The rs9982601 polymorphism of the region between the SLC5A3/MRPS6 and KCNE2 genes associated with a prevalence of myocardial infarction and subsequent long-term mortality

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INTRODUCTION

rs9982601 (C>T) is a polymorphism of the noncoding region between the SLC5A3/MRPS6 and KCNE2 genes. It has been shown to be associated with early-onset myocardial infarction (MI) with T as a risk allele.

OBJECTIVES

The aim of our study was to investigate the association of the rs9982601 polymorphism with long-term overall mortality from MI and prevalence of MI in a Polish population.

PATIENTS AND METHODS

The study involved patients with MI treated invasively. Individuals who underwent paternity testing served as a population group. Genotyping was performed by the TaqMan method. The analyzed endpoint was the overall long-term mortality.

RESULTS

The study group comprised 981 patients (mean age, 62.8 ± 12.1 years; 259 women [26.4%]). The percentages of TT, CT, and CC genotypes were 3.1%, 25.6%, and 71.3%, respectively, in the whole group, and 2.4%, 16.8%, and 80.8% (P = 0.01) in the population group (n = 167). During follow-up (median, 1826 days), 157 patients died (16%). No significant differences were observed between the genotypes either in clinical characteristics or in mortality. However, in a subgroup of high-risk patients (GRACE risk score of 155 points or higher, n = 428), low-risk CC homozygotes had a significantly better survival rate compared with the other genotypes (hazard ratio, 0.64; 95% confidence interval, 0.43–0.96; P = 0.03).

CONCLUSIONS

We showed that the rs9982601 polymorphism of the region between SLC5A3/MRPS6 and KCNE2 genes is associated with long-term mortality in high-risk patients after MI. Additionally, our study supports the previous reports on the correlation of this polymorphism with the prevalence of MI.
and muscle and encodes the membrane subunit of a voltage-gated potassium channel. Loss of function of this protein may lead to long QT syndrome type 6 and sudden cardiac death.\(^6,7\)

According to current guidelines and everyday practice, the assessment of prognosis in patients with MI is based on clinical presentation, which comprises patients’ history, parameters from physical examination, and routine tests.\(^5\) There is an ongoing search for novel risk markers.\(^6\) These studies also concern genetic factors. So far, the best documented influence on outcome has been described for the 9p21 locus.\(^6,12\)

There are still several other genetic loci and SNPs associated with MI that have not been validated for their effect on subsequent prognosis. One of them is rs9982601 SNP.\(^1\) In this case, there are also no studies verifying an association with MI in a Polish population. Therefore, we chose this SNP for further investigation.

The aims of the study were to evaluate the association of the rs9982601 polymorphism with long-term overall mortality after ST-elevation MI (STEMI) and to validate its impact on the prevalence of STEMI in a Polish population.

### PATIENTS AND METHODS

We performed a 2-center study. The study group comprised patients with STEMI treated invasively in the years from 2001 to 2010 in the Departments of Cardiology of the Medical University of Białystok and the Medical University of Warsaw. All patients were of European descent. STEMI was diagnosed based on the most current definition, including chest pain, persistent ST-segment elevation or a new left bundle branch block on electrocardiography, and an increase in the levels of cardiac necrosis markers (in our case, troponin I).\(^13,14\) To make the analysis more sensitive for associations with long-term outcome, patients who died during the first 48 hours from hospital admission were excluded from the study. No other exclusion criteria were applied in the study group. In all cases, coronary angiography was performed within 12 hours from the onset of symptoms. Pharmacological treatment was consistent with contemporary guidelines.

As described previously,\(^1\) the registry comprised data from patients’ history, physical examination on admission, routine laboratory tests, heart imaging (echocardiography, coronary angiography), and results of invasive treatment. Next, every patient also had a GRACE risk score calculated for general risk assessment.\(^15\) The score was calculated retrospectively, based on data on admission.

