PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Design and rationale of a multicentre, randomized, double blind, placebo-controlled clinical trial to evaluate the effect of vitamin D on ventricular remodeling in patients with anterior myocardial infarction: The VITamin D in Acute Myocardial Infarction (VITDAMI) trial
AUTHORS	Tuñón, José; González-Hernández, Ignacio; Llanos-Jiménez, Lucía; Alonso-Martín, Joaquín; Escudier-Villa, Juan; Tarín, Nieves; Cristóbal, Carmen; Sanz, Petra; Pello, Ana; Aceña, Álvaro; Carda, Rocío; Orejas, Miguel; Tomás, Marta; Beltrán, Paula; Calero-Rueda, María José; Marcos, Esther; Serrano-Antolín, José María; Gutierrez-Landaluce, Carlos; Jiménez, Rosa; Cabezudo, Jorge; Curcio, Alejandro; Peces-Barba, Germán; González-Parra, Emilio; Muñoz-Siscart, Raquel; González-Casaus, María Luisa; Lorenzo, Antonio; Huelmos, Ana; Goicolea, Javier; Ibáñez, Borja; Hernández, Gonzalo; Alonso-Pulpón, Luis; Farré, Jerónimo; Lorenzo, Óscar; Mahíllo-Fernández, Ignacio; Egido, Jesus

VERSION 1 - REVIEW

REVIEWER	Nazario Carrabba, MD Department of Cardiology, Careggi Hospital, Florence Italy
REVIEW RETURNED	28-Feb-2016

GENERAL COMMENTS	This is an interesting study about LV remodeling and STEMI, focused on the supplement of Vit D as adjunctive treatment for STEMI in order to reduce the incidence of adverse geometric modification of LV. Although the study is well designed, I suggest a few modifications of protocol to avoid misinterpretation of the final results of the study. Exspecially, the authors should better specify the treatment of STEMI with and without thrombectomy, measure the presence of ischemic mitral regurgitation, and specify the concept of complete revascularization: anatomic or functional, as reported below. This is an interesting study about the topic of LV remodeling and STEMI, focused on the supplement of Vit D other than standard treatment for STEMI in order to counteract the adverse geometric modification of LV. The study is well designed. I suggest only a few modifications of protocol to avoid misinterpretation of the final results of the study. Key question: 1) For the purpose of the VITDAMI study, cardiac MRI should be performed between 2-7 days after index STEMI in order to avoid a misinterpretation of IS and MVO due to delay

	occurring from index event to cardiac MRI examinations. The authors should better specify on the protocol the time of first cardiac MRI examinations 2) Many factors may influence the occurrence of LV remodeling after STEMI and despite current treatment with efficacious primary PCI, the 30% of LV remodeling still is observed. Thus, the author should better clarify the procedure of PCI: a) the use of thrombectomy before PCI, the use of intracoronary abciximab, the use of direct stent, the use of third generation stent, the use of third generation tienopiridine or not tienopiridine agents b) the time elapsed from the chest pain occurrence and the PCI treatment may influence the LV remodeling, thus the authors should selected and use the time <=6h or <=12 h as a major inclusion criteria for the study. c) The functional ischemic mitral regurgitation may influence subsequent LV remodeling. Thus, the authors should measure the presence of mitral regurgitation by MRI (contrast phase) or at least by echo. d) the authors should specify the significance of complete revascularization. In other worlds, before patient's hospital discharge beyond culprit lesion, all vessel with significant lesion suitable for PCI should be treated (anatomic complete revascularization) or a staged procedure is permitted after 1 month after functional evaluation of significant lesion (functional complete revascularization). 3) During the acute phase of STEMI the drug oral administration may be limited by intestinal congestion or vomit. Thus, the authors should take into account this situation and should planned the possibility of a second Vit D capsule administration in these cases. 4) The occurrence of AKI after primary PCI represent a strong marker of adverse prognosis. Thus, beyond the related mechanisms, the authors should planned a separate analysis for AKI patients, to evaluate if the Vit D administration may in some way counterbalance the negative effect of kidney injury occurring during PCI. 5) Finally, I suggest after the end of 12 months of the study, an follow-up of 3 months in order to observe delayed or unexpected events of Vit D supplement.

