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Magical numbers in pharmacological prevention of cardiovascular disease and fractures. A critical appraisal

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Summary

Objectives: To review the principles that sustain the most frequent pharmacological interventions in prevention of cardiovascular disease and osteoporosis directed towards healthy people. **Material and methods:** A review of original trials, meta-analyses and the main clinical guidelines and consensus related to the objectives of the study was performed. The selection of clinical trials was carried out from meta-analyses and clinical guidelines, and by a systematic follow-up of the abstracts from the most relevant publications. **Results:** No evidence that supporting preventive therapy of pre-hypertension, pre-diabetes or osteopenia was found. Nor was there evidence for the indiscriminate treatment of hypertensive and diabetes patients with no cardiovascular disease with statins. In fact, there is no basis to consider diabetes as a "coronary risk equivalent." The size of the global effect of statins is 1.6% (ARR, absolute risk reduction) in 4-5 years with regard to the incidence of coronary events. There is no evidence for the use of statins in healthy women or in patients above 70 years with no cardiovascular disease, as these agents have not shown any efficacy. Aspirin achieved a reduction of myocardial infarction in men in 0.8% in 5-6 years, and in the incidence of stroke in women in 0.2% in 10 years. There was a 0.3% increase of severe digestive hemorrhage and 0.1% in cerebral hemorrhage. In trials investigating diabetes patients, aspirin has not proved effective. The evidence regarding the prevention of fractures is not of sufficient quality. Primary prevention with anti-fracture drugs reduce the incidence of vertebral fractures, but do not clearly or consistently show a reduction in hip and other non-vertebral fractures. There is no data on women under 65 years of age. The evidence available does not support the reduction of blood pressure in diabetes patients below 130/80 mmHg and the general objective of 140/90 mmHg is really a prudent recommendation rather than solidly founded target. In primary prevention there is no evidence to justify the reduction of LDL-c levels below 130 or 115 mg/dL (3.4 or 3.0 mmol/L). There is evidence to reduce HbA1c levels below 6-6.5% against 7-8% which is associated with increased mortality. The use of risk tables to decide on treatment has not shown any clinical impact. The SCORE risk tables have not been validated in the Spanish population and should not be employed in patients above 65 years, as it loses its capacity to discriminate risk. In Spain, the REGICOR table which can be employed in patients up to 75 years has been validated in the Spanish population. **Conclusions:** Inadvertently one of the main ways in which modern society is medicalized is through the pharmacological intervention of healthy people with preventive goals. The use of criteria to initiate treatments based on an unclear and problematic concept of "high risk" and the insistence on attaining even lower therapeutic targets can potentially medicalize an ample group of the population with no solid scientific basis to support them. Physicians today should be aware of this problem and should show prudence in their practice.

Introduction

Within the wide context of preventive interventions the use of drugs in daily clinical practice is one of the most important measures employed by primary care physicians. With the exception of vaccines, oral anticonception, and folic acid, the majority of the preventive pharmacological interventions on healthy people focus on cardiovascular disease with the use of anti-hypertensive agents, lipid-lowering drugs or antiplatelet therapy and on the prevention of fractures related to postmenopause osteoporosis in women[1].

It is known that despite ample consensus on the approach to these interventions, there is wide scientific debate and controversy concerning concrete criteria. This is illustrated by the diversity in guidelines available. In fact it is not at all easy to clarify the basis on which each pharmacological intervention is made. On the one hand, there is a an ample amount of evidence (clinical trials and meta-analyses) and interpretations of evidence available (reviews, guidelines, consensus) all fruits of a laborious undertaking. On the other hand, there are frequent gaps in the evidence on key issues regarding clinical practice.

The objective of this paper is to offer the clinician a general overview of the state of the basis on which pharmacological interventions are justified in healthy people with regard to cardiovascular disease and osteoporosis. These interventions are listed and classified according to the three important questions every physician should ask before making a clinical decision: what should I treat? When should treatment be offered? And up to what point should I intervene? These refer to questions on the definition of disease or risk factor, criteria for intervention and therapeutic goals, as illustrated in table 1.

The perspective chosen to approach the extense material available on this issue gives priority to feasability and synthesis against detail and exhaustive analysis of the evidence. Without renouncing accuracy, we have selected the most relevant evidence in each case and we remit the interested reader to more ample reviews. A review was performed of the original clinical trials, meta-analyses, and the main guidelines and consensus available related to the prevention of diabetes, hypertension, and osteoporosis, the efficacy of statins, aspirin, and drugs to prevent bone fractures in primary prevention. In addition, therapeutic goals in the treatment of hypertension, diabetes and hypercholesterolemia was revised. A review of the scores measuring cardiovascular risk in Spain was performed and that of cardiovascular risk related to diabetes. The selection of clinical trials was performed from guidelines and meta-analyses, and through a systematic follow-up of abstracts from the most relevant journals. In some occasions, when necessary, systematic research was made by consulting *PubMed*.

