USE OF A POLYPILL TO REDUCE CARDIOVASCULAR RISK FACTORS IN PRIMARY AND SECONDARY PREVENTION: REVIEW AND USE GUIDELINES

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ABSTRACT

INTRODUCTION: Primary and secondary cardiovascular prevention programs present less efficacy than desired due to the professionals' lack of adherence when prescribing different drugs to the same patient, and due to patients' lack of adherence in the medium and long term to medications prescribed. Polypills are considered as a possible solution to these problems. An evidence-based review about a cardiovascular prevention polypill efficacy and a guide for its use is presented.

METHODS: Comprehensive bibliographical review of the evidence published on the polypill as a mechanism for facilitating medication adherence in primary and secondary cardiovascular prevention.

RESULTS: A total of 31 published articles were included, showing the options of the polypill as a method of primary and secondary cardiovascular prevention. Polypill can increase the therapeutic adherence of patients in the medium and long term, also increasing therapeutic results compared to the administration of the same different drugs separately. Based on the evidence, a flow chart for the prescription of a polypill has been developed.

DISCUSSION AND CONCLUSIONS: The use of a polypill increases the effectiveness and adherence of patients to primary and secondary cardiovascular prevention programs, without increasing the cost of the intervention. The use of a polypill in cardiovascular prevention can be effective as a prescription tool.

KEYWORDS

Polypill, Cardiovascular Risk, Primary Prevention, Secondary Prevention, Adherence, Cost-effectivity.

DISCLOSURES

Potential conflict of interest: Nothing to report.

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INTRODUCTION

In both primary and secondary cardiovascular (CV) prevention, the effectiveness of the programs depends on the adherence of the professionals to the clinical guidelines, the access to the indicated drugs by the patients and the adherence of the patients to the medication in the medium and long term. Clinical practice indicates that these variables are often not followed by an important part of the stakeholders reducing the effectiveness of those cardiovascular prevention programs. One of the proposed initiatives is the use of polypills to increase the adherence of professionals and patients to these programs in the medium and long term.

A review of the evidence and an algorithm for the use of the polypill is proposed to update knowledge on the indications, uses and prescription techniques.

METHODS

To carry out this narrative review, an exhaustive search on the evidence about cardiovascular prevention polypill was carried out in PubMed and Google Scholar databases during February 2022. The keywords used were those related to the topic of the review: polypill, prevention, cardiovascular risk (CVR) and related terms. The search was carried out based on all those articles published in an indexed journal (Q1, Q2, Q3, Q4) with full text available in English, Spanish for the last 10 years (from 2011 to 2021). Research in humans, with intervention, clinical trial or review design, was included. Other articles as government guidelines and official information brochures were added to increase the information included.

The initial search was limited by using the specified filters and reading the titles and abstracts of the selected articles to analyze their quality and correspondence with the main topics of the investigation.

After the entire process of searching and selecting articles and eliminating duplicates, the critical assessment process of the remaining articles was carried out; at the end of this process, 31 articles were finally included for this review.

RESULTS

After compiling the published evidence and critical assessment of the articles, a total of 31 publications were included in the review, including clinical trials, clinical practice guidelines, evidence with other designs, a polypill data set, expert opinions, government regulations, official brochures and scientific journal editorials.

In primary prevention data seem to demonstrate the efficacy of polypill use in cardiovascular prevention programs when applied to the general population; however, therapeutic strategies aimed at simultaneously controlling different CVR factors in patients without known cardiovascular disease (primary prevention) are valued as expensive and difficult to put into practice by public institutions.[1]

In secondary CV prevention, patients with several CVR factors or with a clinical history of ischemic heart disease (IHD) have a high recurrence risk of new coronary events. Combined pharmacological treatment is a common practice in secondary CV prevention and its benefits in terms of morbidity and mortality are widely documented; however, the complexity of the therapeutic regimen often means that: 1) Professionals tend not to implement a complete preventive regimen, with a lack of adherence to clinical guidelines due to the several drugs that must be prescribed,[2] 2) Professionals tend to not ask the patients about their adherence to treatment [3] and, in turn, that 3) Patients have poor adherence to therapeutic regimens with multiple medications:[1] in these cases, adherence to the therapeutic regimen is usually low 6 months after an Acute Myocardial Infarction (AMI).[4]

This lack of therapeutic adherence produces an increase in the rate of major cardiovascular (CV) events and, consequently, in morbidity and mortality in both primary and secondary prevention. In addition, non-adherence to treatments for other related diseases or delayed diagnosis by going less frequently to the doctor's office (such as diabetes) is added, all this leading to a growth in the care burden and an increase in health costs. Thus, therapeutic adherence to the CV prevention programs is a key factor in ensuring the sustainability of the health system, since non-adherence is linked to worse health outcomes and higher costs for the system.[5,6]

