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Design and validation of a new questionnaire with a gender perspective to measure medication adherence for secondary prevention of ischaemic heart disease: study protocol

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ABSTRACT

Introduction and objectives Only about 50% of chronic patients in high-income countries adhere to their treatment. There are methods to measure medication adherence but none of them can be considered optimal. This study will aim to design and validate a questionnaire to measure medication adherence in patients with ischaemic heart disease using a direct method as a gold-standard adherence measure and taking into account the gender perspective. Moreover, the profile of low adherence in these patients will be determined.

Methods and analysis First study phase consists on the questionnaire design following the next steps: identification of the dimensions, definition of the target population, questionnaire items and order, response coding, questionnaire instructions, content validity by experts and understandability. In the second phase, a cross-sectional study will be performed to end the questionnaire development and validate it. Four hundred and forty patients (50% female) with acute coronary syndrome receiving treatment within the previous 12 months will be included. Patient will answer the initial questionnaire and adherence to aspirin and statin will be measured using a direct method (drug concentration analysis in blood) and other questionnaires. From the set of preselected questionnaire items, those most closely associated with the gold standard measure will be selected using multivariate statistics.

Ethics and dissemination All participants gave their written informed consent before participating in the study. The study protocol follows the recommendations of the Declaration of Helsinki and was approved by the ethics committees of the three participating centres. The results of this study will be displayed at national and international conferences and in peer-reviewed scientific journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Regarding the limitations, there is a chance that the criteria of consulted experts will be heterogeneous.
⇒ Other limitations include those common to self-completed questionnaires in general (if they end up being completed in this way), such as the inability to clarify questions or answers and the conditioning of responses by the patient's state of mind at the time of the interview.
⇒ The main strengths of this study on the design and validation of a medication adherence questionnaire are as follows: it will take into account the main international recommendations for questionnaire design; it will involve both health professionals and patients in the design process; it will use a direct method as a reference standard to assess the criterion validity and it will take into account the gender perspective, both in the questionnaire design and validation stages.

INTRODUCTION

Pharmacological treatments are the main tools to effectively prevent and treat chronic disease. However, despite their importance, the correct use of medication continues to be a challenge,[1] as about 50% of chronic patients in high-income countries have discontinued their treatment after 12 months.[2 3] Lack of medication adherence leads to poor clinical outcomes, and in turn to an increase in mortality, morbidity and health costs. This may be one of the main causes of poorly controlled chronic diseases. Thus, adherence is a crucial issue for population health from the perspectives of both quality of life and health economics.

The WHO defines therapeutic adherence as 'the extent to which a person's behaviour—taking medication, following a diet and/or executing lifestyle changes—corresponds with the agreed recommendations from a healthcare provider' and considers that

improving it may be the best investment to effectively address chronic processes.[4] Specifically, the medication adherence is defined as 'the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation'.[5]

Medication adherence is a multifactorial phenomenon determined by the action of five inter-related domains with several factors:[6] *patient characteristics*, such as age, employment or economic status, culture, educational level, geographic area and race;[7–13] *social and family environment;*[14] *characteristics of the disease; therapeutic regimen* and *health system conditions*, including the characteristics of the health professional.[15 16]

Cardiovascular disease (CVD) is the main cause of premature death in most European populations, including in Spain.[17] Improvements in hygiene, nutrition, and healthcare have favoured better survival, but CVD still represents an important source of disability and contributes substantially to increases in healthcare costs.[18] Ischaemic heart disease is the leading cause of hospital visits in our country, and it has a great health and social impact.[19] Previous studies indicate that most recurrent cardiovascular events occur in survivors of acute coronary syndrome, particularly in the first year after the event.[20] Lack of adherence to medication is common among patients with this disease.[21 22] In Spain, according to the latest published review endorsed by the Spanish Society of Cardiology, the percentage of adherence to medication for secondary prevention is 56% in patients who have had a previous cardiovascular event.[23] In the European Union, around 194 500 deaths are attributed to non-adherence to prescribed medication, and the estimated cost is EUR 125 billion.[24] The optimisation of secondary prevention therapies and especially patients' adherence to them are the key to achieving a greater reduction in cardiovascular mortality and associated costs.[25] According to data from a study on the cost-effectiveness of the polypill, each 10% increase in adherence can reduce CVD complications by 6.7%.[26]

