Author’s response to reviews

Title: Long-term prognosis of patients with Non-ST-segment Elevation Myocardial Infarction according to coronary arteries atherosclerosis extent on coronary angiography: a historical cohort study

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Author’s response to reviews:

Response to the reviewers:

Reviewer #1: Alzuhairi and colleagues have set out to investigate the long-term prognosis of patients with NSTEMI according to coronary arteries atherosclerosis extent on coronary angiography. The study covers a period of 12 years (2000-2011) and comprises a large cohort of patients (N=8,889). Epidemiology-wise this is an interesting analysis, especially when one considers study groups: patients were classified by coronary angiography into: 0-vessel disease (0VD), diffuse atherosclerosis (DA) (0% < stenosis <50%), 1-vessel disease (1VD), 2VD, and 3VD with stenosis >50%.

The study is particularly interesting as it examines the prognosis of patients without obstructive CAD (0VD and DA). This subgroup of patients were classified as MINOCA in the recent 2017 ESC STEMI guidelines.
Response to Reviewer #1:

Thank you very much for your valuable review of our paper entitled "Long-term prognosis of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on coronary angiography"

Indeed the MINOCA subgroup is getting more and more attention, that’s why we think our study could contribute towards examining this subgroup thoroughly to reach in the future the best management for these patients.

Underneath please find our responses to your important comments:

Reviewer #1, Comment no.1:

The definition of MI has changed considerably throughout the study period: unstable angina with elevated troponins vs nonQ-MI vs NSTEMI). This, in my opinion, makes the study group very heterogenous. Thus, the obtained results do not reflect the current NSTEMI population and therefore should not be generalized to the NSTEMI population nowadays.

Our reply:

Thank you for this important comment. To the best of our knowledge, the essentials of MI definition has not been substantially changed since the re-definition of MI (alpert et al. 2000), through the universal definition of 2007 and 2012, with the necessity of rise and fall in biomarkers, accompanied by other criteria, mostly symptoms, but we agree that Troponin assays and the cut-off value used has been changed over the years. This led to increase in the number of patients diagnosed with NSTEMI, whom before were diagnosed with unstable angina, because the sensitive assays led to detection of small injuries to the myocardium, which we referred to in the discussion.

Nevertheless, in accordance to your comment, we have added that to the limitation section.

Changes made to the manuscript (Discussion, page 10, line 240-244):
The proportion of NSTEMI with non-obstructive coronary arteries increased gradually to 18% in 2011 in our data. The reason might be that the cutoff levels of cardiac troponin assays were decreased gradually through the years and the high sensitive assays became available in the last years of the study. This development led to the detection of minor injury to the myocardium.[20]

The percentage of NSTEMI patients with non-obstructive coronary arteries increased gradually during the study to reach 18% in 2011, that might reflect the development of more sensitive troponin and the use of lower cut-off values in the definition of MI, and thus the detection of smaller injuries to the myocardium [20]. This means also that we are dealing with growing subgroup of patients who need more attention in our management.

Changes made to the manuscript: added to (Study Limitation, page 13, line 316-318):

The cut-off values and Troponin assays has been changed during the study years, which might led to that the MI size detected in the later years are smaller than that at the earlier years of the study.

Reviewer #1, Comment no.2:

The paper lacks the information on the treatment modality (conservative therapy, PCI [BMS vs DES], CABG). More importantly, it also lacks the information on the type of antiplatelet therapy (mono vs dual; type of P2Y12 inhibitor; duration of dual antiplatelet regimen). All of these factors could have an unfavorable influence on the prognosis resulting in a higher rate of adverse events.

Our reply:

Thank you for pointing out this very important matter. In response to your comment, we were able to get access to medical and revascularization treatment of study patients and added that (please see underneath).
Changes made to the manuscript: added to (Table 1):

