Author's response to reviews

Title: In-Hospital complications after invasive strategy for the management of Non STEMI: Women fare as well as men.

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Author's response to reviews: see over
We thank Doctor Ioannis Toumpoulis for his useful comments on our work. As a whole his points were quiet positive. We work hard to account on these different points that undoubtedly help us to improve the manuscript.

Item # 1

We studied a small set of patients (133 women and 346 men) as we acknowledged in the limitation section of the manuscript. However, most of the published data deal with inhomogeneous population including STEMI, Non-STEMI and sometime planned PCI for stable angina patients, explaining these large sample sizes quoted by the referee. This aspect could, at least to some extent, undermine the sample size effect raised by the referee. Nevertheless, as required, the statistical power of our study was calculated (package Statmate from GraphPad). This was done using the 'not significant' chi-square test comparing two proportions from the data we report for mortality and bleeding. For both issues our study has at least 80% power to detect a change of 0.04 in mortality and a change of 0.10 for bleeding with a 2-tailed p value of 0.05. We have added this result in the appropriate sections.

Item # 2

We do agree that in order to increase the number of events, we have decided to include all complications. Our interest was to stress only the in-hospital outcome. It could be possible that mid-term and long-term outcome are related to these early complications and we acknowledge that the referee pointed an important issue. However, various papers (such as Weintraub et al JACC 1994; 24: 81-90, quoted in our reference section - #11 but also Bertrand et al, J INVASIVE CARDIOL 2008; 20: 99 dealing with PCI and DES for complex lesions) do not support a gender difference in post-hospital outcome. Moreover, one does not forget the possibility that these very early complications or side effects have little to see, if any, with sex-specific post-hospital outcome.

However, there were mixed reports of in-hospital outcome. Moreover, the reporting of some complications - i.e. bleeding - varies between published data as mentioned in the manuscript. As a result, we were interested in every single side effect in the setting of Non-STEMI (the most frequent form of acute coronary syndromes these days) that could have
been sex-related. In our opinion, this is of interest at least because these problems, though being related to the disease itself and the patient's clinical condition, are the only ones clearly related to the procedure itself, a matter of interest. Though we agree with the referee for its point, we did not study the post-hospital outcome considering that this was beyond our scope.

Item # 3

We used a logistic regression analysis in our study. This is a multivariate analysis allowing to determine which explanatory variables influence outcome and using an individual's values of the explanatory variables evaluate the probability that a subject will have a particular outcome as stated in Petrie A and Sabin C: Medical Statistics at a Glance. “Basic techniques for analysing data”: Regression and correlation section – Binary outcomes and logistic regression pp 79-81. 2nd edition 2005. Blackwell Publishing Ltd. As stated by the referee, we did not report the calibration of the regression model. Now, this has been done in the Statistical section and in the appropriate paragraphs of the Results section. We did not used, as suggested, ROC curves or Hosmer-Lemeshow Goodness of fit test but the -2log likelihood ratio statistics or deviance, which is recognized in this setting. This has been quoted when we report the multivariate analysis results.
Comments from: Referee Shyam Poludasu

We also, thank Doctor Shyam Poludasu for his useful comments on our work. Once again, we could rethink our study in order to improve it.

Item # 1

He stressed with justness the small sample size of our population, a point that we underlined in the manuscript. However, the higher risk of bleeding in women after PCI reported in earlier publications is not obvious in more recent ones and remains poorly understood in those papers reporting such a difference. As we stated in our response to Doctor Ioannis Toumpoulis, our study as a power of at least 80% to detect a 0.04 difference for mortality and a 0.10 change in bleeding. Though this was not a prospective study and that the sample size is small, the mortality rate reported is online with available data in the literature as that of Moriel et al IMAJ 2003; 5: 398-402 for example (not quoted in our reference section). The same holds true for bleeding. We would like to emphasize that in most of the reports, the large sample size is likely related to the aggregation of various clinical conditions sharing the fact that the patients underwent PCI. This could undermine the weakness of the sample size of our study. We hope that these points will satisfy Doctor Poludasu.

