Author's response to reviews

Title: Unanswered clinical questions in the management of cardiometabolic risk in the elderly: a statement of the Spanish Society of Internal Medicine

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Author's response to reviews: see over
Dear Mr. Gilbert Tacbobo,

Thank you very much for giving us the opportunity to revise our manuscript. We have carefully considered the comments made by the reviewers. Each comment has been addressed and we have modified the manuscript accordingly.

We have made major changes in the manuscript related to:

1. Corrections in English language, as suggested by reviewer 1 and 2.
2. In order to facilitate the understanding of the paper, we have modified the title of manuscript to “UNANSWERED CLINICAL QUESTIONS IN THE MANAGEMENT OF CARDIOMETABOLIC RISK IN THE ELDERLY: A STATEMENT OF THE SPANISH SOCIETY OF INTERNAL MEDICINE”.
3. The inclusion of a Methods section, in order to better explain the methodology used in the consensus, and accordingly with the suggestions of the reviewer 2.
   In this section, we have explained that the questions planned to be discussed by the consensus panel, were previously selected by the Clinical Coordinators of the different Working Groups of the Spanish Society of Internal Medicine. These questions were related to the management of cardiometabolic risk in the elderly and were considered questions unresolved or that could produce uncertainty, according to a deep analysis of the medical literature.
4. A different order in the discussion section, dividing this section according to the questions considered for discussion in the consensus statement.
5. Moreover, we have added this sentence in the Background section (line 61):
   “After considering the aforementioned factors, and within the framework of the “Spanish National Health System (SNS) strategy” for approaching
chronicity, the Spanish Society of Internal Medicine (SEMI) has coordinated this expert panel to analyse some relevant questions related to the management of the cardio-metabolic risk in elderly patients.”.

We sincerely hope that the current version of the manuscript will be acceptable for publication in your journal.

Prof. Ricardo Gómez-Huelgas
1. In the background section, many importance is given to multimorbidity, as it has to be in this population, but references are only based in one Spanish "polypathological" participants study. Authors mismatch what they understand by "polypathology" (term not validated in the international literature) with multimorbidity. It would seem that the article refers only to multimorbidity older adults, but recommendations are for all subjects older than 65.

Response:

In the Background section, we have just tried to highlight the well-known association between aging and comorbidity, indicating that elderly subjects frequently experience more than one chronic condition. As the reviewer says, we used Spanish papers (references 5 and 6) in order to support the importance of cardiovascular diseases in the elderly, and in these articles the term “polypathological” was used because they were published in Spanish medical journals and a literal translation was done from the Spanish common term (“pluripatológico”). As suggested by the reviewer we have avoided the term “polypathological” across the whole manuscript. Instead, we have used the term “multi-morbidity”.

On the other hand, our statement is focused generically on the old patients, with or without comorbidities, and we do not therefore establish any age cut-off point.

2. Authors state that the study is within the framework of the "Spanish SNS Strategy in the approach of chronicity", giving a reference. However, revising the document, it is not included in the objectives or implications the design of this study. Moreover, the expert pannel included in that approach is multidisciplinar, and the article has only been written by internists.
Response:

In Spain, internists are responsible for most of the hospital discharges of elderly patients. So, we consider highly pertinent to write a position paper to ease their clinical decisions. Of course, we have not attempted to perform an exclusionary initiative and we are fully aware, as the Spanish National Health Network (“Sistema Nacional de Salud”) Strategy holds, of the importance of a collaborative and interdisciplinary effort to take on this challenge.

3. Authors don’t explain the methodology for the recommendations. Was a systematic review literature conducted? Was a Delphi method employed? Which were the 17 questions and their proposed answers? How did they reached consensus? What about differences? All 59 participants agreed in all the statements? This is difficult to believe. Many problems of the article are due to this lack of rigour.

Response:

Our manuscript is not a systematic review, but rather a summary of statements based on expert opinions.

As we explain in the Methods section, the coordinators have made statements on some relevant questions related to cardiovascular risk factors (CVRF) in the elderly, based on their personal criteria, and have selected some convenient literature references regarding the topic. We have not used a standardized Delphi method. The methodology is described in detail along the text, including both the agreement criteria used and the degree of agreement reached.

