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**PLATELET RESPONSE TO STANDARD ASPIRIN AND CLOPIDOGREL TREATMENT
CORRELATES WITH LONG-TERM OUTCOME IN PATIENTS WITH ACUTE ST-ELEVATION
MYOCARDIAL INFARCTION**

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Running head: Dual antiaggregation therapy response in STEMI

Abstract

Background: Dual antiaggregation therapy with aspirin and clopidogrel represents the therapeutical mainstay in the treatment of patients with acute STEMI. This study prospectively evaluated the dynamic of platelet response to both components during the early phase in patients with acute STEMI with the objective to determine the impact of the variability in antiplatelet response on the clinical outcome in these patients.

Methods: Study population included 90 patients consecutively admitted in the CCU with the diagnosis of acute STEMI who underwent primary PCI. Aggregation testing was done using Multiplate[®] ASPI and ADP tests, and the patients were stratified into 4 quartiles according both to the baseline aggregation as well as to the posttreatment reduction of aggregation from the day 1 to day 6. Follow-up for major adverse cardiac and cerebrovascular events was done at one month, six months and one year.

Results: The posttreatment reduction of platelet reactivity was found to be associated with MACCE during one year follow-up ($P=0.01$), and the patients with suboptimal response to both antiplatelet drugs had a 44.4% incidence of MACCE which was significantly higher than in other patient groups (P for trend = 0.003). Also, the higher level of ADP-induced platelet aggregation before clopidogrel administration was associated with an increase in incidence of MACCE (P for trend=0.009).

Conclusion: The observation of significant correlation between antiplatelet status and the future MACCE suggests that we have an opportunity to stratify the long-term thrombotic risk of patients with STEMI after primary PCI.

Keywords: Aspirin, clopidogrel, antiaggregation therapy, platelet reactivity, STEMI

Introduction

Platelet activation mediated by multiple signaling pathways and consecutive coronary thrombosis plays a central role in the pathogenesis of acute coronary syndromes, including ST-segment elevation myocardial infarction (STEMI) (1, 2). Baseline platelet reactivity in these patients is an independent predictor of both successful myocardial reperfusion and the extent of myocardial necrosis after primary angioplasty (3, 4). Consequently, dual antiaggregation treatment with aspirin and clopidogrel represents the therapeutical mainstay in these patients as it reduces the risk of future cardiac death, myocardial reinfarction and urgent revascularisation.

However, despite antiaggregation, a proportion of patients develops recurrent thrombotic events and the residual rate of re-hospitalization due to worsening of ischemic heart disease or the reoccurrence of MI, stroke and cardiovascular death is around 15% (5). When measured by *ex vivo* platelet function assays, the inhibition of platelet aggregation by aspirin and clopidogrel is highly variable and a substantial percentage of patients shows low response to one or both of these drugs (6, 7). As a result, a considerable concern arises that such a low antiplatelet response might represent one of the risk factors for the development of future adverse cardiovascular events. The impact of antiplatelet variability on the cardiovascular risk was the subject of numerous clinical studies but there is still no definitive answer or guidelines how to manage these patients. The vast majority of studies have enrolled patients with stable coronary disease, non-ST elevation acute coronary syndromes or combined both stable and acute coronary patients, with only one study that exclusively recruited patients with STEMI while solely investigated the impact of clopidogrel response (8).

This study prospectively evaluated the dynamic of platelet response to both components of standard antiaggregation treatment during early phase in patients with acute STEMI to determine the

impact of the variability in antiplatelet response on the clinical outcome in this particular population of coronary patients.

Materials and methods

Patients: The study population included ninety patients consecutively admitted to our Coronary Care Unit (Department of Cardiovascular Diseases, Zagreb University School of Medicine & University Hospital Center Zagreb, Croatia) for the diagnosis of acute STEMI who underwent primary percutaneous coronary intervention (pPCI) with stenting. Diagnosis of STEMI was based on acute prolonged chest pain for ≥ 20 minutes and persistent ST-segment elevation for ≥ 0.1 mV in 2 contiguous leads in ECG, accompanied with elevation of creatine kinase-MB isoenzyme (CK-MB) and/or cardiac troponin T (cTnT) levels.