Polypill creation involves the combination of different drugs without incompatibilities between them, safe, well tolerated, effective, recommended by clinical practice guidelines and physically and chemically compatible with the rest of the components of the pill (excipients, etc.).[7] CNIC (Centro Nacional de Investigaciones Cardiovasculares, Ministerio de Ciencia e Innovación, España) created a polypill containing, in different doses,

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Acetylsalicylic Acid + Ramipril + Atorvastatin, which has shown its clinical effectiveness and high tolerability.[8,9] According to its data sheet,[10] the indication of this polypill focuses on the secondary prevention of CV accidents as substitution treatment in adult patients adequately controlled with the three substances taken at the same time at equivalent doses, aiming to reduce the risk of suffering a CV accident when the patient has already suffered a previous cardiovascular event. At this moment, the data sheet of this product does not include the primary prevention of CV accidents, despite the evidence in providing benefits.

Strategies using polypills for CV secondary prevention have shown greater comfort for the patient and an increase in adherence to treatment of up to 20%,[4,5,11,12] improving not only CVR factors but also reducing CV events and the healthcare cost derived from them; so, it's considered a highly cost-effective strategy.[11,13]

DISCUSSION

COMPOSITION AND INDICATIONS of each component of the polypill:

- Acetylsalicylic Acid (ASA): platelet antiaggregant[14]
  - On primary CV prevention the benefit of antiplatelet therapy is controversial and some documents find no reason for its use;[15] therefore, it must be individualized in each case based on the expected risk-benefit ratio; ASA should only be recommended in patients with high CVR and low risk of bleeding.[5]
  - Secondary CV prevention: in adults for secondary prophylaxis after a first coronary or cerebrovascular ischemic event indications are after AMI or myocardial infarction, in patients with unstable angina pectoris, and to prevent its recurrence in patients with a history of AMI,[14,5] stable or unstable angina, coronary angioplasty, prevention of graft occlusion after aortocoronary bypass, thrombophlebitis, phlebothrombosis and risk of arterial thrombosis,[14] postoperative thromboembolism in patients with biological vascular prostheses or arteriovenous shunts,[14] for treatment of transient ischemic attacks in men with transient cerebral ischaemia to reduce the risk of stroke,[14] prevention of recurrences of transitory or permanent non-hemorrhagic Cerebrovascular Accident (CVA).
  - Other evidence: two systematic reviews and meta-analyses have shown an additive effect on cardiovascular protection with ASA + statin combination.[5] Other evidence show the benefit of ASA in patients with colorectal cancer moderate risk, without risk of bleeding, younger than 70 years (with life expectancy greater than 10 years) and with a CVR greater than 10% in the next 10 years; in them, ASA prescription is recommended and can demonstrate a decrease in the incidence and mortality of colorectal cancer.[16]
- Atorvastatin: lipid-lowering can reduce CV risk in people with and without hyperlipidemia when the response obtained with diet or other non-pharmacological measures has been inadequate.[17]
  - Hypercholesterolemia as additional treatment to diet is indicated in the reduction of high total cholesterol, cholesterol-LDL, apoprotein B and triglycerides in adult patients, adolescents and children from 10 years of age with one or more of the following: primary hypercholesterolemia including familial hypercholesterolemia (heterozygous variant) or combined (mixed) hyperlipidemia (corresponding to Fredrickson classification types IIa and IIb); to lower total cholesterol and cholesterol-LDL (chol-LDL) in adult patients with homozygous familial hypercholesterolemia; in combination therapy with other lipid-lowering therapies (eg, chol-LDL apheresis) or if these therapies are not available.
  - In prevention of CV disease Atorvastatin is indicated in primary prevention of cardiovascular events in adult patients with high CVR, as adjunctive treatment to the correction of other risk factors.
  - Other evidence: statins have shown the ability to provide organ protection in patients with high CVR in primary and secondary CV prevention.[5] At a dose of 20 mg, with a hypocholesterolemic power of 41-43% reduction in chol-LDL, Atorvastatin is the most widely used statin and presents a correct balance between efficacy and adverse effects.[5] Contraindications to doses of 80 mg/d are: previous intolerance to Atorvastatin 80 mg doses, age >75 years, low weight (BMI <20 kg/m2), stage 3 of chronic kidney disease (GFR <60 mL/min /m2),

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hypothyroidism, potential drug interactions (as amiodarone, verapamil).[18]

