3 Guideline recommendations on polypills and single-pill combinations in cardiology

		Class	LoE
Polypill			
2023 ESH guidelines for the management of arterial hypertension[26]	A polypill containing two antihypertensive agents and a statin for reducing LDL cholesterol can be considered for hypertensive patients in primary prevention.	IIa	A
	A polypill containing low-dose aspirin can be considered for hypertensive patients in secondary prevention.	IIa	A
2023 ESC guidelines for the management of acute coronary syndromes[48]	A polypill should be considered to improve adherence and outcomes in secondary prevention after an ACS.	IIa	B
2016 European guidelines on cardiovascular disease prevention in clinical practice[46]	The use of a polypill and combination therapy can be considered to increase adherence to pharmacological therapy.	IIb	B
Single-pill fixed-dose combination			
Hypertension			
2023 ESH guidelines for the management of arterial hypertension[26]	The use of a single-pill fixed-dose combination should be preferred at every therapeutic step (including as the initial treatment).	I	A
2022 World Health Organization. WHO Guideline for the Pharmacological Treatment of Hypertension in Adults[60]	Combination therapy, preferably as a single-pill combination (to improve adherence and persistence), as the initial therapy	CR	Moderate
2019 The Japanese Society of Hypertension Guidelines for the Management of Hypertension[51]	Prescribing a single-pill fixed-dose combination is useful for improving adherence and for blood pressure control.	NA	NA
Hypercholesterolaemia			
2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk[54]	If the recommended goal is not achieved with the maximum tolerated dose of statin, the combination with ezetimibe is recommended.	I	B
	The use of statins or the statin/ezetimibe combination is recommended in patients with Stage 3–5 chronic kidney disease.	I	A
2019 AHA/ACC guideline on the management of blood cholesterol[55]	In patients with symptomatic atherosclerotic cardiovascular disease who are considered at very high risk and are considered for PCSK9 inhibitor therapy, the maximum tolerated therapy to reduce LDL-C should include the combination of statin and ezetimibe.	I	B-R
2023 ESC guidelines for the management of acute coronary syndromes[48]	If the LDL-cholesterol target is not reached after 4–6 weeks of therapy with the maximum tolerated dose of statins, the addition of ezetimibe is recommended.	I	B
2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes[56]	The combination of high-dose statin and ezetimibe can be considered during hospitalization for ACS.	IIb	B
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes[49]			
2019 AHA/ACC guideline on the management of blood cholesterol[55]		I	B-R
2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk[54]	In patients with symptomatic atherosclerotic cardiovascular disease who are considered at very high risk and are candidates for PCSK9 inhibitor therapy, the maximum tolerated therapy to reduce LDL-C should include the combination of statin and ezetimibe.	I	B
	If the recommended goal is not achieved with the maximum tolerated dose of statin, the combination with ezetimibe is recommended.	I	A
	The use of statins or the statin/ezetimibe combination is recommended in patients with Stage 3–5 CKD.	I	A

ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association, B-R: level of evidence B, randomized trials available; CKD, chronic kidney disease; CR, conditional recommendation; LDL-C, low-density lipoprotein cholesterol; EAS, European Atherosclerosis Society; EO, Expert opinion; ESC, European Society of Cardiology; ESH, European Society of Hypertension; LoE, level of evidence; PCSK9, proprotein convertase subtilisin/kexin type 9; WHO, World Health Organization.

adequately controlled with the individual active ingredients taken as monotherapy. Currently, most polypills for cardiovascular prevention available in Italy contain a lipid-lowering agent (statin) in combination with an antiplatelet drug (aspirin) and/or with an antihypertensive drug. A list of available combinations with their respective dosages and approved indications in Italy is provided in *Table 4*. As for secondary prevention,

Table 4 Polypills available in Italy for cardiovascular prevention

Active principles	Doses (mg)	Indication	Form of medication delivery	Reimbursability class
Rosuvastatin + aspirin[61]	5, 10, 20 100	Secondary cardiovascular prevention	Capsule	A
Rosuvastatin + ramipril[62]	10, 20 5, 10	Hypertension + one of the following: • primary hypercholesterolaemia, • homozygous familial hypercholesterolaemia • combined or mixed hyperlipidaemia and/or • high risk of MACE	Capsule	A
Rosuvastatin + amlodipine[63]	1 020 5,10	Hypertension + one of the following: • primary hypercholesterolaemia, • homozygous familial hypercholesterolaemia • combined or mixed hyperlipidaemia and/or • high risk of MACE	Capsule	A
Atorvastatin + perindopril + amlodipine[64]	10, 20, 40 5,10 5, 10	Hypertension and/or stable chronic coronary syndrome in adults with one of the following: primary hypercholesterolaemia or combined/ mixed hyperlipidaemia	Tablet	A
Atorvastatin + ramipril + amlodipine[65]	10, 20, 40 5, 10 5, 10	Hypertension + one of the following: • primary hypercholesterolaemia, • homozygous familial hypercholesterolaemia • combined or mixed hyperlipidaemia and/or • high risk of MACE	Tablet	A
Atorvastatin + ramipril + aspirin[66]	20, 40 2.5, 5, 10 100	Secondary cardiovascular prevention	Capsule	C