Cardiovascular prevention
The definition and classification of risk

Is there evidence available to justify the pharmacological treatment of pre-diabetes?

The term pre-diabetes comprehends two situations which are associated with a high risk for diabetes and cardiovascular disease: impaired fasting glycemia (100-125 mg/dL or 5.5-7.0 mmol/L) and impaired glucose tolerance (glycemias 140-199 mg/dL or 7.8-11.0 mmol/L after an oral glucose tolerance test).

The modification of lifestyle habits has shown a reduction in the incidence of type 2 diabetes mellitus. Moreover, there are studies available showing the superiority or equivalence of lifestyle changes compared to metformin[2].

The XENDOS trial, compared placebo (diet) to the use of orlistat (plus diet), and showed a reduction in the incidence of type 2 diabetes by 0.32% (0.73 vs 1.05)[3]. Rosiglitazone reduced the incidence of type 2 diabetes in 14.4% vs placebo, and at the same time, increased the incidence of heart failure

Table 1. Classification of the measures according to the three operative procedures employed in the medicalization of prevention.

CARDIOVASCULAR PREVENTION
Definition of disease or risk factor. Is there evidence to justify…
…the pharmacological treatment of pre-diabetes?
…pharmacological treatment of patients with normal to high blood pressure?
…decisions on intervetion in accordance with score based cardiovascular risk?
…the use of the SCORE tables instead of REGICOR?
…considering diabetes as a coronary risk equivalent?
Criteria for intervention. Is there evidence to justify…
…the use of stains: in the general population, women, elderly patients, hypertensive and diabetes patients with no previous cardiovacular events?
…anti-platetelet therapy in healthy adults with high cardiovascular risk factors or in diabetes patients?
Therapeutic targets. Is there evidence to justify…
…recommending blood pressure (BP) control under 140/90 mmHg in the general population?
…recommending BP control under 130/80 mmHg en diabetes patients?
…recommending limits to LDL-c to below 130 mg/dL (3.4 mmol/L) in primary prevention?
…recommending limits to LDL-c to below 100 mg/dl (2.6 mmol/L) and to even 70-80 mg/dL (1.8-2.1 mmol/L) in secondary prevention?
…recommending HbA1c limits below 7%?
PREVENTION OF FRACTURES
Definition of disease or risk factor. Is there evidence to justify…
…the use of BMD as diagnostic criteria for osteoporosis?
…the stratification of fracture risk with scores?
…pharmacological treatment of osteopenia or prevention of osteoporosis
Criteria for intervention. Is there evidence to justify…
…prevention of fractures in patients under 65 years and in women with no history of fracture?
Therapeutic targets. Is there evidence to justify…
…follow-up periods and the duration of treatment with antifracture drugs?

by 7 (0.4% ARR absolute risk reduction), the incidence of peripheral oedemas by 1.9% and a mean weight gain of 2.2 kg[4].

From all the above mentioned, systematic pharmacological treatment is not justified in the management of pre-diabetes. The American Diabetes Association (ADA) indicates that metformin may be considered in very particular cases while the European guidelines mention an imprecise "if necessary"[5,6].

Is there evidence to justify the treatment of normal-high blood pressure?

The TROPHY clinical trial investigated whether candesartan reduced the incidence of hipertension in healthy persons with normal-high blood pressure (130-139/85-90 mmHg)[7]. While under treatment with candesartan for a two-year period, the incidence of hypertension was reduced by 26.6% (ARR). Two years after suspending the drug there still persisted a reduction of 10%. However the definition of hypertension employed, as with other methodological aspects, did not give the trial a sufficient base to treat patients with normal-high blood pressure[8].

Is there evidence to justify the use of risk scores for the prediction of cardiovascular risk as a guide to management decisions?

The impact of risk score tables as a guide for decision criteria in initiating treatments has not been

evaluated, and this in itself is a limitation[9]. Moreover, they are instruments with low positive predictive values, sensitivity and specificity (approximately 10%, 20-40% and 70-90% respectively)[10]. Improvements in morbidity and mortality and the control of risk factors with their use has not been demonstrated[11].

Therefore, given these limitations, risk scores do not seem useful as a tool for any definitive decisions nor as a direct indication for prescribing drugs, mainly statins and aspirin, though they may prove useful in making clinical judgements[12]. A potential use of the risk scores could be didactic and persuasive for example with regard to counseling on tobacco cessation.

Is there evidence to justify the use of the SCORE instead of the REGICOR table for estimating cardiovascular risk?

The different risk tables classify patients differently. Since the 1980s it is known that risk tables created from high-risk populations overestimate the risk when applied to populations with low risk. This occurred with the Framingham tables in Spain and in other countries. The SCORE risk tables are created based on European cohorts[13] and the denominated "tables for low risk" are based mainly on cohorts from Belgium and Italy that possess a 30% higher risk than Spain (Spain's participation was reduced to 6%)[14]. These tables show a higher calculated risk than the Framingham scores in patients over 60-65 years. In patients under 60 years the tables show a lower risk than the Framingham's, though probably it is even higher than the real risk[14,15,16]. REGICOR, a calibration of the original Framingham table has been validated successfully (precision and confidence) in the Spanish population, within the context of the limitations that all the risk tables possess[17,18,19].

