CARDIOVASCULAR PATIENTS' DECLARATION REGARDING THERAPEUTIC ADHERENCE

Promoted by:

Cardio Alianza

With the collaboration of:

ferrer

Organisations endorsing the document:

1. CARDIOVASCULAR DISEASE

Cardiovascular diseases (CVD) are due to disorders of the heart and the blood vessels. Acute coronary syndrome, stroke and peripheral arterial disorders in arms or legs are the most frequent symptoms, all related to an alteration in blood flow.

1.1 FIGURES ON CARDIOVASCULAR DISEASE

CVDs are the primary cause of morbidity and mortality in the world. According to the World Health Organization (W.H.O.), 17.7 million people died in 2015 due to cardiovascular diseases, accounting for 31% of all deaths recorded worldwide. Over 75% of these deaths were in medium or low−income countries and, if that were not enough, CVD−related deaths are expected to reach 23.6 million by 2030.[1]

W.H.O. data on CVDs published in 2017 by the *European Heart Network* indicates that 3.9 million people died from this cause, representing a total of 45% of all deaths. In the European Union, this figure stood at around 1.8 million people, which accounts for 37%.

CVDs were the primary cause of death in women in Europe except in two countries (Denmark and Israel). Bulgaria has the highest CVD mortality rate in both men (60%) and women (70%), whereas France (23%) and Denmark (25%) have the lowest mortality rates in men and women, respectively.

EU28 countries	Year	Total deaths EU	Deaths due to the circulatory system	% Mortality due to cardiovascular disease	Total healthcare cost of CVD	Total CVD cost
Germany	2014	868356	338056	38,93	28.306.051 €	57.507.269 €
Austria	2014	78252	33136	42,35	2.522.237 €	4.740.715 €
Belgium	2013	109334	31314	28,64	2.421.246 €	4.668.718 €
Bulgaria	2013	104345	67910	65,08	343.566 €	948.844 €
Croatia	2015	54205	25694	47,40	241.894 €	777.332 €
Cyprus	2013	5272	1823	34,58	80.332 €	212.200 €
Denmark	2014	50993	12109	23,75	961.596 €	2.154.730 €
Slovakia	2014	51345	22889	44,58	657.098 €	1.272.236 €
Slovenia	2015	19834	7982	40,24	247.170 €	541.532 €
Spain	2014	395830	117393	29,66	9.243.461 €	16.850.797 €
Estonia	2014	15470	8250	53,33	177.808 €	488.600 €
Finland	2014	52409	19643	37,48	1.999.312 €	2.924.140 €
France	2013	556031	138894	24,98	15.195.280 €	23.602.232 €
Greece	2013	111794	46342	41,45	1.947.804 €	3.189.507 €
Hungary	2014	126308	62786	49,71	1.511.800 €	2.570.541 €
Ireland	2013	29504	9473	32,11	856.876 €	1.807.823 €
Italy	2012	613520	230160	37,51	15.708.130 €	28.214.832 €
Latvia	2014	28201	16071	56,99	130.396 €	468.134 €
Lithuania	2015	41776	23589	56,47	226.450 €	637.061 €
Luxembourg	2014	3705	1163	31,39	161.863 €	258.146 €
Malta	2014	3270	1231	37,65	47.632 €	110.448 €
Netherlands	2015	147134	39300	26,71	5.527.201 €	8.953.545 €
Poland	2014	376467	169734	45,09	4.352.521 €	8.667.244 €
Portugal	2014	105219	32286	30,68	1.174.407 €	2.828.357 €
Romania	2015	260997	153849	58,95	1.273.766 €	2.833.636 €
United Kingdom	2013	576458	159795	27,72	12.348.406 €	26.666.719 €
Czech Republic	2015	111173	50969	45,85	1.480.739 €	2.780.985 €
Sweden	2015	91002	31999	35,16	1.664.424 €	3.488.063 €
Country total		5097538	1885154	36,98	110.809.466 €	210.164.386 €

* Latest WHO data available. http://apps.who.int/healthinfo/statistics/mortality/whodpms/

In Spain, there were 124,197 CVD-related deaths in 2015[2] (29.3%), this being the primary cause ahead of cancer (26.4%) and respiratory diseases (12.3%). There are an estimated 924,000 patients in a situation of secondary prevention after a cardiovascular event. In Spain, the direct health care cost would have amounted to 5.9 billion euros in 2014 and around 1.8 billion in loss of productivity due to premature death.[3]

Although in general the mortality rate from cardiovascular diseases is decreasing in most EU countries, there is a growing percentage of the population that lives with disability and chronicity caused by CVDs due to the greater longevity and higher survival rates of those who have suffered an event.