MACE, major adverse cardiovascular events. Reimbursability classes in Italy: A, completely reimbursed by the National Health System; C, paid by the patient.

Table 5 Pre-established fixed combinations of lipid-lowering agents and therapeutic indications according to the technical sheet

Active principles	Doses (mg)	Indication	Form of medication delivery	Reimbursability class
Rosuvastatin + ezetimibe[67]	5, 10, 20, 40 10	Primary hypercholesterolaemia (heterozygous and homozygous familial and non-familial) or with mixed hyperlipidaemia	Capsule	A
Atorvastatin + ezetimibe[67]	10, 20, 40 10	Primary hypercholesterolaemia (heterozygous and homozygous familial and non-familial) or with mixed hyperlipidaemia	Capsule	A
Simvastatin + ezetimibe[68]	10, 20, 40, 80 10	Primary hypercholesterolaemia (heterozygous and homozygous familial and non-familial) or with mixed hyperlipidaemia	Tablet	A
Bempedoic acid + ezetimibe[69]	180 10	For patients with primary hypercholesterolaemia or mixed dyslipidaemia, treatment options are expanded beyond diet and the maximum tolerated dose of a statin. In cases where patients are intolerant to statins or have contraindications against them, and do not achieve target LDL-C levels with ezetimibe alone, alternative strategies are considered. This includes monotherapy with an alternative medication for those who cannot take statins or the addition of another active ingredient for patients who have not reached their LDL-C targets with ezetimibe alone. Additionally, for patients previously treated with both active principles separately, a combined treatment approach may be utilized	Tablet	A (with the completion of a prescription form)

LDL-C, low-density lipoprotein cholesterol.

Table 6 Pre-established combinations for the treatment of essential arterial hypertension

Drug class	Available associations	Indication
ACE inhibitor and thiazide diuretic (or thiazide-like diuretic)	Ramipril + hydrochlorothiazide Enalapril + hydrochlorothiazide Lisinopril + hydrochlorothiazide Quinapril + hydrochlorothiazide Perindopril *tert*-butylamine + indapamide Perindopril arginine + indapamide Perindopril tosylate + indapamide Captopril + hydrochlorothiazide Fosinopril + hydrochlorothiazide Benazepril + hydrochlorothiazide Zofenopril + hydrochlorothiazide Moexipril + hydrochlorothiazide Delapril + indapamide Cilazapril + hydrochlorothiazide	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy
ARB and thiazide diuretic	Valsartan + hydrochlorothiazide Irbesartan + hydrochlorothiazide Olmesartan medoxomil + hydrochlorothiazide Losartan + hydrochlorothiazide Candesartan cilexetil + hydrochlorothiazide Telmisartan + hydrochlorothiazide Eprosartan mesilate + hydrochlorothiazide	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy
Beta-blockers and thiazide diuretic and/or other diuretics	Atenolol + chlorthalidone Atenolol + indapamide Nebivolol + hydrochlorothiazide Bisoprolol + hydrochlorothiazide Labetalol + chlorthalidone Oxprenolol + chlorthalidone Metoprolol + chlorthalidone	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy
Calcium channel blocker and ACE inhibitor	Perindopril arginine + amlodipine Ramipril + amlodipine Ramipril + felodipine Enalapril + lercanidipine Delapril + manidipine Perindopril + amlodipine besylate	Treatment of essential hypertension and/or stable coronary artery disease.
ARB and calcium channel blocker	Olmesartan + amlodipine	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy

Continued

Table 6 Continued

Drug class	Available associations	Indication
ACE inhibitors and loop diuretics	Ramipril + piretanide	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy
Loop diuretic and MRA	Furosemide + spironolactone Furosemide + triamterene	Edematous states (congestive heart failure, ascitic phase of liver cirrhosis, nephrotic syndrome) and arterial hypertension due to primary and secondary hyperaldosteronism. Essential arterial hypertension, where other therapies have not been sufficiently effective or tolerated
Direct renin inhibitors and thiazide diuretic	Aliskiren + hydrochlorothiazide	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy
MRA and thiazide diuretic	Spironolactone + hydrochlorothiazide Amiloride hydrochloride + hydrochlorothiazide	Edematous states from secondary hyperaldosteronism (congestive heart failure, ascitic phase of liver cirrhosis, nephrotic syndrome).
ACE inhibitor and beta-blocker	Ramipril + carvedilol Perindopril + carvedilol	Treatment of essential arterial hypertension, stable chronic angina pectoris, and adjunctive treatment of stable chronic heart failure from moderate to severe
Direct renin inhibitors + calcium channel blockers + thiazide diuretics	Aliskiren + amlodipine + hydrochlorothiazide	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy
ACE inhibitors + thiazide-like diuretics + calcium channel blockers	Perindopril arginine + indapamide + amlodipine	Treatment of essential arterial hypertension. These fixed-dose combinations are indicated for patients whose blood pressure is not adequately controlled with the individual active ingredients taken as monotherapy

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

the approved polypills contain rosuvastatin in combination with aspirin or the triple combination of atorvastatin, perindopril, and amlodipine. Specifically, the combination of rosuvastatin (5, 10, and 20 mg) with aspirin at a fixed dosage of 100 mg has been approved for the secondary prevention of cardiovascular events, as substitution therapy in adult patients adequately controlled with the mono-components administered concurrently at equivalent therapeutic doses.[61] The combination of rosuvastatin (10 or 20 mg)/ramipril (5 or 10 mg), according to the product information, is indicated as substitute therapy in adult patients with essential arterial hypertension and one of the following diseases: primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (Type IIb), homozygous familial hypercholesterolaemia, or patients estimated to have a high risk of experiencing a first major cardiovascular event, as additional therapy to the correction of other risk factors.[62] The polypill containing rosuvastatin (10 or 20 mg) and amlodipine (5 or 10 mg) has been approved for the treatment of essential arterial hypertension in adult patients at high risk of a first cardiovascular event (for the prevention of major cardiovascular events) in addition to the correction of other risk factors or with one of the aforementioned hypercholesterolaemias.[63] Atorvastatin (10, 20, or 40 mg) is currently available on the market in combination with perindopril (5 or 10 mg) and amlodipine (5 or 10 mg) for the treatment of essential arterial hypertension and/or coronary artery disease, in association with primary hypercholesterolaemia or mixed hyperlipidaemia.[64] Similarly, the combination of ramipril, atorvastatin, and amlodipine is indicated in the treatment of arterial hypertension associated with primary hypercholesterolaemia or mixed hyperlipidaemia, but not in coronary artery disease.[65,66]

Several combinations for the management of dyslipidaemia are available (*Table 5*), whose use is approved in adults who are already taking the individual molecules simultaneously. Both the combination of atorvastatin with ezetimibe and that of rosuvastatin and ezetimibe can be used for secondary prevention in patients with known coronary disease and/or with a history of ACS.[67,68] Regarding the ezetimibe–bempedoic acid combination, recently introduced into clinical practice, its product information indicates primary hypercholesterolaemia or mixed dyslipidaemia, in addition to diet and the maximum tolerated dose of statin, or as monotherapy in patients who are intolerant or with contraindications to statins and who do not achieve LDL-C target levels with ezetimibe alone, and in patients already treated with the two active principles separately.[69]

Numerous combinations are available for arterial hypertension and can improve adherence to therapy.[70]

Details regarding the indications of the different combinations and available dosages are listed in *Table 6*.

Conclusions and position of the Associazione Nazionale Medici Cardiologi Ospedalieri

There is a growing evidence supporting the safety and efficacy of SPCs and polypills in managing individual risk factors and preventing cardiovascular events,[15,16,19] as well as pharmacoeconomic studies indicating a favourable cost-effectiveness ratio for their use.[42] Adopting a therapeutic strategy centred on SPCs and polypills is then increasingly advocated for secondary cardiovascular prevention. Consequently, understanding the array of fixed-dose combinations in the market, including the specific dosages of their constituent components and their indications established by the Italian Medicines Agency, is essential.

Initiating treatment with multiple drugs, each containing a single active principle, is typically preferred to gauge the distinct effects of the agents in terms of clinical benefits and potential adverse effects. However, for patients at higher risk, where a more potent therapeutic approach is necessary to meet the recommended therapeutic targets (for example, following an acute coronary event or among individuals with significantly elevated blood pressure or LDL-C levels), the early integration of SPCs and polypills into the treatment regimen is a reasonable approach that aims to expedite the achievement of therapeutic goals and limit the exposure to an increased cardiovascular risk.[29,71]

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