Despite this data, the main consensus on prevention in Spain, PAPPS (Programme for Preventive Actions and Health Promotion - Programa de Actividades Preventivas y Promoción de la Salud)[20] and the CEIPC (Spanish Committee for Cardiovascular Prevention - Comité Español Interdisciplinario para la Prevención Cardiovascular)[21] that adapts the European guidelines on cardiovascular prevention, recommends the use of the SCORE tables, without any mention that the tables should not be employed in patients over 65 years of age, its upper limit[22]. The SCORE table classifies the 65 year old population, with the exception of non-smoking women with a risk equal or greater than 5% independent of the value of the risk factors. These circumstances annul its capacity to discriminate between diverse risk groups, which is the goal for which the tables are developed. One way of palliating this technical problem is by elevating the threshold of risk to initiate pharmacological treatment in elderly patients at 10% instead of the habitual 5% risk value. The European guidelines for cardiovascular prevention have adopted this measure, though it is necessary to find the recommendation in one table. Only the CEIPC has eliminated the recommendation when adapting the European guidelines[22].

The PAPPS guidelines explicitly recommend calculating the risk in patients over 65 years as if they were 65 years old, without any further considerations. The immediate clinical consequence of this decision is to classify as "high risk" an ample group within the population, with the single criteria of age, which could lead to unjustified and unnecessary interventions. It is worth recalling that the amount of patients over 65 years of age is considerable in consultancy, and strictly speaking, the SCORE tables should not be employed above this limit.

The REGICOR risk table for example, allows for a "moderate risk" classification of an important group of the population. By doing so, it facilitates the introduction of an individually based clinical judgement when deciding to treat, using other additional criteria or risk modifiers[12,16].

Is there sufficient evidence to justify that diabetes mellitus should be considered as a coronary risk equivalent?

Diabetes patients have higher coronary risk than non-diabetes patients, but those who have suffered from infarction show higher risk of mortality by infarction than diabetes patients by 1.8 to 2.9 times while the risk for non-fatal infarction is 3 times higher in the latter, as shown by well designed studies[23,24]. The error originated from a biased study by Haffner and Grundy in 2001 when applying the North American NCEP-ATP III consensus as an argument to consider all diabetes patients as coronary patients with regard to preventive intervention options[25]. The rest of the studies that supported the results from Haffner were carried out with biased cohorts[23,24].

Therefore, intervention in all diabetes patients with the same criteria for coronary disease patients does not seem justified. In fact the latest and most consistent study showed there are varying degrees of risk in diabetes patients that depend on the co-existence of other additional risk factors. In

other words there is an ample variety of clinical situations among diabetes patients[26].

Criteria for pharmacological intervention

Is there evidence to justify the prevention of cardiovascular disease with statins in healthy people?

Of the eight large clinical trials carried out to study primary prevention with statins the conclusions were that these agents do not reduce either total or coronary mortality. These trials include WOSCOP, AFCAPS, MEGA, the ASCOT and ALLHAT studies (both in hypertensive patients), the CARDS and ASPEN trials (in diabetes population) and the PROSPER study, which evaluated a subgroup in primary prevention in patients over 70 years. The most recent study (JUPITER), which found a reduction in total mortality (ARR = 0.6%), is an atypical trial carried out among patients with high C protein levels and LDL-c < 130 mg/dL or 3.4 mmol/L[27]. The meta-analyses including all these trials (Brugst and Thavendiranathan)[28,29] confirmed that statins do not reduce mortality, although Brugst found a reduction in total mortality (ARR = 0.6%) on including the JUPITER trial and the results of the extended observational period of the ASCOT trial. Lastly, there is a meta-analysis by Mills that included 20 trials in primary prevention, but the majority were small, not very homogeneous, and presented methodological problems[30].

Coronary events were reduced in primary prevention by between 1.4%[28], and 1.66%[29], and stroke in 0.3%28 or 0.4%[29]. The corresponding number of patients needed to treat (NNT) were 60-63 and 268-313 persons to avoid an new event in the next 5 years27. These effects have been shown in populations with a cardiovascular risk 3 times that of the Spanish population (in USA, United Kingdom and the Nordic countries) and basically in men with other cardiovascular risk factors. In the Japanese population which is characterized by a low risk (MEGA study) the effect is reduced to half. In absolute terms, coronary events are reduced by 0.84% (NNT= 129 in 5 years) and cardiovascular events by 1.1% (NNT=91)[31].

Therefore, given the low efficacy of statins in this indication in absoulte terms, it would be prudent to carefully select patients that could obtain some benefit.

Is there evidence to justify the use of statins in women with no cardiovascular disease?