According to the suggestion from the reviewer, we have added the following paragraph at the end of the Discussion section:
4. As a general comment, recommendations are vague and imprecise.

Response:

We specifically selected unresolved questions in the management of cardiometabolic risk in the elderly. They were unresolved because there were no definitive studies that could undoubtedly give an answer to them. For that reason, these recommendations have to be obligatory vague at some point, in accordance to the lack of supporting evidence. However, our manuscript provides clinicians with some general recommendations to support their decision-making processes based on fair clinical judgment.

5. In the dyslipidemia section, authors advise for the use of SCORE, although they say that the original one does not account over 65 years, and the Spanish correction over 75. They can’t make this suggestion. Also, in the metaanalysis by Savarese, mean age is 73, and there are no valid data for adults older than 80. Authors don´t state this problem, and furthermore, NNT is 83 por MI and 142 for Stroke. Are this values acceptable? Finally, authors neither state the importance of function, quality of life, and frailty in the decision making on this population, nor the lag time to benefit in very old adults.

Response:

We repeatedly acknowledge in the manuscript that the use of risk charts in subjects above 65 years, underestimates the calculated risk. However we considered that there were not any other way of solving the problem, due to the lack of national
charts or calibrated charts that had included subject above that age. It was a much-debated question that ended up with this consensus statement.

We completely agree with the reviewer about the critical importance of including a comprehensive clinical assessment for making clinical decisions in elderly people. We also agree with the reviewer about the importance to take into account functionality and quality of life before prescribing statins in primary prevention. Certainly, these aspects have not been well reflected in the writing step of the manuscript.

To clarify our recommendation, and to respect the consensus achieved by the experts, we have modified the text in statement 1 as follows:

- Are vascular risk equations useful for estimating the cardiovascular risk in the elderly Spanish population?

Line 88: “The vascular risk estimation in the elderly must be addressed by a comprehensive evaluation, including other important considerations (function, frailty, cognitive state, quality of life and life expectancy).”

Line 95: “… when vascular risk needs to be estimated…”

Line 103: “We also admit that there is an urgent need to develop national risk equations that could be applied to subjects of all ages. In the meantime, and considering the need of estimating the risk in older individuals, we should use the available risk charts with the chance of risk underestimation.”

Line 108: “Cardiovascular risk scores should never replace clinical judgment, especially in older patients. An individualized decision-making process based on functional and cognitive status, quality of life and life expectancy, comorbidities and the patient’s preferences is critical in the elderly. Elderly-specific validated scales
that include relevant markers for this population such as frailty and disability, have to be developed” [Rodondi N, Locatelli I, Aujesky D, Butler J, Vittinghoff E, Simonsick E, Satterfield S, Newman AB, Wilson PW, Pletcher MJ, Bauer DC, Health ABC Study: Framingham risk score and alternatives for prediction of coronary heart disease in older adults. PLoS One 2012, 7(3):e34287; Rodondi N. PloS ONE 2012.]

The meta-analysis of Savarese included subjects above 65 years (mean age 73 years). Although patients 80 years of age were included in the analysis, their number was probably small. However this study is the best approximation we can choose to evaluate the effect of statin treatment in the primary prevention of elderly subjects. Whether the NNTs are or not cost/effective is a different question, which is not discussed but is mentioned in the text.

We have added the following phrases in the answer to the question:

- Is statin treatment useful for the primary prevention of CVD in the elderly?”

Line 123: “Life expectancy in Spain at 80 years is approximately 5-6 years in males and 8 years in females, a sufficient time frame for obtaining a benefit from statins.”

Line 128: “However, it must be underscored that this meta-analysis did not give information about patients older than 80, and the numbers needed to treat were relatively high (83 for MI and 142 for stroke).”

6. Regarding diabetes, authors dont include the main guidelines on this problem in older adults, those from IDF 2014 and Sinclair 2010. Moreover, authors include as a reference one of their papers [25], but this article is about chronic kidney disease and not about older adults. Recommendations in this section
are more vague. Morover, they don’t explain what, when, how, and to whom exercise and nutritional supplementation must be prescribed.