If physicians fail to identify non-adherence as the cause of poor disease control, a drug may be mistakenly regarded as ineffective, unnecessarily intensifying treatments or even leading to unnecessary diagnostic tests. In addition, clinical trial results may not be well interpreted if adherence to the drug in question is unknown.[27]

Methods to measure medication adherence can be direct (through direct observed therapy, therapeutic drug monitoring or ingestible sensor-based system) or indirect (patient self-report questionnaires, tablet counting, medication event monitoring systems, among others).[28] The direct method is objective, specific and the most accurate, but it is expensive and unfeasible in clinical practice. The indirect method is usually based on self-report questionnaires. This method has limitations, including subjectivity, recall bias and response bias, since the information is reported by the patient themselves, but it is the most widely used because it is practical and inexpensive.[28] There is a wide variety of adherence questionnaires, most of which are validated for chronic diseases such as arterial hypertension, AIDS, tuberculosis, diabetes and dyslipidaemia; however, they do not use a direct method as a reference measure of adherence or account for gender in the design process. Previous literature[29] reports that there are differences between the factors associated with non-adherence between men and women, thus to introduce the gender perspective in research on adherence is important. The most widely used, validated questionnaires in Spain are the Haynes-Sackett[30] and Morisky-Green tools, which generally have a low negative predictive value and low sensitivity[31] and are sometimes used in diseases for which they have not been validated. In general, while there are numerous tools to measure medication adherence, currently none of them can be considered optimal.

Therefore, the main aim of this study will be to design and validate a questionnaire to measure medication adherence in patients with ischaemic heart disease, taking into account the gender perspective. Secondary aims are to compare this new questionnaire with the most widely used instruments for measuring medication adherence in clinical practice, and to determine the profile of low adherence in patients with ischaemic heart disease in Spain, according to sociodemographic and clinical variables as well as gender.

METHODS AND ANALYSIS

The study protocol has been approved by the ethics committees of the four participating centres: San Juan de Alicante University Hospital (Alicante), Elda General Hospital (Alicante), Alicante General Hospital (Alicante) and HM Sanchinarro (Madrid). The study has two phases (figure 1).

PHASE 1: QUESTIONNAIRE DESIGN (FROM JANUARY 2022 TO SEPTEMBER 2023)

We will follow the methodology and recommendations proposed by the American Research Association.[32]

Definition of the construct: identification of the dimensions

A literature review will be carried out to develop the theoretical framework for analysing adherence to medications. Subsequently, a consensus group made up of researchers in the fields of cardiology, primary care and nursing who investigate medication adherence will identify possible causes of non-adherence to treatment in patients with ischaemic heart disease, defining these as possible dimensions of the questionnaire. Likewise, consultations will be carried out with community pharmacy professionals and with women and men with ischaemic heart disease in drug treatment for at least 1 year, using qualitative (focus groups) and quantitative (closed-question surveys) methods.

