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USE OF A POLYPILL TO REDUCE CARDIOVASCULAR RISK FACTORS: REVIEW AND USE GUIDE

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Conflicts of interest

No conflict of interest is declared.

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ABSTRACT

Primary and secondary cardiovascular prevention is less effective than expected due to the concern about polymedication by professionals and the lack of patient adherence to medications prescribed in the medium and long term. Polypills have been presented as a possible solution. A comprehensive bibliographic review is presented about polypills as mechanisms for facilitating adherence and a proposed guide for the use of polypills for the prevention of cardiovascular risk. 41 articles were included, showing options for the polypill as a method of primary and secondary cardiovascular prevention.

The polypill increases therapeutic adherence in the medium and long term, also increasing the therapeutic results compared to the administration of the various drugs separately. Based on the evidence, a flow diagram is proposed for the prescription of a polypill.

Polypills increase 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.

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INTRODUCTION

Both in primary cardiovascular prevention and in secondary prevention, the effectiveness of the programs depends on the adherence of the professionals to the clinical guidelines, on the access to the drugs indicated by the patients and on the adherence of the patients to the guidelines prescribed by the and long-term clinical practice indicates that often these variables are not followed by an important part of the actors, decreasing the effectiveness of cardiovascular prevention programs. One of the proposed initiatives is the use of polypills to increase the adherence of professionals and patients to these programs.

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

METHODS

To carry out this narrative review, an exhaustive search was carried out in the PubMed and Google Scholar databases during September and October 2022. The keywords used were those related to the theme of the review: polypill, prevention, cardiovascular risk and related terms The search was carried out based on all articles published in indexed journals (Q1, Q2, Q3, Q4) with full text available in English and Spanish from the last 10 years (from 2011 to 2022). Research on humans, with an intervention design, clinical trial or review, was included.

The initial search was narrowed down by using the specified filters and reading the titles and summaries of the selected articles to analyze the correspondence of the topic of each of the articles with the main topic of the investigation.

After the entire process of searching and selecting articles and eliminating duplicates, the process of critical reading of the remaining articles was carried out; After this process, 39 articles and other publications were finally included for this review.

RESULTS

After more than 20 years of existence of the so-called polypill,[1] the compilation of the published evidence and the critical reading of the articles included in the review a total of 39 publications including clinical trials, systematic reviews, clinical practice guidelines, evidence with other designs, expert, and editorial opinions.

In primary prevention there are data that demonstrate the effectiveness of cardiovascular prevention programs, even when they are applied to the general population or people with low cardiovascular risk;[2] however, therapeutic strategies aimed at simultaneously controlling several factors of CVR in patients without declared cardiovascular disease (primary prevention) are expensive and difficult to put into practice.[3]

In secondary prevention, patients with various cardiovascular risk factors (CVR) or with a clinical history of ischemic heart disease (IC) have a high risk of recurrence of new coronary episodes. Combined pharmacological treatment is a common practice in secondary cardiovascular prevention, including in geriatric patients[4] and its benefits in morbidity and mortality are widely documented;[4] however, the complexity of the therapeutic regimen often means that: 1) Professionals tend not to implement a complete preventive regimen, with lack of adherence to clinical guidelines,[5] 2) Professionals do not question the patient about their adherence to treatment[6] and, in turn, that 3) Patients show poor adherence to the therapeutic regimen with multiple medications;[3] in these cases adherence to the therapeutic regimen is usually low after 6 months after an acute myocardial infarction (AMI),[7] while the use of a polypill after this period reduces the rate of major cardiovascular events.[8,9]

The consequences of this lack of therapeutic adherence are increase in the rate of major cardiovascular (CV) episodes[2] and, consequently, of morbidity and mortality in both primary and secondary prevention, non-adherence to the

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treatments of other related diseases, or its delayed diagnosis due to less frequent medical consultations (such as diabetes), all of which lead to an increase in the care burden and an increase in healthcare costs.