Response:

According to the suggestion of the reviewer, we have added in the Discussion section of the manuscript the following paragraph:

Line 148: “Avoiding hypoglycemias is critical in this population, since elderly patients are at an increased risk of hypoglycemia, often the unaware type, which may have serious consequences (falls and functional and cognitive impairment).


Also, we have modified the reference 25 (now it is the #30) including the correct one:


7. In the high blood pressure section change fragility by frailty.

Response:

We have changed in the text the term “fragility” by “frailty”.

8. In the antiaggregation section, there is no reference to CHADS2VASC or CHADS scales and HAS-BLED to determine the risk of anticoagulation. New anticoagulants are not described.

Response:

The reviewer is right. We have not included in the manuscript these issues although these topics were analyzed during the meeting. We have corrected this omission, adding the following sentences in the statements and in the Discussion section

- When is antiplatelet therapy indicated in elderly patients without CVD?

Line 246: “The use of aspirin in primary prevention confers a modest benefit on nonfatal MI and CVD events and greatly increases the risk of bleeding associated with aspirin.”

- Is antiplatelet therapy a more reasonable (risk/benefit) alternative than anticoagulation in elderly patients with atrial fibrillation?
Overall, anticoagulation, anti vitamin K and new oral anticoagulants, provide a net benefit over antiplatelet therapy in elderly patients with atrial fibrillation. One possible exception, due to lack of evidence, would be patients with CHADS-VASc = 1, especially if they have a high bleeding risk (HAS-BLED >=3).”

Due to the higher risk of major bleeding associated with anticoagulation, the selection of antithrombotic therapy in this population should balanced the risk for embolism and the risk for hemorrhage. In this setting the use of CHADs-VASC and HAS-BLEED scores is mandatory. The net clinical benefit is higher in subjects with a higher risk of stroke, including the oldest age category, despite their higher bleeding risk.”

- Does aging involve any exceptions regarding the general recommendations on antiplatelet therapy in CVD? (37, 41)

The evaluation of both CHADS-VASc and HAS-BLED is very important in the elderly, although patients with a high CHADs-VASC usually also have a high HAS-BLED. “

9. It seems surprising that in one article about older adults, only one reference is about geriatric journals.

Response:

All our references are focused on geriatric patients.

10. there is a recent and excellent Statement From the American Heart Association 2013 regarding secondary prevention of cardiovascular risk factors in older adults not included.

Response:
We have added this paragraph in the Introduction section:

The abstract & summary are very promising; they identify a genuine area of need, in an area where insufficient research and knowledge is applied. It sets the reader up for something clinically useful and sits nicely within a framework of other consensus statements by similar groups. Statements issued in lieu of guidelines must be seen as the opinion – only – of a group of independent experts, without the weight of a National body (eg NICE in the UK) or International body (eg ADA/EASD, IOTF, WHO) to back them, and need to offer high quality evidence and recommendations in order to be sufficiently persuasive. Unfortunately the body of the statement doesn’t fulfil these criteria; it constitutes neither a thorough review of the evidence, nor an effective guideline for clinical management of a patient. For example, if an elderly patient with diabetes is suffering frequent hypoglycaemic episodes, what exactly should be done? The guideline should review glucose-lowering agents and their propensity for inducing hypoglycaemia, and suggest alternatives as appropriate for the benefit of practising clinicians. Should sulphonylurea use be restricted? And what should be used instead? What are the problems associated with hypoglycaemia and the elderly – hypo unawareness, falls, cardiac autonomic neuropathy, functional and cognitive impairment, polypharmacy and concordance with treatment. The importance of renal and hepatic impairment, plus drug interactions must be discussed. Special populations are important – care home residents, cognitive impairment and end of life care. Similarly, weight loss is glossed over; what nutritional and lifestyle changes are appropriate? The obesity paradox reminds us that someone who has achieved old age...
probably shouldn’t be encouraged to lose weight, although health improvement and risk reduction should be encouraged. Initiatives such as the Institute for Diabetes in Older People (IDOP) strive more effectively to improve care in this population. Each section needs expanding with these points in mind prior to consideration for publication.