- Ramipril: antihypertensive inhibitor of the Angiotensin Converting Enzyme (ACEI)[19]
  - Indicated as treatment of Arterial Hypertension (high Blood Pressure, BP), symptomatic heart failure, AMI (reduction of mortality in the acute phase).
  - As kidney disease treatment in incipient diabetic glomerular nephropathy (with microalbuminuria), diabetic glomerular nephropathy (macroproteinuria) with one or more CVR factors, non-diabetic glomerular nephropathy (macroproteinuria ≥ 3 g/day.)
  - As CV prevention is indicated in CV morbidity and mortality reduction in patients with atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral vascular disease)[5], diabetes with at least one CVR factor[5], AMI with clinical signs of heart failure (when treatment is started 48 hours after the AMI). In secondary prevention Ramipril can be prescribed after acute myocardial infarction achieving a mortality reduction in the acute phase of myocardial infarction in patients with clinical signs of heart failure when their treatment is started 48 hours after AMI.
  - Other evidence: only telmisartan and ramipril are indicated to reduce CVR, based on available clinical trials.[5]

Polypill main OPPORTUNITIES:[5,12] switching to a polypill may increase ASA use and more favorably modify total cholesterol levels,[6] col-LDL, [6,20] col-HDL[6] and blood pressure[6,9] than patients following treatment with the three separate drugs,[21] especially in patients with a history of non-adherence or who present any of the predictors of pharmacological non-adherence (patients who are not well controlled with equipotent doses and with adherence problems, patients who are controlled with individual drugs, and patients with comorbidities and under polymedication regimes).

According to scientific evidence, the benefits of using the association of ASA + Ramipril + statins are:[12] 1) the increase in therapeutic compliance more accentuated in antihypertensive drugs and in ASA (because they generally present less adherence) above statins;[21] 2) simplification of the therapeutic regimen and increased adherence in the short, medium and long term:[6] for every 10% increase in adherence, cardiovascular complications decrease by 6.7%; 3) Assuming that the polypill increases adherence by up to 20%, the reduction in CV complications would be around 12.6%[21] (up to 11 fatal and 46 nonfatal events per 1,000 patients treated),[5,13] pointing out its enormous cost-effectiveness, especially at a time when, as in Spain, the polypill available on the market has a price identical to the sum of its components in a separate generic version (see Annex); 4) in polymedicated patients, the simplification of the therapeutic regimen also results in better compliance with the treatment guidelines for other conditions and diseases.

INDICATIONS for the polypill: according to the most recent evidence, indications may include patients with high or very high CVR (as a subclinical cardiovascular disease) in order to control their CVR factors and as organ protection as long as they do not have a high risk of hemorrhage:[5,8,12,18]

- Hypertensive patients with high CVR (not included in the technical data sheet of marketed products),[22] defined by one or more of the following criteria: age ≥70 years [10,19,23], risk ≥10% at 10 years in the SCORE2 table[23] risk-adjusted for each European region, risk ≥5% at 10 years in the SCORE table calibrated for each country,[24] risk ≥10% for REGICOR or Framingham tables,[25] left ventricular hypertrophy, microalbuminuria/proteinuria, renal failure, increased pulse wave velocity, increased carotid intima media thickness, presence of atherosclerotic plaques, and abnormal ankle-brachial index.[26]
- Primary prevention of cardiovascular events (not included in the technical data sheet of marketed products) in patients with the three components (ASA, Ramipril and statin) indications for prescription and with subclinical CV disease: patients with high or very high CVR (determined by risk tables, diabetes mellitus or subclinical vascular disease: atherosclerotic carotid artery plaques, increased intima-media thickness, low ankle-brachial index, or chronic renal failure) and low risk of bleeding in the following circumstances: [26,27] diabetics older than 50 years with at least one associated CVR factor, diabetics older than 50 years with chronic kidney disease and micro or macroalbuminuria, hypertense patients with high CVR or high CVR patients with clinical or subclinical ventricular dysfunction.

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- In secondary prevention of CV events polypill can be prescribed in adult patients with CV accidents adequately controlled with the three components administered concomitantly in equivalent therapeutic doses,[10] in coronary complications,[28] ischemic cerebrovascular disease,[29,30] in patients with coronary stents[26] or in symptomatic peripheral arterial disease[18] (in this kind of patient, a reduction in the rate of CV complications greater than the reduction of each of the drugs separately will be achieved).

