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Statins in Primary Prevention of Cardiovascular Disease: Incidence of Potentially Inappropriate Prescriptions in Very Low Risk Primary Care Patients and Associated Factors

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Abstract

Objective: To quantify and characterize the initiation of Potentially Inappropriate Prescription (PIP) of statins in primary prevention of Cardiovascular Disease (CVD) in patients with low cardiovascular risk in the Basque Health Service (Osakidetza) by estimating the annual incidence rate and identifying the associated clinical and socio-demographic factors.

Methods: Analytical retrospective observational study on the incidence of PIP of statins and provision of advice for changing lifestyles in 2018. Patients aged 40 to 75 years with cardiovascular risk <5% (REGICOR) and LDL-cholesterol levels between 70 and 189 mg/dl and/or Total Cholesterol (TC) between 200 and 289 mg/dl. Sociodemographic and clinical characteristics and deprivation index were evaluated. Global incidence, factors associated with PIP and the variability between Integrated Health Organizations (IHOs) were analyzed.

Results: 70,526 people met the selection criteria. Of them, 741 started a PIP for statins with an overall incidence of 10.5 prescriptions per 1,000 person-years (ranging in IHOs from 2.3 to 18.0). Less than 40% of these people received preventive advice on physical activity and diet and approximately 50% received advice on cessation of smoking. PIPs were higher in men (RR 1.36), people with arterial hypertension (RR 1.86) and other comorbidities (RR 3.93 if ≥ 5 comorbidities); PIPs also increased with age (RR 1.02 per year) and TC levels (RR 1.21 per 10mg/of the increase).

Conclusion: This study shows that practice in primary CVD prevention in low-risk primary care patients does not seem to follow the recommendations of current guidelines. It is necessary to identify determinants associated with this low-value practice in order to inform the design and implementation of strategies to favor its abandonment.

Keywords: Cardiovascular disease • Primary prevention • Low-value practice • Potentially inappropriate prescription • Statins • Primary care

Abbreviations: CVD: Cardiovascular Disease; CVR: Cardiovascular Risk; TC: Total Cholesterol; LDL-C: LDL Cholesterol; PIP: Potentially Inappropriate Prescription; IHO: Integrated Health Organization; RR: Relative Risk

Introduction

Health care quality can be defined as the degree to which the health care delivered services increase the probability of obtaining the desired health results and are consistent with current knowledge [1]. However, a considerable number of patients receive interventions without adequate prior evaluation of their safety, effectiveness or cost-effectiveness [2,3]. Consequently, patients may receive inappropriate care, with non-beneficial or even harmful interventions [4]. In 2011, it was estimated that up to 30% of medical practices in the US could be classified as low-value practices, with a cost of between 158 and 226 billion dollars [2]. In addition to the financial cost, low-value practices have various negative physical and emotional consequences [5]. Therefore, a strategy aimed at improving the health of the population, promoting an efficient use of resources and minimizing damage must address the option of abandoning interventions whose benefit has not been demonstrated and/or adapt them in terms of their form of administration, targeting a population where the benefit/risk ratio is appropriate [6].

A growing interest in the study of low-value practices has been observed with the emergence of initiatives that encourage their identification, reduction and/or optimization, such as the "Choosing Wisely" programme, present in 12 countries, or the NICE "Do not do" initiative in the United Kingdom [7-10]. In Spain, several initiatives have been launched, for example the "Commitment to the Quality of Scientific Associations in Spain" project of the Ministry of Health, Social Services and Equality and the MAPAC initiative to Improve Care and Clinical Practice, with its "DianaSalud" ('Diana Health') website [11,12].