Thus, therapeutic adherence is a key factor to ensure the sustainability of the healthcare system since non-adherence is linked to worse health outcomes and higher costs for the system.[10–12]

The creation of polypills involves the combination of different drugs without incompatibilities between them, safe, well tolerated, effective, recommended by clinical practice guidelines and physicochemically compatible with the rest of the components of the pill (excipients, etc.) .[13] The CNIC (Centro Nacional de Investigaciones Cardiovasculares, Ministerio de Ciencia e Innovación, España) created a polypill containing, in different doses, Acetylsalicylic Acid + Ramipril + Atorvastatin, which has shown its clinical effectiveness and high tolerability.[14,15] According to its technical sheet,[16] the indication of the polypill containing AAS + Atorvastatin + Ramipril focuses on the secondary prevention of cardiovascular accidents as replacement treatment in adult patients adequately controlled with the three substances taken at the same time in equivalent doses, to reduce the risk of suffering a cardiovascular accident, when the patient has already suffered a previous cardiovascular event; at the moment the technical data sheet of this product does not include the primary prevention of cardiovascular accidents, despite the evidence in the sense of providing benefits.[11,17]

The strategies using polypills for secondary cardiovascular prevention have shown greater comfort for the patient and an increase in treatment adherence up to 20%,[7,12,17–20] improving not only cardiovascular risk factors but also decreasing CV events and the health expenditure derived from them, being considered a strategy of great cost-effectiveness.[20–22]

DISCUSSION

COMPOSITION AND INDICATIONS of each component of the polypill:

- Acetylsalicylic acid (AAS): antiplatelet[23]
    - Primary prevention: the benefit of antiaggregation in primary prevention is controversial and some documents do not find reasons for its use,[24] because it must be individualized in each case, depending on the expected risk/benefit; they could only be recommended in patients with high RCV and low risk of bleeding.[12]
    - Secondary prevention, in adults for secondary prophylaxis after a first coronary or cerebrovascular ischemic event of:
        - AMI or myocardial infarction in patients with unstable angina pectoris and to prevent its recurrence in patients with a history of AMI[12.23]
        - Stable angina or unstable
        - Coronary angioplasty
        - Prevention of graft occlusion after aortocoronary bypass Thrombophlebitis
        - , phlebothrombosis and risk of arterial thrombosis[23]
        - Post-operative thromboembolism in patients with biological vascular prostheses or arteriovenous shunts.[23]
        - Treatment of transient ischemic attacks in men with transient cerebral ischemia to reduce the risk of cerebrovascular accident.[23]
        - Prevention of recurrences of cerebrovascular accidents (CVA) without hemorrhagic transitory or permanent
    - Other evidence:
        - Two systematic reviews and meta-analyses have shown an additive effect on the cardiovascular protection of the combination of AAS with statin.[12]
        - Evidence shows the benefit of the use of AAS in patients with a moderate risk of colorectal cancer, without risk of bleeding, under 70 years of age (with a life expectancy greater than

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10 years) and with a cardiovascular risk greater than 10% in the next 10 years The use of AAS is recommended, demonstrating a decrease in the incidence and mortality of colorectal cancer in these patients.[12.25]