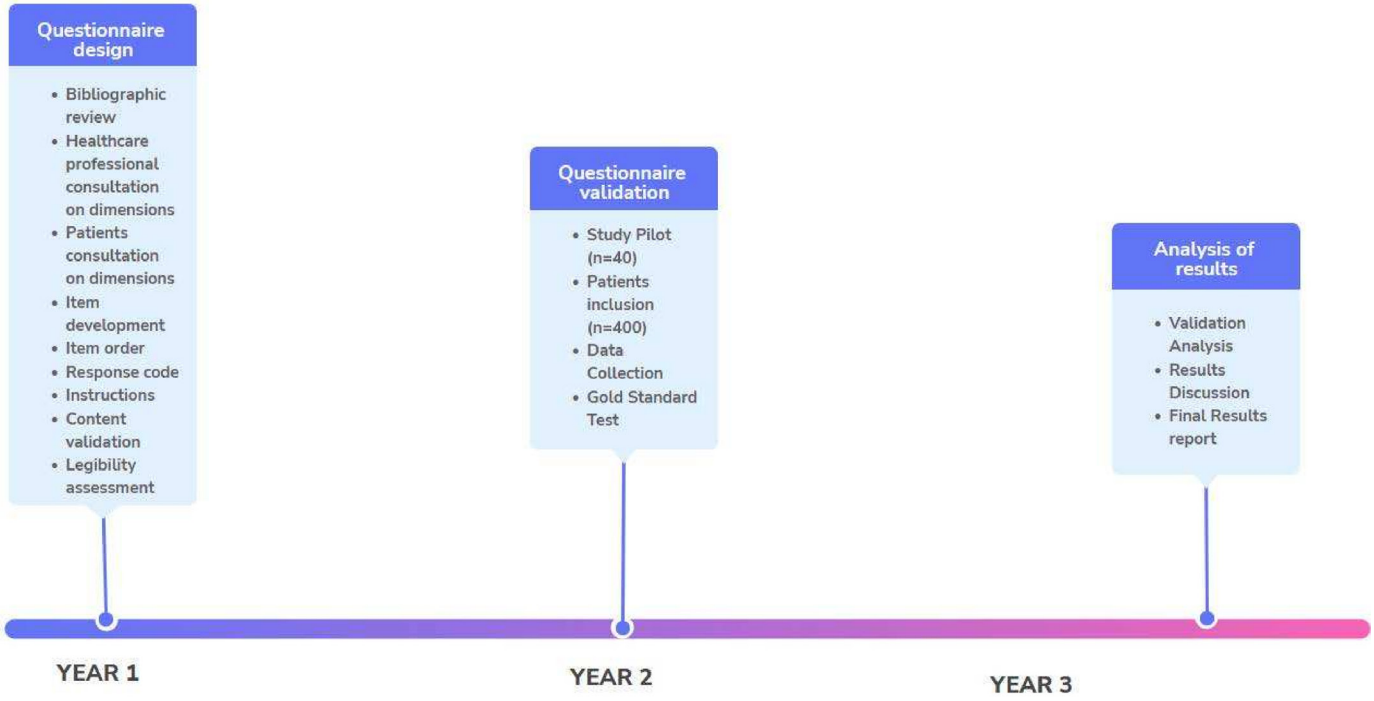

Figure 1 Timeline diagram.

Purpose of the scale

The target population (age, disease and setting) and the form of administration of the questionnaire will be defined. In this case, the questionnaire is aimed at people with ischaemic heart disease undergoing drug treatment for at least 1 year, and it will be self-completed.

Definition of questionnaire items

Questionnaire items will be formulated based on the dimensions identified and will be adapted to the target population. Items and their possible answers will be collectively exhaustive, mutually exclusive, brief and easy to understand, avoiding negative forms and the use of the question 'Why'. No questions will be formulated in such a way that one of the answers is so desirable that it can hardly be rejected. Likewise, we will avoid questions that require calculations or recall effort. Possible biases (central tendency error, social desirability, learning or proximity bias, logical error and information collection bias) will be monitored. A control type item will be introduced to verify, as far as possible, the consistency of the responses obtained. Two expert psychologists in questionnaire design will review the items against the recommendations.

Determination of the number of items in the questionnaire

In the initial phase of questionnaire development, it is recommended to include twice as many items as those that will make it into the final version, with a minimum of 6 and a maximum of 90. Each dimension should have a minimum of three items.

Logical ordering of the items

The items will be ordered by dimension and type of response, placing the most conflictive or direct items at the end of the questionnaire.

Coding of the item responses

We will choose the most appropriate response scale (dichotomous, multiple choice or Likert), and scoring system (simple or weighted) for each item.

Development of questionnaire instructions

The instructions for the questionnaire will appear above the items, with an explanation of how the patient should complete the responses in language that is understandable to patients of any cultural level.

Expert assessment: content validity

Subsequently, the questionnaire will be reviewed by two experts in the design and validation of questionnaires as well as two experts in CVD who did not participate in the questionnaire design; their recommendations will be used to eliminate irrelevant aspects, add other essential concepts and/or modify the existing items when needed. The experts will be invited to make a qualitative assessment of each item (representativeness of the dimension, relevance, clarity and comprehensibility), of the response options and the order and structure of the complete content of the questionnaire. The researchers will review each of the items in light of the experts' suggestions as long as at least two of them do not answer that they 'agree' on what is being asked.

Assessment of understandability

Individual interviews will be carried out with patients with the same profile as the target population in order to

identify the most appropriate types of questions, identify correct and understandable statements, adjust the length of the questions, identify psychological resistance to some questions, determine whether the internal ordering is logical and assess whether the overall length of the questionnaire is acceptable.