Cardiovascular disease (CVD) is one of the main causes of premature death in Europe, accounting for 42% of deaths in women and 38% in men under 75 years of age, and its great frequency and impact have stimulated the development of preventive programmes [13]. Clinical practice guidelines rec-

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ommend a global approach, using the concept of cardiovascular risk (CVR), or the probability of developing a cardiovascular event over a given period of time (generally 10 years) based on the combined levels of various well-established risk factors. Additionally, a series of CVR prediction equations have been developed and validated, recommending that preventive and/or therapeutic decisions be based on these estimates. They also recommend the promotion of healthy lifestyles as the first option in patients with low CVR (<10%) and as a follow-up measure to a pharmacological approach to risk factors in people with a CVR of ≥ 10% [14-17]. One of the risk factors included in these equations is the presence of hyperlipidemia and, specifically, high levels of total cholesterol (TC) and/or LDL cholesterol (LDL-C). Although there is general agreement on the indication of lipid-lowering treatment, mainly with statins, in patients with a CVR measurement greater than 10% over 10 years or in secondary prevention, there is some controversy regarding the use of these drugs in primary prevention. Especially in cases with low CVR, a possible excessive emphasis on the weight assigned to cholesterol levels in isolation without considering CVR as a whole, has been postulated [18]. Consequently, the prescription of lipid-lowering drugs and, more specifically, of statins, has increased notably. In the Basque Health Service (Osakidetza), the consumption of these drugs grew by 93% between 2006 and 2013, increasing from 46 DHD (defined daily doses per 1,000 person-days) in 2006 to 90 DHD in 2013. Statins constituted 90% of these lipid-lowering drugs in 2013, with a cost of more than 35 million euros for the Basque Health Service [19].

There is evidence showing that statins are effective and offer clear benefits in specific population groups (in secondary prevention or those who present a 10-year CVR higher than 15%) [20]. However, there is insufficient evidence to support statin therapy in primary prevention of CVD [21,22]. Furthermore, the promotion of healthy lifestyles through diet, physical activity and cessation of smoking should remain the preferred practice. Therefore, the pharmacological prescription of statins in primary prevention of CVD in patients with low cardiovascular risk can be considered a potentially inappropriate prescription (PIP).

There are few studies that have evaluated the practice of prescribing statins in low-risk populations. A study carried out in the United Kingdom looked at the relationship between having a statin prescription and a CVR record, and found that the majority of people who started a prescription did not have their CVR assessed [23]. In addition, one out of every six people in whom a prescription was started after a CVR calculation had a low risk value. Moreover, other authors who analyzed the characteristics of patients who receive statin prescriptions in primary prevention according to their CVR found even higher figures, with 24.3% of prescriptions in the low-risk population (<10%) [24]. However, these studies were carried out in an epidemiological context that is different from ours, using a different risk measurement tool, the QRISK, so it is necessary to have specific data that provides information on the magnitude and characteristics of the problem in our area. The general objective of this study is to identify and characterize a clinical practice of potentially low value in the primary prevention of CVD in our healthcare context, specifically the initiation of PIP of statins in people with very low overall CVR and moderately high cholesterol levels.

The specific objectives are:

1. To determine the incidence of the PIP of statins in CVD primary prevention in a population with very low cardiovascular risk (risk <5% estimated by REGICOR) with moderately high cholesterol attended in the Basque Health Service in 2018.
2. To quantify the proportion of these people who have not received a recommendation for the promotion of healthy lifestyles: physical activity, diet and smoking cessation.
3. To describe the variability in this PIP pattern among the Integrated Health Organizations (IHOs: equivalent to regional healthcare organizations with comprehensive management of the different levels of health care in a geographical area) of our regional health system.
4. To explore factors associated with the start of statin PIP in primary prevention of CVD in this very low-risk population.
5. To quantify the proportion that these newly identified PIPs represent out of the total number of possible new PIPs for statins in primary prevention in 2018.

Methods

Study design

A descriptive analytical retrospective observational study was carried out on the incidence rate of statin PIPs and the provision of healthy lifestyle advice in patients with very low CVR (REGICOR) and moderately high cholesterol levels. This study is part of the project De-implementation of low-value pharmacological prescriptions 'DE-imFAR', whose objective is to design, evaluate and implement feasible and effective strategies to favor the de-implementation of low-value practices using a methodology based on scientific evidence and behavioral change models within the framework of implementation science [25].