All patients received 300 mg of chewable aspirin on admission and 100 mg/day thereafter. Clopidogrel was administered as a loading dose of 600 mg before PCI and followed by 75 mg/day. Unfractionated heparin was administered during PCI. Eptifibatid infusion was used periprocedurally in 63% of patients during 8 ± 3 hours.

Population excluded: previous ingestion of aspirin, clopidogrel and/or nonsteroidal anti-inflammatory drugs, history of bleeding disorders, platelet count $\leq 100 \times 10^9/L$, hematocrit ≤ 0.30 and renal failure (creatinine $\geq 140 \mu\text{mol/L}$).

Ethics: All patients had given informed consent according to the protocol approved by the institutional review board of Zagreb University Hospital Center and in compliance with the Declaration of Helsinki.

Platelet function test: Aggregation testing was done in the whole blood using Multiplate[®] ASPI and ADP tests (Dynabyte Medical, Munich, Germany) (9). Multiplate[®] is a computerized «point-of-care» instrument that measures the platelet response to antiplatelet therapy based on the impedance, where a change of the resistance between two electrodes immersed into the testing blood is determined after

the addition of specific platelet agonists. Arachidonic acid (AA) with its final concentration of 0.5 mM is used in ASPI test for the measurement of antiplatelet response to aspirin, while ADP at 6.4 mM is used in ADP test for the measurement of clopidogrel effect.

The instrument continuously measures the change in resistance between two silver-coated copper wires that is proportional to the amount of activated platelets adhering to the electrodes and transforms it into "aggregation units" (U). Because two pairs of electrodes are immersed in a single measuring cell, platelet aggregation is always double determined during each test and the final result is calculated from the mean values of the two curves. Pearson's correlation coefficient of the data points detected by each channels is calculated. If the correlation coefficient was lower than 0.98 we have repeated the measurement. In addition, the areas under the aggregation curve detected by each channel are compared and if the difference was higher than 20% vs. the mean value of the two curves, the measurement was also repeated. The Multiplate[®] is comparable to the classical «gold standard» i.e. light transmission aggregometry (LTA) as well as to PFA-100[®] (10, 11).

Platelet response to aspirin (ASPI test) and clopidogrel (ADP test) were expressed as an absolute value (U) as well as relative to the baseline aggregation measured at admission (day 1). Patients were stratified into 4 quartiles according both to the baseline aggregation as well as to the posttreatment reduction of aggregation from the day 1 to day 6.

Blood samples were drawn from antecubital vein and tested within a recommended range of 30 min and 3 h after collection. The compliance to aspirin and clopidogrel was easy to control in the hospital environment. Blood samples for platelet aggregation studies were drawn before loading with dual antiaggregation therapy and primary PCI (day 1), and then daily during the next five days (days 2-6).

All samples after the admission day were taken in the morning after an overnight fast to exclude circadian variation of platelet function. Blood samples were also analyzed for: LDL-cholesterol, triglycerides, blood glucose, glycosylated hemoglobin A (HbA1c), high sensitivity C-reactive protein (hsCRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and homocysteine. Creatine phosphokinase (CK) and cardiac troponin T (cTnT) were determined on daily basis, as peaks of total CK and cTnT were recorded.

