INTRODUCTION
Secondary prevention of cardiovascular diseases is strongly recommended by international guidelines [1–2]. However, several trials have shown that adherence to therapy recommended at discharge from hospital dramatically decreases among patients after acute coronary syndromes (ACS) [3–8]. To date limited data about medication adherence and ST-segment elevation myocardial infarction (STEMI) treatment in Ukraine are available.

THE AIM
The general objective of the present study was to evaluate the adherence to medications prior and within a two-year period after STEMI and to estimate its impact on the average lifespan of patients after STEMI.

MATERIALS AND METHODS
Details of the prospective STIMUL survey have been described previously [9]. In brief, 1,103 patients with STEMI [2] were enrolled to the registry. This study analysed a whole range of data on patients with STEMI at discharge from hospital entered two-year follow-up observation with clinical assessment after 6, 12, and 24 months. The recommended post-STEMI management analysed in the present study included statins, dual antiplatelet therapy (DAPT – acetylsalicylic acid, continuously, and P2Y12 inhibitors during the first year); angiotensin-converting enzyme inhibitors (ACE-I), or angiotensin receptor blockers (ARB) in the case of ACE-I intolerance and beta-blockers. The primary end-points were cardiovascular death and non-fatal myocardial infarction.
STATISTICAL ANALYSIS
All analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA). All tests were considered statistically significant if p < 0.05. The use of medications was assessed as a proportion of patients who took medications to the total number of patients at the end of each follow-up period. Adherence was considered high when the number of medications was ≥ 80.0% when compared with the number of medications at discharge. The relationship between adherence and average lifespan was evaluated by the cross-tabulation analysis based on the Pearson’s χ² (chi-squared) test. The association between two variables was calculated by the phi and Cramer’s V coefficients. The Kaplan-Meier curves were constructed to graphically present crude survival estimates, with a log-rank test for the equality of survivor functions used to assess group differences.

RESULTS
BASELINE DATA AND TREATMENT BEFORE STEMI
The baseline characteristics of all patients included in the study are presented in Table I. In addition, 34.5% of the patients had a high risk of in-hospital mortality according to their GRACE score. 11.9% and 19.5% of the patients, respectively, had high and very high bleeding risk as assessed by the CRUSADE score. According to the baseline data, the STIMUL population was characterized by high or very high cardiovascular risk. However, only a few of them reported regular use of medicines prior to STEMI. The frequency of regular use of medications among patients prior to STEMI is presented in Table II. The antiplatelet therapy was used in 57.0% and 54.5% of the individuals with a history of MI and stroke, respectively. Among patients with high blood pressure at admission, 78.0% (n = 659) of the patients were aware that they had hypertension. Hypotensive therapy was used in 51.0% (n = 431) of the individuals, but only in 35.4% of the individuals on a regular basis (n = 299). Half of the patients with hypertension were treated with monotherapy. As a result, only 7.5% of them achieved target levels of blood pressure. Statins were predominantly used in patients who experienced cardiovascular events (ACS or stroke). Lipid targets were achieved only in 5.5% of patients. The main reasons for statin discontinuation or dose reduction were: a fear of side effects or perceived side-effects (25.6%) based on negative media coverage, advice from friends or family members, or lack of clinicians’ guidance; the absence of clinical symptoms of dyslipidaemia making it easy to forget to take statins (forgetfulness) (18.3%), and the cost of statins (8.3%). 47.9% of patients did not take statins because of a lack of medical appointments/medical control. The main reasons for the discontinuation or episodic use of blood pressure lowering therapy were forgetfulness (22.0%), the fear of: side effects (21.6%), taking too many drugs at the same time (3.0%) and damage caused by long-lasting medication use (5.6%).