- Atorvastatin: hypolipidemic and cardiovascular risk reducer in people with and without hyperlipidemia when the response obtained with diet or other non-pharmacological measures has been inadequate.[26]
    - Hypercholesterolemia: additional treatment to the diet in the reduction of high total cholesterol, LDL cholesterol, apoprotein B and triglycerides, in adult patients, adolescents and children from 10 years of age with:
        - Primary hypercholesterolemia, including familial hypercholesterolemia (heterozygous variant) or
        - combined (mixed) hyperlipidemia (corresponding to types IIa and IIb of the Fredrickson classification).
        - To reduce total cholesterol and LDL cholesterol (LDL-cholesterol) in adult patients with homozygous familial hypercholesterolemia, in combination therapy with other lipid-lowering treatments (for example, LDL apheresis) or if these treatments are not available.
    - Prevention of cardiovascular disease:
        - Primary prevention of cardiovascular events in adult patients with high CVR, as an adjunct treatment to the correction of other risk factors.
    - Other evidence:
        - Statins have demonstrated the ability to provide organic protection in patients with high CVR in primary CV prevention and secondary prevention.[4.12]
        - At a dose of 20 mg, with a hypocholesterolemic power of 41-43% reduction of c-LDL, Atorvastatin is the statin most used and presents a correct balance between efficacy and adverse effects.[12]
        - Contraindications to doses of 80 mg/d.: previous intolerance to the dose of Atorvastatin 80 mg., age >75 years, low weight (BMI <20 kg/m2), chronic kidney disease stage 3 (GFR <60 mL/ min/m2), hypothyroidism, drug interactions (amiodarone, verapamil).[27]
- Ramipril: antihypertensive inhibitor of the Angiotensin Converting Enzyme (ACEI).[28]
    - Treatment of Hypertension (HT)
    - Treatment of symptomatic heart failure
    - Treatment of AMI (reduction of mortality in the acute phase): treatment of renal disease: incipient diabetic glomerular nephropathy (with microalbuminuria), overt diabetic glomerular nephropathy (macroproteinuria) with one or more factors of CRV, overt non-diabetic glomerular nephropathy (macroproteinuria ≥ 3 g/day.)
    - Cardiovascular prevention[4]
        - Reduction of cardiovascular morbidity and mortality in patients with overt atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or vascular enf. peripheral)[12], diabetes with at least one RCV factor[12], AMI with clinical signs of heart failure (when treatment begins 48 hours after the AMI)
        - Secondary prevention after an acute myocardial infarction: reduction of mortality in the acute phase of myocardial infarction in patients with clinical signs of heart failure here when your treatment starts 48 hours after the acute myocardial infarction and when it is established up to 6 months later.[8,9]
    - Other evidence:
        - Only telmisartan and ramipril are indicated to reduce RCV, based on the available clinical trials.[12]

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OPPORTUNITIES of the polypill:[12,18] the change to a polypill can increase the use of AAS and modify more favorably the levels of total cholesterol,[10] LDL-cholesterol, [10,29] HDL-cholesterol[10] and blood pressure[10,14] than in patients who were following treatment with three separate drugs,[30] especially in: patients with a history of non-adherence or who have any of the factors predictive of pharmacological non-adherence, patients who are not well controlled with equipotent doses and with problems of adherence, patients who are controlled with individual drugs, and patients with comorbidities and polymedicated patients.

According to the scientific evidence, the benefits of using the combination of AAS + Ramipril + statins are:[18] The increase in therapeutic compliance is more pronounced in antihypertensive drugs and in AAS (due to lower adherence in general), over statins ;[30] simplification of the therapeutic regimen and increase in adherence in the short, medium and long term:[10] for every 10% increase in adherence, cardiovascular complications decrease by 6.7%; assuming that the polypill increases adherence by up to 20%, the reduction in complications would be around 12.6%[30] (up to 11 fatal and 46 non-fatal episodes per 1000 patients treated),[12.22] pointing out its enormous cost-effectiveness,[21] maximum at a time when the polypillora available in the market has a price identical to the sum of its components in the generic version separately (see Annex); in polymedicated patients, the simplification of the therapeutic regime also results in better compliance with treatment guidelines for other ailments and diseases.

INDICATIONS for the polypill: according to the most recent evidence, the indications may include patients with high or very high CVR (subclinical cardiovascular disease) to control their CVR factors and as organic protection, provided that they do not present a high risk of bleeding:[12 ,15,18,27]