Current evidence does not recommend the recent medicalization of life

In contrast with those trials carried out on hypertensive drugs, those carried out with statins showed very little participation of women, except for the ALLHAT, MEGA and PROSPER trials. In no study was any effect found in the sub-group of women, a fact which was confirmed by a meta-analysis which did show effects in secondary prevention in women[24,32]. It is worth taking into account that in the MEGA study (Japan, low risk) the global effect on morbidity and mortality was due to the minority sub-group of men (31% of 7,832) and did not appear among the majority of the women[31]. Therefore the current evidence does not support the use of statins in healthy women.

Is there evidence to justify the use of statins in healthy adults over 70 years with no cardiovascular disease?

There is a specific study of statins in the population above 70 years, the PROSPER trial[33]. In this study statins showed effects in secondary prevention but not in primary prevention. In addition, there was a higher incidence of cancer in the group treated with statins (ARR = 1.6% and RRR 20%). In the rest of the studies (subgroup data) the results were negative or were not provided[24]. Therefore the evidence available does not support the use of statins in healthy adults above the age of 70.

Is there evidence to justify the use of statins in all hypertensive patients with no cardiovascular disease?

There are two trials on primary prevention in patients with hypertension, the ALLHAT and ASCOT trials[34,35]. The ALLHAT study showed negative results, while the ASCOT trial had favorable findings (ARR of coronary events, 1.6%). Besides hypertension, the patients included in the ASCOT trial had an average of 3.7 cardiovascular risk factors and poor control of their blood pressure (mean 179/102). In the rest of the trials the results within subgroups were negati-

ve[24]. Therefore, the indication for statin therapy in all hypertensive patients does not seem justified without further considerations.

Is there evidence to justify the use of statins in all type 2 diabetes mellitus patients with no cardiovascular disease?

There are two trials on diabetes patients: the ASPEN and CARDS trials[36,37]. Diabetes patients included on the CARDS trial were also hypertensive (84%) or had other cardiovascular risk factors (30% with retinopathy, 17% with either micro or macro albuminemia and with a 7.8 year evolution). Cardiovascular events as a whole were reduced by 4%. The ASPEN trial, with a similar population to the CARDS trial, did not show any positive results. With regard to other trials, the results from the subgroups were not statistically significant, except for the sub-sub group in primary prevention in the HPS trial within the context of an evaluation of 80 subgroups[24]. Therefore, being diabetic does not seem to justify therapy with statins[38].

Is there evidence to recommend acetylsalicylic acid (ASA) to all healthy patients with a high cardiovascular risk?

Despite the trials including a high participation (up to 39,000 participants) to study the effects of ASA in the healthy population, no effect was found in either the corresponding primary endpoints or in total mortality. There were however favorable effects in secondary endpoints and in data from sub-groups which suggested reductions in myocardial infarctions on men and stroke in women with an effect of less than 1%. At the same time, the risk for severe gastrointestinal bleeding was increased by 0.32% and cerebral hemorrhage by 0.12%. The NNT was 333 men and 270 women to avoid any new cardiovascular event and 400 men and 203 women to provoke any major bleeding[27,39].

From this data, it is not strange that the European Cardiovascular Prevention Guidelines and their corresponding Spanish adaptation, CEIPC, place the threshold of high risk to indicate treatment with ASA in healthy people with a SCORE ≥ 10, instead of the habitual 5%[21,22]. Although the PAPPS[20] and the Prescrire journal[40] make no indication on when to treat, they do advise against treatment in the population with low risk. With the same evidence, the US Preventive Task Force makes a tentative to establish cutoff points according to age and sex in which the potential benefit is greater than the risk incurred (for example men between 70-79 years with a risk estimation ≥ 12%)[41]. In a recent editorial, however, Hiatt argued that the negative results from the seven high-quality available trials did not justify the use of ASA in primary prevention including the high-risk population[42].

Is there evidence to justify recommending ASA to all diabetes patients over 40/50 years of age?

With expectations for the results from two large ongoing clinical trials in diabetes patients (ASCEN and ACCEPT-D), two recent trials in diabetes patients with no cardiovascular disease showed negative results (POPADAD[43] and JPAD[44]). The findings from the sub-groups of diabetes patients in the trials on primary prevention are contradictory: effects were similar, greater or lower than non-diabetes patients[45]. The results of the main meta-analysis in secondary prevention and high risk did not find any effect in the ample group of diabetes patients (5,126 participants)[46].

In an editorial by Nicolucci it was remarked that the same evidence has led the ADA to recommend ASA to all diabetes patients over 40 years and the ESC-EADJ to recommend it only in secondary prevention[47].

Therapeutic goals

Does the available evidence justify maintaining blood pressure below 140/90 mmHg in the general population?