IN-HOSPITAL TREATMENT
The median time from symptom onset to hospital admission was 5.1 ± 0.3 hours. 59.8% (n = 660) of the patients were admitted to cardiology units. However, only a half of them (51.4%, 339 patients) were hospitalized in interventional units and 73.4% (n = 237) of the patients admitted to interventional units underwent primary percutaneous coronary intervention (pPCI). Fibrinolytic therapy was performed in 8.4% (n = 93) of the cases. Therefore, in the entire cohort, only 29.9% of the study population underwent reperfusion therapy. The major reasons for the non-performance of reperfusion therapy were late arrival (40.5%) and unavailability of catheterization laboratories (31.4%). Additional reasons were contraindications (7.4%), uncertain diagnosis (6.3%), patient refusal (6.1%).

In-hospital mortality rate was 11.3% (125 cases) in the STIMUL cohort and 7.0% (23 cases) among patients who underwent coronary reperfusion.

Finally, 872 (79.1%) patients were discharged from hospital with STEMI. They were included in a further two-year follow-up.

As shown in Table III, at discharge, the majority of the STIMUL population received recommendations to take the main cardiovascular medications, except for P2Y12 inhibitors. A lower level of recommendation to take P2Y12 inhibitors was related with a patient’s high bleeding risk at admission.

TREATMENT DURING FOLLOW-UP AFTER ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION
Post-discharge events were followed for 636 (72.9%) patients for six months, 480 (55.1%) patients for 12 months, and 278 (31.9%) patients for 24 months. During the first six months after STEMI, 64 patients (7.3%) had died and 8.0% of the patients had experienced a non-fatal myocardial infarction. After 12 months, 140 patients (16.1%) had died and 15.6% had a non-fatal myocardial infarction. After 24 months, 169 patients (19.4%) had died and 21.9% had a non-fatal myocardial infarction.

The adherence to medical treatment recommended at discharge from hospital progressively decreased (p<0.001) during the 24-month follow-up period (Table IV). After 24 months, regular use of ASA decreased by 35.2%, statins by 80.5%, beta-blockers by 38.1%, and ACE-I by 43.9% (p < 0.001), when compare with the recommendations of the clinicians at discharge from hospital.

DAPT adherence was 21.4% during the six-month follow-up period and 16.3% during the first 12 months after STEMI. The main reasons for DAPT discontinuation were the fear of side effects in 26.4% of the cases (n = 106), price in 22.4% of the cases (n = 90), and forgetfulness due to the lack of noticeable benefits in 18.4% of the cases (n = 74).

At the end of 24-month follow-up, further reduction of ASA, statin, ACE-I/ARB and beta-blockers adherence was observed (Table IV). The main reasons for medication discontinuation were similar as in the prior myocardial
MEDICATION ADHERENCE AND ITS IMPACT ON THE AVERAGE LIFE EXPECTANCY AFTER ST-SEGMENT ELEVATION...

As shown in Table V, significant correlations were determined between two-year death risk and complete cessation of medications (ASA and statins) within 24 months after STEMI (p<0.05) or ASA discontinuation (p<0.05). We did not find any correlation between statin discontinuation and two-year death risk after STEMI (p<0.05) because of the small cohort of patients (n=27) still using statins after the two-year period.

The continual use of ASA and statins for two years after STEMI was associated with a 7.0% mortality rate, while discontinuation of antiplatelet and lipid-lowering therapy