PHASE 2: FINAL DESIGN AND VALIDATION OF THE QUESTIONNAIRE (FROM OCTOBER 2022 TO SEPTEMBER 2024)

Study design and population

A descriptive, cross-sectional observational study will be performed to validate the questionnaire, using a direct method as a gold standard adherence measure. This multicentre study will be carried out in the hospital setting for 24 months. The study population will be recruited from the cardiology service of four hospitals in Spain (in San Juan de Alicante, Elda, Alicante and Madrid).

Eligible patients will be adults (≥18 years) with a diagnosis of acute coronary syndrome who have been undergoing treatment for at least the last 12 months with the drugs recommended for secondary prevention of CVD (at least acetylsalicylic acid (ASA), atorvastatin or rosuvastatin), and who understand and speak Spanish. Exclusion criteria will be treatment interruptions in the last 12 months, a neurological or psychological condition that prevents the completion of questionnaires, life expectancy of less than 1 year, a disease that affects the capacity for self-assessment, disease-related or physical circumstances that may affect their adherence and/or having problems reading or writing.

Participant selection and data collection

The researchers from the cardiology services will be responsible for recruitment, participant inclusion and data collection during their daily clinical practice. Sample selection will be carried out consecutively among patients attending the cardiology clinic for a follow-up visit during the inclusion period. The researchers will explain the purpose of the study to eligible patients and invite them to take part. After the patient and the researcher sign informed consent, the following data will be collected as detailed as follows.

- Sociodemographic variables and information on medication-taking behaviour will be collected through a self-administered ad-hoc form.
- Variables on medical history, treatments and clinical variables will be collected through a review of the patient's electronic medical record.
- The patient will be asked to complete our proposed adherence questionnaire in Spanish, plus the eight-item Morisky Medication Adherence Scale (MMAS-8),[33 34–36] validated in Spanish, and the Haynes-Sackett[30] questionnaire.
- Gold-standard adherence test: the patient's blood will be extracted in the clinic on the same day of study inclusion by the research staff for the subsequent analysis of ASA and statin concentrations (atorvastatin or rosuvastatin).

All information will be collected anonymously, with a code generated for each patient.

Processing, storage and sample analysis

Three EDTA-K2 tubes (4 mL) of blood, previously chilled in an ice bath, will be drawn from each patient and gently inverted eight times. The tubes will be kept cold with an ice bath (2°C to 8°C) until centrifugation. Within 15 min of extraction, they must be centrifuged at 3000 rpm (1000 g) for 10 min at 4°C.

Within 20 min (maximum) after centrifugation, 2.5 mL plasma will be separated and extracted from the tube for ASA determination, into a tube previously cooled in an ice bath and containing 250 µL of 1 mol/litr hydrochloric acid (HCl 1N). The acidified plasma will be mixed gently for 5 s, divided into two tubes of 1 mL aliquots, identified with the patient number (first aliquot and backup). These tubes will be stored at −80°C.

Within 15 min (maximum) after centrifugation, plasma will be separated and extracted from the tube for statin determination, into two aliquots of 1 mL each (two tubes identified with the patient number and differentiating the first aliquot from the backup). Both tubes will be stored at −80°C. Therefore, in total, four tubes per patient will be stored—the respective first aliquots and backup aliquots for ASA and statin determination. At the end of the inclusion period or when the maximum storage limit set by each centre is reached, the samples will be sent to the contracted laboratory for analysis. The frozen tubes will be sent in dry ice containers together with the technical data sheet.

An external national laboratory will perform the analysis of drug plasma levels. The determination of ASA will be carried out by means of partial validation of an analytical method for ASA measurement in human plasma samples by LC-MS/MS (liquid chromatography coupled with tandem mass spectrometry (triple quadrupole) with electrospray probe). For the statins, determination will be performed using liquid chromatography coupled with tandem mass spectrometry (triple quadrupole) with ESI probe in multiple reaction monitoring detection mode (UHPLC-MS/MS).