Currently the interpretation of the direct evidence with regard to the optimum targets to achieve in the management of hypertension still remains unresolved. The European guidelines on the management of hypertensión affirms: “in the 2003 guidelines (...) we admitted that maintaining BP under 140/90 mmHg was only a prudent recommendation” and did not derive from clinical trials[48]. Although the authors attempt to argue that currently there is “additional indirect evidence” (VALUE and INVEST trials) and “direct” evidence (FEVER study) available they are not convincing. Such studies, presented by authors some of whom happen to be on the panels that determine the guidelines, do not support this conclusion. The indirect trials are a post hoc analysis that did not respect the intention to treat and the FEVER trial is one of the many comparative studies published whose objective was not to evaluate the goals of treatment. In fact some of the authors affirmed in a document published in 2009 that “more direct evidence was

necessary to support the reduction of systolic blood pressure below 140 or 130 mmHg"[49].

In reality only negative results are available. The great classical trial on this issue, that attempted to demonstrate that it was better to reduce diastolic blood pressure (DBP) to 80 or 90 mmHg (HOT with 18,790 hypertensive patients and 3.8 years of follow-up) did not find differences in either morbidity or mortality[50]. In a secondary analysis that obviated the analysis to treat, the morbidity and mortality was similar in the ranges between 150-120 and 90-75 mmHg[51].

Two recent trials with a two year follow-up, focussing on systolic blood pressure (SBP), have obtained different results. The larger trial (JATOS study, 4,418 hypertensive patients between 65-80 years)[52], did not find differences between situating the SBP below 140 mmHg or maintaining it between 140 and 160 mmHg with regard to the endpoints under study (cardiovascular morbidity and mortality and renal failure), despite obtaining differences in SBP in the groups of 9.8 mmHg. The Cardio-Sis trial, included 1,111 patients with isolated systolic hypertension and one additional risk factor found in the group assigned to achieve a SBP below 130 mmHg (against <140 mmHg) a reduction of 5.6% (ARR, CI 95% 1.2-10) in the incidence of left ventricular hypertrophy (primary endpoint) and 4.6% (1.5-7.6) in the incidence of a composite endpoint of cardiovascular and total morbidity and mortality[53]. The difference in SBP achieved was by 3.8 mmHg. The number of drugs and the distribution of the different agents was similar in both groups, except for the use of diuretics, which was employed in higher quantities in the group under intensive therapy.

At last, a Cochrane review in 2009 on the issue concluded that the treatment of the patients with lower therapeutic goals to the standard 140-160/90-100 mmHg, did not reduce either mortality or morbidity[54]. The review included trials studying the general population, patients with diabetes and renal failure.

It is worth recalling that the clinical trials compared to placebo had blood pressure goals of 170-150/95-90 mmHg while in more recent comparative trials the targets were set to 140/90 mmHg[27,55-56].

Preventive interventions must be effective and the extent of their effects should be worthwhile both economically and socially with a favourable risk-benefit relationship

Is there evidence to support maintaining blood pressure under 130/80 mmHg in the diabetes population?

The recommendations of the three most influential consensus on hypertension (JNC[57], the European consensus[58] and the WHO[59]) explicitly recognize the weakness of the evidence that supports the option of recommending blood pressure goals of under 130/80 mmHg, provided by the HOT[50], UKPDS[59] and the ABCD[60] trials. In effect the data from the HOT trial corresponded to a sub-group of diabetes patients whose initial baseline distribution was not provided that presented an improbable result (a reduction in cardiovascular mortality of not less than 70% in relative terms in the groups assigned to achieve DBP <80 and <85 mmHg with respect to <90 mmHg).

The UKPDS trial compared intensive treatment to a standard regimen (goal of 150/85 mmHg compared to 200-180/105 mmHg) and achieved 144/82 compared to 154/87 mmHg.

Finally the ABCD trial obtained negative results. Consequently the consensus before mentioned insists on prudence and does not strictly apply this recommendation. In fact, the latest national and international guidelines are correcting this figure. The NICE guidelines and the American College of Physicians recommend the target of 140/80-85 mm Hg[61,62]. At the same time, in our context the second edition of the Basque Health Services-Osakidetza guidelines on hypertension have modified their previous objective of 130/80 mmHg to 140/80 mmHg[63]. The guidelines of the National Health Services also coincide with the 140/80 mmHg recommendation[64], while the PAPPS[20] and the CEIPC[21] still maintain the 130/80 mmHg goal with no further warning or special consideration.

Is there evidence to justify the setting the objectives of LDL-c below 130 mg/dL (3.4 mmol/L) in primary prevention?

There are no studies that have attempted to compare the results in morbidity and mortality in rela-

tion to the different levels of LDL-c. Even more so, the trials with statins, in contrast to those trials with anti-hypertensive agents, do not adjust doses according to targets, but employ a standard dose, or as in two trials employ lower doses than the standard (AFCAPS[65], lovastatin 20-40 mg if the LDL-c after three months was above 110 mg/dL or 2.8 mmol/L, and the MEGA trial, pravastatin between 5-20 mg to achieve total cholesterol levels under 220 mg/dL or 5.7 mmol/L)[24,27].