Response:

As the reviewer rightly points out, this manuscript is neither a guideline nor a systematic review, but a general selection of important unresolved questions about the management of cardiovascular risk factors in the elderly answered by experts. So, we have not tried to make a comprehensive approach and many relevant points (for instance, hypoglycemia or special populations) have not been addressed in the text. Most of these questions should be broaden in future manuscripts. In fact, we have previously published specific guidelines for the management of certain condition in the elderly (Treatment of type 2 diabetes in the elderly: A consensus document of the treatment of type 2 diabetes mellitus in the elderly. R. Gómez Huelgas et al. Med Clin (Barc) 2013 Feb <2;140(3):134.e1-134.e12), where many of the questions suggested by the reviewer are already answered. With this statement, the Spanish Society of Internal Medicine just wanted to call the attention of important general gaps in the cardiometabolic risk management of older adults. This statement should, either encourage to develop specific clinical guidelines, or help clinicians to be aware of the uncertainties in some frequent and relevant questions in this area. In order to better explain our intention, we have included the term “general questions” for referring to the questions we have selected and we have included this
sentence at the end of the document: “Far from trying to increase the available information, this document is intended to provide general recommendations for clinicians and to promote the effective use of procedures and medications. We must underscore that this manuscript is not a systematic review, but rather a statement based on expert opinions. “

However it is true that some relevant questions that were treated in the meeting have not been reflected in the final document.

Therefore, according to the reviewer’s suggestions, we have added the following sentences in the *Diabetes, obesity and nutrition* section:

Line 148: “Avoiding hypoglycemias is critical in this population, since elderly patients are at an increased risk of hypoglycemia, often the unaware type, which may have serious consequences (falls and functional and cognitive impairment) [Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E, Tschope D: Oral antidiabetic treatment in type-2 diabetes in the elderly: balancing the need for glucose control and the risk of hypoglycemia. Cardiovasc Diabetol 2012, 11:122.]

Line 155: “Renal and hepatic impairment and potential drug interactions should be also taken into account. The use of sulphonylureas should be restricted in the elderly, favoring the use of antidiabetic drugs with a low risk of hypoglycemia (metformin, DPP-4 inhibitors) [Gómez Huelgas R, Díez-Espino J, Formiga F, Lafita Tejedor J, Rodríguez Mañas L, González-Sarmiento E, et al; en nombre del Grupo de Trabajo para el Documento de Consenso sobre el tratamiento de la diabetes tipo 2 en el anciano. Tratamiento de la diabetes tipo 2 en el anciano. Med Clin (Barc). 2013;140:134.e1-134.e12.]. Initiatives such as those of the Institute for Diabetes in
Older People (IDOP) (http://instituteofdiabetes.org) can be useful for increasing the quality of care in this population, including diabetes care at home."


Line 179: “Increasing physical activity in older adults should reduce sedentary behavior and emphasize moderate-intensity aerobic activity. The activity plan must take into account the older adult's abilities and aerobic fitness. Activities aimed to increase flexibility, muscle-strengthening and balance are also recommended.”

Reviewer: Pamella Cristine Anunciação

Reviewer’s report:

Minor Essential Revisions:

Line 35: missing space between words “with” and “morbidity”

Line 114: missing the meaning of abbreviation of "Ca"

Linie: 151: missing space between words “no” and “metaanalysis”

Response:

We have corrected the misspellings indicated by the reviewer.

Discretionary Revisions:

Line 133: "Those older than 79 years with a reduction on nonfatal vascular events (mainly strokes) but having a potential increase in overall mortality when the diastolic BP is under 70 mmHg." This sentence is meaningless. Lacked a connection to the previous sentence. I suggest rewriting the sentence.

Response:

We have rewritten the sentence as following:

Line 201: “In subjects older than 79 years, antihypertensive drugs reduce nonfatal vascular events (mainly strokes), but increase total mortality when the diastolic BP decrease below 70 mmHg.” [Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard R, Casiglia E, Kerlikowske K, Coope J: Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group.]