In fact, cardiovascular diseases are one of the four main diseases within the so-called "non-communicable or chronic diseases" that, together with cancer, respiratory diseases and diabetes, cause 70% of all deaths worldwide and 80% of all premature deaths[4].

At present, the total cost of CVDs in Europe stands at around 201 billion euros a year, of which 53% are from direct costs, 26% from loss of productivity and 21% from the indirect care of people with CVD.[5]

Costs for the health care systems due to chronic diseases are high and are expected to increase. In fact, economic analyses suggest that every 10% increase in chronic diseases is associated to a 0.5% drop in annual economic growth[6].

In light of this situation, in its "Global status report on non-communicable diseases"[7] the WHO indicates a 25% relative reduction in general mortality due to cardiovascular diseases, cancer, diabetes or chronic respiratory diseases by 2025. Furthermore, the WHO Member States have reached an agreement regarding a set of another eight voluntary global targets that should be reached by 2025. These targets focus on reducing the harmful use of alcohol, insufficient physical activity, the intake of salt or sodium, the use of tobacco and raised blood pressure, halt the rise in diabetes and obesity and improve the coverage of treatment to prevent heart attacks and strokes. There is also a target aimed at improving the availability and accessibility of basic technologies and medicines to treat non-communicable diseases. The countries have made progress in them all towards reaching the general target of reducing premature mortality from the four main non-communicable diseases by 2025.

1.2 RISK FACTORS OF CARDIOVASCULAR DISEASE

Preventing cardiovascular disease is primordial. Such is the case that experts acknowledge that 90% of all cardiovascular disease responds to seven risk factors, which in most cases are a reflection of our behaviour: smoking, sedentary lifestyles, high blood pressure, high blood sugar, high cholesterol, diet and excess weight or obesity[8].

It is important to note that the population control of the main cardiovascular risk factors (RF) remains very low in Spain: 22.7% for high blood pressure (HBP) and 13.2% for cholesterol. In fact, together with the regional differences regarding prevalence and degree of control of risk factors, this factor shows the extensive margin that still exists for prevention in our environment[9].

Along these lines, the W.H.O. estimates that the episodes of this type would be halved through minor prevention of the RFs. Furthermore, over three quarters of all cardiovascular-related deaths could be prevented through a healthier lifestyle. [10] Therefore, the population health strategies focus on promoting healthy lifestyles and reducing the risk factors in the population.

More specifically, the most common cardiovascular risk factors can be grouped into three subgroups: *metabolic risk factors,* where high blood pressure (hypertension), high blood sugar levels (diabetes) and high lipid concentration (hypercholesterolemia), as well as excess weight and obesity, are highlighted; *behavioural risk factors*, arising from the individual's lifestyle, such as a rather unhealthy diet rich in salt, fats and/or calories, physical inactivity and tobacco and/or alcohol abuse; and *other factors* that includes those of a socioeconomic nature (such as a low income level, poor education, old age, female, etc.) and others of a more psycho-biological nature (family background, genetic predisposition, or mental disorders such as stress or depression).

To control the risk factors, the latest therapeutic guide to the secondary prevention of cardiovascular events in clinical practice [11] specifies how health care professionals and the authorities must intervene individually and jointly to propose actions to reduce the RF, such as: influence the lifestyles of people with CVD, providing individualised behaviours and strategies to the population regarding sedentary behaviour, with the prescribing of exercises to promote physical activity, reducing smoking habits, and ensuring a balanced diet through healthy eating. Although it is not just limited to behavioural habits, but also includes metabolic risk factors such as the control of high blood pressure, body weight or blood lipids through pharmacological treatments (polypharmacy or combined treatments), in which adherence to therapy plays a vital role to correctly monitor the secondary prevention of CVDs.