Table 1: Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>0VD (N=988)</th>
<th>DA (N=302)</th>
<th>1VD (N=3295)</th>
<th>2VD (N=2114)</th>
<th>3VD (N2190)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 (53, 72)</td>
<td>66 (56, 74)</td>
<td>63 (54, 71)</td>
<td>67 (59, 75)</td>
<td>71 (63, 78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>585 (59.9)</td>
<td>131 (44.0)</td>
<td>966 (29.6)</td>
<td>489 (23.3)</td>
<td>587 (27.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>368 (39.2)</td>
<td>143 (49.7)</td>
<td>1290 (41.6)</td>
<td>875 (44.4)</td>
<td>1088 (53.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>427 (45.5)</td>
<td>144 (49.5)</td>
<td>1517 (48.9)</td>
<td>1060 (53.6)</td>
<td>1093 (53.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>106 (11.0)</td>
<td>51 (17.2)</td>
<td>413 (12.9)</td>
<td>342 (16.6)</td>
<td>488 (23.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IHD in the family</td>
<td>347 (37.4)</td>
<td>113 (40.1)</td>
<td>1231 (40.5)</td>
<td>765 (39.3)</td>
<td>750 (37.9)</td>
<td>0.3072</td>
</tr>
<tr>
<td>Current smoker</td>
<td>293 (32.4)</td>
<td>100 (36.6)</td>
<td>1303 (42.7)</td>
<td>772 (39.4)</td>
<td>654 (33.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Overweighta</td>
<td>463 (57.7)</td>
<td>143 (55.6)</td>
<td>1764 (67.3)</td>
<td>1097 (66.7)</td>
<td>1059 (64.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Renal insufficiencyb</td>
<td>107 (13.8)</td>
<td>39 (15.4)</td>
<td>353 (13.8)</td>
<td>310 (19.0)</td>
<td>457 (28.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EF&lt;50%</td>
<td>107 (22.1)</td>
<td>37 (25.2)</td>
<td>282 (19.5)</td>
<td>258 (28.7)</td>
<td>427 (42.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Parameters Presented as Numbers (Percentages From Non-Missing Data) or Median (25th, 75th Percentile).</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Previous Stroke</td>
<td>36 (3.6)</td>
<td>15 (5.0)</td>
<td>113 (3.4)</td>
<td>111 (5.3)</td>
<td>189 (8.6)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Any Revascularizationc</td>
<td>26 (2.6)</td>
<td>15 (5.0)</td>
<td>2764 (83.9)</td>
<td>1816 (85.9)</td>
<td>1688 (77.1)</td>
</tr>
<tr>
<td></td>
<td>(77.1)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCI</td>
<td>21 (2.1)</td>
<td>11 (3.7)</td>
<td>2728 (82.8)</td>
<td>1588 (75.1)</td>
<td>769 (35.1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>CABG</td>
<td>5 (0.5)</td>
<td>4 (1.3)</td>
<td>36 (1.1)</td>
<td>228 (10.8)</td>
<td>919 (42.0)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Aspirin</td>
<td>883 (90.9)</td>
<td>288 (95.7)</td>
<td>3177 (96.6)</td>
<td>2039 (96.5)</td>
<td>2048 (93.8)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
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<td></td>
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<tr>
<td></td>
<td>P2Y12 Receptor Inhibitor</td>
<td>668 (67.7)</td>
<td>235 (78.1)</td>
<td>3097 (94.2)</td>
<td>1920 (90.9)</td>
<td>1642 (75.2)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>Beta Blocker</td>
<td>758 (78.1)</td>
<td>263 (87.4)</td>
<td>2964 (90.1)</td>
<td>1892 (89.6)</td>
<td>1975 (90.5)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>ACE-Inhibitor</td>
<td>428 (44.1)</td>
<td>147 (48.8)</td>
<td>1641 (49.9)</td>
<td>1175 (55.6)</td>
<td>1363 (62.4)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Statin</td>
<td>808 (83.2)</td>
<td>277 (92.0)</td>
<td>3103 (94.3)</td>
<td>1968 (93.2)</td>
<td>1978 (90.6)</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
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</tbody>
</table>

Parameters presented as numbers (percentages from non-missing data) or median (25th, 75th percentile).

