

# The effect of glycoprotein IIIa A1/A2 gene polymorphism on one-year outcome in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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## Abstract

**Introduction:** Glycoprotein IIb/IIIa (GP IIb/IIIa) is a platelet receptor composed of two subunits coded by individual genes. GP IIIa gene has two alleles: A1 and A2. The A2 allele determines higher platelet activity and was investigated many times as a potential risk factor of ACS. The influence of A1/A2 polymorphism on the prognosis in patients with ST-segment elevation myocardial infarction (STEMI) has not been analysed so far.

**Aim:** Evaluation of the relationship between GP IIb/IIIa A1/A2 gene polymorphism and one-year prognosis in patients with STEMI treated with primary percutaneous coronary intervention (pPCI).

**Methods:** 171 patients (23.9% – women, 39.7% – anterior MI) with STEMI treated successfully with pPCI as well as 121 healthy subjects from a reference group were enrolled in the study. Genotyping was performed using restriction fragment length polymorphism analysis (RFLP). In one-year follow-up the primary end point included deaths and infarctions. The following methods were used in statistical analysis:  $\chi^2$  as well as Mann-Whitney test, Kaplan-Meier survival analysis, Cox regression model and multivariate analysis.

**Results:** The percentage of A2 allele carriers was similar in STEMI patients and in subjects from the reference group (27.4% vs. 21.5%,  $p=0.24$ ). No statistically significant difference in the incidence of primary end point between the A1A1 homozygotes and A2 allele carriers (A1A2/A2A2 genotype) was observed among STEMI patients. In Cox regression analysis, the variables associated with death or MI were: ejection fraction (RR 0.912,  $p=0.01$ ) and systolic blood pressure on admission (RR 0.97,  $p=0.049$ ). The variables categorised as unfavourable predictors included: Killip class >2 and heart ratio on admission >100/min ( $p < 0.05$ , log-rank test).

**Conclusion:** No relationship between GP IIb/IIIa A1/A2 gene polymorphism and STEMI incidence as well as one-year prognosis in patients with STEMI treated with pPCI was documented.

**Key words:** glycoprotein IIb/IIIa (GP IIb/IIIa), polymorphism, RFLP, STEMI, pPCI

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## Introduction

Glycoprotein IIb/IIIa (GP IIb/IIIa) is an integrin receptor located on the platelet surface, binding

fibrinogen and von Willebrand factor. GP IIb/IIIa plays a key role in platelet aggregation and adhesion, which determines the process of haemostasis.

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Glycoprotein IIb/IIIa is composed of 2 subunits coded by individual genes. The role of GP IIIa A1/A2 gene polymorphism has been investigated extensively. The A2 allele is a product of point mutation within the 2<sup>nd</sup> exon in the 1565<sup>th</sup> nucleotide (Cytosine→Thymine), which results in a change in the 33<sup>rd</sup> position of the amino acid chain (Leu→Pro) [1].

Molecular investigations indicate a potential relationship between GP IIIa A1/A2 gene polymorphism and increased risk of thromboembolic events, with myocardial infarction (MI) among them. The A2 allele has also been implicated as a potential risk factor of atherosclerosis and acute coronary syndromes (ACS). However, the results of previous studies are inconsistent. There is no unequivocal evidence that presence of the A2 allele predisposes to MI. Data on its influence on prognosis in patients with ACS are limited. In the aspect of prognosis in patients with coronary artery disease, its role has been evaluated so far only in patients after coronary artery bypass graft surgery (CABG) – presence of A2 allele increased by 2.4 times the risk of periprocedural myocardial ischaemia (OR 2.4, 95% CI 1.2-6.2) [2]. The possible role of the A2 allele as a cause of complications after revascularisation is still unknown.

The aim of the present study was to analyse prospectively the relationship between GP IIIa A1/A2 gene polymorphism and prognosis in patients with ST-segment elevation myocardial infarction (STEMI) treated successfully with primary percutaneous coronary intervention (pPCI).