The population group included 84 adult men and 83 adult women, whose genetic material was collected for paternity testing. Their clinical data were not available; however, it was assumed that they were representative in terms of the genetic background for our region, as has been described previously.\(^16\)

Blood samples for genotyping were collected in EDTA tubes and stored at −20°C. DNA was extracted with a commercial kit (Blood Mini, A&A Biotechnology, Gdynia, Poland). The genotypes were determined with a TaqMan SNP Genotyping Assay on the ABI 7500 real-time polymerase chain reaction platform (Applied Biosystems, Carlsbad, California), according to the manufacturer’s instructions. Ten percent of the samples were genotyped in duplicates.

The analyzed endpoint was long-term all-cause mortality. Information concerning survival status was retrieved from the local population registry run by a government office.

Proxies for the rs9982601 SNP were searched with an SNP Annotation and Proxy Search (SNAP) browser (Broad Institute).\(^17\) We used the following settings: SNP dataset, 1000 Genomes Pilot 1; population panel, CEU; \(r^2\) threshold, 0.8; distance limit, 500 kb. Next, the proxies were investigated for a potential effect on gene expression in the PubMed database, based on the approach described previously.\(^18\)

Statistical analysis was performed with STATISTICA 9.0 software (StatSoft Polska, Kraków, Poland). Variable distribution was assessed with the Shapiro–Wilk test. Next, clinical parameters were compared between the genotypes with the \(\chi^2\) test or Kruskal–Wallis test. The difference in probability of survival was evaluated with the log-rank test. A univariate analysis for long-term survival was performed with a Cox proportional hazards model. Variables with a significant association with survival except for the GRACE risk score were included in a primary

### TABLE 1 Distribution of alleles in the groups

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Study group, n = 981</th>
<th>High-risk patients from the study group, n = 428</th>
<th>Population group, n = 167</th>
<th>CEU population(^a), n = 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>31 (3.1)</td>
<td>12 (2.8)</td>
<td>4 (2.4)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>CT</td>
<td>251 (25.6)</td>
<td>101 (23.6)</td>
<td>28 (16.8)</td>
<td>17 (33.3)</td>
</tr>
<tr>
<td>CC</td>
<td>699 (71.3)</td>
<td>315 (73.6)</td>
<td>135 (80.8)</td>
<td>32 (62.7)</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) of patients.

Study group vs. population group: \(OR = 1.53; 95\% CI, 1.07–2.2, P = 0.018\) (per T allele); after adjustment for sex, \(OR = 1.79; 95\% CI, 1.1–2.9, P = 0.02\).

### Abbreviations:

CEU, Utah residents with Northern and Western European ancestry; CI, confidence interval; OR, odds ratio

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\(^a\) CEU; Yates \(P = 0.053\), \(\chi^2\) test, compared with the population group.\(^19\)

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The percentages of specific genotypes in the study group and in the population group are shown in TABLE 1. The odds ratio for STEMI was 1.53 (95% confidence interval [CI], 1.07–2.2) per T allele and remained significant after adjusting for sex (TABLE 1). Allele distribution in our population group varied from the frequencies observed in the Utah Residents with Northern and Western European ancestry (CEU) population, but the difference was not significant (TABLE 1; Yates $P = 0.053$; $\chi^2$ test).

No significant deviations from the Hardy–Weinberg equilibrium were found in either group ($P = 0.15$ for the study group, and $P = 0.2$ for the population group). The clinical characteristics of specific genotypes are shown in TABLE 2. No significant differences were found between the genotypes.

The study was designed to have a statistical power of at least 80% to detect a 50% percent relative risk increase in 5-year mortality of T-allele carriers compared to CC low-risk homozygotes. Assuming an overall mortality rate of 18% $^6$ and a percentage of low-risk homozygotes around 75%, $^1$ the target of events would be achieved in a group of 862 patients. Assuming a percentage of high-risk homozygotes of 40% and a mortality rate of 27% in this subgroup, $^1$ the number of 981 patients included in our analysis would allow to detect an increase in relative risk of 60% in this subgroup. The sample sizes in survival functions were estimated with the 2-sample $Z$-test.