Study variables

- Results for each item of the proposed adherence questionnaire.
- Gold standard test results: concentration of ASA and statins in the patient's blood. Based on theoretically calculated range of plasma drug concentration at steady-state condition, patients will be categorised into three different levels of adherence: fully adherent (within the range), partially adherent (below or above the range) or non-adherent (not detectable).
- Outcomes of the MMAS-8 questionnaire: level of adherence to medication

- Outcomes of the Haynes-Sackett questionnaire: level of adherence to medication.
- Sociodemographic variables: sex, age, country of origin, educational level, current employment situation, marital status, zip code, net household income, household unit, caregiver, independence in the basic activities of daily living and self-perceived health.
- Health-related behaviours: tobacco, alcohol, special diet, main daily activity and physical activity in leisure time.
- History of disease: date of diagnosis of acute coronary syndrome, type of event in the first episode, number of episodes, revascularisation, weight, height, blood pressure, heart rate, cardiovascular risk factors, other CVDs, comorbidities, type of cardiovascular medication that the patient takes, other treatments, date when ASA treatment began and dose prescribed, date when current statin treatment began and dose prescribed, modification of statin or ASA regimen treatment during the last month adherence as perceived by the cardiologist.
- Medication intake: person in charge of administering the patient's medication, number of pills per day, number of doses per day and approximate time of taking medication (ASA and statin).

Sample size calculation

According to Costello and Osborne,[37] a minimum correct factorial structure of 70% is empirically obtained with 20 participants per questionnaire item. Therefore, the final sample will be a minimum of 20 participants per item, plus 10% to account for losses. We estimate a maximum of 20 items in the questionnaire, so at least 440 patients are required. In order for the questionnaire to adequately represent both men and women and to include the gender perspective, patients will be included until the proportion of men and women is similar and the calculated minimum is achieved.

Pilot study

A pilot study with 40 patients (20 women and 20 men) from a single-study centre will be conducted to test the entire research process, from patient enrolment to validation analysis in order to detect potential errors or unexpected problems.

Statistical analysis

From the set of preselected items in the questionnaire design stage, the items most closely associated with the gold standard measure (max. 20 items) will be selected using multivariate statistical techniques. In this selection, the specific weights of each item by gender will be taken into account.

A descriptive analysis of the different variables will be performed to characterise the sample. Categorical variables will be described using absolute and relative frequencies, and quantitative variables using means, SD and range. A separate analysis will be carried out by gender.

The following tests will be performed to validate the questionnaire:

- Reliability: internal consistency will be measured using the McDonald Omega coefficient and its 95% CI for all the items and for each dimension. Temporal stability will be measured using a test–retest of 50 randomly selected participants and calculated using the intraclass correlation coefficient of the total score along with its 95% CI.
- Validity: content validity will have been assessed at the end of the questionnaire design phase. Construct validity will be measured through an exploratory and confirmatory factor analysis, using polychoric matrices for categorical items. The sample will be equally divided into two subsamples: the exploratory analysis will be carried out in an adjustment sample and the confirmatory analysis in the other test sample. Criterion validity will be measured by comparing the scores of the items with the gold standard, that is, the concentration of the active principle of ASA and statins. Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, overall hit and error rate and the area under the receiver operating characteristic curve will be calculated.

To assess the gender perspective, the gender variable will be taken into account as a weighting variable in the calculation of the total score of the questionnaire, which will be calculated based on the specific scores of each item using weighted sums or another function, as appropriate. An optimal cut-off point for the total score will be determined to define adherence, optimising validity parameters against the gold standard.

To determine patients' adherence profile according to the classification obtained by the questionnaire and the categorical explanatory variables, 2×2 tables will be constructed and the χ^2 test applied. For quantitative variables, student's t test or Mann-Whitney U test will be used, as appropriate. A multivariable logistic regression model will be fitted to assess the OR for low adherence and its 95% CI according to the explanatory variables. The results of the MMAS-8 and Haynes-Sackett adherence questionnaires will be compared with the gold standard (direct method), calculating predictive indicators.

Patient and public involvement statement

None

DISCUSSION

This project could produce a simple, freely accessible questionnaire, with better predictive values than existing questionnaires and validated in patients with ischaemic heart disease. The questionnaire would also take into account the gender perspective, since none of the tools currently available to measure medication adherence are

optimal, allowing an exact assessment that is sensitive to differences between genders.[28] This questionnaire could be used by family physicians, cardiologists, the pharmaceutical industry, pharmacists, nurses, psychologists, and the scientific community in general.