Statistical analysis: MedCalc V 7.2.1.0 statistical software was used for all statistical analyses. Continuous variables are presented as median with range, categorical variables as absolute and relative frequencies. Platelet aggregation measured by ASPI test or ADP test is expressed as absolute value as well as relative to the aggregation measured at admission (as a percentage of baseline value). Non-parametric tests (Wilcoxon's and Kruskal-Wallis as appropriate) tests were used for group comparisons of continuous variables; chi-squared test was used for comparisons of categorical variables. Spearman's correlation was used for correlation analysis. Friedman's test for repeated measurements was used to compare results of more than two aggregation tests on different days. Wilcoxon's signed rank test for paired samples was used to compare results of two consecutive aggregation measurements. Statistical significance was set at $P < 0.05$.

Study endpoints: Measured clinical endpoint was the composite of cardiovascular death, non-fatal myocardial infarction, definite or probable stent thrombosis, target vessel revascularization as well as cerebrovascular accident (MACCE, major adverse cardiac and cerebrovascular events).

Data collection and follow-up: Patients were examined after 1 and 6 months, and then contacted by telephone one year after hospital discharge and interviewed about adverse events. Investigators who performed follow-up interviews were blinded to antiplatelet response. Compliance with aspirin and clopidogrel treatment after hospital discharge was determined on examination and by telephone

interview during follow-up. Causes of death were determined by examination of hospital charts, autopsy results and medical files of the patients' general practitioners. For patients who have reached any other clinical end point, a medical chart review was done to determine whether the event met its definition.

Results

Patient characteristics. Among 90 patients enrolled, 87 have completed anticipated daily platelet aggregation measurements (from day 1 to day 6) and were successfully followed-up for a one year. Their median age was 59 years (range 35-88 years) and 60 (69%) were male (Table 1).

Dynamic of platelet response to aspirin and clopidogrel. Arachidonic acid (AA) dependent aggregation significantly drops on day 2 ($P<0.001$) and then rises slightly but significantly on day 3 ($P=0.012$). After day 4 there was no significant difference in measured aggregation: day 4 vs day 5 ($P=0.132$) and day 5 vs day 6 ($P=0.489$). Friedman's test for repeated measurements showed significant differences if measurements of all days were included ($P<0.001$). But when only measurements of day 4 and following days were included, it showed no statistically significant difference ($P=0.831$) (Figure 1a).

The similar dynamic was observed in ADP-dependent platelet aggregation: the significant reduction on day 2 ($P<0.001$) and the increase on the following two days (day 3 and day 4). However, after day 4 there was no significant change in measured aggregation: day 4 vs day 5 ($P=0.143$) and day 5 vs day 6 ($P=0.213$). Friedman's test for repeated measurements has also showed no significant differences in ADP-dependent antiaggregation after day 4 ($P=0.748$) (Figure 1b).

Variability in pretreatment platelet reactivity. Patients were stratified into quartiles based on the baseline AA-dependent platelet aggregation in ASPI test: 1st quartile (Q1): 13.6-35.0, 2nd quartile (Q2): 35.6-58.7, 3rd quartile (Q3): 66.7-97.3 and 4th quartile (Q4): 98.1-180.7. Similarly, patients were stratified into quartiles based on the baseline ADP-induced platelet aggregation in ADP test, i.e. before loading with clopidogrel: 1st quartile (Q1): 6.1-73.2, 2nd quartile (Q2): 74.5-96.6, 3rd quartile (Q3):

100.0-120.9 and 4th quartile (Q4): 121.0-167.0. The values in the fourth quartiles were defined as high pretreatment platelet reactivity.

Variability in response to aspirin and clopidogrel. Patients were also stratified into four quartiles based on the percentage of reduction of AA- and ADP-induced platelet aggregation at day 5 (the day when antiplatelet response to both aspirin and clopidogrel has stabilized) compared with the baseline (day 1). Quartiles of relative aggregation reduction in ASPI test were: 1st quartile (Q1): -29-8%, 2nd quartile (Q2): 8.5-44.6%, 3rd quartile (Q3): 46.5-73.8% and 4th quartile (Q4): 73.9-96.7% (Figure 2a). Quartiles of relative aggregation reduction in ADP test from day 1 to day 5 were: 1st quartile (Q1): -57.4-4%, 2nd quartile (Q2): 5-27%, 3rd quartile (Q3): 28-50% and 4th quartile (Q4): 52-78% (Figure 2b).