Table I. Baseline, demographic and clinical characteristics of STIMUL registry population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.4 ± 11.5</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>819</td>
<td>74.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>845</td>
<td>76.6%</td>
</tr>
<tr>
<td>Hyperlipidemia (defined as total cholesterol ≥ 4.5 mmol/l)</td>
<td>565</td>
<td>50.7%</td>
</tr>
<tr>
<td>Body mass index (BMI) &gt; 30 kg/m²</td>
<td>353</td>
<td>32.0%</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>351</td>
<td>31.8%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>275</td>
<td>24.9%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>300</td>
<td>27.2%</td>
</tr>
<tr>
<td>Past smoker</td>
<td>354</td>
<td>32.1%</td>
</tr>
<tr>
<td>Prior angina</td>
<td>380</td>
<td>34.5%</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>267</td>
<td>24.2%</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>23</td>
<td>2.1%</td>
</tr>
<tr>
<td>Prior coronary bypass graft surgery</td>
<td>3</td>
<td>0.3%</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>251</td>
<td>22.8%</td>
</tr>
<tr>
<td>Prior stroke/transient ischemic attack</td>
<td>72</td>
<td>6.5%</td>
</tr>
<tr>
<td>Prior renal failure</td>
<td>19</td>
<td>1.7%</td>
</tr>
<tr>
<td>Heart rate, mean bpm</td>
<td>83.4 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>138.6 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Killip class, ≥ II</td>
<td>262</td>
<td>23.8%</td>
</tr>
<tr>
<td>cardiogenic shock</td>
<td>39</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Fig. 1. Average life expectancy among patients taking and without taking acetylsalicylic acid (ASA) plus statin therapy within two-year follow-up after ST-segment elevation myocardial infarction.

infarction period: fear of side effects, especially in case of ASA (15.7%) and statins (18.4%), and forgetting to take the medication.
led to a 15.0% mortality rate during the two-year follow-up (Table VI). Therefore, the risk of two-year death in the case of discontinuation of the abovementioned treatment increased four times (OR 4.2; 95% CI 0.2–0.9; p<0.05). Among the patients with regular ASA intake, the rate of two-year death was 6.5%. Meanwhile, the cessation of the regular use of ASA was associated with a 15.5% mortality rate. As a result, the discontinuation of ASA during the first two years after STEMI increased the mortality risk three times (OR 3.8; 95% CI 0.2–0.9; p<0.05).

Regular statin intake was associated with a 6.9% mortality rate, whereas statin discontinuation increased this risk to 14.9%. Therefore, the two-year death risk in the case of the discontinuation of lipid-lowering therapy increased by four times (OR 4.2; 95% CI 0.1–0.9; p>0.05). However, the risk appears to be not significant statistically because of the small number of patients using statin treatment after two years.

The impact of adherence to treatment on average lifespan during the two-year follow-up period after STEMI is presented in Figure 1 and Table VII.

To conclude, the average lifespan in the case of regular use of antithrombotic and lipid-lowering therapy during the first two years after STEMI was 62.3 ± 1.1 years (95% CI 60.1–64.4; p<0.05) and 61.2 ± 0.9 years in the case of discontinuation of the recommended treatment (95% CI 59.4–62.9; p<0.05). Therefore, regular use of ASA and statins during the 24 months after STEMI prolonged lifespan by one year.

**DISCUSSION**

The results of our study indicate the poor level of cardiac prevention in the STIMUL registry population of Ukrainian patients before STEMI. In the present study, we observed a low and irregular rate of use of statin and hypotensive therapy prior to STEMI. This resulted in the non-achievement of target lipid and blood pressure goals and substantially increased the risk of adverse cardiovascular outcomes. The results of the STIMUL registry are much worse than those obtained in the EUROASPIRE V survey [10].

In our study, the rate of reperfusion therapy in Ukrainian patients with STEMI was dramatically low. Late hospitalization was the main barrier to invasive reperfusion treatment and had a great impact on in-hospital mortality. The importance of time in the management of STEMI was shown to directly affect both mortality and morbidity [11]. General in-hospital mortality in the STIMUL registry population was high (11.3%), when compared with international registries: 4.6% in the GRACE registry [12]; 4.0% in the second Euro Heart Survey on acute coronary syndromes [13] or 5.9% in the Polish PL-ACS registry.
Another problem that should be emphasized when discussing the low pPCI rate in the STIMUL population is limited access to PCI procedures at the time of registry due to the lack of an organized PCI network in Ukraine. Kämpfer et al. have shown significant differences in the number of pPCI procedures for ACS in 2010 between three different socioeconomic environments [15]. In Switzerland and Poland, coronary interventions were the first choice therapy, whereas in Ukraine 30% of patients with ACS received fibrinolysis therapy and pPCI was not performed at all, as it was unavailable at this time in the study centre in Ukraine. Our results also correspond with the Euro Heart Survey 2009 Snapshot where, in comparison to western European countries, the use of pPCI for STEMI treatment in eastern European countries was low (23%), and 44% of patients called within 12 hours of symptom onset did not receive reperfusion therapy. Similarly to the our data, the low rate of reperfusion therapy resulted in a high in-hospital mortality rate (10.1%) [16].