A number of questionnaires have been developed to measure medication adherence in patients with chronic diseases. The MMAS-8,[34] Haynes-Sackett test,[30] Maastricht Utrecht Adherence in Hypertension questionnaire,[38] Martin-Bayarre-Grau scale,[39] Hill-Bone scale,[40] VOILS questionnaire,[41] Battle test[42] and Hermes test[43] were all initially designed and validated for hypertensive patients. In addition, the Self-Efficacy for Appropriate Medication Use Scale[44] was designed for patients with coronary disease, the Adherence to Refill and Medication Scale[45] for multimorbid patients and the Beliefs about Medicines Questionnaire (BMQ)[46] for assessing patients' beliefs about medication and how these influence on adherence to medication. Subsequently, some of these questionnaires have been validated in other populations, obtaining different predictive values, specificity and sensitivity for each type of disease or country. Each questionnaire provides different information, some more focused on the patient's behaviour in terms of taking medication and others more focused on beliefs about medication adherence.[47] Therefore, depending on the type of patient and the type of information needed, one or the other can be used.[5] All these questionnaires are based on self-report, and none have used a direct method as the gold standard to analyse criterion validity, nor have they taken into account the gender perspective during their design as we do. Furthermore, some of them are not freely accessible.

Using the new questionnaire that will be developed in our study, the health professional could assess the degree of adherence in patients with ischaemic heart disease and could direct their efforts at reinforcement to those who present a low adherence profile, anticipating future events and improving the patient's quality of life. In short, knowing if a patient with ischaemic heart disease adheres to their treatment can help healthcare professionals identify the causes of the lack of adherence and try to correct them, which will allow better control of their risk factors and avoid possible complications.

The main strengths of this study on the design and validation of a medication adherence questionnaire are as follows: it will take into account the main international recommendations for questionnaire design; it will involve both health professionals and patients in the design process; it will use a direct method as a reference standard to assess the criterion validity and it will take into account the gender perspective, both in the questionnaire design and validation stages.

Regarding the limitations, there is a chance that the criteria of consulted experts will be heterogeneous and any relevant issue could not be included in the questionnaire. Other limitations include those common to self-completed questionnaires in general (if they end up being completed in this way), such as the inability to clarify questions or answers that can lead to misunderstandings, the reading ability of the patients that can generate comprehension problems, the occasional forgetting of any of the questions asked and the conditioning of responses by the patient's state of mind at the time of the interview. To control for this variability, the questionnaire instructions will be short and precise, and the items will be well defined in an operational manner, with clear and unambiguous language, avoiding wording that leads to biased responses and ordered in a controlled manner. In addition, the gold standard test result will be limited to a certain time window when analysing the plasma concentration of the drug; therefore, there may be a possibility that a patient who takes the medication correctly could be considered non-adherent or partially adherent. Desirability bias will be controlled for by informing the patient that all the data and questionnaires that they complete will be anonymous, and they will fill in the questionnaire in a waiting room without the presence of healthcare personnel. Finally, there could be a selection bias if non-adherent patients tend not to accept the invitation to participate in the study.

Ethics and dissemination

All participants gave their written informed consent before participating in the study. The study protocol follows the recommendations of the Declaration of Helsinki and was approved by the ethics committees of the three participating centres. Only the investigators had access to the study data. The results of this study will be displayed at national and international conferences and in peer-reviewed scientific journals.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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REFERENCES