2. ADHERENCE TO THERAPY

In Europe, 3 out of every 10 patients do not adhere to therapeutic treatment, and in Spain the data is even worse, with 5 out of every 10 people not doing so[12] Another relevant piece of data is that, in Europe, 5 out of every 10 patients fail to complete long-term treatments.

More specifically in the cases of CVD, adherence stands at 57% in Europe[13] In Spain, according to the latest review written and endorsed by the Spanish Society of Cardiology (SEC), the percentage of adherence in secondary prevention (i.e. among patients who have had a prior cardiovascular event) is 56%, which means that 44% of patients did not adhere[14].

In the EU, the number of deaths associated to poor adherence to prescribed medicine accounts for 194,500 a year, and the estimated cost is 125 billion euros[15].

In Spain, the health care and economic cost of failing to adhere was shown in a recent study that indicated that, by adding just one percentage point to the completion of therapy for the secondary prevention of cardiovascular diseases (i.e. That prescribed after having suffered an incident of this type), would involve an avoidable cost of 10,900,627 euros to public health care. Furthermore, an increase of 10 percentage points in improving adherence would prevent 8,700 deaths and 7,650 episodes caused by CVD, with an avoidable cost of 75 million euros to the health care system[16].

According to the WHO, adherence to therapy is defined as the *extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider[17]*.

Adherence involves two issues: non-pharmacological treatment based on modifications in lifestyles, such as improved diet, daily physical activity and stopping alcohol and tobacco, and pharmacological treatment, i.e. appropriately taking medicine (according to the dosage and programme prescribed by the health care professional). Hence, adherence to therapy is considered a complex behavioural process that requires: "the active, voluntary, and collaborative involvement of the patient in a course of behaviour" to produce a therapeutic result.

2.1 CAUSES AND CONSEQUENCES OF THE LACK OF ADHERENCE

Good adherence to therapy is related to improved quality and life expectancy of the patient, whereas bad adherence involves a worse control of the disease, leading to a greater number of complications in the patient's health and the subsequent socioeconomic cost to the system.

Despite the benefits associated to adherence to therapy, the aforementioned data shows that the level of compliance is low, which means that there is still a great deal to be done. Poor adherence to therapy is a major problem worldwide and represents one of the main obstacles for improving patient health and quality of life and reducing the socio-health care cost[18].

As the WHO indicates, "*poor adherence is the primary reason for not achieving the full health benefits medicines can provide to patients. It causes medical and psychosocial complications of disease, reduces patients' quality of life, increases the likelihood of development of drug resistance, and wastes health care resources*"[19].

On one hand, for the patient it means an increase in the rate of CVD-related, which involves a lower quality of life and event death, whereas for the health care professional it means an increase in workload given the increasingly severe complications and subsequent hospitalisations. What is more, this also has repercussions on the health care system, generating greater financial costs and worse health results.

"Poor adherence to therapy is a significant barrier in the secondary prevention of cardiovascular disease (CVD) and, as a result, in being able to reach certain levels of health care excellence"[20]. There are different reasons behind this poor adherence: related to the patient (such as age, sex and low educational and socio-economic status), to the chronicity (complexity of the treatment, medication costs, side effects) and the asymptomatic nature of the disease itself, and to the health care system and the professionals working in it (absence of infrastructures, lack of tools, suitability of the relationship between patient and professional, etc.).

The main reason for abandoning CVD treatment is linked to an inadequate understanding of the disease, which is due to three main factors: the patient's lack of perception of his or her vulnerability, the patient's lack of information on the treatment and the lack of precise instructions from health care professionals. When the treatment is complex, i.e. a large number of medicines, adherence drops. Adherence is inversely proportional to the number of doses, i.e. The greater the number of tablets/doses, the poorer the adherence[21]. In short, taking a lot of tables every day is a determining factor in poor adherence, which ends up threatening patient health.