Abbreviations: 0VD zero-vessel disease, DA diffuse atherosclerosis, 1VD one-vessel disease, 2VD two-vessel disease, 3VD three-vessel disease, IHD ischemic heart disease, EF ejection fraction, PCI percutaneous coronary intervention, CABG coronary bypass graft operation.

a Overweight defined as body mass index ≥25

b Renal insufficiency defined as estimated glomerular filtration rate <60ml/min/1.73m² using MDRD equation.

c Revascularisation defined as PCI within 30 days, and CABG within 60 days of non-ST-elevation myocardial infarction.
Changes made to the manuscript (Results, page 7, line 153-156):

Patients with all sub-groups of obstructive CAD were significantly more frequently treated with revascularization (either percutaneous coronary intervention or coronary by-pass grafting (Table 1), they were also more likely to receive double anti-platelet therapy than patients with 0VD or DA (Table 1).

Changes made to the manuscript (Discussion, page 10, line 251-255):

In our study 2.6% of 0VD and 5.0% of DA were treated with revascularization (either PCI or CABG). In the DA group, the explanation could be proven plaque rupture in non-obstructive lesion, and in the 0VD group, one of the explanations could be complications to the coronary angiography like perforation or dissection either with the diagnostic catheter or with optical coherence or IVUS wire. These complications might have led to revascularization in a patient without CAD.

Changes made to the manuscript (Discussion, page 10, line 265-270):

A possible explanation for our findings could be that patients with NSTEMI with non-obstructive CAD were less likely to receive recommended medical treatment after MI according to ESC guidelines,[23] and more likely to discontinue double platelet inhibitors if these were started.[1,2].

A possible explanation for our findings could be that as our results showed that patients with NSTEMI with non-obstructive CAD were less likely to receive double anti-platelet therapy and other recommended medical treatment after MI according to ESC guidelines,[23] . This was also shown in another study, where these patients were also more likely to discontinue double platelet inhibitors if these were started.[1,2].

Reviewer #1, Comment no.3:

Noteworthy, the demonstration of non-obstructive CAD in a patient presenting with symptoms suggestive of ischemia does not preclude an atherothrombosis etiology, as thrombosis is a very dynamic phenomenon and the underlying atherosclerotic plaque can be non-obstructive.
Our reply:

Thank you for this comment. We totally agree with you, and that was one of our arguments in the discussion, page 10, line 229-231:

There are several reported mechanisms of myocardial injury in these patients, like plaque disruption without significant stenosis on the angiogram proven with intra vascular ultrasound (IVUS) examination

Reviewer #1, Comment no.4:

Keeping in mind MINOCA is a working diagnosis and thus should result in a further investigation of the underlying causes. Failure to identify the underlying cause may result in inadequate and inappropriate therapy in these patients, which may lead to worse outcomes. The identification of the underlying cause of MINOCA should lead to specific treatment strategies. Although the outcome of MINOCA strongly depends on the underlying cause, its overall prognosis is serious, with a 1-year mortality of about 3.5%.

Our reply:

Thank you for this comment, and we agree on your considerations, and that an extensive examination should be done, which we are planning to do in a future separate research project. In this study, as you pointed out, we stress the adverse outcome of these patients to draw more attention of the cardiology community to these sub-groups of patients.

Reviewer #1, Comment no.5:

The authors need to discuss in more detail the phenomenon of a worse prognostic profile in patients with non-obstructive CAD.

Our reply:

Thank you for this comment. The prognosis of patients with non-obstructive CAD was as severe as 1VD and 2VD group, which is emphasized in the conclusion:
“Patients with NSTEMI with normal coronary arteries or atherosclerosis without significant stenosis have substantial risk of future cardiovascular events. Both patients with 0VD without diabetes and patients with DA have higher risk of mortality and heart failure compared with patients with 1VD; and patients with DA have a similar risk of recurrent MI compared with those with 1VD. Moreover, patients with 0VD have favorable risk profile, lower mortality (if patients were diabetic) and lower recurrent MI risk than patients with diffuse atherosclerosis. These findings call for considering these two subgroups of NSTEMI separately in future research and urge for further investigations to explore the best management and follow-up plans for each of these two subgroups.”

Response to reviewer #2:

Reviewer #2, Comment no.1:

Francesco Fioravanti (Reviewer 2): Editor comment.

Lenght of DAPT represents a hot issue for these patients, both for those treated and not. (Quote on PMID 27134057).

Our reply:

Thank you for this suggestion, we have added this important reference and discuss it.