For this reason, the recommendations of the NICE guidelines[66] seem coherent in not setting fixed therapeutic targets in relation to LDL-c in primary prevention, or even in carrying out cholesterol level controls and insist on not employing doses above the standard. To be precise the recommendation is to employ a fixed dose of 40 mg simvastatin, which is the most cost-effective option in their context.

Is there evidence to justify setting targets for LDL-c below 100 mg/dL (2.6 mmol/L) and even lowering it to 70-80 mg/dL (1.8-2.1 mmol/L) in secondary prevention?

From the studies comparing placebo in secondary prevention the same affirmations can be made as with primary prevention, that doses are not titrated except for the 4S trial[67], which did not employ doses above the standard 40 mg simvastatin to obtain LDL-c levels between 115-200 mg/dL (3.0-5.2 mmol/L). Even so, the 4S trial represents the only clinical trial to achieve the greatest effect and by a considerable difference. Neither do the trials that compare doses question the best objective in terms of morbidity and mortality, but compare fixed high doses to standard doses. It should be noted that these studies are carried out on very selected patients that have not suffered from adverse effects previously with standard doses, and with baseline LDL-c levels around 100 mg/dL (2.6 mmol/L). Moreover, they reduce LDL-c levels to 70 mg/dL (1.8 mmol/L) employing statins at doses 8 times higher than the standard[24,68].

Therefore no solid recommendation can be made to achieve LDL-c levels <70-80 mg/dL (1.8-2.1 mmol/L) from any baseline level of LDL-c[69].

Recent trials that have studied the effect of the association of statins with ezetimibe (SEAS[70] and ENHANCE[71]). They have not shown differences in morbidity or mortality (SEAS) or in doppler studies of the carotid artery (ENHANCE) despite important reductions of LDL-c. In addition, in the SEAS study there was an absolute increase by 3.6% (50% in relative terms) in the incidence of cancer after four years in the group under intensive therapy. Therefore there is no support for the additional use of ezetimibe to "reach targets".

Is there evidence to justify attaining HbA1c levels below 7% in all diabetes patients?

Up to 2008 there were no specific studies carried out to discover the optimum glycemic level or HbA1c target to reduce microvascular complications in diabetes patients (except for metformin, no reduction in macrovascular complications has been shown with other hypoglycemic agents)[72].

That year three trials were published evaluating the potential benefits of lowering HbA1c below 6% (ACCORD[73] and VADT[74]) or below 6.5% (ADVANCE75) compared to 7-8%. In one of the studies (ACCORD), there was a 1% increase in cardiovascular and total mortality in the group assigned to intensive treatment which obliged the suspension of the trial. The only positive result obtained among the three trials proceeded from one of them, a 1% reduction in the composite endpoint of renal impairment and a 1.9% reduction in a composite endpoint including micro and macrovascular complications, at the expense of renal impairment. All the trials showed an increase in hospitalization and severe hypoglycemias (with an incidence double or triple that of the control)[76].

With these results, the ADA has recently issued a statement in which it maintains that the general target for HbA1c levels should be less than 7%, but in addition considers that this target should be reviewed carefully and on an individual basis when there is a high risk of hypoglycemias, co-morbidity or advanced complications (preferably higher levels). In addition the preferences of the patients and quality of life should be taken into account[77].

Prevention of fractures

Definition of risk factor and classification of risk

Is there evidence available to justify the use of bone density as a criteria for diagnosing osteoporosis?

Before 1993, the diagnosis of osteoporosis was established when a fracture due to weakness ocurred. In 1994 the WHO proposed a definition based on the bone mineral density (BMD) determined by densitometry (DXA). Thus osteoporosis was considered to exist when the T-score points were equal or

greater than 2.5 times the standard deviation of the mean score in young adult women. Thus definition was initially constructed for epidemiological purposes, but an operative definition was later imposed with the subsequent need to make clinical decisions with regard to management.

Whereas it is known that the DXA measurements have little precision in defining bone density (the confidence interval is wide), BMD is not a good predictor of fracture. The most important risk factor for fracture are falls, not BMD[78]. The strength of the bone, whose alteration is a key element in osteoporosis, depends on its physical and structural properties and and a complex process of bone remodeling[79]. The BMD is only one of the determinants of the strength of the bone. In fact the increase in BMD attained from antifracture agents shows a poor correlation in the reduction of the incidence of bone fracture in clinical trials[80]. Even so, there may be a paradoxical increase in fractures (as shown in the case of flouride)[81].

For these reasons, population screening for osteoporosis is not advised and the indication for DXA should be reserved for women over 60-65 years with some risk factor for additional fracture, factors that vary according to the different consensus. Consideration of these factors should be made prior to the DXA determination and bone densitometry may be even dissuaded if no advantage could be afforded from it when making management decisions[82,83,84].

Is there evidence to justify stratifying the risk for fracture?