There was no statistically significant difference between patients in 1st quartile and 2nd to 4th quartiles of reduction in AA-induced platelet aggregation in ASPI test with respect to baseline demographic and clinical characteristics, medications assigned to patients as well as to biochemical markers of cardiovascular risk, infarct size or heart failure. However, patients in 1st quartile of reduction in ADP-induced platelet aggregation in ADP test, i.e. those with the lowest response to clopidogrel had significantly more frequent previous myocardial infarction, higher platelet count as well as plasma glucose when compared to patients in 2nd to 4th quartiles (Table 1).

Association of baseline platelet reactivity with clinical outcomes. During the one year follow-up, 14 patients (16.1%) developed MACCE: 4 patients died (4.6%), 4 patients had recurrent MI (4.6%), 2 patients had stent thrombosis (2.3%), 3 patients had target vessel revascularization (3.4%) and 2 patients developed ischemic stroke (2.3%), one of whom had also recurrent MI. Thus, 14 patients had 15 MACCE in total. There was a gradual increase in incidence of MACCE from the 1st to the 4th quartile of the baseline ADP-induced platelet aggregation.

Almost half of adverse events (47%) occurred in the 4th quartile, 33% occurred in the 3rd quartile, 13% in the 2nd and only 7% in the 1st quartile of baseline ADP-dependent platelet aggregation. Seven patients (32%) in the 4th quartile sustained an adverse cardiovascular event, 4 (19%) in the 3rd quartile, 2 (9%) in the 2nd quartile and only one (5%) in the 1st quartile i.e. the one with the lowest baseline ADP-induced aggregation (P for trend=0.009) (Figure 3). On the other hand, there was no association between baseline AA-induced platelet aggregation and future MACCE.

Association of posttreatment reduction in platelet reactivity with clinical outcomes: While 8 out of 23 patients in the quartile with the lowest reduction of AA-dependent platelet aggregation from day 1 (baseline) to day 5 sustained MACCE, this occurred in only 6 out of 64 patients from the 2nd to the 4th quartiles (34.8% vs 9.4%; P=0.012).

Similarly, the extent of posttreatment reduction in ADP-dependent platelet aggregation was associated with clinical outcome. Seven out of 23 patients in the quartile with the lowest reduction in aggregation and 7 out of 64 patients in the 2nd to the 4th quartile had MACCE (30.4% vs. 10.9%; P=0.033).

Among 87 patients, 26 patients (29.9%) showed unfavorable response to a single antiplatelet drug, while 52 patients (59.8%) were responders to both aspirin and clopidogrel. Nine patients (10.3%) had suboptimal platelet response to both aspirin and clopidogrel, i.e. belonged to both quartiles of the lowest reduction in AA- and ADP-dependent platelet aggregation. While only 4 patients who were responsive to both components of dual antiaggregation therapy developed some of MACCE (7.7%), this has occurred in 6 patients with suboptimal response to a single antiplatelet drug and in 4 patients who resembled suboptimal platelet inhibition with both aspirin and clopidogrel (44.4%) (P for trend = 0.003) (Figure 4).

Discussion

In this study we have evaluated the platelet response to both aspirin and clopidogrel and their relation to clinical outcome exclusively in patients with STEMI. In the landmark study of clopidogrel resistance in STEMI reported by Matetzky et al, patients were treated with 300 mg loading dose while 600 mg used in this study is now considered as a standard loading dose for its more rapid and stronger inhibition of platelet aggregation (12, 13).

Platelet response to standard dual antiaggregation therapy changes significantly in first days of acute phase STEMI, but than stabilizes after the fourth day of treatment with both aspirin and clopidogrel. This is in concordance with the observation from study of Matetzky et al where no further changes in ADP-dependent aggregation were observed at days 4 through 6 (8).