The study protocol was approved by the Ethics Committee of the Medical University of Białystok and Ethics Committee of the Medical University of Warsaw. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed written consent was obtained from all subjects before their inclusion in the study.

RESULTS. The study comprised a total of 1017 patients, of whom 19 were lost to follow-up (1.86%). In 17 subjects, the genotype was not determined because of poor sample quality. No genotyping errors were detected in samples genotyped in duplicates. The final study group included 981 patients (mean age, 62.8 ±12.1 years; 259 women [26.4%]; percutaneous coronary intervention successful [Thrombolysis In Myocardial Infarction flow 3] in 897 patients [91.4%]). Standard pharmacotherapy after hospital admission included the use of acetylsalicylic acid (915 patients [93.3%]), clopidogrel or ticlopidine (843 patients [85.9%]), β-blockers (893 patients [91%]), angiotensin-converting enzyme inhibitors (828 patients [84.4%]), and statins (823 patients [83.9%]). In 2001, statins were prescribed only for hypercholesterolemia, and since 2003, it has been a standard treatment (no patients were enrolled in the year 2002).

The percentages of specific genotypes in the study group and in the population group are shown in TABLE 1. The odds ratio for STEMI was 1.53 (95% confidence interval [CI], 1.07–2.2) per T allele and remained significant after adjusting for sex (TABLE 1). Allele distribution in our population group varied from the frequencies observed in the Utah Residents with Northern and Western European ancestry (CEU) population, but the difference was not significant (TABLE 1; Yates $P = 0.053$; $\chi^2$ test). $^1$ No significant deviations from the Hardy–Weinberg equilibrium were found in either group ($P = 0.15$ for the study group, and $P = 0.2$ for the population group). The clinical characteristics of specific genotypes are shown in TABLE 2. No significant differences were found between the genotypes.

Long-term follow-up was performed with a median of 1826 days (minimum, 846 days; maximum, 1827 days). During this time, 157 patients (16%) died, including 110 CC homozygotes (15.7%), 42 heterozygotes (16.7%), and 5 TT homozygotes (16.1%). No significant differences in the probability of survival were found between the genotypes, when the entire study group was analyzed. Kaplan–Meier survival curves for specific genotypes of the rs9982601 polymorphism are shown in FIGURE 1.
and long-term mortality are shown in FIGURE 1 (P = 0.74, log-rank test). TABLE 3 shows the results of the univariate and multivariate analyses (Cox proportional hazards model) in the whole study group.

In the subgroup of high-risk patients (GRACE risk score, ≥155 points; n = 428; 25% mortality [n = 107]; percentages of genotypes shown in TABLE 1) 70 CC homozygotes (22.2%), 35 heterozygotes and 560 CC homozygotes (34.6%), and 2 TT homozygotes (16.7%) died. In this subgroup, CC homozygotes had a significantly higher probability of survival than patients with other genotypes (P = 0.033, log-rank test). FIGURE 2 shows Kaplan–Meier survival curves for rs9982601 genotypes and long-term mortality in a subgroup of high-risk patients.

In the Cox proportional hazards model performed in a subgroup of high-risk patients (TABLE 4), the rs9982601 polymorphism was one of the variables associated with time of survival (hazard ratio [HR] for CC genotype vs. T-allele carriers, 0.64; 95% CI, 0.43–0.96; P = 0.032; HR for CC genotype vs. CT genotype, 0.61; 95% CI, 0.4–0.9; P = 0.16). In the multivariate model, the parameters independently associated with outcome were age, Killip class on admission, ejection fraction, and serum creatinine concentrations.

Proxies for the rs9982601 SNP are listed in TABLE 5. The PubMed database search revealed no reports describing the effect of SNPs on gene expression at any level.