The approach to managing the prevention of fractures has mimicked that employed for stratifying cardiovascular risk. The scores established for cardiovascular risk come after some delay in years, given that trials on hypertension were carried out in the 1970s, hypolipidemic agents in the 1980s and statins at the onset of the 1990s while the trials studying antifracture agents were only published since the end of the 1990s. In contrast to the main cardiovascular risk factors which have been well established for a long time and to which new emergent factors have been added, the risk factors for bone fracture initially described were numerous and in occasions overlapped those risk factors for falls.

In order to make management decisions, qualitative criteria have been adopted (aggregation of risk factors) and in the last few years score tables have been constructed to predict fracture in 5 and 10 years intervals. These include proposals by Black, Kanis (who in addition elaborated the FRAX tool endorsed by the WHO)[85] and the Dutch model (recommended in Madrid)[82]. The clinical impact of these models has not been evaluated or validated in Spain.

The criteria for intervention, therapeutic goals and the definition of disease or risk factors should all be considered with clinical prudence

Therefore the adequacy of their use to make management decisions still remains undefined[82,86]. For instance the NICE guidelines do not recommend the FRAX tool, because the authors do not agree with all the clinical risk factors included and because the absolute risk of fracture calculated by FRAX is not related directly to its cost effectiveness[83].

Is there evidence to justify the prevention of fractures with pharmacological agents in women with osteopenia (or to prevent osteoporosis)?

There is no existing data from clinical trials that support pharmacological intervention in women without osteoporosis, even if they have antecedents of fracture. The indication to “prevent osteoporosis” is registered by the European Medicines Agency (EMEA) and national drug agencies when an active substance, having demonstrated reduction in the incidence of fractures in women with osteoporosis, also demonstrates the increment in bone density in women with osteopenia and there exists some additonal risk factors, for example early menopause, ovariectomy, or history of maternal fracture. This indication (authorized for risedronate and raloxifen) aims at reducing the loss of bone mass related to early estrogen deprivation or other genetic traits. However, the results published with regard to this indication do not offer a basis for pharmacological intervention as they do not proceed from clinical trials but rather from an overall analysis of data available (pooled studies)[82,86,87,88].

Criteria for pharmacological intervention

Is there evidence to justify the prevention of fractures?

The evidence on the prevention of osteoporosis-related fractures in post-menopause women is very variegated. The systematic review for the preparation of the NICE guidelines in September 2008 contains more than 100 papers. Many studies have been carried out in different parts, have been duplicated partially, with posterior follow-up periods, separated subgroups or have included populations from various studies (pooling), among other complex adjustments[89]. The task of ordering all the evidence is therefore primordial. Below are the most important trials, by acronym, that have conditioned the recommendations, with some clarifications made on those trials with various publications and evolutions: alendronate (FIT, Liberman and FOSIT), risedronate (VERT and HIP), ibandronate (Chestnut), raloxifen (MORE), strontium ranelate (TROPOS and SOTI), teriparatide (NEER) and calcitonin (PROOF)[82,83,84,86,87].

The clinical importance of osteoporosis is that it is a risk factor for fractures and the goal of treatment is the prevention of fractures, especially those affecting the hip and any other not affecting the vertebral column. However the evidence available on the efficacy of the anti-osteoporotic agents is very limited, both in population groups and in size of effect.

In women with no history of fracture, there is no agent that has shown any consistent efficacy in reducing the incidence of hip or non-vertebral column fractures. The data from subgroups of patients suggest that alendronate could reduce the incidence of hip fractures by 1% in women with osteoporosis. The risk of fractures affecting the vertebral column is reduced by ralendronate and raloxifen in about 2%, and strontium ranelate shows a reduction of 8.2% (data from a subgroup, and with a greater basal risk than the trials with bisphosphonates)[82,83,84,86,87].

In women with a history of fracture, some trials showed reductions of approximately 1% in the incidence of hip fracture, 2% in non-vertebral column fractures and 6% of fractures affecting the vertebral column.

It should be insisted that the validity of the clinical trials and their results are also limited (important losses of patients, subgroup data, pooled studies, statistical significance found at the limit), which makes it difficult to evaluate the clinical relevance and effectiveness of these drugs[82,83,84,86,87].

The clear lack of relation between all the evidence available and corresponding recommendations is shown by the enormous disparity of the latter. The recommendations are not easy to summarize with precision, nor is it the objective of our paper. It is enough to say that some consensus (The North American Menopause Society-NAMS[90] and National Osteoporosis Foundation, NOF[91]) recommend pharmacological intervention in all women over 50 years (and including men)[91] with osteoporosis demonstrated by densitometry and/or with a history of fractures, and also in cases of ostepenia with risk factors. At the same time, there are consensus that restrict the intervention in women with no previous fracture or in cases of osteoporosis with diverse risk factors with more or less strict criteria with regard to age, and in no way recommend the treatment of osteopenia (as in the case of the Spanish consensus in the Madrid province and the whole of the scientific societies and the Latinamerican Cochrane centre, and the NICE guidelines).