Baseline ADP-dependent platelet reactivity has been already recognized as a predictor of future adverse clinical outcome (3, 4). Also, a recent study showed that the initial patency of the infarct-related artery in patients with acute STEMI during primary PCI was related to platelet response to aspirin (14). We detected almost geometrical rise in the incidence of recurrent major adverse cardiovascular events among patients from the 1st to the 4th quartile of pretreatment ADP-induced aggregation. While the pretreatment ADP-dependent platelet reactivity strongly correlated with long-term follow-up, the level of pretreatment AA-induced aggregation in patients with STEMI did not. Borna et al have demonstrated higher ADP levels among patients with STEMI in comparison to patients with both non-ST elevation MI or patients with no coronary disease, and speculated that higher ADP serum concentration in these patients may be responsible for their weaker antiplatelet response (15). It is possible that the magnitude of ADP release during myocardial infarction actually reflects the extent of ongoing myocardial necrosis that subsequently correlates with the risk for future adverse clinical outcome.

After the introduction of dual antiaggregation treatment in patients with STEMI, the relative reduction of pretreatment platelet reactivity and not the absolute level of posttreatment platelet reactivity was found to be associated with major adverse cardiovascular events during one year follow-up. Whereas 34.8% of patients in the first quartile of reduction of AA-induced aggregation i.e. those who were the least responsive to aspirin sustained a recurrent cardiovascular event in long-term follow-up, this occurred in only 9.4% of "non-resistant" patients with STEMI ($P=0.012$). The similar finding was observed in the terms of patients' response to clopidogrel. The incidence of MACCE among clopidogrel "resistant" patients was 30.4% in comparison to responders with 10.9% ($P=0.033$). It is not clear why the relative reduction in platelet aggregation and not the absolute level of platelet reactivity after the introduction of aspirin and clopidogrel in therapy was associated with the future outcome in patients with acute STEMI. It is possible that relative changes in platelet reactivity better reflects the complexity of platelet physiology during acute and dynamic event such as the case in STEMI.

Study limitations

The study population and subsequently the number of adverse clinical events were relatively small. In this study we had to take two blood samples to assess a reduction of platelet reactivity from baseline to posttreatment level as a measure of response to antiplatelet treatment. Such measurements are not always suitable for daily clinical practice. For example, in the settings of 24/7 unavailable aggregometry, a baseline aggregation usually can not be obtained due to need for urgent antiplatelet loading in patients with ACSs. However, in the case of point-of-care method like Multiplate[®] this should not be the real problem. Besides, there is increasing number of patients that are already taking chronic antiplatelet therapy and in that case the "true" baseline platelet reactivity can not be assessed.

Conclusions

Even though these data are limited to a relatively small number of cases and require a conformation by larger studies, the observation of significant correlation between antiplatelet status and the future adverse cardiocerebrovascular events (MACCE) suggests that we have an opportunity to stratify the long-term thrombotic risk of patients with STEMI after primary PCI using a simple "point-of-care" aggregometry test like Multiplate[®].

In the future we should examine whether clinical outcome in these patients can be improved by adapting the standard antiplatelet regimen on the basis of the individual risk profile with targeting poor responders to aspirin and/or clopidogrel using higher loading and/or maintenance doses, introduction of GpIIb/IIIa inhibitors or novel antiplatelet drugs like prasugrel, ticagrelor or cangrelor.