Expected results: fixed combination treatments use is associated with a greater than expected reduction in blood pressure and lipid levels, due to increased therapeutic adherence.[5,28,31] In phase IV studies, the reduction in blood pressure and chol-LDL was maintained after one year of treatment, reducing cardiovascular risk factors.[28]

Prescription:[5] when to prescribe polypill: after an acute ischemic event, both during hospitalization or at discharge[26] if compliance or adherence problems, polypharmacy or difficulties in accessing medication are expected. The therapeutic goals are BP <140/90 mmHg, chol-LDL <70 mg/dl or a reduction of more than 50% of baseline chol-LDL values. Additional measures:[12] all patients with cardiovascular risk need to follow heart-healthy lifestyle habits such as quitting tobacco consumption, following a heart-healthy diet, performing regular physical activity, avoiding obesity, and controlling classic cardiovascular risk factors (diabetes mellitus, high blood pressure, dyslipidemia). Dose modification: in case of insufficient control of blood pressure or chol-LDL, it may be necessary to prescribe other fixed doses of the same polypill, add extra doses of the same or other drugs, or even return to individualized treatment.[12] Marketed doses available of polypill: the fixed combinations of ASA + Atorvastatin + Ramipril marketed in Spain can be seen in Table 1.

Change of individual drugs to polypill and dose equivalences:[8] approximate effective daily dose for switching from other ACE inhibitors to Ramipril (extracted from Coca et al.)[8] can be seen in Table 2. The approximate effective daily dose of angiotensin II receptor blockers (ARBs) to Ramipril (extracted from Coca et al.)[8] can be consulted in Table 3. The potency and approximate effectiveness of other statins compared to Atorvastatin (extracted from Coca et al.)[8] can be consulted in Table 4.

Based on the existing bibliography, a flow chart has been drawn up (see Figure 1) to facilitate the indication and follow-up of a polypill for primary and secondary CV prevention, maximizing the use of prevention programs and facilitating their prescription to professionals to achieve greater patient adherence in the medium and long term.

The annexes specify, for the Spanish reality, approved prices of the components for an example dosification of a polypill, warnings and precautions, possible interactions, contraindications, and adverse reactions, based on its components.

CONCLUSSION

The use of a polypill, based on the available evidence, could increase patient adherence to the medication and reduce CV risk in the medium and long term, resulting in greater effectiveness of cardiovascular prevention programs, without increasing costs or pressure on the health system.