Study population

A population in which no evidence-based recommendation promotes the use of statins for preventive purposes was selected [14-17]. The study population is made up of men aged 40-74 years and women aged 45-74 years, without known CVD, without a previous registered prescription of statins and: a) with a CVR measurement registered in 2018 in the electronic medical record; b) moderately high LDL-C levels in the 70-189 mg/dl range and/or TC of 200-289 mg/dl in the period between two years before and six months after that CVR measurement; and c) an estimated CVR <5%, according to the REGICOR scale in 2018 and in all CVR measured in the two previous years or six months after [16]. Those people with a) LDL-C levels greater than or equal to 190 mg/dl and/or TC at 290 mg/dl and/or b) with a family history of dyslipidemia (familial hypercholesterolemia or other dyslipidemias of genetic origin) were excluded.

Information sources

The data was extracted from the electronic information systems of the Basque Health Service; the OSABIDE electronic clinical record for information on clinical practice and the PRESBIDE electronic prescription system. In 2015, the PRESBIDE system grouped and integrated all the healthcare system prescriptions, both at the primary and specialized care levels. The Bizkaia Primary Care Research Unit is formally authorized by the Osakidetza Health Directorate for the extraction and use of data from these electronic medical records for research purposes.

Variables and definitions

CVR reference measurement: CVR measurement recorded in OSABIDE in 2018, on the occasion of a visit to the general practitioner. Given that the Basque Health Service protocol for periodic preventive evaluations in this population recommends a periodic assessment of CVR and a biannual assessment of lifestyles, and also to rule out a measurement or recording error, any record of CVR in this population during the two years before and six months after the CVR index measurement was also identified.

Very low cardiovascular risk: one or more measurements recorded in 2018 with a <5% estimated risk according to the REGICOR scale. If there was a record of CVR in the two previous years or six months after, all must have been <5%.

Incidental statin PIP: start of a statin prescription registered in the PRESBIDE system between January 1st 2018 and December 31st 2018 in people: a) without CVD, b) without any measurement of ≥ 5% CVR for two years before and six months after the start of prescription and c) without any measurement of TC ≥ 290 mg/dl or LDL-C ≥ 190 mg/dl in the same period of time. In our study population, we focused on those people who also had at least one CVR measurement in 2018. The incidence rate was calculated as the proportion of patients in the study population with a record of incidental statin PIP.

Lifestyle modification advice: any recommended activity (physical activity, diet or smoking cessation) registered in OSABIDE two years before or six months after the CVR reference measurement date of each person. Since the time relationship between CVR measurement, advice to promote healthy lifestyles and prescription of statins can vary (for example, concurrent registration of CVR and advice and/or prescription, or advice and/or prescription before or after registration of CVR), a time window was used that encompassed the practice records on advice for healthy lifestyles and measurement of CVR and cholesterol levels between two years before and six months after the year of study, 2018.

The additional variables obtained from OSABIDE were sociodemographic variables (gender and age), clinical variables (TC and LDL-C levels, diagnosis of arterial hypertension, number of chronic diseases and smoking habit) and the MEDEA deprivation index [26].

Statistical analysis

Firstly, a descriptive analysis of the study population was carried out based on its sociodemographic and clinical characteristics and the deprivation index. Subsequently, the incidence of statin PIPs in this population was analyzed globally and in each of the 13 IHOs, as well as the proportion of cases in which a recommendation was prescribed to promote healthy lifestyles (physical activity, healthy diet and smoking cessation). In addition, the factors associated with the start of PIP in the study population were explored through a mixed log-binomial model that took into account the correlation between patients in each IHO (PROC GLIMMIX). Using an empirical Bayesian approach, the differences in the incidence of PIP between the different IHOs were estimated. All estimators were exponentiated to express the results as Relative Risk (RR), and 95% confidence intervals were calculated [27].