Item # 2

Like the first referee, Doctor Poludasu pointed out the absence of long-term follow-up in our report, as this was associated with major bleeding events occurring during the in-hospital phase. As we say, in the answer to Doctor Toumpolis, there are conflict published data on this point. In a recent paper from Casterella et al J INVASIVE CARDIOL 2008; 20: 94-98, dealing with the safety and the efficacy of GP IIb/IIIa antagonists during PCI in the real world, the reported rate of TIMI major bleeding was low (1.9 -3.1%) in a large population of 3082 patients (male subjects = 72.2%). In this paper, there was no difference between genders for bleeding. As we said to the first referee, various papers (such as Weintraub et al JACC 1994; 24: 81-90, quoted in our reference section - #11 but also Bertrand et al, J INVASIVE CARDIOL 2008; 20: 99 dealing with PCI and DES for complex lesions) do not support a gender difference in post-hospital outcome. One does not forget the possibility that these very early complications or side effects have little to see, if any, with sex-specific post-hospital outcome.
However, there were mixed reports of in-hospital outcome. Moreover, the reporting of some complications - i.e. bleeding - varies between published data as mentioned in the manuscript. As a result, we were interested in every single side effect in the setting of Non-STEMI (the most frequent form of acute coronary syndromes these days) that could have been sex-related. In our opinion, this is of interest at least because these problems, though being related to the disease itself and the patient’s clinical condition, are the only ones clearly related to the procedure itself, a matter of interest. To our knowledge, no clear evidence was stressed to explain a sex-related difference for bleeds in PCI. Though we agree with the argument of Doctor Poludasu about the interest of a long-term follow-up of such patients, we did not perform this analysis as we thought that it was beyond our scope.

Item # 3

As suggested by Doctor Poludasu, we change the conclusion by removing the too strong sentence previously proposed.

Item # 4

Doctor Poludasu pointed out the modality of administration of antiplatelets drugs. The antiplatelet regimen used was the association of acetyl salicylic acid (standard dose of 75 mg once a day) and clopidogrel (75 mg once a day). These dosages are online with the ESC guidelines. In our study population, suffering from Non-STEMI, a few patients, primarily seen by non-cardiologists in the emergency department, received a loading dose of clopidogrel. These patients did not suffer significantly more bleeding than the others. The efficacy of clopidogrel was not evaluated by specific tests such as VASP or Verify Now. These tests were not available at that time and are still not recommended by the Guidelines.

Heparin was also used as stated by the Guidelines. When Non Fractionated Heparin was onboard, the APTT was set between 2 and 3 times as usual. When Low Molecular Weight Heparin was used, the dose was according to the patient weight but without blood testing as usual.

The use of GP IIb/IIIa was not widely spread as reported in the Table 5 of the manuscript. These drugs were used according to the cardiologist on duty at the patient entry or during the PCI procedure as required by the interventionist cardiologist. The same holds for the choice between bare metal stent and drug eluting stent. As a result, we could not go
further in our analysis, suggested by Doctor Poludasu. This is a single centre practice, likely representing another weakness, though small, of our study.

Pentasaccharide and Bivalirudin were not used in our study. These drugs were not yet approved in France.

Item # 5

We agree that the complication rate reported was high. However, it must be stressed that we were interested in any single side effect as already mentioned. This is likely the explanation for such a rate. However, regarding the major bleeds or the mortality rate, our data are online with the other published data. We don’t think that accounting for all possible complications might reduce the reported benefit of the invasive approach of Non STEMI. With regard to bleeding, as we discussed in the manuscript, the way you choose to report them (i.e. TIMI score or CRUSADE) may change significantly the final conclusion. Having reported all bleeds including the groin ones, could avoid any misinterpretation of the data.

As required, the use of closure devices was added in the manuscript. There was no difference whatsoever between the groups (appropriate section and Table 4).

Item # 6

Doctor Poludasu has some concerns with the Chi-Square test used for the analysis of the reported data in Table 6. We must apologize for that. We think that we induce a misunderstanding of our previous statement: “Counts and percentages were compared using the Chi-Square test with Fischer exact test if necessary”. It is likely that the referee has wrongly interpreted our statement and thought about the use of the Chi-Square test for relationship (Lang Than Secic M: Testing for relationships. in How to report statistics in Medicine. Chap 6; pp 73 – 84. 2nd Edition. 2006. American College of Physicians Editions). This Chi-Square test is different from the one for comparing proportions. As stated in the book cited here, this latter is a hypothesis test largely used and recommended in the Lang and Secic book (chap 4, pp 45- 60). As we think that our previous formulation could have been misleading, we replace it by “Proportions were compared using…” . The multivariate analysis using a logistic regression was already performed and altered as required by the first referee.

We hope that all the comments of Doctor Poludasu were properly argued and that the alterations made fitted his requirements. We thank him once more for his global appreciation of our work and to give us the opportunity to improve the paper.