1 Bosworth HB, Granger BB, Mendys P, *et al*. Medication adherence: a call for action. *Am Heart J* 2011;162:412–24.
2 Haynes RB, McDonald H, Garg AX, *et al*. Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev* 2002:CD000011.
3 Fernandez-Lazaro CI, García-González JM, Adams DP, *et al*. Adherence to treatment and related factors among patients with chronic conditions in primary care: a cross-sectional study. *BMC Fam Pract* 2019;20:132.
4 World Health Organization. *Adherence to long term therapies: evidence for action*. Geneva: Ginebra.2004, 2003.
5 Vrijens B, De Geest S, Hughes DA, *et al*. A new Taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
6 Dilla T, Valladares A, Lizán L, *et al*. Adherencia Y Persistencia Terapéutica: Causas, Consecuencias Y Estrategias de Mejora [Treatment adherence and persistence: causes, consequences and improvement strategies]. *Atención Primaria* 2009;41:342–8.
7 Solera Camarasa G, Solera Albero J, Tárraga Marcos L, *et al*. Evaluación de la Efectividad del Farmacéutico en La Mejora de la Adherencia Terapéutica de Pacientes con diabetes mellitus Tipo 2: Revisión Sistemática Y meta-Análisis. *Med Gen Fam* 2018;7:60–5.
8 Orueta Sánchez R. Estrategias para Mejorar La Adherencia Terapéutica en Patologías Crónicas [strategies to improve therapeutic adherence in chronic diseases]. *Inf Ter Sist Nac Salud* 2005;29:40–8.
9 Núñez Montenegro AJ, Montiel Luque A, Martín Aurioles E, *et al*. Adherencia al Tratamiento en Pacientes Polimedicados Mayores de 65 Años con Prescripción Por Principio Activo [Adherence to treatment, by active ingredient, in patients over 65 years on multiple medication]. *Atención Primaria* 2014;46:238–45.
10 Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the Economics of noncompliance. *Room for Methodological Improvement Health Policy* 2002;59:65–94.
11 Murray MD, Morrow DG, Weiner M, *et al*. A conceptual framework to study medication adherence in older adults. *Am J Geriatr Pharmacother* 2004;2:36–43.
12 Roberts MC, Wheeler SB, Reeder-Hayes K. Racial/ethnic and socioeconomic disparities in endocrine therapy adherence in breast cancer: a systematic review. *Am J Public Health* 2015;105 Suppl 3(Suppl 3):e4–15.
13 Wu X-C, Lund MJ, Kimmick GG, *et al*. Influence of race, insurance, socioeconomic status, and hospital type on receipt of guideline-concordant adjuvant systemic therapy for Locoregional breast cancers. *J Clin Oncol* 2012;30:142–50.
14 Conthe P, Márquez Contreras E, Aliaga Pérez A, *et al*. Treatment compliance in chronic illness: Current situation and future perspectives. *Rev Clin Esp (Barc)* 2014;214:336–44.
15 Gagnon MD, Waltermaurer E, Martin A, *et al*. Patient beliefs have a greater impact than barriers on medication adherence in a community health center. *J Am Board Fam Med* 2017;30:331–6.
16 Yap AF, Thirumoorthy T, Kwan YH. Systematic review of the barriers affecting medication adherence in older adults. *Geriatr Gerontol Int* 2016;16:1093–101.
17 Soriano JB, Rojas-Rueda D, Alonso J, *et al*. Colaboradores de GBD en España; Lista de Colaboradores de GBD en España:. The burden of disease in Spain: results from the global burden of disease 2016. *Med Clin (Barc)* 2018;151:171–90.
18 Lobos Bejarano JM, Royo-Bordonada MA, Brotons C, *et al*. Comité Español Interdisciplinario para La Prevención cardiovascular (CEIPC). *Guía Europea de Prevención Cardiovascular En La Práctica Clínica Adaptación Española Del CEIPC 2008 [European Guidelines on Cardiovascular Disease Prevention in Clinical Practice CEIPC 2008 Spanish Adaptation] Aten Primaria* 2009.
19 Maiques Galán A, Broton Cuixart C, Villar Álvarez F, *et al*. Recomendaciones Preventivas Cardiovasculares.[Cardiovascular preventive recommendations]. *Aten Primaria* 2012;44:3–15.
20 Briffa TG, Hobbs MS, Tonkin A, *et al*. Population trends of recurrent coronary heart disease event rates remain high. *Circ Cardiovasc Qual Outcomes* 2011;4:107–13.
21 Chowdhury R, Khan H, Heydon E, *et al*. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–8.
22 Piepoli MF, Hoes AW, Agewall S, *et al*. European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for cardiovascular prevention & rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81.
23 Alianza C. Declaración de los pacientes respecto a la adherencia terapéutica.[Heart Alliance. Declaration of patients regarding therapeutic adherence], Available: https://cardioalianza.org/wp-content/uploads/2018/07/ [Accessed 20 Sep 2022].
24 Leslie KH, McCowan C, Pell JP. Adherence to cardiovascular medication: a review of systematic reviews. *J Public Health (Bangkok)* 2019;41:e84–94.
25 Quiles J, Miralles-Vicedo B. Estrategias de Prevención Secundaria del Síndrome Coronario Agudo [secondary prevention strategies for acute coronary syndrome]. *Revista Española de Cardiología* 2014;67:844–8.
26 Becerra V, Gracia A, Desai K, *et al*. Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a Polypill in the UK. *BMJ Open* 2015;5:e007111.
27 Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int* 2015;2015:217047.
28 López-Romero LA, Romero-Guevara SL, Parra DI, *et al*. Adherencia al Tratamiento: Concepto Y Medición [Adherence to treatment: concept and measurement]. *Hacia Promoc Salud* 2016;117–37.
29 Chen SL, Lee WL, Liang T, *et al*. Factors associated with gender differences in medication adherence: a longitudinal study. *J Adv Nurs* 2014;70:2031–40.
30 Sackett DL, Haynes RB, Gibson ES, *et al*. Patient compliance with antihypertensive regimens. *Patient Couns Health Educ* 1978;1:18–21.
31 Culig J, Leppée M. From Morisky to hill-bone; self-reports scales for measuring adherence to medication. *Coll Antropol* 2014;38:55–62.
32 Standards for educational and psychological testing. In: *National Council on Measurement in Education*. Lanham, MD: American Educational Research Association, 2014.
33 Morisky DE, Ang A, Krousel-Wood M, *et al*. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)* 2008;10:348–54.
34 Bress AP, Bellows BK, King JB, *et al*. Cost-effectiveness of intensive versus standard blood-pressure control. *N Engl J Med* 2017;377:745–55.