**DISCUSSION** We report for the first time the association between the rs9982601 polymorphism and adverse long-term outcome after MI. This finding was limited to a subgroup of high-risk patients according to the GRACE risk score. Additionally, our data support previous reports concerning the relation between the investigated SNP and a prevalence of STEMI.

All potential explanations for those phenomena are highly hypothetical. No biological mechanism linking the rs9982601 polymorphism with the reported phenotype has been described. The SNP is located in the intergenic region, and there are no studies investigating the effect of the rs9982601 C>T SNP on the expression of the nearby genes (SLCSA3/MRPS6 and KCNE2). We have verified a hypothesis that rs9982601 SNP is just a genetic risk marker, in a strong linkage disequilibrium with another functional SNP. However, none of those SNPs were ever reported to influence gene expression on any level. None of the proxies are located within the nearby genes (SLCSA3/MRPS6 and KCNE2), although the genes
hand, it is theoretically possible that this region encodes a different type of ribonucleic acid part-

ticle than mRNA, such as miRNA. Pairing miRNA with complementary mRNA usually leads to

its degradation and gene silencing.

were included in a distance limit of 500 kb that we used in our search. Another option is that the

surrounding genes might be silenced in a pro-

cess of genomic imprinting, which is based on
cytosine methylation and blocking the access of

transcription factors to chromatin. On the other

hand, it is theoretically possible that this region

encodes a different type of ribonucleic acid par-
ticle than mRNA, such as miRNA. Pairing miRNA
with complementary mRNA usually leads to

its degradation and gene silencing.20

Conversion factor to SI unit for creatinine is 88.49.

Abbreviations: PCI, percutaneous coronary intervention; others, see TABLE 1

TABLE 3 Univariate and multivariate analyses for long-term mortality in the whole study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, y</td>
<td>1.06</td>
<td>1.045–1.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>type 2 diabetes</td>
<td>1.9</td>
<td>1.3–2.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>hypertension</td>
<td>1.75</td>
<td>1.2–2.4</td>
<td>0.001</td>
</tr>
<tr>
<td>previous myocardial infarction</td>
<td>2.0</td>
<td>1.4–3.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>heart rate, bpm</td>
<td>1.014</td>
<td>1.006–1.022</td>
<td>0.0009</td>
</tr>
<tr>
<td>systolic blood pressure, mmHg</td>
<td>0.993</td>
<td>0.987–0.999</td>
<td>0.03</td>
</tr>
<tr>
<td>Killip class</td>
<td>1.8</td>
<td>1.5–2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI 3 flow after PCI</td>
<td>0.52</td>
<td>0.32–0.84</td>
<td>0.008</td>
</tr>
<tr>
<td>ejection fraction, %</td>
<td>0.94</td>
<td>0.93–0.96</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>creatinine, mg/dl</td>
<td>2.0</td>
<td>1.7–2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>1.018</td>
<td>1.014–1.022</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>rs9982601 CC genotype</td>
<td>0.94</td>
<td>0.67–1.3</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age, y</td>
<td>1.05</td>
<td>1.03–1.06</td>
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<td>type 2 diabetes</td>
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<td>0.03</td>
</tr>
<tr>
<td>hypertension</td>
<td>1.55</td>
<td>1.07–2.26</td>
<td>0.02</td>
</tr>
<tr>
<td>Killip class</td>
<td>1.4</td>
<td>1.2–1.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>ejection fraction, %</td>
<td>0.96</td>
<td>0.94–0.98</td>
<td>0.0001</td>
</tr>
<tr>
<td>creatinine, mg/dl</td>
<td>1.6</td>
<td>1.2–2.0</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

FIGURE 2 Subgroup of high-risk patients; Kaplan–Meier survival curves for specific genotypes of the
rs9982601 polymorphism and long-
term mortality. The difference between the groups was statistically significant
\( P = 0.033: \text{CC homozygotes vs T-allele carriers}; P=0.016: \text{CC homozygotes vs. CT genotype; log-rank test}.\)
In our study, we observed a remarkably high effect size of the investigated SNP on survival. The relative risk associated with the CC genotype was 0.64 and the encoding genes belong to the main susceptibility genes for this disease. Nevertheless, the arrhythmia hypothesis suggests the potential link to survival after MI, but not to atherosclerosis and the prevalence of MI.