## Methods

### Patients and control group

171 patients with STEMI treated successfully with pPCI (23.9% – women, 39.7% with anterior MI; all patients were receiving 150 mg of aspirin daily) were enrolled in the study. Additionally, a group of healthy subjects, with genotype representative for the population of Podlasie district (50.4% women), was examined [3]. Diagnosis of STEMI was established based on typical clinical symptoms, ECG changes and increase of myocardial necrosis markers.

All patients were followed for one year. Primary composite end point included cardiac deaths and recurrent MI, while secondary end point additionally included another coronary angiography, PCI, CABG or cerebral stroke during the follow-up.

### Genetic analysis

DNA was extracted from whole blood samples using chelex [4]. Genotyping was performed using restriction fragment length polymorphism analysis (RFLP). In the

first stage of PCR, exon 2 GP IIIa gene was amplified (primers: 5'-CTG CAG GAG GTA GAG AGT CGC CAT AG-3' and 5'-GCC GGA GTG CAA TCC TCC GGG GAC TGA CTT G-3'). Next, the PCR product was incubated with NciI restrictase and then subjected to electrophoresis on agarose gel. In the case of the A2 allele, a new restriction site appears as a result of mutation. In electrophoresis, the A1 allele is visible as a single fragment (234 base pairs), whereas the A2 allele forms two fragments (157 and 77 base pairs).

### Statistical analysis

Patients with STEMI were divided according to genotype into two groups: a group of A1 homozygotes and a group of A2 allele carriers (genotype A1A2 or A2A2). Statistica 6.0 software (StatSoft Inc.) was used for statistical analysis. The groups were compared by means of  $\chi^2$  as well as Mann-Whitney tests. The results were statistically significant for p value below 0.05. Kaplan-Meier curves with log-rank test were applied to survival analysis. Cox regression model was used in univariate analysis of uncategorised variables, and log-rank test analysis for categorised variables. Furthermore, multivariate logistic regression analysis was performed. Predictive value of A1/A2 polymorphism for the occurrence of unfavourable cardiovascular events was established based on an ROC curve, plotted by means of Analyse-it software.

## Results

171 patients with STEMI as well as 121 subjects from the reference group underwent genotype analysis. There was a slightly increased incidence of the A2 allele in patients from the study group (A1A2 or A2A2 genotype); however, the difference was not significant (27.4% vs. 21.5%,  $p=0.24$ ). The percentages of various haplotypes are shown in Table I.

Among patients with STEMI, 124 (72.5%) subjects were found to be in the group of A1 homozygotes, whereas 47 (27.5%) patients were A2 allele carriers (genotype A1A2 or A2A2). General characteristics of

**Table I.** The percentage of various genotypes in patients with STEMI and reference group (differences NS)

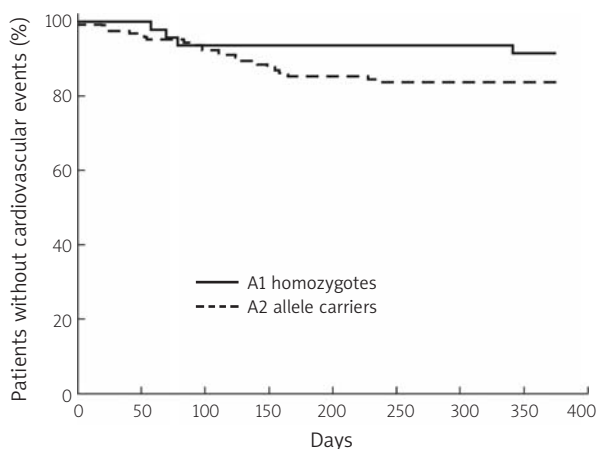
| Genotype | Patients with STEMI (N=171) | Reference group (N=121) |
|----------|-----------------------------|-------------------------|
| A1A1     | 124 (72.5%)                 | 95 (78.5%)              |
| A1A2     | 44 (25.7%)                  | 22 (18.2%)              |
| A2A2     | 3 (1.7%)                    | 4 (3.3%)                |