35 Berlowitz DR, Foy CG, Kazis LE, *et al*. Effect of intensive blood-pressure treatment on patient-reported outcomes. *N Engl J Med* 2017;377:733–44.
36 Martinez-Perez P, Orozco-Beltrán D, Pomares-Gomez F, *et al*. Validation and Psychometric properties of the 8-item Morisky medication adherence scale (MMAS-8) in type 2 diabetes patients in Spain. *Aten Primaria* 2021;53:101942.
37 Costello AB, Osborne J. Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. *Practical Assessment, Research, and Evaluation* 2005;10.
38 Wetzels G, Nelemans P, van Wijk B, *et al*. Determinants of poor adherence in hypertensive patients: development and validation of the "maastricht utrecht adherence in hypertension (MUAH)-questionnaire." *Patient Educ Couns* 2006;64:151–8.
39 Alfonso LM, Bayarre HD, Grau Abalo JA. Validation of MBG questionnaire for the evaluation of therapy adherence in blood hypertension patients. *Rev Cubana Salud Pública* 2008;34.
40 Kim MT, Hill MN, Bone LR, *et al*. Development and testing of the hill-bone compliance to high blood pressure therapy scale. *Prog Cardiovasc Nurs* 2000;15:90–6.
41 Voils CI, Maciejewski ML, Hoyle RH, *et al*. Initial validation of a self-report measure of the extent of and reasons for medication Nonadherence. *Med Care* 2012;50:1013–9.
42 Batalla Martínez C, Blanquer Laguarta A, Ciurana Misol R, *et al*. Cumplimiento de la Prescripción Farmacológica en Pacientes Hipertensos. [compliance with the pharmacological prescription in hypertensive patients]. *Aten Prim* 1984;185–91.
43 Jabary NS, Castrodeza J, Monfa JM, *et al*. Validación de UN Nuevo test para Determinar El Cumplimiento Terapéutico en Pacientes Hipertensos[Screening tests for measuring adherence used in clinical practice]. *Hipertensión* 1999;16:298–303.
44 Risser J, Jacobson TA, Kripalani S. Development and Psychometric evaluation of the Self- efficacy for appropriate medication use scale (SEAMS) in low-literacy patients with chronic disease. *J Nurs Meas* 2007;15:203–19.
45 Kripalani S, Risser J, Gatti ME, *et al*. Development and evaluation of the adherence to Refills and medications scale (ARMS) among low-literacy patients with chronic disease. *Value Health* 2009;12:118–23.
46 Svarstad BL, Chewning BA, Sleath BL, *et al*. The brief. medication questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient Education and Counseling* 1999;37:113–24.
47 Nguyen T-M-U, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. *Br J Clin Pharmacol* 2014;77:427–45.