The reduction in co-payment, automatic reminders via mobile apps, the provision of orders by mail to chemists, the advice of a health care professional and fixed-dose combination therapies are measures that have proven to improve therapy compliance[22]. The simplification of therapeutic regimes in fixed-dose combination therapies is an additional strategy to improve adherence to the treatment of many different types of disease and are also favourably perceived by patients[23]. Fixed-dose combinations also allow for a reduction in production and distribution costs, thus improving treatment affordability[24].

Promoting changes with patient empowerment, involving them in decisions regarding their treatment and considering their experiences and preferences, simplifying treatment or improving communications between health care professionals and patients would provide a clear improvement in adherence to therapy for the secondary prevention of CVDs.

3. DECLARATION FOR CARDIOVASCULAR PATIENTS

This document seeks to **promote adherence to therapy in patients with cardiovascular disease, preventing disability and reducing avoidable deaths for the improved quality of life and wellbeing of patients and their families.**

General goal

To have an impact on the optimisation of adherence to therapy (pharmacological and non-pharmacological) in order to improve patient health and quality of life and, as a result, reduce the possibility of suffering a second cardiovascular event that might worsen the situation or lead to a disability or event death.

Specific goals

- To make patients aware of the importance of good, maintained adherence to therapy, especially to prevent a new event.
- To promote a more active role in patients, involving them in the decisions affecting their health.
- Early detection of poor adherence to therapy.
- To ensure access to the best treatment and generate measures and recommendations to ensure health care quality.
- To contribute towards the sustainability of the Health Care System.

> Cardioalianza, together with the European CVD organisations signing this declaration,
>
> **URGE ALL PLAYERS INVOLVED IN CARDIOVASCULAR HEALTH**
>
> to work towards improving adherence to therapy in Europe and propose a series of recommendations that will help patients, their families and all other stakeholders in the health care system to control and improve the wellbeing of people with CVD.

We therefore DECLARE that all patients should:

- **Control the main cardiovascular risk factors and follow a healthy lifestyle.** Undertaking the regular examinations regarding the main risk factors and following the recommended guidelines for everyday life, such as regular exercise, the responsible use of alcohol and stopping smoking.

- **Undertake the commitment to be jointly responsible for the disease.** Patients must be acutely aware of the cardiovascular disease and its possible causes and consequences and must follow the recommendations to be able to prevent a new cardiovascular event.

- **Follow the pharmacological guidelines prescribed by their doctor.** Patients must understand the importance of following the prescribed treatment and the consequences of not doing so.

- **Ask for help if necessary.** Tackling the disease and its different facets is a complex process for patients and one which they do not have to face alone. They can share their experience with other patients suffering the same symptoms, with their specialist or GP and with patient organisations. All players can help them in different ways: patient organisations are formed to provide support activities for other people in the same situation and talking to other patients "among peers" has proven to have a positive effect on the course of the disease. In turn, health care professionals can offer psychological help, if required, given that the diagnosis of any disease is bound to have repercussions on an individual's mental health.

- **Take a more active role in the consultation.** Get ready for the visit before a consultation, i.e. be aware of the different treatments available and ask for the most beneficial in each case, know the names of the drugs/active ingredients if asked, know which queries you want the doctor to explain, or ask for printed information to be read at home.

- **Never be carried away by the "white coat" syndrome.** Never leave the consultation without having previously made sure that you understand all the information provided by the health care professional. If there is anything you have not understood, ask again and, if necessary, ask them to use a language that is easier to understand. Doctor–patient communication must be flowing, and this also partly depends on the patient.

- **Wherever possible always go to the consultation with someone else.** The context of the doctor's visit is sometimes stressful for patients and this affects their understanding of all the information and means that they sometimes do not ask the right questions. Taking someone with you may make the consultation easier and enable that someone to become more involved in managing the disease.

For this to be possible, a series of conditions must be encouraged by other health care players involved in handling the cardiovascular patient. Only in this way can we all ensure improved adherence to therapy.

WE ASK health care professionals:

- **To explain the benefits and the importance of compliance with the full treatment to the patient,** as well as the consequences of poor adherence. If you want patients to follow the prescribed treatment, they must understand the benefits it will have on their quality of life and the possible consequences of poor adherence.