- Hypertensive patients with high RCV,[31] defined by one or more of the following criteria (not included in the technical sheet of the commercialized products): age ≥70 years[16,28,32], risk ≥10% a at 10 years in the SCORE2 table[32] adapted to the risk of your European region, risk ≥5% at 10 years in the SCORE table calibrated for Spain,[33] risk ≥10% for the REGICOR or Framingham tables,[34] left ventricular hypertrophy, microalbuminuria /proteinuria, renal insufficiency, increased pulse wave velocity, increased carotid intimo-medial thickness, presence of atheroma plaques and pathologic ankle-arm index[35]
- Primary prevention of cardiovascular events (does not include do in the technical sheet of the marketed products): in patients with indications for treatment with the three components (ASA, Ramipril and statin), patients with subclinical CV disease: patients with high or very high CVR (determined by means of risk tables, presence of diabetes mellitus or subclinical vascular disease: carotid atheroma plaques, increased intima-media thickness, low ankle-brachial index or chronic renal insufficiency) and low risk of bleeding in the following circumstances: [35.36] diabetics older than 50 years with al minus an associated CVR factor, diabetics over 50 years of age with chronic renal disease and microalbuminuria or macroalbuminuria, hypertensive patients with high CVR, patients with high CVR with clinical or subclinical ventricular dysfunction
- Secondary prevention of cardiovascular events: of cardiovascular accidents in controlled adult patients adequately with monocomponents administered concomitantly in therapeutic doses equivalent tics,[4.16] of coronary complications,[36] cerebrovascular ischemic[37,38] or symptomatic peripheral arterial disease;[27] in this type of patients, a reduction in the rate of cardiovascular complications has been demonstrated that is greater than the reduction of each of the drugs separately) and patients with coronary stents.[35]

Expected results: the use of treatments in a fixed combination is associated with a greater than expected reduction in blood pressure and lipid figures, due to the increase in therapeutic adherence.[12,36,39] In phase IV studies, the reduction in blood pressure and LDL cholesterol was maintained after one year of treatment, reducing cardiovascular risk factors.[36]

Prescription:[12] moment: after the acute ischemic episode, including during hospitalization or upon discharge,[35] if compliance or adherence problems, polymedication or difficulties in accessing medication are anticipated. Therapeutic objectives: BP <140/90 mmHg, LDL-cholesterol <70 mg/dl or a reduction greater than 50% of baseline values. Additional measures:[18] all patients with cardiovascular risk are required to follow heart-healthy lifestyle habits such as quitting

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smoking, eating a heart-healthy diet, exercising regularly, avoiding obesity and controlling classic cardiovascular risk factors (diabetes mellitus, high blood pressure, dyslipidemia). Modification of doses: in case of insufficient control of blood pressure or LDL-cholesterol, 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.[18] Commercialized doses: the fixed combinations of AAS + Atorvastatin + Ramipril commercialized in Spain can be seen in Table 1.

Change of individual drugs to polypill and dose equivalences:[15] the approximate effective doses of daily doses for the change from other ACE inhibitors to Ramipril[15] can be seen in Table 2. The approximate effective doses of daily doses of angiotensin II receptor blockers (ARA-II) in Ramipril[15] consulted in Table 3. The potency and approximate effectiveness of other statins compared to Atorvastatin[15] can be consulted in Table 4.

Based on the existing bibliography, a flow diagram has been drawn up (see Figure 1) to facilitate the indication of a polypill for primary and secondary cardiovascular prevention, maximizing the use of prevention programs and facilitating their prescription to professionals to achieve greater patient adherence in the medium and long term.[19]

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

CONCLUSION

The use of a polypill, based on the available evidence, could increase patients' adherence to medication that reduces their cardiovascular risk in the medium and long term, resulting in greater effectiveness of cardiovascular prevention programs, without increasing costs or the pressure on the healthcare system.

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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: Polypill doses marketed in Spain (Source: 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 (ACEI).

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 equivalence of different angiotensin II receptor blockers (ARA-II).

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: Equivalencies of effective doses of different statins.

