Review paper

Dual antiplatelet therapy for reduction in mortality in patients with acute and chronic coronary syndromes

Maciej Lesiak, Anna Komosa

1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland

A b s t r a c t

Dual antiplatelet therapy (DAPT) is a foundation of successful coronary artery disease management. DAPT is recommended according to ESC guidelines for 6 months following elective percutaneous coronary intervention and for 12 months following the acute coronary syndrome (ACS). ACS are the most cost-consuming type of the ischemic heart disease, which prominently requires hospital treatment. This risk significantly increases shortly after stopping DAPT, which is typical in most patients after 12 months following acute myocardial infarction (AMI). Therefore, one of the goals of long-term treatment of such patients should be the identification of those at increased risk of subsequent events, for whom prolonged DAPT will bring clinical benefits. It has been documented that prasugrel and ticagrelor, compared to clopidogrel, significantly reduce the incidence of major adverse cardiovascular events (MACE) in ACS patients. In addition to lowering composite ischemic endpoint, ticagrelor significantly reduced all-cause and cardiovascular mortality. The long-term use of ticagrelor in patients with a previous myocardial infarction was also related to a significant reduction in MACE. In patients who had a myocardial infarction 1–3 years earlier, the addition of ticagrelor to aspirin resulted in a substantial reduction in the composite endpoint of cardiovascular death, myocardial infarction, or stroke at the expense of a small but significant increase in bleedings. Hypothetical calculations have shown that replacing clopidogrel with ticagrelor in all patients with AMI in Poland would save more than three thousand lives within 12 months after AMI and more than a thousand within the following 2 years.

Key words: antiplatelet therapy, acute coronary syndromes, mortality, ticagrelor, clopidogrel.

The global burden of ischemic heart disease

Ischemic heart disease is the most common cause of morbidity and mortality in Poland and worldwide. Coronary artery disease (CAD) affects around 3.5% of the population of the European Union [1]. According to IHME data, in 2017 in Poland, 4.2% of the population suffered from CAD, which was 0.1 percentage point more than in 2012 [2]. The number of new cases of CAD in Poland decreased in the years 1990–2017. It was evident in the case of male morbidity, for whom the values in 1995 were much higher than in females, and by 2017 it had dropped to a similar level. The clinical presentation of CAD ranges from chronic (stable) coronary syndromes (CCS) to various forms of acute coronary syndromes (ACS). According to the European Society of Cardiology (ESC), two types of ACS can be distinguished: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS). The latter group comprises of two sub-groups: non-ST-segment elevation

myocardial infarction (NSTEMI) and myocardial ischaemia without cell damage, known as unstable angina (UA). Acute coronary syndromes are the most frequent CAD presentation, which leads to death. ACS are also the most cost-consuming type of the ischemic heart disease, which prominently requires hospital treatment. In 2019, in Poland, expenses provided for ACS accounted for 61.4% of the value of hospital reimbursement due to the ischemic heart disease. In 2019, the total number of ACS cases recorded by the Polish National Health Fund was 102,700, the number was 19% lower compared to the data from 2014. This decrease mainly concerned the number of cases of unstable angina (by 55%, $n = 30,000$), whereas the number of myocardial infarctions increased by 9% ($n = 6,000$). Among women, an increase of 3% was noted, and by over 10% in men. The mean age of patients with acute coronary syndromes in 2019 was 66.3 years. Men dominated in the 60–74 age group, whereas predominance of women was noted in the group over 80 years of age [2]. There was also an

Corresponding author:
Prof. Maciej Lesiak, 1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland, phone: +48 61 854 92 23, e-mail: maciej.lesiak@skpp.edu.pl

increase in the proportion of ACS patients treated with coronary angioplasty within 7 days from the onset of symptoms. Angioplasty was most often performed in the case of STEMI (88% in 2018), in a smaller percentage of NSTEMI (64%) and unstable angina (48%). A substantial number of ACS patients were treated with a coronary artery bypass grafting (CABG) procedure within 90 days of the event. The highest percentage was observed in UA patients (14%), followed by NSTEMI (6%) and STEMI patients (3%) [2].