REFERENCES

1. Fuster V, Sanz G. Compuestos de dosis fija en la prevención secundaria de la cardiopatía isquémica. Rev Esp Cardiol. 2011;64(SUPPL. 2):3–9.
2. Sanz G, Fuster V. Maximizing Therapeutic Envelope for Prevention of Cardiovascular Disease: Role of Polypill. Mt Sinai J Med. 2012;79:683–8.
3. Armstrong PW, McAlister FA. Searching for Adherence: Can We Fulfill the Promise of Evidence-Based Medicines? J Am Coll Cardiol. 2016;68(8):802–4.
4. Castellano JM, Sanz G, Peñalvo JL, Bansilal S, Fernández-Ortiz A, Alvarez L, et al. A polypill strategy to improve adherence. J Am Coll Cardiol. 2014;64(20):2071–82.
5. González-Juanatey JR, Mostaza JM, Lobos JM, Abarca B, Llisterri JL, Baron-Esquivias G, et al. Consensus document for the use of the Polypill in the secondary prevention of cardiovascular disease. Med Clin (Barc) [Internet]. 2017;148(3):139.e1-139.e15. Available from: http://dx.doi.org/10.1016/j.medcli.2016.10.031
6. González-Juanatey JR, Cordero A, Castellano JM, Masana L, Dalmau R, Ruiz E, et al. Reduction of cardiovascular events in patients with cardiovascular disease with the CV-polypill: a retrospective and propensity score matching study. In: European Society of Cardiology, editor. ESC Congress 2021 - The Digital Experience [Internet]. 2021. Available from: https://esc365.escardio.org/presentation/237242
7. Tamargo J, Castellano JM, Fuster V. The Fuster-CNIC-Ferrer Cardiovascular Polypill: a polypill for secondary cardiovascular prevention. Int J Cardiol. 2015;201:S15–23.
8. Coca A, Kreutz R, Manolis AJ, Mancia G. A practical approach to switch from a multiple pill therapeutic strategy to a polypill-based strategy for cardiovascular prevention in patients with hypertension. J Hypertens. 2020;38(10):1890–8.
9. González-Juanatey JR, Tamargo J, Torres F, Weisser B, Oudovenko N. Pharmacodynamic study of the cardiovascular polypill. Is there any interaction among the monocomponents? Rev Española Cardiol (English Ed. 2021;74(1):51–8.
10. AEMPS. Ficha Técnica - Trinomia [Internet]. CIMA. Madrid; 2021. Available from: https://cima.aemps.es/cima/pdfs/es/ft/78575/78575_ft.pdf
11. Castellano JM, Bueno H, Fuster V. The cardiovascular polypill: Clinical data and ongoing studies. Int J Cardiol. 2015;201:S8–14.
12. González-Juanatey JR, Mostaza JM, Lobos JM, Abarca B, Llisterri JL. A Step Ahead in Secondary Prevention of Cardiovascular Risk. Consensus Document on Clinical Use of the Polypill. Rev Esp Cardiol. 2016;69(6):547–50.
13. Barrios V, Kaskens L, Castellano JM, Cosin-Sales J, Ruiz JE, Zsolt I, et al. Utilidad de un policomprimido cardiovascular en el tratamiento de pacientes en prevención secundaria en España: un estudio de coste-efectividad. Rev Esp Cardiol. 2017;70(1):42–9.
14. AEMPS. Ficha Técnica - Ácido AcetilSalicílico. [Internet]. Madrid; 2019. Available from: https://cima.aemps.es/cima/pdfs/es/ft/42991/FT_42991.pdf
15. Vivas D, Roldán I, Ferrandis R, Marın F, Roldan V, Martın A, et al. Manejo perioperatorio y periprocedimiento del tratamiento trombótico : documento de consenso de SEC , SEDAR , SEACV , SECTCV ,. Rev Esp Cardiol. 2018;71(x):553–64.
16. Liang PS, Shaukat A, Crockett SD. AGA Clinical Practice Update on Chemoprevention for Colorectal Neoplasia: Expert Review. Clin Gastroenterol Hepatol [Internet]. 2021;19(7):1327–36. Available from: https://doi.org/10.1016/j.cgh.2021.02.014
17. AEMPS. Ficha Técnica - Atorvastatina [Internet]. Madrid; 2019. Available from: https://cima.aemps.es/cima/pdfs/es/ft/75191/75191_ft.pdf
18. Marzal D, Rodríguez Padial L, Arnáiz JA, Castro A, Cosín J, Lekuona I, et al. Use of the cardiovascular polypill 40 mg in secondary cardiovascular prevention. Clin e Investig en Arterioscler. 2018;30(5):240–7.
19. AEMPS. Ficha Técnica - Ramipril [Internet]. Madrid;

2019. Available from: https://cima.aemps.es/cima/pdfs/es/ft/67932/67932_ft.pdf

20. Gómez-Álvarez E, Verdejo J, Ocampo S, Ponte-Negretti CI, Ruíz E, Ríos MM. The CNIC-polypill improves atherogenic dyslipidemia markers in patients at high risk or with cardiovascular disease: Results from a real-world setting in Mexico. IJC Hear Vasc. 2020;29.

21. Lafeber M, Spiering W, Visseren FLJ, Grobbee DE, Bots ML, Stanton A, et al. Impact of switching from different treatment regimens to a fixed-dose combination pill (polypill) in patients with cardiovascular disease or similarly high risk. Eur J Prev Cardiol. 2017;24(9):951–61.

22. Mazón-Ramos P. Cardiovascular risk in the 21st century: Identifying risk in primary prevention. Controlling risk in secondary prevention. Rev Esp Cardiol. 2012;65(SUPPL.2):3–9.

23. SCORE2 working group, ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: New models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439–54.

24. Sans S, Fitzgerald AP, Royo D, Conroy R, Graham I. Calibración de la tabla SCORE de riego cardiovascular para España. Rev Esp Cardiol. 2007;60(5):476–85.

25. Buitrago Ramírez F, Cañón-Barroso L, Díaz-Herrera N, Cruces-Muro E, Escobar-Fernández M, Serrano-Arias JM. Comparación de las tablas REGICOR y SCORE para la clasificación del riesgo cardiovascular y la identificación de pacientes candidatos a tratamiento hipolipemiante o antihipertensivo. Rev Esp Cardiol. 2007;60(2):139–47.

26. González-Juanatey JR. Actualización del documento de consenso del uso clínico del policomprimido: nueva dosis con atorvastatina 40 mg. Rev E [Internet]. 2018;71(7):595–7. Available from: https://www.revespcardiol.org/es-pdf-S030089321830071X

27. González-Juanatey JR, Abarca B, Lobos JM, Llisterri JL, Mostaza JM. Nuevo enfoque terapéutico para la prevención secundaria del riesgo cardiovascular Actualización del documento de consenso del uso clínico de la Polypill: nueva dosis con 40 mg de atorvastatina. Korupsi. 2017. 98–115 p.