From the evidence however it could be deduced that the use of drugs in women with no history of fracture is not justified, because this intervention does not prevent hip fractures. The adoption of measures to prevent falls, diet and hygiene should be insisted on periodically. In an ample cohort of women followed for a 12 year period, it was found that walking 4 hours a week reduced the incidence of hip fracture by 1.5% (ARR)[92]. The evidence is also in accordance with a restrictive approach to pharmacological intervention in women with a history of fracture.

Is there evidence to justify the use of pharmacological drugs in the prevention of fractures in women under 65 years?

There is no information available on the efficacy of antifracture agents outside the range of the mean age of the population studied in the clinical trials, which lies between 68-83 years[86,87,89].

Therapeutic goals

Is there evidence to justify the follow-up and the duration of antifracture agents?

The aim of pharmacological management is to reduce the incidence of fractures. As explained earlier, the reduction in BMD does not explain the majority of the therapeutic effect, nor does it always precede it and is very sensitive to the regression to the mean[82]. Despite these limitations, the North American consensus recommends a follow-up

DXA every 2 years[90,91] while other guidelines do not make any statement on this issue[82,83,84,87].

There is no information to determine the duration of treatment. There is a trial (FLEX)[93] whose objective was to compare the efficacy of the interruption of treatment with alendronate after 5 years with respect to its continuation for another 5 year period in a selected group of women (a third of the patients from the original FIT trial). The interruption of treatment was associated with a progressive reduction in the BMD, but not with an increase in fractures, except for clinical fractures affecting the vertebral column that were 2.9% (ARR) lower than those in the group that continued treatment. Although this study affirms that there were no problems with regard to safety, no numerical data was provided, and women who were not treated for at least 3 years during the FIT study and those with a low BMD were not included.

The long term safety of these agents is unknown. The displacement of the curative role (limited in its indication and with a known risk-benefit relationship) to pharmacological interventions in large groups of the population for preventive purposes favours the incidence of adverse effects, for example osteonecrosis of the jaw related to biphosphonates or hypersensitivity reactions related to strontium ranelate, circumstances that oblige the drug agencies to issue alerts periodically[97].

Final comment

A large part of clinical practice in primary care in the last few years is characterized by implementing preventive measures, in many occasions with the employment of pharmacological agents and technologies. In contrast to curative practice, prevention offers little choice for clinical feedback and its efficacy relies on the results from well designed and interpreted clinical trials. The clinician is immersed in a sea of confusion when he or she perceives that the recommendations which were taken for consistent show their more vulnerable side by the naked evidence.

The review performed allows us to confirm that a large part of the pharmacological interventions recommended in daily clinical practice lacks solid justification with regard to the evidence available. This situation becomes more important when it is known that any pharmacological intervention in healthy people should comply three basic conditions: that efficacy is clearly shown, that the size of the effect is clinically and socially worthwhile, and that there is a clearly demonstrated risk-benefit relationship.

During the last few years there has been a wide debate on the issue of the medicalization of the western world even among the general public[94,95,96]. The unnecessary use of drugs, due to inefficacy, or potential harm, or the extension of the medical use of drugs to other fields that excede their role is now well understood. From this point of view, it is important to note that besides the so-called “disease mongering,” a concept which often overlaps with the pathologization of normal vital processes, there exists a great territory susceptible for medicalization within the heart of daily clinical practice. To be more precise the prevention of cardiovascular events and fractures are especially susceptible to pharmacological intervention.

The potential medicalization of these interventions that can affect large groups of the population has become even more sophisticated in the last few years. To the classic “criteria for pharmacological intervention” as a gateway to potential medicalization, two other fields have been affected in a subtle way, though not less effectively: therapeutic targets, that may in many occasions oblige the use of high doses and the association of drugs, and the operative definition of what is disease or a risk factor, which can acquire special relevance depending on the instruments employed to define or classify “high risk”.

The real problem the clinician faces when making management decisions is that it seems difficult to distinguish between evidence and recommendations on the one hand, which belongs to true scientific debate, and on the other hand, the bundle of interests that surround modern medicine immersed in a free market. Given this context the clinician therefore needs to develop a new skill, which is to identify and disregard the bias created by the market when consulting the recommendations in the three vulnerable fields mentioned to introduce unjustified practices of medicalization. Clinical prudence remains a fundamental guide in the clinicians practice.

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Conclusiones

A considerable part of the pharmacological recommendations to prevent cardiovascular events and fractures in healthy persons lack any solid justification. No clear efficacy, nor the size of the effect of these agents or a clear balance between risk and benefit make the intervention clinically and socially worthwhile.

The "therapeutic targets" and the "operative definition" of disease or risk factor that include instruments or tables to calculate risk are new gateways to unnecessary medicalization.

In the context of modern medicine, immersed in conflicts of interest, the physician is obliged to interpret the results of trials and the recommendations from guidelines and consensus at a critical distance, and to place emphasis on the development of clinical prudence as a desired skill.

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