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Figure 1. Dynamics of platelet response

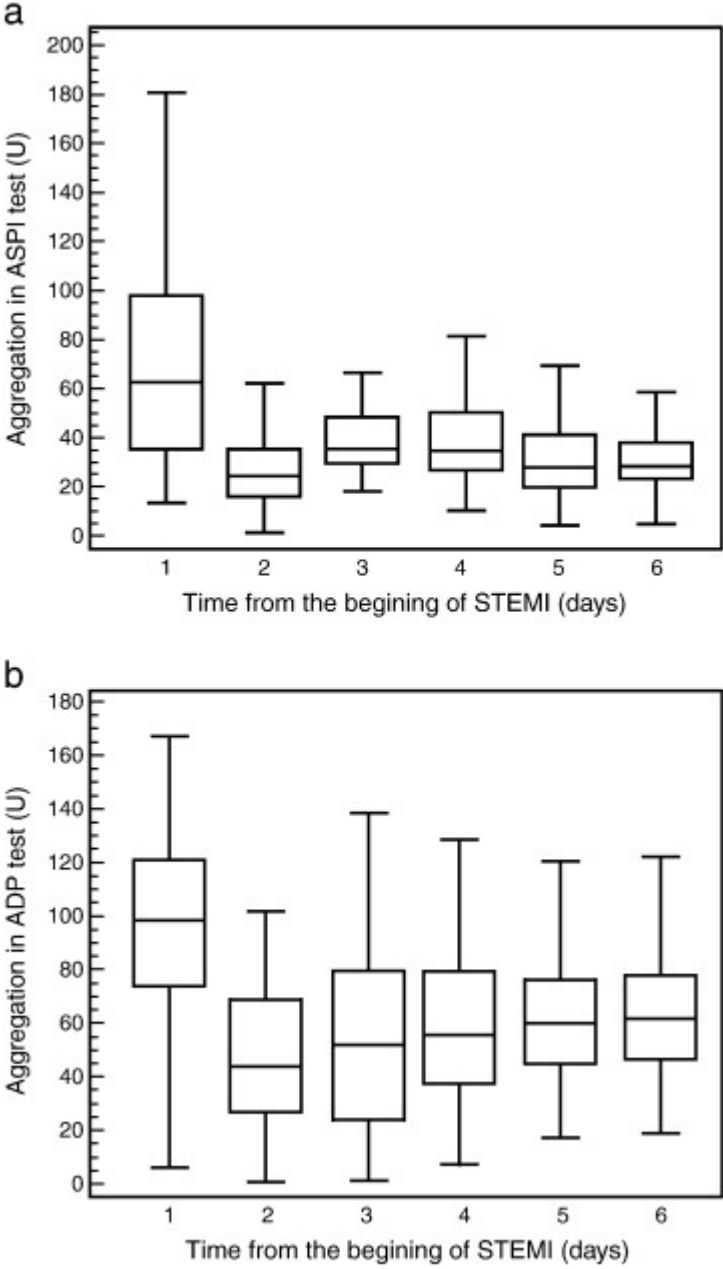


Figure 2. Relative aggregation reduction in ADP and ASPI test

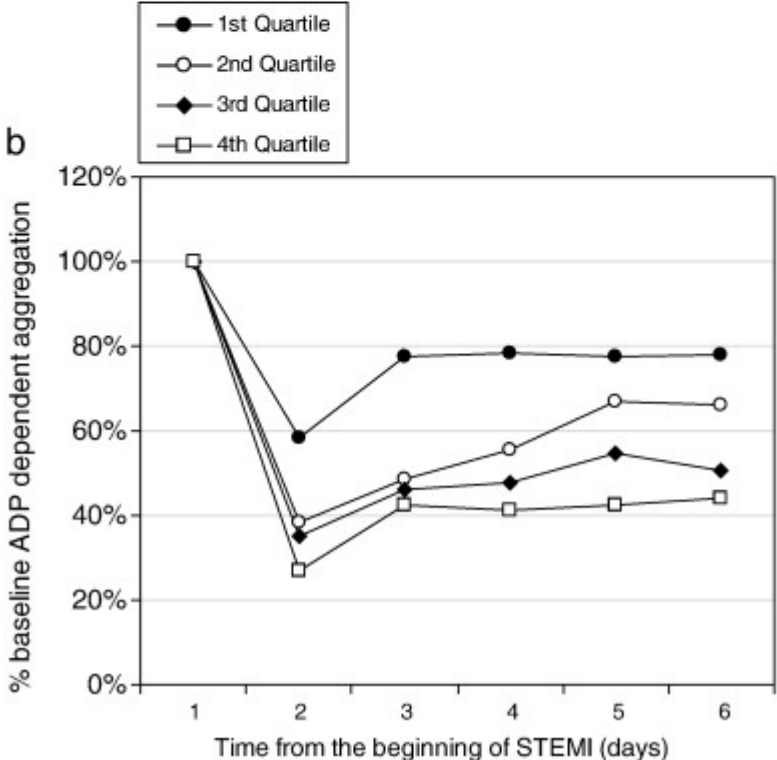