Early and late outcomes following acute myocardial infarction

The nationwide AMI-PL database 2009–2012 revealed that among all AMI patients admitted in 2009, in-hospital mortality was as high as 10.5% and was strongly related to patients' age [3]. The total mortality at 1 year was 19.4%, indicating that the mortality after discharge was 8.9%. As already mentioned, AMI patients who survived the first year after the event are still at increased risk of cardiovascular events.
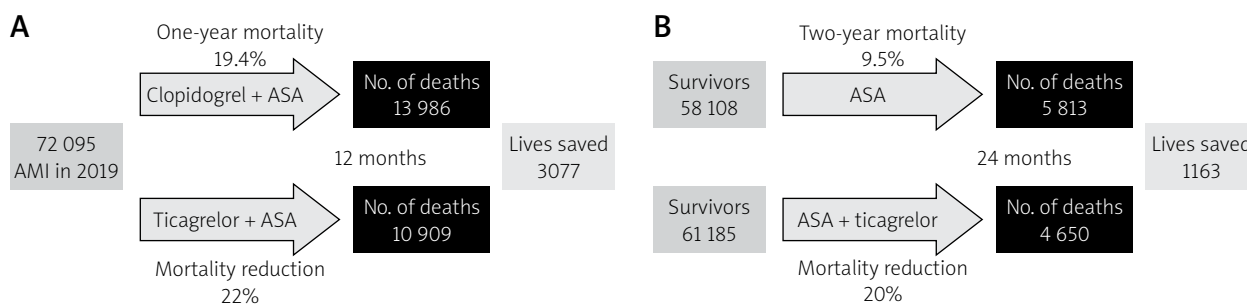
Wojtyniak *et al*. have published data from the Polish nationwide AMI-PL registry that included 134,602 patients hospitalized for acute myocardial infarction (AMI) in 2009–2010 [4]. Five-year outcomes of all patients discharged alive were assessed. The AMI definition included patients with STEMI, NSTEMI and unspecified AMI. Data concerning all-cause mortality, a need for further hospitalization for cardiovascular reasons and procedures performed after discharge were collected. The outcomes were presented separately in 4 age groups: below 55, 55–64, 65–79 and above 80 years. Survival dropped the most in the first year after the index hospitalization, whereas further decline remained constant in the following years. The 5-year survival rates differ across the age groups. In males below 55 years, there was the highest survival rate, and in those above 80, the lowest one: 0.915 vs. 0.383, respectively. However, after adjustment for the overall mortality of the entire Polish population, this relationship was substantially attenuated. An even more substantial reduction in the impact of age was observed in women. However, data from the Polish registry differ from those surveyed in SWEDEHEART [5] and other European registries [6, 7]. In Poland, the absolute and relative survival rate was higher in women than in men. Whereas in other countries, this correlation was the opposite. A possible explanation of this phenomenon may be caused by poor guidelines application in clinical practice, level of education, the diversity of cardiovascular risk factors and poor management of numerous comorbidities in a real-life setting. The reported high mortality rate of AMI patients after the first year following the event was consistent with other Polish data published previously [8]. This risk significantly increases shortly after stopping dual antiplatelet therapy (DAPT), typically in most pa-

tients after 12 months following AMI [9]. An observational study of numerous patients treated with percutaneous coronary angioplasty (PCI) for AMI showed that recurrent myocardial infarction originating from a previously untreated lesion was twice higher than from a previously stented lesion [10]. Therefore, one of the goals of long-term treatment of such patients should be the identification of those at increased risk of subsequent events, for whom prolonged DAPT will bring clinical benefits. At the same time, patients at high risk of bleeding should be excluded from such an approach.

It has already been demonstrated that among various risk factors, some are vital for both ischemic and bleeding events. Lindholm and coauthors studied the impact of risk factors such as age > 65, chronic kidney disease, diabetes mellitus, multivessel coronary artery disease, prior myocardial infarction and prior bleeding on the incidence of new ischemic and bleeding events [11]. The study was based on the SWEDEHEART registry and Swedish National Patient Register that combined data obtained between 2006 and 2014. The primary outcome was the composite of MI, stroke and cardiovascular death. The majority of patients had two or more risk factors (53.5%). The authors found a strong cumulative correlation between the number of risk factors and the rate of ischemic events. With each risk factor added, there was a marked, gradual increase in the incidence of cardiovascular death, myocardial infarction or stroke. Also, a similar but less pronounced correlation with bleeding events has been found. Prior bleeding was the strongest predictor of this complication. After excluding such patients from analysis, an increasing number of risk factors remained associated with a substantial rise in the ischemic events. In contrast, the bleeding rate increased only minimally. This finding is consistent with the PRECISE-DAPT score that is recommended in ESC Guidelines for bleeding risk assessment in ACS patients and those undergoing PCI [12, 13].

The role of antiplatelet therapy in mortality reduction following acute myocardial infarction

Dual antiplatelet therapy (DAPT) is a foundation of successful coronary artery disease management. DAPT is recommended according to ESC guidelines for 6 months following elective PCI and for 12 months following ACS. It has been documented that more potent and predictable P2Y12 inhibitors – prasugrel and ticagrelor, compared to clopidogrel, significantly reduce the incidence of major adverse cardiovascular events (MACE) in broad-spectrum ACS patients [14, 15]. In addition to lowering composite ischemic endpoint, ticagrelor significantly reduced all-cause and cardiovascular mortality [15]. This beneficial effect has been recently confirmed in a network meta-analysis of 52,816 ACS patients from 12 randomized