REVIEWER	Juan Guillermo Gormaz Molecular and Clinical Pharmacology Program, Faculty of Medicine, University of Chile, Chile.
REVIEW RETURNED	07-Mar-2016

GENERAL COMMENTS	General Comments Tuñón et al. present a rationale and design of a randomized clinical

	trial aimed at evaluate the effects of oral vitamin D supplementation in cardiac remodeling, evaluated by magnetic resonance imaging. The authors will perform the trial in patients undergoing an anterior ST-elevation myocardial infarction (STEMI), based in the administration of single doses of 0.266 mg of calcifediol or placebo every 15 days during one year. Additionally it has been proposed to evaluate several biomarkers associated to mineral metabolism. The theoretical background that supports the hypothesis seems to be solid as well as the explanations regarding the unsuccessful results of previous trials. The design of the study is also robust and, in general, seems to correctly address to the most important aspects of interventional clinical trials. However there are a few major things that it is necessary to clarify and specify. Based in the analysis of this reviewer and their collaborators, the research is appropriate to be published in this journal but it is necessary to correct previously certain major and minor aspects. Major Revisions: 1) From our point of view, to be consistent with the interest of the authors to optimize the model in order to demonstrate the effects of the intervention, they must limit the recruitment of STEMI patients, to only those that will be treated by primary angioplasty (PA), excluding pharmacologic thrombolysis and coronary artery bypass grafting surgery. Even more, among the PA patients, it would be optimal to select those who start the intervention with TIMI 0 and end it with TIMI 3. These procedures ensure homogeneity in the STEMI model, as they give the absolute certainty that an ischemia-reperfusion injury will happen. The latter will be important because those injuries are closely linked with the future reduction of left ventricle function and their remodeling. Additionally, these restrictions to recruitments facilitate future repeats of the study as well as to perform a larger study. Therefore, please limit enrollment to PA patients mentioned above. 2) In the proposed protocol it is not clear the clinical and/or epidemiological bases that the authors use to define cardiac remodeling in the primary outcome as an increase in LV end-diastolic volume ≥10%. Therefore, it is necessary to explain why it will be used that definition and supporting that explanation with strong references. 3) We understand that the cardiac morph-functional study will be performed by Echocardiography and Magnetic Resonance at time 0 and after 12 month. We believe that there are too much time between the evaluations and it should be considered an intermediate evaluation, at least only with Echocardiography. The latter, considering that morphological changes and functional alterations not necessarily have the same temporality. Please incorporate an imagenological intermediate evaluation. Minor Revisions 1) In the abstract it is mentioned that: “To our knowledge, this is the first study to evaluate this outcome in patients with STEMI and the possible influence of FGF-23 and klotho on this benefit”. However in the protocol it is clear that the evaluation of these biomarkers are a fairly secondary objective and that regarding them, it is only evaluating a potential relationship with the cardiac outcome. In any

	case, it does not seem to have been considered in the study an evaluation of the pathophysiological role of both markers. Therefore, we suggest to remove that paragraph and instead, to emphasize in other most relevant aspects of the study. 2) Please add an epidemiological reference to support the phrase in page 4 line 8. 3) Please add a primary epidemiological reference to support the phrase in page 4 line 17. The reference 2 is not an epidemiological quote.

VERSION 1 – AUTHOR RESPONSE

− Reviewer: 1
Reviewer Name: Nazario Carrabba, MD
Institution and Country: Department of Cardiology, Careggi Hospital, Florence, Italy Competing Interests: None declared

This is an interesting study about LV remodeling and STEMI, focused on the supplement of Vit D as adjunctive treatment for STEMI in order to reduce the incidence of adverse geometric modification of LV. Although the study is well designed, I suggest a few modifications of protocol to avoid misinterpretation of the results of the study.
Especially, the authors should better specify the treatment of STEMI with and without thrombectomy, measure the presence of ischemic mitral regurgitation, and specify the concept of complete revascularization: anatomic or functional, as reported in attached file.