**Table II.** General characteristics of patients from group of A1 homozygotes and A2 allele carriers

|  | A1 homozygotes N=124 | A2 allele carriers N=47 | p      |
|--|----------------------|-------------------------|--------|
| Age (years)                                | 60.6±11.5            | 58.6±11.9               | NS     |
| Gender – women (%)                         | 30 (24.1%)           | 11 (23.4%)              | NS     |
| Arterial hypertension (%)                  | 62 (50%)             | 19 (40%)                | NS     |
| Type 2 diabetes mellitus (%)               | 28 (22.%)            | 7 (14.8 %)              | NS     |
| Hypercholesterolaemia (%)                  | 36 (29%)             | 21 (44.6%)              | NS     |
| Smoking status (%)                         | 59 (47.5%)           | 26 (55.3%)              | NS     |
| Previous MI (%)                            | 13 (10.4%)           | 3 (6.3%)                | NS     |
| Anterior MI (%)                            | 52 (41.9%)           | 16 (34%)                | NS     |
| Inferior MI (%)                            | 68 (54%)             | 28 (59%)                | NS     |
| TIMI >0 before pPCI (%)                    | 64 (51.6%)           | 23 (48%)                | NS     |
| Stent implantation (%)                     | 47 (37.9%)           | 14 (29.7%)              | NS     |
| Ticlopidine (%)                            | 85 (68.5%)           | 32 (68%)                | NS     |
| GP IIb/IIIa inhibitors                     | 31 (25%)             | 12 (25.5%)              | NS     |
| Killip scale >1 (%)                        | 61 (49.1%)           | 14 (29.7%)              | 0,0224 |
| Total cholesterol (mmol/l)                 | 5.13±0.91            | 5.37±1.06               | NS     |
| LDL cholesterol (mmol/l)                   | 3.32±0.82            | 3.36±0.93               | NS     |
| HDL cholesterol (mmol/l)                   | 1.16±0.38            | 1.2±0.39                | NS     |
| Triglycerides (mmol/l)                     | 1.5±0.71             | 1.73±0.95               | NS     |
| Fibrinogen (g/l)                           | 3.85±0.94            | 3.75±0.94               | NS     |
| Body mass index – BMI (kg/m <sup>2</sup> ) | 27.66±5.17           | 26.8±4.64               | NS     |
| Ejection fraction (%)                      | 44.4±8.9             | 46.6±8.2                | NS     |

both groups are given in Table II. Patients with A1A1 genotype presented signs of cardiac failure on admission with significantly higher incidence (class >1 according to Killip scale: 49.1% vs. 29.7%,  $p=0.0224$ ).

In one-year follow-up the percentage of patients with primary end point (death or MI) was insignificantly higher in the group of A1 homozygotes (6.4% vs. 2.1%, NS). Also in this group secondary end point was

**Figure 1.** Kaplan-Meier survival curves

observed (death, MI, coronary angiography, PCI, CABG or stroke) insignificantly more often – 17.7% vs. 8.5% (NS). No significant differences between groups were found in the Kaplan-Meier survival analysis (Figure 1).

In univariate analysis, the variables influencing the occurrence of primary end point were: systolic blood pressure on admission (as a continuous variable, relative risk (RR) 0.97,  $p < 0.05$ ), ejection fraction assessed on the second day after MI (as a continuous variable, RR 0.912,  $p < 0.05$ ), heart rate on admission >100/min. (survival rate of 80% vs. 96.23%,  $p < 0.05$ ) and haemodynamic status class >2 according to the Killip scale (survival rate of 60% vs. 95.78%,  $p < 0.05$ ). A1/A2 polymorphism did not affect death or MI (survival rates in the group of homozygotes and A2 allele carriers were 93.55% and 97.87%, respectively;  $p > 0.05$ ). In multivariate analysis, the variables independently associated with primary end point were: ejection fraction (as a continuous variable) (OR 0.914, 95% CI 0.84-0.99) and Killip class >2 (OR 13.6, 95% CI 1.7-107.3).