During the first two years after STEMI, adherence to treatment of all medications recommended at the moment of discharge from hospital progressively decreased (p<0.001). These results correspond with data obtained by other researchers [17–23].

Data from the STIMUL registry revealed a high frequency of ASA administration at discharge. The rate of clopidogrel administration was lower, and this can be partially explained by the low rate of pPCI procedures and the high bleeding risk among the registry cohort. In the Ukrainian registry, adherence to DAPT was 16.3% at the end of the 12-month follow-up after STEMI. Despite strong evidence for a significant correlation between adherence with respect to antiplatelet and statin therapy and a decrease in mortality for patients with ACS, a reduction in adherence to DAPT and statins in patients after myocardial infarction has been commonly described [3-4, 6, 17–19, 21–22, 24]. Jackevicius et al. reported 44% of unfilled ASA prescriptions and almost 70% of unfilled prescriptions for medication other than ASA in 120 days for acute coronary syndrome [24]. According to Moalem et al., 6.5% of patients discontinued DAPT due to non-compliance at the end of a year [4]. Similar results have been shown in the international GRACE registry [19, 21], where only one third of the patients took clopidogrel after 6-month observation.

Adherence to therapy with statins decreased during the two-year follow-up period by almost 80%. In another observational study undertaken in one Ukrainian clinical centre, the rate of statin discontinuation after ACS was lower (about 64% during 3.5-year follow-up), but still higher than in western European countries or United States clinical centres [15]. In a large prospective multicentre cohort of patients with ACS, the discontinuation rate for statins was 6.7% and the main reason for discontinuation was the presence of side effects [23]. Low adherence to statins in the STIMUL population absolutely cannot be explained by the presence of side effects [6, 20]. The most common reasons for statin cessation in the Ukrainian registry were: the fear of side effects or the perceived side effects, a low disease awareness, and a lack of motivation or medical guidance. Our results correspond with the results obtained in the nationwide study in Denmark, where early statin discontinuation was significantly associated with negative statin-related news stories [25].

Among the Ukrainian population of STEMI patients, the frequency of ACE-I/ARB and beta-blocker use remained low after two years. Despite the high prevalence of hypertension in the STIMUL patients prior ACS, only 26.3% and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Two-year risk of death</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes N [%]</td>
<td>No N [%]</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>ASA</td>
<td>Take</td>
<td>10</td>
<td>6.5%</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>19</td>
<td>15.5%</td>
<td>145</td>
</tr>
<tr>
<td>Statins</td>
<td>Take</td>
<td>2</td>
<td>6.9%</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>37</td>
<td>14.9%</td>
<td>212</td>
</tr>
<tr>
<td>ASA + statins</td>
<td>Take</td>
<td>11</td>
<td>7.0%</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>18</td>
<td>15.0%</td>
<td>102</td>
</tr>
</tbody>
</table>