Thank you for this observation. As you know, a first study showed benefit of thrombectomy that finally has not been confirmed, and the guidelines do not indicate to perform thrombectomy. However, following your advice we are going to pre-specify an analysis in patients with/without thrombectomy.

Concerning the presence of ischemic mitral regurgitation, baseline echocardiographic assessment will be performed to detect the degree of valve regurgitation. Moderate to severe mitral regurgitation represents a reason for exclusion (Table 1, exclusion criteria). In patients included in the trial, the existence of mild regurgitation will be registered in the protocol.

Regarding the definition of Complete Revascularization, we mean that patients should undergo satisfactory revascularization of all the severe lesions in the three main coronary arteries as estimated by either an angiographic severity higher of 70% or borderline angiographic stenosis but with a positive intracoronary adenosine test. Similarly, lesions in secondary vessels fulfilling these criteria should be revascularized unless the attending cardiologists do not estimate this to be relevant or feasible because of technical limitations such as small diameter, distal lesion, calcification or tortuous vessel. We have specified this in the new version of the paper.

− Reviewer: 2
Reviewer Name: Juan Guillermo Gormaz
Institution and Country: Molecular and Clinical Pharmacology Program, Faculty of Medicine, University of Chile, Chile.
Competing Interests: None declared

General Comments

Tuñón et al. present a rationale and design of a randomized clinical trial aimed at evaluate the effects of oral vitamin D supplementation in cardiac remodeling, evaluated by magnetic resonance imaging. The authors will perform the trial in patients undergoing an anterior ST-elevation myocardial infarction (STEMI), based in the administration of single doses of 0.266 mg of calcifediol or placebo every 15 days during one year. Additionally it has been proposed to evaluate several biomarkers associated to mineral metabolism.

The theoretical background that supports the hypothesis seems to be solid as well as the explanations regarding the unsuccessful results of previous trials. The design of the study is also robust and, in general, seems to correctly address to the most important aspects of interventional clinical trials. However there are a few major things that it is necessary to clarify and specify. Based in the analysis of this reviewer and their collaborators, the research is appropriate to be published in this journal but it is necessary to correct previously certain major and minor aspects.

Major Revisions:

1. From our point of view, to be consistent with the interest of the authors to optimize the model in order to demonstrate the effects of the intervention, they must limit the recruitment of STEMI patients, to only those that will be treated by primary angioplasty (PA), excluding pharmacologic thrombolysis and coronary artery bypass grafting surgery. Even more, among the PA patients, it would be optimal to select those who start the intervention with TIMI 0 and end it with TIMI 3. These procedures ensure homogeneity in the STEMI model, as they give the absolute certainty that an ischemia-reperfusion injury will happen. The latter will be important because those injuries are closely linked with the future reduction of left ventricle function and their remodeling. Additionally, these restrictions to recruitments facilitate future repeats of the study as well as to perform a larger study. Therefore, please limit enrollment to PA patients mentioned above.

We agree that it is optimal to narrow inclusion criteria to select only those patients with anterior STEMI and PA to make the population more homogeneous. We did not want to exclude these patients to avoid missing a significant number of patients for the trial. However, after discussing this matter with all the investigators we believe that thrombolysis is very infrequent in our setting. Then we accept to exclude these patients. We have added this exclusion criterion in the new version of the manuscript.

You are right regarding exclusion of patients that undergo surgical coronary revascularization. In fact, if an interval longer than 7 days from admission to inclusion in the trial is not allowed, a patient undergoing CABG is not expected to be included in the trial. For the sake of clarity, we have added coronary artery by-pass grafting surgery as a separate exclusion criterion in the new version of the paper.