28. Castellano JM, Verdejo J, Ocampo S, Rios MM, Gómez-Álvarez E, Borrayo G, et al. Clinical Effectiveness of the Cardiovascular Polypill in a Real-Life Setting in Patients With Cardiovascular Risk in Mexico: The SORS Study. Arch Med Res. 2019;50(1):31–40.

29. Ros-Castelló V, Natera-Villalba E, Gómez-López A, Sánchez-Sánchez A, Chico-García JL, García-Madrona S, et al. Use of the Cardiovascular Polypill in Secondary Prevention of Cerebrovascular Disease: A Real-Life Tertiary Hospital Cohort Study of 104 Patients. Cerebrovasc Dis Extra. 2020;10(3):166–73.

30. Masjuan J, Gállego J, Aguilera JM, Arenillas JF, Castellanos M, Díaz F, et al. Use of cardiovascular polypills for the secondary prevention of cerebrovascular disease. Neurologia. 2021;36(1):1–8.

31. Gómez-Álvarez E, Verdejo J, Ocampo S, Ruiz E, Martinez-Rios MA. Reaching blood pressure guideline targets with the CNIC polypill in patients with a previous cardiovascular event in Mexico: A post hoc analysis of the SORS study. Future Cardiol. 2019;16(1):53–60.

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TABLES

100 mg/20 mg/5 mg Cáps. dura
100 mg/40 mg/10 mg Cáps. dura
100 mg/40 mg/2,5 mg Cáps. dura
100 mg/40 mg/5 mg Cáps. dura
100/20/10 mg Cáps. dura
100/20/2,5 mg Cáps. dura

Table 1: Dose of polypill marketed in Spain (Source: www.Vademecum.es).

ACE inhibitor	Ramipril 2.5 mg	Ramipril 5 mg	Ramipril 10 mg
Benazepril	10 mg	20 mg	40 mg
Captopril	50 mg	100 mg	200 mg
Cilazapril	2.5 mg	5 mg	10 mg
Enalapril	10 mg	20 mg	40 mg
Fosinopril	15 mg	30 mg	60 mg
Lisinopril	10 mg	20 mg	40 mg
Moexipril	15 mg	30 mg	60 mg
Perindopril erbumine	2 mg	4 mg	8 mg
Perindopril arginine	2.5 mg	5 mg	10 mg
Quinapril	10 mg	20 mg	40 mg
Tradolapril	2 mg	4 mg	8 mg
Zofenopril	30 mg	60 mg	120 mg

Table 2: Dose equivalences of different Angiotensin Converting Enzyme Inhibitors (ACEIs) (Source: Coca et al.[8]).

ARB	Ramipril 2.5 mg	Ramipril 5 mg	Ramipril 10 mg
Candesartan	4–8 mg	8–16 mg	16–32 mg
Eprosartan	150 mg	300 mg	600 mg
Irbesartan	75–150 mg	150 mg	300 mg
Losartan	25–50 mg	50 mg	100 mg
Olmesartan	5–10 mg	10–20 mg	20–40 mg
Telmisartan	20 mg	40 mg	80 mg
Valsartan	40–80 mg	80–160 mg	160–320[a] mg
Azilsartan	20 mg	40 mg	80 mg

Table 3: Dose equivalences of different angiotensin II receptor blockers (ARA-II) (Source: Coca et al.[8]).

Statin Percent LDL-C reduction	Atorvastatin 20 mg 41%	Atorvastatin 40 mg 47%
Lovastatin	80 mg	–
Pitavastatin	4 mg	–
Pravastatin	80 mg	–
Rosuvastatin	5 mg	10 mg
Simvastatin	40 mg	80 mg

Table 4: Equivalences of effective doses of different statins (Source: Coca et al.[8]).

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FIGURES:

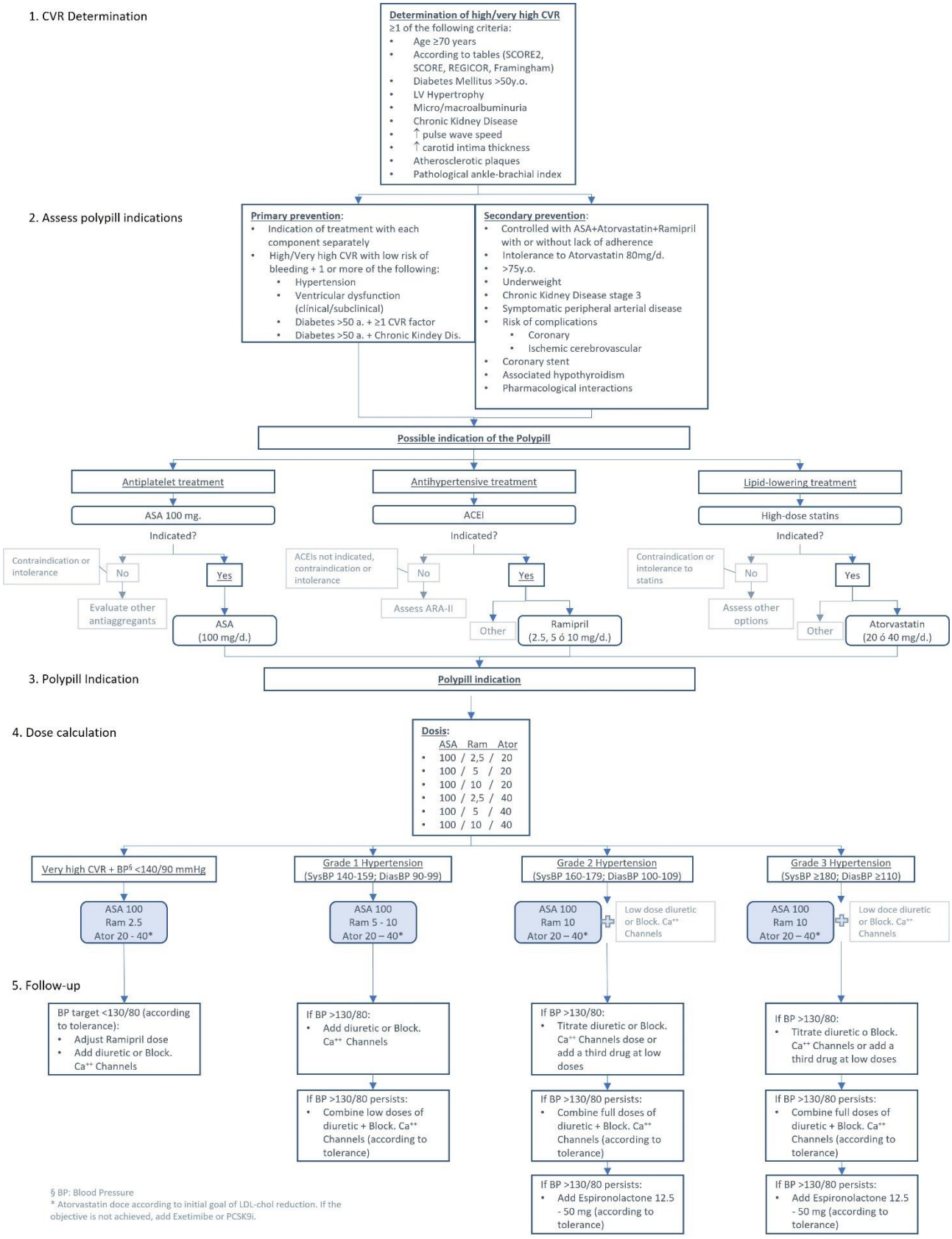

Figure 1: Polypill prescription and use algorithm (modified and adapted from Marzal et al.[18] y Coca et al.[8]).

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ANNEXES:

Average prices of the polypill with respect to its components marketed individually (Spain):

	Unit price	Traded Combination 28c.
ASA 100mg, 30c.	1.45€ (1.3533€/28c.)	Acetylsalicylic acid 100mg
Atorvastatin 20mg, 28c.	9.21€	Atorvastatin 20mg
Ramipril 10mg, 28c.	9.68€	Ramipril 10mg
	20.2433€	20.25€

Combination, same price as its components separately (calculation based on generic drug prices).

Polypill Warnings and Precautions [10,14,17,19]

- Hypersensitivity to ASA, Atorvastatin, Ramipril, to other salicylates, NSAIDs, to any other ACEI.
- History of asthma attack or other allergic reaction to ac. salicylic acid and other non-steroidal anti-inflammatory/analgesics.
- Active or history recurrent peptic ulcer and/or gastric/intestinal bleeding, or other kinds of bleeding such as cerebrovascular hemorrhages.
- Hemophilia and other bleeding disorders. I.H. and go. serious.
- Hemodialysis patients.
- Insuf. severe cardiac
- Concomitant with methotrexate in weekly doses ≥ 15 mg.
- Concomitant with aliskiren is contraindicated in diabetes mellitus or I.R. (GFR < 60 ml/min/1.73m^2).
- Nasal polyps associated with asthma induced or exacerbated by ASA.
- Active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the ULN.
- Pregnancy and lactation and in women of childbearing potential not using reliable contraception.
- Concomitant with tipranavir, ritonavir or cyclosporine, due to the risk of rhabdomyolysis.
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or angiotensin II receptor antagonists.
- Treatment. extracorporeal injuries involving blood contact with negatively charged surfaces.
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.
- Ramipril should not be administered to hypotensive or hemodynamically unstable patients.
- Children and adolescents < 18 years.
- In children <16 years with fever, flu or chickenpox, there is a risk of s. of King.