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FIGURES:

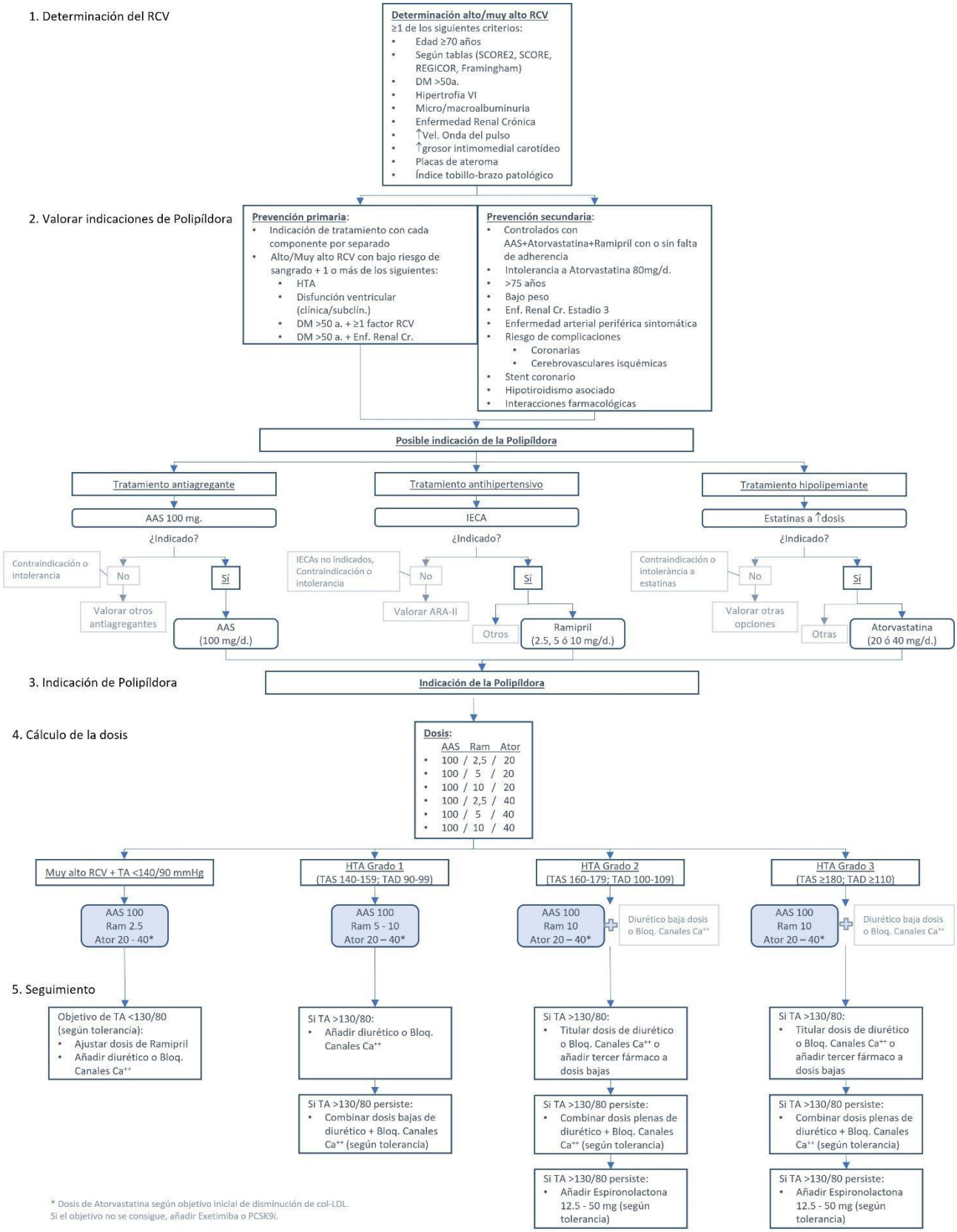

Figure 1: Algorithm for prescribing and using the Polypill (modified and adapted from Coca et al.[15] and Marzal et al.[27]).

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ATTACHMENTS: Average prices

of the polypill with regard to its individually marketed components:

	Precio unidad	Combination marketed 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 prices of generic medicines).