To estimate the relative magnitude of the incident PIPs identified by our population selection strategy with respect to all new prescriptions of statins in primary prevention in 2018 in the Basque Health Service, an additional search for new statin prescriptions was carried out in the PRESBIDE system in the same population. All the statistical analyses were carried out using the SAS 9.4 programme (SAS Institute Inc., Cary, NC, USA).

Ethics

The DE-imFAR study was reviewed and approved by the Basque Ethics Committee for Drug Research-CEIm (PI2019102, approved on 04/10/2019). At all times, the legal and ethical requirements for anonymity and confidentiality established by the Organic Law on the Protection of Personal Data (3/2018 of December 5, LOPD) were guaranteed. The study was carried out in accordance with the principles of the Declaration of Helsinki. The inclusion in the study of the cohort of individuals does not involve any new diagnostic or therapeutic practice, which is why the Basque drugs research ethics committee approved the exemption from the request for informed consent.

Results

Incidence

There were 70,526 people who met the selection criteria. Of them, 741 started a statin PPI in 2018, with an overall incidence of 10.5 prescriptions per 1,000 person-years. This incidence varied among IHOs with a range of 2.1 to 18.0 prescriptions per 1,000 person-years (Table 1).

Sociodemographic characteristics of the study population

Table 2 describes the profile of the population that received a new

Table 1. Incidence of potentially inappropriate prescription (PIP) of statins in very low estimated cardiovascular risk primary care patients in 2018.

	Incidence	
Integrated Healthcare Organization (IHO)	**Without statin prescription**	**With statin PIP**
	N (%)	**N (%)**
IHO 12	2521 (99.8)	6 (0.2)
IHO 11	3407 (99.8)	8 (0.2)
IHO 8	2608 (99.5)	12 (0.5)
IHO 6	2405 (99.4)	15 (0.6)
IHO 9	13151 (99.3)	89 (0.7)
IHO 1	1743 (99.2)	14 (0.8)
IHO 2	6848 (99.2)	58 (0.8)
IHO 10	5430 (98.9)	59 (1.1)
IHO 4	3172 (98.7)	40 (1.3)
IHO 5	9566 (98.6)	134 (1.4)
IHO 7	12328 (98.5)	185 (1.5)
IHO 3	242 (98.4)	4 (1.6)
IHO 13	6365 (98.2)	117 (1.8)
Total	69785 (98.9)	741 (1.1)

Table 2. Sociodemographic and clinical characteristics of primary care patients with very low estimated cardiovascular risk, according to whether or not a new potentially inappropriate prescription (PIP) of statins was prescribed.

	Without Statin Prescription (N = 69785)	**With Statin PIP (N = 741)**	**Total (N = 70526)**
Gender (N. %)			
Woman	42089 (60.3)	468 (63.2)	42557 (60.3)
Age (years) [a]	56.2 (9.2)	59.1 (8.9)	56.3 (9.2)
Level of cholesterol (mg/dl) [a]	211.6 (32.1)	231.9 (38.9)	211.8 (32.3)
Deprivation index - quintile (N.%) [b]			
1	14386 (20.7)	183 (24.9)	14569 (20.7)
2	15468 (22.2)	159 (21.7)	15627 (22.2)

3	14874 (21.4)	132 (18.0)	15006 (21.3)
4	12991 (18.7)	143 (19.5)	13134 (18.7)
5	11876 (17.1)	117 (15.9)	11993 (17.0)
Smoker (N. %)			
Yes	11442 (16.4)	126 (17.0)	11568 (16.4)
Ex	12713 (18.2)	147 (19.7)	12860 (18.2)
No	45600 (65.4)	467 (63.1)	46067 (65.4)
Number of chronic diseases (N. %)			
0	16736 (24.0)	62 (8.4)	16798 (23.8)
1-2	36403 (52.2)	400 (54.0)	36803 (52.2)
3-4	14576(20.9)	239 (32.3)	14815 (21.0)
>5	2070 (3.0)	40 (5.4)	2110 (3.0)
Hypertension (N. %)			
Yes	23789 (34.1)	378 (51.0)	24167 (34.3)
No	45996 (65.9)	363 (49.0)	46359 (65.7)

[a] Mean (SD); [b] Deprivation index: quintile 5 identifies people who live in an area with lower socioeconomic level and with less access to services.