- **To personalise the treatment, depending on the personal, social and clinical context of patients,** especially in patients with poor adherence or who do not follow the treatment guidelines. It is therefore important to identify patient expectations and try to mitigate the barriers to be able to choose the best alternative treatments together.

- **To adapt the language used for medical explanations depending on the profile of the patient** being treated in order to make sure he or she has understood the information given. In patients asking as such, to offer additional material for an easier understanding of the information provided.

- **To involve patients in the management of their disease and in the controlling of risk factors.** Empower patients, including them in the decisions related to the treatment and monitoring of the disease so that they are involved. It is important to motivate them so that they feel acknowledged when they successfully follow the guidelines set by their health care professional.

- To try to **shorten the intervals between visits**, especially in patients at risk of poor adherence. This will enable the professional to monitor patients more closely and ensure they are complying with treatment.

- **To detect whether the patient needs psychological assistance/emotional help.** Know how to identify whether patients have accepted their disease in order to offer psychological assistance if required and recommend a visit to an association of patients affected by the same symptoms.

- **To coordinate with the other specialities and with primary care, where poor adherence is detected.** Share with and/or ask other health care professionals dealing with the same patients in order to be able to assess the best treatment together. Follow a strategy of comprehensive care with regard to the therapeutic plan.

WE DEMAND that the Public authorities:

- **Design and create specific programmes for early detection** in patients who do not comply correctly with the treatment, paying special attention to patients at risk due to their socio-economic situation.

- **Promote campaigns on the importance of correctly controlling cardiovascular risk factors** (cholesterol, high blood pressure, diabetes, obesity, smoking, etc.), and the promotion of healthy life styles (exercise and a balanced diet).

- **Guarantee access to the best alternative therapies available for all patients,** without exception, regardless of their geographic area, their financial resources or their level of education.

- **Provide patients with tools and alternatives that enable them to manage their medication in a better way**, such as pill boxes, reminder apps, drug combinations taken just once a day, etc. In short, providing the polymedicated patient and his or her carers with tools to enable them to keep a record of the prescriptions or notify/remember the administering of doses.

- **Encourage coordination among the different levels of health care** (primary and specialist). Design programmes of collaborative and comprehensive health care among GPs, nursing staff, specialists and pharma industry, focusing on ensuring compliance with adherence especially among those patients with different comorbidities.

4. BIBLIOGRAFÍA

[1] World Health Organization (WHO). (2017) Cardiovascular diseases (CVDs) – Factsheet Nº317. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/.

[2] Instituto Nacional de Estadística (INE): Defunciones según la causa de muerte 2015. Defunciones por causas (lista detallada) sexo y edad. Disponible en: http://www.ine.es/jaxi/Tabla.htm?path=/t15/p417/a2015/l0/&file=01000.px&L=0.

[3] Centre for Economics and Business Research. The rising cost of cvd 2014. Available at: https://cebr.com/reports/the-rising-cost-of-cvd/

[4] WHO. (2017) Enfermedades no transmisibles – Factsheets N) 355. Available at: http://www.who.int/mediacentre/factsheets/fs355/es/

[5] Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. (2017). European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels. Available at: http://www.ehnheart.org/images/CVD-statistics-report-August-2017.pdf .

[6] WHO (2010) Informe sobre la situación mundial de las enfermedades no transmisibles 2010. RESUMEN DE ORIENTACIÓN. Disponible en: http://www.who.int/nmh/publications/ncd_report_summary_es.pdf

[7] WHO (2014) Informe sobre la situación mundial de las enfermedades no transmisibles 2014. Disponible en: http://apps.who.int/iris/bitstream/10665/149296/1/WHO_NMH_NVI_15.1_spa.pdf

[8] Entrevista a Valentí Fuster.4 de septiembre 2017. Disponible en: http://www.larazon.es/atusalud/salud/valentin-fuster-el-90-de-la-patologia-cardiovascular-responde-a-siete-factores-de-riesgo-GM15919069