Prognostic value of GP IIb/IIIa A1/A2 gene polymorphism was low and amounted to 0.586 (95% CI 0.41-0.76,  $p > 0.05$ ) for primary end point and 0.571 (95% CI 0.46-0.68,  $p > 0.05$ ) for secondary end point.

## Discussion

No significant correlation between GP IIIa A1/A2 gene polymorphism and MI occurrence and one-year prognosis in patients with STEMI successfully treated with pPCI was found. Slightly worse prognosis in patients with A1A1 genotype should be related to significantly worse haemodynamic state of these patients including higher Killip-Kimball class and more frequent anterior MI. That has been confirmed in multivariate analysis.

There are some convincing reports about mechanisms leading to increased propensity toward thrombosis in the case of A2 allele presence. In molecular studies, the A2 variant was associated with higher activation of GP IIb/IIIa receptor after ADP stimulation [6]. In vitro cultivated cells with mutated receptor expression are characterised by higher capability of immobilised fibrinogen binding [7]. A similar relationship was not observed for free fibrinogen binding. There are also some reports on the A2 allele being responsible for increased thrombin generation and interfering with antithrombotic aspirin actions [8].

A number of case-control analyses were performed in which the A2 allele was assessed as a potential risk factor for ACS. In the first of them, the A2 allele was more than two times more frequently observed in patients with ACS than in the control group [9] (3.6 times more frequently in the subgroup of patients aged <60 years). The hazard ratio for ACS related to the A2 allele was 2.8. Larger analyses have been performed to verify the results obtained in relatively small groups of patients (n=139). The conclusions from further studies are inconsistent. ECTIM and ARIC studies did not show a relationship between A1/A2 polymorphism and MI [10] or occurrence of coronary artery disease (sudden cardiac death, MI, coronary artery revascularisation) [11]. Conversely, a statistically significant difference in the number of A2 allele carriers between the study and control group was observed in a Dutch programme (n=2210) [12]. A comparison of young patients with MI (below 45 or 47 years) and age-matched subjects from the control groups showed divergent results [13, 14]. Also in a prospective analysis (Copenhagen City Heart Study, follow-up of 22 years) young men with A2A2 genotype had 3 times greater risk of coronary heart disease and 4 times greater risk of MI than subjects with A1A1 genotype [15].

The effect of a gene on the presence of a disease is complex due to numerous interactions with other genes and environmental factors. It has been demonstrated that there is a relationship between A2 allele carrier state and higher fibrinogen level in patients with coronary artery disease [16]. In patients from the fourth quintile of fibrinogen level the A2 allele had a significant impact on time to death or MI.

A relationship between A2 variant and higher serum cholesterol levels has been reported [12, 14]. Also, significantly worse prognosis in patients with coronary artery disease who were A2 allele carriers and smokers has been observed [17].

There are some reports on the relationship between A1A1 genotype and more severe atherosclerosis of coronary arteries. Such a relationship was also observed in autopsy material [18] and in patients with coronary artery disease who underwent coronary angiography [5]. A hypothesis has been proposed that the A1 allele predisposes to atherosclerosis, whereas the A2 allele predisposes to thrombus formation [18]. However, in the present study a higher incidence of thromboembolic complications in A2 allele carriers was not observed.