Table 3. Proportion of patients with a potentially inappropriate prescription (PIP) of statins who received a preventive advice on physical activity, healthy diet and smoking cessation by Integrated Health Organization (N = 741).

Integrated Healthcare Organization (IHO)	People with Potentially Inappropriate Prescription who were recommended		
	Physical activity	Healthy diet	Cessation of smoking
	N (%)	N (%)	N (%)
IHO 12	3 (50.0)	3 (50.0)	4 (57.1)
IHO 11	6 (75.0)	6 (75.0)	6 (75.0)
IHO 8	5 (41.7)	4 (33.3)	7 (58.3)
IHO 6	4 (26.7)	4 (26.7)	5 (33.3)
IHO 9	29 (32.6)	28 (31.5)	40 (44.9)
IHO 1	4 (28.6)	4 (28.6)	5 (35.7)
IHO 2	16 (27.6)	14 (24.1)	22 (37.9)
IHO 10	22 (37.3)	21(35.6)	33 (55.9)
IHO 4	14 (35.0)	14 (35.0)	20 (50.0)
IHO 5	59 (44.0)	56 (41.8)	71 (53.0)
IHO 7	70 (37.8)	63 (34.1)	91 (49.2)
IHO 3	2 (50.0)	2 (50.0)	4 (100.00)
IHO 13	47 (40.2)	46 (39.3)	60 (51.3)
Total	281 (37.9)	265 (35.8)	367 (49.5)

prescription in 2018. The mean age of the population, with 60.3% women, is 56.2 years. The subgroup of patients starting PIP had a higher average age, cholesterol level and number of chronic diseases than the subgroup of patients without starting prescription. They also presented a greater active consumption of tobacco and diagnosis of arterial hypertension, but no differences were found in their level of deprivation.

Lifestyles

In Table 3, we can see that 37.9% and 35.8% of the patients in our study who started a statin PIP in 2018 had received preventive advice on physical activity and diet, respectively, from their health professionals between two years before and six months after the CVR measurement. The percentages vary between 24% and 75% in the different IHOs, but in only three of them they are all above 50%. Further, 49.5% of patients received preventive advice on smoking cessation, this being the most common advice both globally and in each of the IHOs.

Associated factors

The start of a statin PIP in our study population is associated with age, gender, total plasma cholesterol level, arterial hypertension, and number of chronic diseases (Table 4). It is seen that those who have a higher risk of receiving a PIP of statins are men (36% higher risk) and people with a diagnosis of high blood pressure (84% higher risk). The number of identified comorbidities increases the risk of receiving a new statin PIP. This risk also increases as the number of comorbidities rises: patients with one or two chronic diseases have double the risk than those who do not have any; those with between three and five registered health problems heighten the risk likelihood, reaching an increase of almost 3.2 times in those with more than five comorbidities. Likewise, a 10 mg/dl increase in cholesterol level (within the moderate hypercholesterolemia range of the study) is associated with a 21% increment in the risk that the doctor will start a statin PIP. Similarly, each year of increase in age is associated with a 1.4% increment in the probability of starting PIP.

Figure 1 shows the variability of the incidence of PIP between the different IHOs in the model adjusted for the above factors. Two of them show an RR that is significantly lower than the mean, while three are significantly higher.