We showed a strong effect of the rs9982601 SNP on survival after MI in a relatively small study group. On the other hand, a genome-wide study performed in over 18,000 individuals revealed no association between this polymorphism and either lipid response to simvastatin therapy or risk of major vascular events during a 5-year follow-up. However, patients enrolled in that research were definitely at lower cardiovascular risk compared with our study group. The eligibility criteria included diagnosis of previous coronary artery disease, ischemic stroke, peripheral artery disease, diabetes mellitus, or, in men aged at least 65 years, hypertension. The primary endpoint was defined as coronary death, nonfatal MI, coronary or noncoronary revascularization, or any stroke. During the 5-year follow-up, major vascular events occurred in 20.2% of simvastatin-associated patients and in 25.4% of patients on placebo therapy. Our study, however, investigated the occurrence of all-cause death in a group of patients at a notably higher risk of cardiovascular events (subjects after MI). Owing to these differences in design, the studies cannot be directly compared.

The association between the rs9982601 genotype and mortality was observed only in a subgroup of high-risk patients according to the GRACE risk score. No such effect was found in patients with low or medium risk. It might be that the effect of the genotype on phenotype is triggered under conditions of increased risk. Alternatively, we might have simply missed it in low- and medium-risk patients due to the generally low event rate. A detailed analysis of mortality in a subgroup of high-risk patients revealed that the best prognosis had a small fraction of TT homozygotes with CC homozygotes and was underpowered to analyze TT homozygotes separately. Moreover, there are no theoretical concepts supporting a theory of the so-called heterozygote effect of the investigated SNP. It seems that TT homozygotes had a favorable risk profile (age, creatinine, GRACE risk score), but the differences were not significant when compared with C-allele carriers (P values not reported). Therefore, we assume that low mortality in the case of TT genotype is an accidental finding.

We observed a remarkably high effect size of the investigated SNP on survival. The relative risk associated with the CC genotype was 0.64 long QT syndrome (type 6, 2, or 1, respectively) and the encoding genes belong to the main susceptibility genes for this disease. In our study, the investigated endpoint was all-cause death, and we had no possibility to investigate the underlying mechanism. Nevertheless, the arrhythmia hypothesis suggests the potential link to survival after MI, but not to atherosclerosis and the prevalence of MI.

A potential option explaining our findings would be the association of the rs9982601 SNP with the KCNE2 gene. This gene encodes a subunit of the voltage-gated potassium channel that couples with the KCNH2 pore-forming protein (potassium voltage-gated channel, subfamily H [age-related], member 2) to modify its function. It is also associated with KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) and suppresses its current amplitude, which results in slowing down the deactivation gating process. Loss of function of any of those 3 proteins (KCNE2, KCNH2, and KCNQ1) may lead to
compared with the T-allele carriers. By comparison, in studies by the Myocardial Infarction Genetics Consortium and the CARDIOGRAM Consortium, the odds ratios for MI were estimated at 1.19 and 1.18 per T allele, respectively.\textsuperscript{1,2} In our case, however, the absolute risk associated with an unfavorable genotype was incomparably higher than in the case-control association studies due to the high event rate. Based on the available literature, every fifth patient with STEMI admitted to the hospital dies within a 5-year follow-up.\textsuperscript{13} Therefore, even a small reduction in relative risk results in a pronounced influence on absolute risk. This fact increases the potential for genotype-tailored interventions in clinical practice.