Changes made to the manuscript (Discussion, page 11, line 282-289:

A recent meta-analysis ([28] showed that shorter duration (<6 months) of double antiplatelet therapy, was associated with higher incidence of MI, less incidence of bleeding, and the same mortality and stent thrombosis rates. However, this study was in patients treated with PCI with second generation drug eluting stent, nevertheless, about 40% of patients were acute coronary syndrome patients. Although, our study population is different, but our results also indicated that a non-unreasonable anticipation is that some of the recurrent MI incidence in DA group is because of either not been given double anti-platelet therapy or shorter duration of treatment compared with obstructive CAD group.
Reviewer #2 Comment no.2:

This article reports a well done analysis on an imponent NSTEMI registry (almost 9000 patients). Alzuhairi et al stratified prognosis, considering different coronary artery disease patterns. Notably, they show that NSTEMI patients without evident coronary stenosis have similar prognosis to patients with one- or two-vessel disease. This finding makes it an interesting article to publish.

Our reply:

Thank you for this comment; we agree that this article can add to increase the focus on this important sub-group of MI patients.

Reviewer #2, Comment no.3:

Major issue:

- Although useful, I think that the overall mortality should be flanked by CV mortality or MACE.

Our reply:

Thank you very much for this comment, we have added below the analysis for CV mortality as you kindly suggested. Regarding MACE, in our article we analyzed the individual components of the classical MACE: mortality, recurrent MI, and stroke, and we also analyzed HF. Because we have enough patients, we decided to analyze the individual component to emphasize the effect on each event, rather than taking a composite of all, where it is difficult to see which component contributes more than the others.

Changes made to the manuscript (Results, page 9, line 205-216):

Cardiovascular mortality

Considering only cardiovascular (CV) mortality and not all-cause mortality: for patients without DM, the CV mortality for 0VD group was higher compared to 1VD (HR: 1.52; 95% CI: 1.19-1.94, P= <0.001), not different compared to DA and 2VD groups, and lower than 3VD group (HR: 0.69; 95% CI: 0.50-0.96, P=0.02). While patients in the DA group had a CV mortality which was higher than both 1VD and 2VD groups (HR: 1.82; 95% CI: 1.27-2.60, P= <0.001), (HR: 1.76; 95% CI: 0.91-1.82, P= 0.03), respectively, and not different compared to 3VD.
For patients with NSTEMI and DM, whose in the 0VD group had CV mortality which was not significantly different compared to both 1VD, and 2VD groups, but lower than CV mortality of both 3VD, and DA groups (HR: 0.06; 95% CI:0.007-0.47,  P=0.007). While patients in the DA group had higher CV mortality than 1VD (HR:2.88; 95% CI:1.29-6.43,  P=0.009), and not different compared to 2VD, and 3VD groups.

Minor issues:

Reviewer #2, Comment no.4:

- The "background" section, in the abstract, seems more like an "aim of the study". I suggest to rethink this section.

Our reply:

Thank you for this comment; we have changed the Background accordingly.

Changes made to the manuscript (Background, page 1, line 27-30:

Background: To examine the long-term prognosis of patients with non-ST-segment elevation myocardial infarction (NSTEMI) according to the degree of coronary artery disease (CAD).

Background: patients with non-ST-segment elevation myocardial infarction (NSTEMI) without obstructive coronary artery disease (CAD) are often managed differently than those with obstructive CAD, therefore we aimed in this study to examine the long-term prognosis of patients with NSTEMI according to the degree of CAD on coronary angiography (CAG).

Reviewer #2, Comment no.5:

- ".. median follow-up period of 4.5 years ..". Are there any difference between the groups?

Our reply:

The median follow-up time for each group is as follows: 4.3 years for 0VD , 3.2 years for AS, 4.6 years for 1VD, 4.9 years for 2VD, 4.3 years for 3VD.
Reviewer #2, Comment no.6:

- Check citations 17 and 18. I do not see them in the text.

Our reply:

Citations 17 and 18 (which become 19 because of adding a new reference 18) are mentioned in the Discussion, page 10, as follows:

This was also observed in another study.[2] An explanation of more females among both groups of non-obstructive CAD group could be that one half of females without significant stenosis have microvascular dysfunction.[17]

There are several reported mechanisms of myocardial injury in these patients, like plaque disruption without significant stenosis on the angiogram proven with intra vascular ultrasound (IVUS) examination,[19]