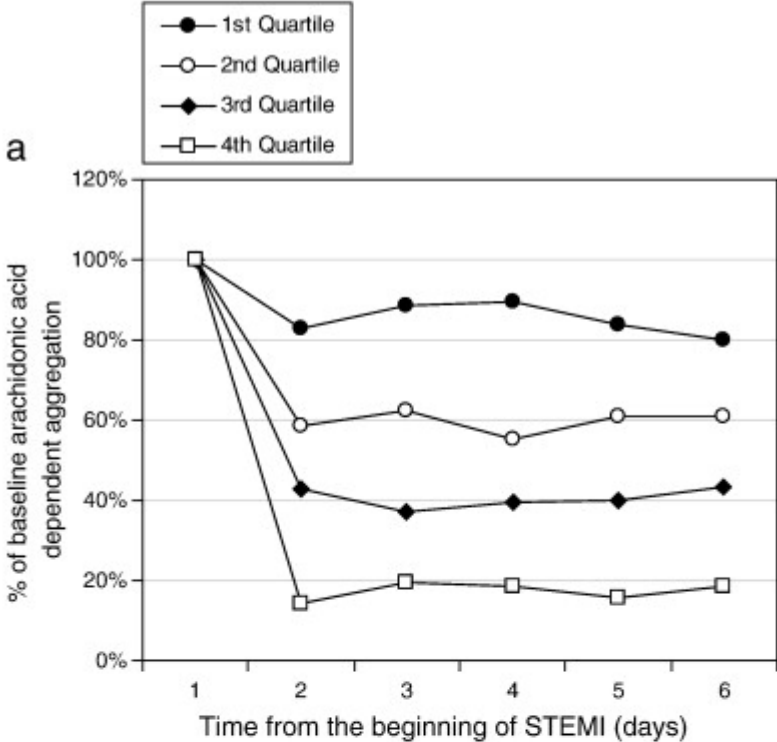


Figure 3. ADP-aggregation reduction related incidence of MACCE

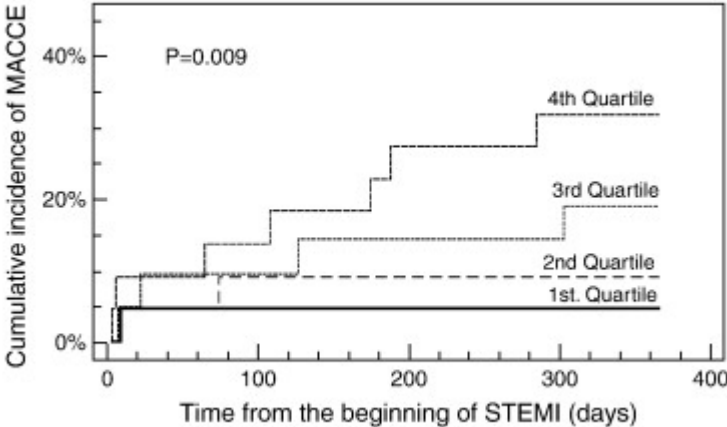


Figure 4. Suboptimal drug response related incidence of MACCE