Limitations of the study The study has several limitations. First, the number of patients was relatively small. Several thousand study participants certainly enable the finding of significant associations of very small effects, but these frequently have no real clinical impact, as cost-ineffective. However, we aimed to search for large-effect sizes. Next, the study was designed to compare mortality in CC homozygotes and T-allele carriers. It was underpowered to analyze TT homozygotes separately. We assume that very low mortality in TT homozygotes from the high-risk group is an accidental finding.

Moreover, the analysis was performed retrospectively. As a result, the smoking status is missing in a substantial number of patients. The long period over which we enrolled the patients in our study covers a variety of changes in the standard of care.

The next major limitation is that the population group was used instead of a typical control group. It limits the interpretation of our report of association between the investigated SNP and STEMI prevalence. Typically, controls are disease-free and matched for age and sex. Such a design was used in our reference literature.\textsuperscript{1} In the case of our controls (adult subjects who took part in paternity testing), the clinical status was not available. It is highly probable that they were not age-matched and some of them might have been MI survivors. Therefore, we decided not to match them for sex to receive a group highly representative for our region in terms of the genetic background.

Finally, the study was not designed to investigate the mechanisms of deaths during follow-up. This research would be less sensitive to assess the impact of genotype on the mechanisms of deaths during follow-up. Therefore, even a small reduction in relative risk results in a pronounced influence on absolute risk. This fact increases the potential for genotype-tailored interventions in clinical practice.

Conclusions The rs9982601 polymorphism of the region between SLC5A3/MRP56 and KCNE2 genes is associated with long-term mortality after STEMI, but only in a subgroup of high-risk patients according to the GRACE risk score. This preliminary finding should be validated in an external cohort. Afterwards, owing to a very high-effect size, it could potentially be translated into clinical practice, if only appropriate methods are developed. Additionally, this study supports previous reports on the correlation between this SNP and the prevalence of STEMI.

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REFERENCES
The rs9982601 polymorphism of the region between the SLC5A3/MRPS6...
ARTYKUŁ ORYGINALNY

Polimorfizm rs9982601 regionu między genami SLC5A3/MRPS6 i KCNE2 jest związany z występowaniem zawału serca oraz odległą śmiertelnością pacjentów po zawale

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SŁOWA KLUCZOWE

KCNE2, polimorfizm, rokowanie, rs9982601, zawał serca

STRESZCZENIE

WPROWADZENIE rs9982601 (C>T) to polimorfizm regionu niekodującego między genami SLC5A3/MRPS6 i KCNE2. Wykazano jego związek z występowaniem zawału serca (myocardial infarction – MI) w młodym wieku (allel ryzyka – T).

CELE Celem badania była ocena związku polimorfizmu rs9982601 z odległą śmiertelnością pacjentów po MI oraz z występowaniem MI w populacji polskiej.


WYNIKI Grupa badana objęła 981 pacjentów (średni wiek 62,8±12,1 lat; 259 kobiet [26,4%]). Odsetki genotypów TT, CT i CC wyniosły odpowiednio 3,1%, 25,6% i 71,3% w całej grupie oraz 2,4%, 16,8% i 80,8% (p = 0,01) w grupie populacyjnej (n = 167). W trakcie obserwacji (mediana 1826 dni) zmarło 157 pacjentów (16%). Nie obserwowano istotnych różnic między pacjentami o różnych genotypach w charakterystyce klinicznej ani w śmiertelności. Jednak w podgrupie chorych wysokiego ryzyka (>155 punktów według skali ryzyka GRACE, n = 428), homozygoty niskiego ryzyka CC miały istotnie lepsze przeżycie w porównaniu do pozostałych genotypów (HR = 0,64; 95% CI 0,43–0,96; p = 0,03).

WNIOSEKI Wykazaliśmy, że polimorfizm rs9982601 regionu między genami SLC5A3/MRPS6 i KCNE2 jest związany z odległą śmiertelnością pacjentów wysokiego ryzyka po MI. Ponadto nasze badanie potwierdza wcześniejsze donosienia o związku powyższego polimorfizmu z występowaniem zawału serca.