Finally, we strongly agree with the idea of including only patients with TIMI 0 at the beginning and TIMI 3 at the end of the procedure. However, this could limit the number of patients to be included, compromising the feasibility of the trial, given that the design has necessarily many exclusion criteria. We believe that a good point may be to pre-specify a subgroup analysis in patients with TIMI 3 flow. We have added this change to the present version of the paper.

2) In the proposed protocol it is not clear the clinical and/or epidemiological bases that the authors use to define cardiac remodeling in the primary outcome as an increase in LV end-diastolic volume ≥10%. Therefore, it is necessary to explain why it will be used that definition and supporting that explanation with strong references.

To our knowledge, there is no universal definition of remodeling. Then, we estimated that we should

use a definition avoiding that changes due to inter- or intraobserver variability could be interpreted as remodeling. In previous literature, intra-observer and inter-observer variability as assessed by MRI was 2.9-6.8% and 3.9-10.2% (Luijnenburg SE et al. Int J Cardiovasc Imaging 2010 Jan;26:57-64). Then, given that the probability of a change in LV end-diastolic volume >10% due to observational variability is very low, and we decided to use this limit. We now add this explanation and its reference to the new version of the manuscript.

3) We understand that the cardiac morph-functional study will be performed by Echocardiography and Magnetic Resonance at time 0 and after 12 month. We believe that there are too much time between the evaluations and it should be considered an intermediate evaluation, at least only with Echocardiography. The latter, considering that morphological changes and functional alterations not necessarily have the same temporality. Please incorporate an imagenological intermediate evaluation.

We agree with you that an intermediate imaging analysis would add valuable information, allowing to seeing if a potential benefit of vit D is already present by this time and also providing data on the timing of remodeling. However, in our setting, performing MRI and/or an echocardiogram at six months is not included in daily clinical practice. Adding this exploration would complicate the protocol. You must take into account that some of the involved institutions have not specific staff to do research. That is, the investigators are cardiologists that will participate in the study in addition to performing their clinical task. Then, please accept that we cannot include this exploration in the protocol.

Minor Revisions

1) In the abstract it is mentioned that: “To our knowledge, this is the first study to evaluate this outcome in patients with STEMI and the possible influence of FGF-23 and klotho on this benefit”. However in the protocol it is clear that the evaluation of these biomarkers are a fairly secondary objective and that regarding them, it is only evaluating a potential relationship with the cardiac outcome. In any case, it does not seem to have been considered in the study an evaluation of the pathophysiological role of both markers. Therefore, we suggest to remove that paragraph and instead, to emphasize in other most relevant aspects of the study.

Following your kind recommendation, we have replaced the sentence by a reference to the primary objective of the trial: “This is the first study to evaluate the effect of VD on cardiac remodeling in patients with STEMI". Please, find attached the draft document with track changes.

2) Please add an epidemiological reference to support the phrase in page 4 line 8.

References number 1 and 2 apply to this point. We have added also a paper from Larsson et al showing the relationship between renal function and FGF-23, PTH and Vitamin D (Ref 3).

3) Please add a primary epidemiological reference to support the phrase in page 4 line 17. The reference 2 is not an epidemiological quote.
Reference 3 is valid for this purpose; also, references 1 and 2 are relevant to this point.

We would like to thank you once again for your contributions to the manuscript.

VERSION 2 – REVIEW

REVIEWER	Nazario Carrabba Department of Cardiololgy, Careggi Hospital, Florence Italy
REVIEW RETURNED	25-Apr-2016

GENERAL COMMENTS	The value about the use of thrombectomy as adjunctive therapy in setting of primary angioplasty is not fully solved and some issues remain matter of debate at least in case of culprit IRA vessel with high thrombus burden (CCI 2015, SMART MRI study). However, the design of the study is robust, and the Authors have responded appropriately to all remaining questions.

REVIEWER	Juan Guillermo Gormaz Universidad de Chile, Chile
REVIEW RETURNED	25-Apr-2016

GENERAL COMMENTS	I agree with the corrections and accept those points that the authors could not modify.