Interactions of polypill components

Acetylsalicylic acid (ASA)[14]

- Prolongation of coagulation time with: ticlopidine, clopidogrel.
- Increased risk of bleeding with: NSAIDs, systemic glucocorticosteroids (except hydrocortisone as replacement therapy in Addison's disease), alcohol, anticoagulants, thrombolytics
- Risk of acute renal failure with: diuretics, ACEI, ARA II.
- Plasma concentrations increased with: uricosurics

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- Increases nephrotoxicity of: cyclosporine
- Increases the effect of: insulin and sulfonylureas.
- Decreases the effect of: alpha interferon, beta-blocker antihypertensives, uricosurics (probenecid and sulfinpyrazone), ACE inhibitors, ARA II.
- Increases risk of ototoxicity from: vancomycin.
- Increases plasma concentrations of: barbiturates, digoxin, phenytoin, lithium, zidovudine, valproic acid, methotrexate (do not associate with methotrexate at doses of 15 mg/week or higher and at low doses monitor blood count and kidney function).
- Potentiates the action and toxicity of: acetazolamide.
- Renal clearance increased by: antacids
- Plasma concentrations increased by: uricosurics.
- Toxicity potentiated by: cimetidine, ranitidine, zidovudine.
- Lab: in blood: increased glucose, paracetamol and total proteins; reduced ALT, albumin, alkaline phosphatase, cholesterol, CPK, LDH, and total protein. In urine: reduction of ac. 5-hydroxy-indoleacetic, ac. 4-hydroxy-3-methoxy-mandelic acid, total estrogens and glucose.

Atorvastatin[17]

- Plasma levels increased by: strong CYP3A4 inhibitors (eg, cyclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, and HIV protease inhibitors such as ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.); moderate CYP3A4 inhibitors (eg, erythromycin, diltiazem, verapamil, and fluconazole), grapefruit juice, cyclosporine
- Plasma levels decreased by: inducers of cytochrome P450 3A4 (eg, efavirenz, rifampin, hypericum)
- Risk of rhabdomyolysis with: Gemfibrozil/fibric acid derivatives, ezetimibe, fusidic acid
- Risk of myopathy with colchicine
- Increases plasma concentrations of: norethindrone and ethinylestradiol, digoxin.

Ramipril[19]

- Extracorporeal procedures involving contact of blood with negatively charged surfaces are contraindicated, such as dialysis or hemofiltration with certain high-flux membranes and low-density lipoprotein apheresis with dextran sulfate, due to the increased risk of severe anaphylactoid reactions.
- Potentiation of hypotension with: diuretics, nitrates, tricyclic antidepressants, anesthetics.
- Antihypertensive effect reduced by: sympathomimetic vasopressors, NSAIDs, isoproterenol, dobutamine, dopamine, epinephrine.
- Increased blood count abnormalities with: allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics.
- Increases toxicity of: lithium.
- Increases hypoglycemic effect of: insulin and sulfonylurea derivatives.
- Increased risk of hyperkalemia: potassium salts, heparin, potassium-sparing diuretics, angiotensin II antagonists, trimethoprim, tacrolimus.
- Increased risk of hypotension with: antihypertensives (eg, diuretics), nitrates, tricyclic antidepressants, anesthetics, acute alcohol ingestion, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin.

Contraindications [10,14,17,19]

- Alcohol
- Grapefruit juice
- Pregnancy
- Lactose intolerance
- Peanut allergy
- Soy allergy

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Adverse reactions [10,14,17,19]

- Heartburn, nausea, vomiting, gastralgia, diarrhoea, minor gastrointestinal bleeding (microhemorrhage), constipation, flatulence, dyspepsia
- paroxysmal bronchospasm, severe dyspnea, rhinitis, nasal congestion, pharyngolaryngeal pain, epistaxis
- nasopharyngitis
- allergic reactions
- hyperglycaemia, hyperkalaemia, hypotension, orthostatic hypotension, syncope; headache, dizziness
- myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain, chest pain, fatigue
- liver function test abnormalities, blood creatine kinase increased
- rash, especially maculopapular.