[9] Royo-Bordonada MÁ, Armario P, Lobos Bejarano JM, Botet JP, Villar Alvarez F, Elosua R et al en nombre del Comité Español Interdisciplinario para la Prevención Cardiovascular (CEIPC). Adaptación española de las guías europeas de 2016 sobre prevención de la enfermedad cardiovascular en la práctica clínica. Rev Esp Salud Pública. 2016;Vol.90: 24 de noviembre: e1-e24. Disponible en: http://www.msssi.gob.es/biblioPublic/publicaciones/recursos_propios/resp/revista_cdrom/VOL90/C_ESPECIALES/RS90C_CEIPC2016.pdf

[10] Plaza Celemín, L. (Coordinador) et. Al. (2015) Disminuir la enfermedad cardiovascular, un objetivo prioritario: Informe sobre la enfermedad cardiovascular en España. FEC

[11] Piepoli M, Hoes A, Agewall S, Albus C, Brotons C, Catapano A, et al. (2016) European Guidelines on cardiovascular disease prevention in clinical practice Eur Heart J; 37(29):2315-81.

[12] Universidad de Pacientes. Infografía extraída de: http://www.universidadpacientes.org/calidad_asistencial/info/16/

[13] Naderi SH, Bestwick JP, Wald DS.(2012) Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med; 125:882-887.

[14] Restovic Camus, G. et al. (2016) Plan de adherencia al tratamiento. Uso responsable del medicamento. Farmaindustria y EY. Santander.

[15] Pharmaceutical Group of the European Union. "Targeting Adherence: Improving Patient Outcomes in Europe through Community Pharmacists' Interventions". Accessed at: http://www.pgeu.eu/en/policy/5-adherence.html

[16] Restovic Camus, G. et al. (2016) Plan de adherencia al tratamiento. Uso responsable del medicamento. Farmaindustria y EY. Santander

[17] Sabaté, E. (2003) Adherence to long-term therapies: evidence for action. Geneva: World Health Organization. Available in: http://www.who.int/chronic_conditions/adherencereport/en/

[18] Organización Mundial de la Salud (OMS). Informe sobre enfermedades crónicas 2008.

[19] Declaraciones del Dr. Derek Yach, Director Ejecutivo de Enfermedades No Transmisibles y Salud Mental, Organización Mundial de la Salud (OMS). Nota de prensa OMS 2003.

[20] López–Sendón J, González–Juanatey JR, Pinto F, Cuenca Castillo J, Badimón L, Dalmau R, et al. Indicadores de calidad en cardiología. Principales indicadores para medir la calidad de los resultados (indicadores de resultados) y parámetros de calidad relacionados con mejores resultados en la práctica clínica (indicadores de práctica asistencial). INCARDIO (Indicadores de Calidad en Unidades Asistenciales del Área del Corazón): Declaración de posicionamiento de consenso de SEC/SECTCV. Rev Esp Cardiol. 2015;68:976–995.e10.

[21] Gutiérrez–Angulo, M. L., Lopetegi–Uranga, P., Sánchez–Martín, I., & Garaigordobil Landazabal, M. (2012). Cumplimiento terapéutico en pacientes con hipertensión arterial y diabetes mellitus 2. *Revista de Calidad Asistencial*, *27*(2), 72-77. https://doi.org/10.1016/j.cali.2011.09.008

[22] Phan K, Gomez YH, Elbaz L, Daskalopoulou SS. Statin treatment non–adherence and discontinuation: clinical implications and potential solutions. Curr Pharm Des. 2014;20:6314–24.

[23] Bryant L, Martini N, Chan J, Chang L, Marmoush A, Robinson B, et al. Could the polypill improve adherence? The patient perspective. J Prim Health Care. 2013;5:28–35.

[24] Fuster V. Un problema alarmante en prevención secundaria, bajo cumplimiento (estilo de vida) y baja adherencia (farmacológica). Rev Esp Cardiol. 2012;65(Supl 2):10–6.