ASA – acetylsalicylic acid

<table>
<thead>
<tr>
<th>Adherence to medication</th>
<th>Average lifespan</th>
<th>SD</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low</td>
<td>high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA and statin adherence</td>
<td>62.3</td>
<td>1.1</td>
<td>60.1</td>
<td>64.4</td>
</tr>
<tr>
<td>ASA adherence</td>
<td>62.2</td>
<td>1.1</td>
<td>60.1</td>
<td>64.4</td>
</tr>
<tr>
<td>ASA and statin non-adherence</td>
<td>61.2</td>
<td>0.9</td>
<td>59.4</td>
<td>62.9</td>
</tr>
</tbody>
</table>
17.7% of the patients used these medicines regularly. After STEMI adherence to ACEI/ARB and beta-blockers decreased with time from the time of discharge and was 58.0% and 45.3%, respectively at two-year follow-up. It is a much lower rate than the current data from the EUROASPIRE V survey [10], where in the population with confirmed coronary artery disease 81% of the population were on beta-blockers and 75% were on ACE-I/ ARBs. The major reasons for discontinuation or dose reduction of blood pressure were fear of side effects, lack of self-motivation based on low disease awareness. It correspond with the results obtained by Khan et al., where strong myths responsible for the fear of antihypertensive medication use as well as for the poor acceptance of hypertension as a main risk factor of ACS and stroke have been described [26].

In our registry, we observed a high mortality rate and a high risk of recurrent myocardial infarction in a two-year period. The risk was the highest during the first year after STEMI. The high risk for adverse incidents was contributed by the low rate of reperfusion therapy and the discontinuation of evidence-based treatment with antiplatelets and statins. Discontinuation of treatment with ASA in the two-year observation period increased the risk of death three times, whereas discontinuation of both ASA and statin therapy increased the risk of death four times. In multivariable analysis, Ho et al. reported lower one-year survival after the discontinuation of both ASA and statins [27]. In our registry, regular use of ASA and statins for 24 months after STEMI prolonged average lifespan by one year. This corresponds with the results of Rodriguez et al. [6].

CONCLUSIONS
1. The population of Ukrainian patients in the STIMUL registry was predominantly at a high and very high cardiovascular risk before STEMI with a poor level of cardiovascular risk. The level of reperfusion therapy among patients with STEMI was low, due to late hospitalization and limited access to primary PCI. This had a great impact on in-hospital death. The frequency of recommendation of evidence-based therapy was high at discharge from hospital.

2. In a real-life setting, adherence to medications for secondary prevention after STEMI was low to moderate in Ukraine. The cessation of ASA and lipid-lowering therapy in two-year follow-up after STEMI led to a reduction of average lifespan by one year.

3. Our study revealed the immense need of improvement of cardiac care for patients at high and very high cardiovascular risk in Ukraine by increasing accessibility to invasive reperfusion procedures in ACS and specialist healthcare, by implementing national educational programs about the symptoms of ACS. This is required to decrease both in-hospital and long-term mortality of patients with STEMI. Currently, according to the Ukrainian Ministry of Health reports, the total number of catheterization laboratories (Cath Labs) is 42 whereas the population of Ukraine is over 44 million (1 Cath Lab for 1,048,000 people) [28]. In Switzerland it is 1 Cath Lab for 230,000 people and in Poland, a country neighbouring Ukraine, with a population of 37.97 million it is 1 Cath Lab for 239,000 people.

LIMITATIONS OF THE STUDY
Our study has several limitations that need to be addressed. Extrapolation of local results to the whole country needs to be performed with caution. The PCI results, in-hospital and general mortality since 2013 for STEMI in Ukraine could have changed. In regards to follow-up data, the reliability of the data with regards to medication is somewhat compromised by the fact that two-year follow-up was limited to 31.9% (278) of the patients of the whole registry cohort who entered the follow-up period at the time of discharge from hospital.

REFERENCES


**ORCID and contributionship:**

Svitlana Korol: 0000-0002-9656-6732A-F

Agnieszka Wsół: 0000-0001-7221-8103B-F

Liana Puchalska: 0000-0002-4717-7677C-F

Alexander Reshetnik: 0000-0002-9951-8410B,E-F

**Conflict of interest:**

The Authors declare no conflict of interest.

**CORRESPONDING AUTHOR**

Agnieszka Wsół

Department of Experimental and Clinical Physiology, Laboratory of Centre for Preclinical Research, Medical University of Warsaw, Poland

e-mail: awsol@wum.edu.pl

**Received:** 08.08.2021

**Accepted:** 19.02.2022

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article