Author's response to reviews

Title: Revascularization and cardioprotective drug treatment in myocardial infarction patients: How do they impact on patients survival when delivered as usual care

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Submission of the revised manuscript: « Revascularization and cardioprotective drug treatment in myocardial infarction: How do they impact on patients’ survival when delivered as usual care»

To the editor,

On behalf of my colleagues, I am pleased to submit this revised manuscript. We want to thank Drs Fuster and Quinn for their valuable and pertinent comments. We seriously considered each comment. We are confident that this revised manuscript will be at their satisfaction and will meet the high standard quality of your journal. You will find below a point-by-point description of the changes made. Should you have any question, please feel free to e-mail the first author. We are looking forward to hearing from you.

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RESPONSES TO THE REVIEWER VALENTIN FUSTER:

Major Compulsory Revisions

1. ... Some of the results are particularly surprising, like the better survival during the acute episode of those patients with more comorbidities ...However, the ‘unexpected’ results mentioned above together with the reasonable uncertainty that those subjects taking more drugs have necessarily more severe diseases raises doubts on the validity of such an index.

   We agree with the reviewer that the Comorbidity score defined as the total number of drugs taken may not be a valid indicator of Comorbidity. For example, patients not taking any medication can just reflect of an absence or poor follow-up by physicians, not necessarily an absence of diseases. Consequently, we defined
another Comorbidity score, the D’Hoore score (D’Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson Comorbidity index with administrative data bases. J Clin Epidemiology 1996; 49(12): 1429-33). This index, which is an adaptation of the so-called Charlson comorbidity index, is a weighted score of comorbid conditions, these conditions being defined by the secondary diagnoses available in the MED-ECHO database in the year preceding the index hospitalization. We adapted this index simply by subtracting the quantity 1 to the D’Hoore index, corresponding to the weight associated to the MI comorbid condition. This new comorbidity score provides less ‘unexpected results’ in our study.

2. …it might be possible that revascularization ‘per se’ was necessarily better than medical treatment, as the survival curves appear to imply. Although this may be the case in the setting of STEMI (at least the restoration of coronary patency) it is still controversial in the case of NSTEMI or unstable angina. Therefore, reaching the latter conclusion requires great caution…

We understand that according to specific acute coronary conditions different care must be provided and different outcomes can be expected. Unfortunately, MED-ECHO administrative database does not allow distinction between STEMI and NSTEMI but we can distinguish between MI and unstable angina. In order to raise the specificity of the condition presented by the patient in the cohort, the inclusion criteria have been restricted to patients with MI (ICD-9 code 410).

3. Another important issue is if revascularization and cardiovascular drugs had an impact in non-cardiovascular mortality (and if so why this could be) or if the whole benefit in total mortality came from the reduction in cardiovascular mortality alone. This should be included in the results.

In order to simplify the manuscript, we removed all analyses on all-cause mortality. Instead, as proposed by the reviewer, we added a column in Table 3 to include non cardiovascular death rates. We observed that non cardiovascular death decreases with revascularization and cardioprotective drugs but the extent of this decrease is less important than the one observed in cardiovascular survival. We can put forward the hypothesis that the use of revascularization and cardioprotective drugs can reflect a better health care management in general, leading to an increase in non cardiovascular survival as well as in cardiovascular survival.

Minor Comments
1. **All abbreviations (ACE, ASA, etc) should be defined on first use.**
   This is done in the revised version.

2. **Page 7. Methods, Statistical analysis, last line: The version etc. of SAS needs not be included as a reference.**
   This reference has been removed.

3. **Table1: please add 2 columns: one with the total numbers for the population, and another one with the p values of the comparisons between survivors and deceased.**
   Two columns have been added to Table 1.

4. **The statistical analysis in Tables 2 and 3 are confusing. ... These tables should be modified so that statistically significant differences are clear. In addition, what type of test was used for these comparisons should be mentioned in the Methods.**
   We rearranged tables 2 and 3 so that statistical significance becomes clear. Also, we added the information on the tests used in the Methods.

5. **Data shown in the tables needs not be repeated in the text...**
   We agree with the reviewer and the results have been simplified to avoid repetitions.

6. **Which survival curves are significantly different from others? The scale of the survival curves is somewhat misleading, as the lowest value in the y axis is very high. Figures 2-3 could be divided in 2 figures each...In addition, if the age and gender adjusted curves were similar why did they choose to show the unadjusted curves instead?**
   The figures have been divided in order to simplify the curves and the y axis is rescaled to 0 to avoid misleading information. Statistical significance has been added to the curves. We could not produce adjusted curves since the Kaplan-Meier estimates do not allow this kind of adjustment. Stratified curves could have been done, but showing all these curves would make results cumbersome. Instead, we used Cox proportional hazard models to adjust for covariates, including age and gender.

7. **In Table 4, adjusted hazard ratios are adjusted for what? All other 4 co-variables? Why in the regression trees some of the branches include comorbidities but not others?**
   All hazard ratios are adjusted for all other 4 co-variables. This is now specified in the table. In the regression tree approach, the first step is to divide the sample in two subgroups, each of which is as homogeneous as possible (within-group homogeneity), the division being carried out through one covariate, that is, the covariate that splits the sample into separate subgroups the most heterogeneous (between-group heterogeneity) but each being the most homogeneous. The second
step is to repeat the process of splitting on the two subgroups independently from one another, so that one covariate, say age, can enter in the model at one branch or subgroup while another covariate, say Comorbidity index, enters in the model at another branch. This process continues recursively and permits for instance the inclusion on the Comorbidity index as an important determinant of death for some subgroups but not for other subgroups.

**RESPONSES TO THE REVIEWER TOM QUINN:**

**Major Compulsory Revisions**

1. *The data are almost a decade old (1998) and I wondered if longer term (more than 2 years) outcome data were available.*

   Unfortunately, data on mortality were available only until the end of 2000, so that a longer follow-up of the cohort was impossible. This is another limitation of administrative databases.

2. *ACS is poorly defined and it may be helpful to have information available on the baseline characteristics of patients on entry – type of ACS presentation (STEMI, non-STEMI, biomarker release, blood pressure, etc.).*

   We agree with the reviewer and we understand that according to specific acute coronary conditions (ACS) different care must be provide and different outcomes can be expected. Unfortunately, MED-ECHO administrative database does not allow distinction between STEMI and NSTEMI but we can distinguish between MI and unstable angina. Also, because of the administrative goal of the MED-ECHO data base, other important information regarding biomarker release, blood pressure, etc. is not available either. In order to raise the specificity of the condition presented by the patient in the cohort, the inclusion criteria have been restricted to patients with MI (ICD-9 code 410).