The total number of new statin prescriptions in 2018 in primary prevention for men between 40-75 years and women between 45-75 years was 7,121. Of these, 2,947 (41.4%) could be considered potentially inappropriate as there was no measurement of CVR (≥ 5%) or cholesterol (TC ≥ 290 mg/dl, LDL-C ≥ 190 mg/dl) during the two years before and six months after the prescription date. This group of PIPs is made up, in addition to the 741 PIPs found in our study population, of 2,143 new prescriptions in people without CVR measurement in 2018 and by 63 new prescriptions in people with TC levels less than 200 mg/dl and/or LDL-C less than 70 mg/dl (upper limit of normality in our laboratories). Therefore, the PIPs identified in our study would account for 25.1% of all PIPs in 2018.

Table 4. Factors associated with the incidence of potentially inappropriate statin prescriptions in very low estimated cardiovascular risk primary care patients.

Associated factors	RR[a]	CI[b] 95%	*P*-value
Gender			
Woman	Ref	-	-
Man	1.36	1.16-1.59	<0.001
Age (years)	1.01	1.00-1.02	<0.001
Cholesterol level [c]	1.21	1.19-1.24	<0.001
Smoker			
No	Ref	-	-
Former	1.01	0.84-1.21	0.945
Yes	1.21	0.99-1.48	0.064
Hypertension			
No	Ref	-	-
Yes	1.84	1.58-2.14	<0.001
Number of chronic diseases			
0	Ref	-	-
1-2	2.40	1.84-3.15	<0.001
3-4-5	3.08	2.32 -4.10	<0.001
>5	3.19	2.13-4.78	<0.001
Deprivation index[d]			
5	Ref	-	-
1	1.26	0.99-1.60	0.062
2	1.10	0.86-1.40	0.468
3	1.08	0.84-1.38	0.569
4	1.21	0.94-1.54	0.135

Multiple multilevel log-binomial regression model with the following explanatory variables: gender, age, total cholesterol level, smoking habit, arterial hypertension, number of chronic diseases and deprivation index. [a]RR relative risk; [b]CI: confidence interval; [c]Plasma cholesterol level for every 10 mg/dL increase; [d]The last quintile (5) of the deprivation index has been used as the reference level for this factor in the analysis, identifying people who live in an area with the lowest socioeconomic level and with least access to services.