Warnings and precautions of the polypill[16,23,26,28]

- Hypersensitivity to AAS, Atorvastatin, Ramipril, to other salicylates, NSAIDs, to any other ACEI.
- Antecedents of asthmatic crisis or other allergic reaction to the ace. salicylic and other non-steroidal analgesics/anti-inflammatories.
- Active or previous recurrent peptic ulcer and/or gastric/intestinal bleeding, or other types of bleeding such as cerebrovascular bleeding.
- Hemophilia and other coagulation disorders. Severe IH and IR.
- Patients on hemodialysis.
- Insuf. severe cardiac
- Concomitant with methotrexate in weekly doses ≥ 15 mg.
- Concomitant with aliskiren is contraindicated in diabetes mellitus or IR (GFR < 60 ml/min/1.73 m^2).
- Nasal polyps associated with asthma induced or exacerbated by AAS.
- Active liver disease or unexplained persistent elevations of serum transaminases that exceed 3 times the ULN.
- Pregnancy and lactation and in women of childbearing age who do not use reliable contraceptive methods.
- Concomitant with tipranavir, ritonavir or ciclosporin, due to the risk of rhabdomyolysis.
- Antecedents of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or angiotensin II receptor antagonists
- . All extracorporeal drugs involving contact of blood with negatively charged surfaces.
- Significant bilateral stenosis of the renal artery or stenosis of the renal artery in a single functioning kidney.
- Ramipril should not be administered to hypotensive or hemodynamically unstable patients.
- Children and adolescents < 18 years old.
- In children < 16 years old with fever, flu or chicken pox, there is a risk of Reye's syndrome.

Possible interactions

Acetylsalicylic acid (AAS)[23]

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

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- Aumenta nef rototoxicity of: ciclosporin
- Increases the effect of: insulin and sulfonylureas.
- Decreases the effect of: alpha interferon, beta-blocking antihypertensives, uricosurics (probenecid and sulfinpyrazone), ACEI, ARA II.
- Augmenta risk of ototoxicity of: 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 renal function).
- Enhances the action and toxicity of: acetazolamide.
- Renal elimination increased by: antacids Plasma
- concentrations increased by: uricosurics.
- Toxicity enhanced by: cimetidine, ranitidine, zidovudine.
- Lab: in blood: increase in glucose, paracetamol and total proteins; reduction of ALT, albumin, alkaline phosphatase, cholesterol, CPK, LDH and total proteins. In urine: reduction of acid. 5-hydroxy-indole lactate, acid. 4-hydroxy-3-methoxy-mandelic, total estrogens and glucose.

Atorvastatin[26]

- 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 (e.g. erythromycin, diltiazem, verapamil and fluconazole), grapefruit juice, ciclosporin
- Plasma levels decreased by: cytochrome P450 3A4 inducers (e.g. efavirenz, rifampicin, 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[28]

- are contraindicated. extracorporeal that involve blood contact with negatively charged surfaces, such as dialysis or hemofiltration with certain high-flow membranes and apheresis of low-density lipoproteins with dextran sulfate, due to the increased risk of serious anaphylactoid reactions.
- Potentiation of hypotension with: diuretics, nitrates, tricyclic antidepressants, anesthetics.
- Antihypertensive effect reduced by: sympathomimetic vasopressors, NSAIDs, isoproterenol, dobutamine, dopamine, epinephrine.
- Increase in changes in blood count with: allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics.
- Increases toxicity of: lithium.
- Increases the 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 (e.g., diuretics) nitrates, tricyclic antidepressants, anesthetics, acute alcohol ingestion, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin.

Contraindications[16,23,26,28]

- Alcoholor
- grapefruit juice
- Pregnancy
- Lactose intolerance

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- Peanut
- Soy

Adverse reactions[16,23,26,28]

- Heartburn, nausea, vomiting, gastralgia, diarrhea, minor gastrointestinal bleeding (microbleeding), constipation, flatulence, dyspepsia
- paroxysmal bronchospasm, severe dyspnea, rhinitis, nasal congestion, pharyngolaryngeal pain, epistaxis
- nasopharyngitis
- allergic reactions
- hyperglycemia, hyperkalemia, hypotension, orthostatic hypotension, syncope; headache, dizziness,
- myalgia, arthralgia, pain in the extremities, muscle spasms, joint inflammation, back pain, chest pain, fatigue,
- abnormalities in liver function tests, increased creatine kinase in the blood
- exanthema, especially maculopapular.