In the analysis of the effects of A1/A2 allele polymorphism on the occurrence of thrombotic episodes and prognosis after STEMI, its potential relationship with antiplatelet drug actions should be taken into consideration. In several in vitro experiments the influence of aspirin on platelet function, dependent on GP IIb/IIIa receptor variant, was evaluated. The results were divergent. The A2 allele [8] or A1A1 genotype [19] were associated with defective aspirin activity. The relationship between platelet receptor variation and aspirin resistance phenomenon was not confirmed in another study [20]. In the case of the A2 variant worse clopidogrel activity [6] but higher platelet sensitivity to abciximab was observed [19].

Limitations of the present study include the small size of the analysed group and lack of a control group. Instead of gender- and age-matched controls we used a group with a genotype representative for the geographic area [3]. Precise clinical characteristics of this group are not known because the study assessed anonymous subjects. Though the relationship between A1/A2 polymorphism and STEMI was not assessed, analysis of its influence on prognosis after MI treated with pPCI was the main aim of the study.

## Conclusions

Our results do not confirm the presence of a relationship between GP IIIa A1/A2 gene polymorphism and STEMI. Also, a significant influence on prognosis in patients hospitalised due to STEMI was not observed.

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## Wpływ polimorfizmu A1/A2 genu glikoproteiny IIIa na roczne rokowanie pacjentów z zawałem serca z uniesieniem odcinka ST leczonych pierwotną przezskórną interwencją wieńcową

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### Streszczenie

**Wstęp:** Glikoproteina IIb/IIIa (GPIIb/IIIa) jest receptorem płytek krwi zbudowanym z 2 podjednostek kodowanych przez oddzielne geny. Gen GPIIIa ma allele A1 i A2. Allel A2 warunkuje wyższą aktywność płytek i był wielokrotnie badany jako potencjalny czynnik ryzyka ostrych zespołów wieńcowych. Dotychczas nie oceniano wpływu polimorfizmu A1/A2 na rokowanie pacjentów z zawałem serca z uniesieniem odcinka ST (STEMI).

**Cel:** Zbadanie związku między polimorfizmem A1/A2 genu GPIIIa a rocznym rokowaniem pacjentów ze STEMI leczonych pierwotną przezskórną interwencją wieńcową (pPCI).

**Metodyka:** Do badania włączono 171 chorych ze STEMI skutecznie leczonych pPCI (23,9% kobiet, 39,7% zawał przedni) oraz 121 osób z grupy referencyjnej. Genotyp oznaczano metodą polimorfizmu długości fragmentów restrykcyjnych (RFLP). W rocznej obserwacji pierwotny punkt końcowy uwzględniał zgony i zawały. W analizie statystycznej użyto testów  $\chi^2$  i Manna-Whitneya, analizy przeżycia Kaplana-Meiera, modelu regresji Coxa oraz analizy wieloczynnikowej.

**Wyniki:** Odsetek nosicieli allele A2 był zbliżony u chorych ze STEMI i w grupie referencyjnej (27,4% vs 21,5%;  $p=0,24$ ). Wśród pacjentów ze STEMI nie obserwowano istotnej statystycznie różnicy w występowaniu dodatniego punktu końcowego między grupą homozygot A1A1 i nosicieli allele 2 (genotyp A1A2/A2A2). W modelu regresji Coxa zmiennymi związanymi z wystąpieniem zgonu lub zawału były: frakcja wyrzutowa (RR 0,912;  $p=0,01$ ) i ciśnienie skurczowe przy przyjęciu (RR 0,97;  $p=0,049$ ). Ze zmiennych kategoryzowanych z niepomyślnym rokowaniem wiązały się klasa wg Killipa  $>2$  oraz HR przy przyjęciu  $>100/\text{min}$  ( $p < 0,05$ , *log-rank test*).

**Wnioski:** Nie wykazano związku między polimorfizmem A1/A2 genu GPIIIa a występowaniem STEMI ani też rocznym rokowaniem pacjentów ze STEMI poddanych pPCI.

**Słowa kluczowe:** glikoproteina IIIa (GPIIIa), polimorfizm, RFLP, STEMI, pPCI

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