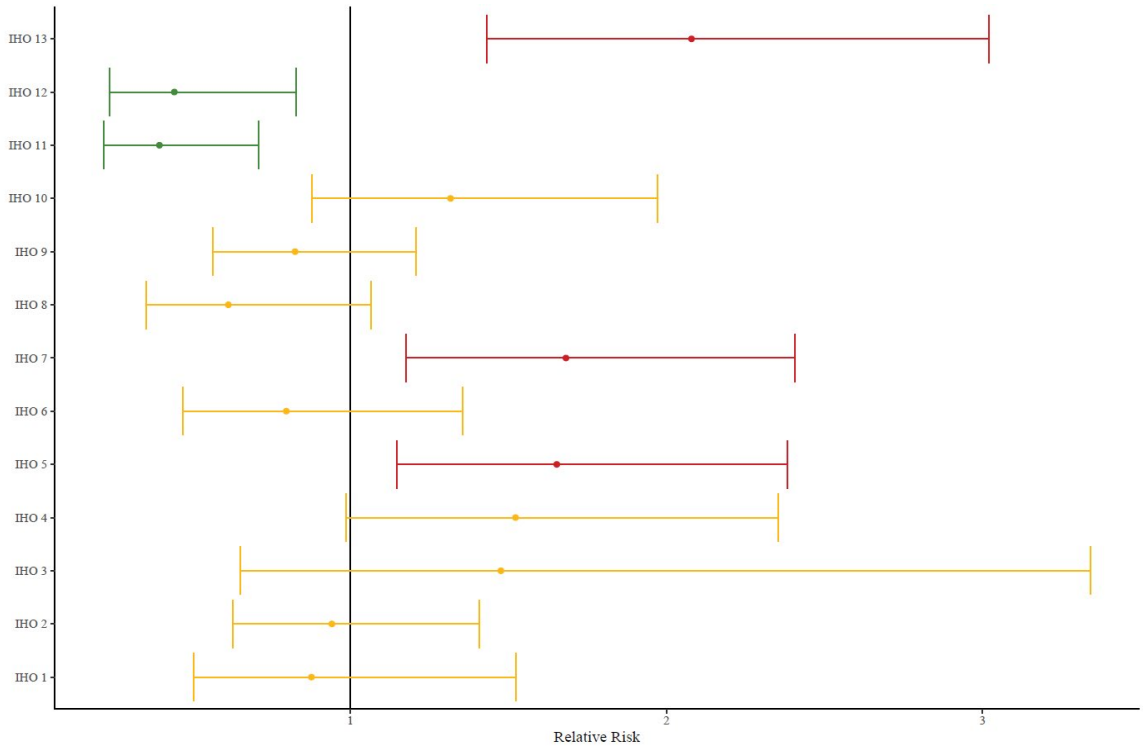

Figure 1. Variability in incidence of potentially inappropriate statin prescription among the different Integrated Health Organizations (IHO).

Discussion

Main findings

This study examined the magnitude and characteristics of the PIP of statins in primary prevention of CVD, in a scenario of less than 5% CVR and moderately elevated cholesterol, where the recommended preventive practice is the promotion of healthy lifestyles, based on a global assessment of CVR. An estimated incidence of 10.5 per 1,000 person-years (range in IHOs: 2.3 to 18.0 per 1,000 person-years) was identified in the Basque Health Service in 2018. Likewise, the advice on physical activity, diet and smoking cessation associated with these new prescriptions seems scarce, when the current

guidelines indicate that this should be the first preventive action to be carried out in a population with low CVR. Finally, factors associated with this PIP in the evaluated population were: being male, cholesterol level, the presence of arterial hypertension and comorbidities.

Comparison with literature

To date, there are some studies that have quantified statin prescriptions in primary prevention of CVD in different settings [23, 24]. However, they measured the prevalence of prescription in other populations, other study periods, and using different CVR measurement tools. Therefore, we cannot directly compare our results with these studies. Its authors have also identified practices of little value in the use of statins in primary prevention of CVD. For example, in a cohort in the United Kingdom, of 91,735 people considered to have low CVR (QRISK2 <10%), 2.7% (N=2,481) started a statin prescription in the period from 2012 to 2015 [23]. In another study, 3.7% (N=5,444/146,676) of patients with QRISK <10% had a statin prescription in 2014 in primary prevention. These prescriptions accounted for 24% of all prescriptions in primary prevention in the population with measured CVR [24].

Moreover, we observed that most patients with PIP do not received advice on promoting healthy lifestyles. Approximately half of them were advised to give up smoking, while in physical activity and a healthy diet the proportion that received advice is much lower still. In other words, in addition to receiving a potentially inappropriate pharmacological treatment, patients do not receive advice on changing their lifestyles, which represents the first-line preventive measure according to the guidelines of our health system [16]. No other studies that evaluate the frequency of advice to promote healthy lifestyles in a population with PIP have been found. A recent study carried out in Germany on the advice received on healthy lifestyles in primary and secondary prevention observed that in secondary prevention a greater number of people received advice on a healthy diet (73.1%) and physical activity (71.4%), compared with in primary prevention (43.9% in diet and 52.1% in physical activity). In contrast, a higher recommendation was made for smoking cessation in primary prevention (44.0%) compared to secondary prevention (36.7%) [28]. Therefore, advice on physical activity, healthy diet and smoking cessation is still scarce in primary prevention of CVD. According to the World Health Organization (WHO), with suitable changes in lifestyle, more than 75% of cardiovascular mortality could be prevented [13]. Population strategies for the general promotion of healthy lifestyles should be applied, with individualized advice when there is moderate to high risk of CVD or an established CVD [29].