OTHER BIBLIOGRAPHY CONSULTED:

Barrios, V., Kaskens, L., Castellano, J., Cosin–Sales, J., Emilio Ruiz, J., Zsolt, I., ; Gracia, A. (2016). *Usefulness of a Cardiovascular Polypill in the Treatment of Secondary Prevention Patients in Spain: A Cost–effectiveness Study*. *Revista Española de Cardiología (English Edition)*. https://doi.org/10.1016/j.rec.2016.05.009

Becerra V, Gracia A, Desai K, Abogunrin S, Brand S, Chapman R, et al. (2015) Cost–effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK. BMJ Open [Internet];5(5):e007111. *Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4452741/*

Bernick, S. (2014) The economic cost of cardiovascular disease from 2014–2020 in six European economies. Cebr. London.

Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S, Fuster V. (2014) A polypill strategy to improve global secondary cardiovascular prevention: from concept to reality. J Am Coll Cardiol 64:613-21.

Chowdhury, R., Khan, H., Heydon, E., Shroufi, A., Fahimi, S., Moore, C., Franco, O. H. (2013). Adherence to cardiovascular therapy : a meta–analysis of prevalence and clinical consequences, 2940-2948. https://doi.org/10.1093/eurheartj/eht295

Cosin–sales, J., Ruiz, E., Barrios, V., Kaskens, L., & Zsolt, I. (2017). Utilidad de un policomprimido cardiovascular en el tratamiento de pacientes en prevención secundaria en España : un estudio de pacientes en prevención de coste–efectividad, Revista española de Cardiología *70*(1), 42-49.

Fuster, V., Gambús, F., Patriciello, A., Hamrin, M., & Grobbee, D. E. (2017). The polypill approach - An innovative strategy to improve cardiovascular health in Europe, 1-8. https://doi.org/10.1186/s40360–016–0102–9

González–Juanatey JR, Mostaza JM, Lobos JM, Abarca B, Llisterri JL. (2016) Nuevo enfoque terapéutico para la prevención secundaria del riesgo cardiovascular. Documento de consenso del uso clínico de la

Polypill.Disponible   en: http://www.revespcardiol.org/contenidos/static/docs/Consenso%20Polypill_v4_2.pdf.

Kolandaivelu, K., Leiden, B. B., Gara, P. T. O., & Bhatt, D. L. (2014). Clinical update Non–adherence to cardiovascular medications, 3267-3276. https://doi.org/10.1093/eurheartj/ehu364

Jan S, Usherwood T, Brien JA, et al. (2011). What determines adherence to treatment in cardiovascular disease prevention? Protocol for a mixed methods preference study. BMJ Open 2:e000372. doi:10.1136/bmjopen–2011–000372

Jin, J., Sklar, G. E., Min, V., & Oh, S. (2008). Factors affecting therapeutic compliance : A review from the patient ' s perspective, 4(1), 269-286.

Ho M, Bryson CL, Rumsfeld JS. (2009) Medication adherence. Its importance in cardiovascular outcomes. Circulation 119:3028-35.

Laba TL, Howard K, Rose J, et al. (2015) Patient preferences for a polypill for the prevention of cardiovascular diseases. Ann Pharmacother 49: 528-39.

Mclinpharm, L. B., Martini, N., Bpharm, J. C., Bpharm, L. C., Robinson, B., Yu, K., & Wong, M. (2013). Could the polypill improve adherence ? The patient perspective, 5(1), 28-36.

Mendis S, Puska P, Norrving B. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization, 2011.

Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al.(2012) Sociedad Europea de Prevención y Rehabilitación cardiovascular (EACPR). Guía europea sobre prevención de la enfermedad cardiovascular en la práctica clínica (versión 2012). Rev Esp Cardiol 65(10):937. e1–e66

Tamargo, J., Castellano, J. M., & Fuster, V. (2015). The Fuster–CNIC–Ferrer Cardiovascular Polypill : a polypill for secondary cardiovascular prevention, 1, 15-23. https://doi.org/10.1016/S0167–5273(15)31028–7

WHO. (2016) Hearts: technical package for cardiovascular disease management in primary health care. Geneva. Available at: http://apps.who.int/iris/bitstream/10665/252661/1/9789241511377–eng.pdf?ua=1