The factors associated with PIP in our study generally coincide with those of other studies [24,30]. Regarding gender, although there are conflicting results in the literature both in our case and in the O'Keeffe study, a lower probability of receiving a PIP has been observed in women [30]. In contrast, other studies have found no association between gender and prescription [21,24]. In our study, we did not see a relationship between the deprivation index and PIP. Other authors have found differences, with a lower probability of receiving statins in the population with a higher socioeconomic level, corresponding to a lower rate of deprivation [31].

Strengths and Limitations

Information is provided on the magnitude and determinants of an under evaluated problem. We have adopted an approach based on the recommended practice of guiding primary prevention based on global estimates of CVR, rather than plasma cholesterol levels. In addition, our study simultaneously evaluates the pattern of provision of healthy lifestyle advice together with the start of statin PIPs and it is, to our knowledge, the first study with this approach. We have focused the study on the beginning of prescription, which makes it possible to identify more clearly a specific area susceptible to the implementation of educational strategies and other measures to match scientific evidence with actual practice.

As limitations, we highlight the use of secondary databases, which reflect the activity registration patterns of professionals in their healthcare practice. It is likely that, at the time of making the decision for a new prescription, there was additional information that was not recorded in the clinical information system. The same could be said of the record for the activity of providing advice on healthy lifestyles.

We evaluated the prescription practice over a year. To do so, based on the recommendations of periodic preventive evaluations of the Basque Health Service, we selected a window that includes two years before and six months after the CVR reference measurement or the beginning of the prescription. This decision was discussed and unanimously agreed on by the research team and could be different in other healthcare contexts. Finally, we did not evaluate professional practice factors such as perceived efficacy and safety of statins, attitude towards prevention, perception of risk, expectations and preferences of patients or the influence of other health professionals, which probably also influence prescription [32].

Recommendation for Future Studies

Additional research is needed on the multi-level determinants behind PIP of statins in low-risk patients, in order to propose specific implementation and de-implementation strategies to favor both the abandonment of low-value practices and the increase of recommended and evidence-based practices.

Conclusion

Our study has identified and quantified the start of statin treatment prescription for preventive purposes in a population with a very low risk of CVD, but with moderately high cholesterol levels. This clinical practice does not conform to the recommendations of the current evidence-based clinical practice guidelines for this population. Moreover, sociodemographic and clinical factors that significantly increase the probability of starting PIPs have been identified. The degree of recommendation of healthy lifestyles by primary care physicians is very low in this population, especially with regard to a healthy diet and physical exercise. There is significant variability in the pattern of initiation of PIPs in CVD primary prevention among the different health organizations that make up our public health system. Other additional groups of patients of similar age with the start of PIP of statin in the same study period were identified, and in these groups, CVR was not recorded or was recorded but is less than 5% at 10 years, with normal cholesterol levels in the year of the study.

Conflict of Interest

The authors declare there is no conflict of interest.

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Ethical Considerations

The study was authorized by the Basque Ethics Committee for Drug Research (CEIm) (Ref: PI2019102, approved on 10/04/2019). The study was carried out in accordance with the principles of the Declaration of Helsinki and it complies with the provisions of the Spanish Organic Law 3/2018, December 5th, on the Protection of Personal Data and Guarantee of Digital Rights. The Primary Care Research Unit of Bizkaia is explicitly authorized by the Healthcare Management of the Basque Health System to extract and use data from its electronic health records for research purposes.

Availability of Data and Materials

Since data supporting the present study will mostly concern to process and/or data from professionals of the Basque Health Service-Osakidetza, it will be only shared upon justified request to the study guarantors.

Authors' Contributions

AS, JIP and GG conceived the idea and are the study guarantors. They are primarily responsible for the study design and planning, as well as the funding obtained, and were responsible for project coordination and supervision, analysis and interpretation of results and manuscript preparation. UE, MMM, AG, IL and RS collaborated in the study design, and funding obtained, and was responsible for study coordination, interpretation of results and manuscript preparation. AS, JIP, UE and AG were responsible for the analysis of results and critically reviewing the manuscript. All authors have read and approved the final manuscript version submitted for publication.

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