A

72 095
AMI in 2019

One-year mortality
19.4%

Clopidogrel + ASA

No. of deaths
13 986

12 months

Lives saved
3077

Ticagrelor + ASA

No. of deaths
10 909

Mortality reduction
22%

B

Survivors
58 108

Two-year mortality
9.5%

ASA

No. of deaths
5 813

24 months

Lives saved
1163

Survivors
61 185

ASA + ticagrelor

No. of deaths
4 650

Mortality reduction
20%

Figure 1. A – Hypothetical reduction in mortality in patients up to 12 months after myocardial infarction. **B** – Hypothetical reduction in mortality in patients 12–36 months after myocardial infarction

trials [16]. The long-term use of ticagrelor in patients with previous myocardial infarction was also related to a significant reduction in MACE [17]. In patients who had a myocardial infarction 1 to 3 years earlier, the addition of ticagrelor on top of a low dose of aspirin resulted in a significant reduction in the composite endpoint of cardiovascular death, myocardial infarction, or stroke at the expense of a small but significant increase in bleedings. No excess fatal bleeding or intracranial hemorrhage has been observed. In the approved European label, ticagrelor at a dose of 60 mg b.i.d. was associated with a significant reduction in cardiovascular and all-cause death – hazard ratio 0.71 (0.56–0.90) and 0.80 (0.67–0.96), respectively [18]. The EU label group consisted of patients who were randomized ≤ 2 years from qualifying MI or ≤ 1 year from stopping DAPT.

Given the well-documented positive effect of ticagrelor on mortality and its major underuse in ACS patients in Poland, it is worth calculating the hypothetical number of deaths that might be prevented by using ticagrelor instead of clopidogrel. These are theoretical calculations as it will never be possible to replace clopidogrel for everyone because of contraindications or side effects. The calculations assume the number of patients who had AMI in Poland in 2019 because the statistics for 2020, due to the COVID-19 pandemic, differ significantly from previous years. The early benefit (12 months) was calculated based on the results of the PLATO study [15], whereas the long-term effect (another 24 months) was based on the approved European label, patients from PEGASUS-TIMI 54 study [18]. As shown in Figure 1 A, the strategy of replacing clopidogrel with ticagrelor in all patients with AMI in Poland would result in more than three thousand lives saved within the 12 months following AMI. Moreover, another 1163 deaths could be avoided by adding a low dose of ticagrelor to ASA in the following 2 years (Figure 1 B). These hypothetical calculations should be corrected for the actual use of antiplatelet drugs in patients with myocardial infarction in Poland. The recent analysis of the PL-ACS registry shows that in 2020, ticagrelor was used in less than 40% of patients in the first year after AMI and in less than 5% of patients in > 12 months post-AMI.

Conclusions

In Poland, routine replacement of clopidogrel with ticagrelor would save around three thousand lives within 12 months following AMI. Adding a low dose of ticagrelor to ASA for another 24 months would prevent more than one thousand deaths.

Conflict of interest

Maciej Lesiak: speaking bureau/consulting for Astra Zeneca and Gedeon Richter. Anna Komosa: speaking bureau for Gedeon Richter.

References

1. IHME, 2020. Global Health Data Exchange. URL: http://ghdx.healthdata.org/gbd-results-tool
2. NFZ o zdrowiu. Choroba niedokrwienna serca. Warszawa, kwiecień 2020.
3. Gierlotka M, Zdrojewski T, Wojtyniak B, et al. Incidence, treatment, in-hospital mortality and one-year outcomes of acute myocardial infarction in Poland in 2009-2012-nationwide AMI-PL database. Kardiol Pol 2015; 73: 142-58.
4. Wojtyniak B, Gierlotka M, Opolski G, et al. Observed and relative survival and 5-year outcomes of patients discharged after acute myocardial infarction: the nationwide AMI-PL database. Kardiol Pol 2020; 78: 990-8.
5. Alabas OA, Gale CP, Hall M, et al. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: national cohort study using the SWEDEHEART registry. J Am Heart Assoc 2017; 6: e007123.
6. Raphael CE, Singh M, Bell M, et al. Sex differences in long-term cause-specific mortality after percutaneous coronary intervention: temporal trends and mechanisms. Circ Cardiovasc Interv 2018; 11: e006062.
7. Bucholz EM, Butala NM, Rathore SS, et al. Sex differences in long-term mortality after myocardial infarction: a systematic review. Circulation 2014; 130: 757-67.
8. Gierlotka M, Gąsior M, Poloński L. Jak długo stosować podwójną terapię przeciwpłytkową po ostrych zespołach wieńcowych? Kardiologia po Dyplomie 2016: 3: 34-43.
9. Bonaca MP, Bhatt DL, Steg PG, et al. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. Eur Heart J 2016; 37: 1133-42.
10. Varenhorst C, Hasvold P, Johansson S, et al. Culprit and nonculprit recurrent ischemic events in patients with myocardial in-

farction: data from SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence Based Care in Heart Disease Evaluated According to Recommended Therapies). J Am Heart Assoc 2018; 7: e007174.

11. Lindholm D, Sarno G, Erlinge D, et al. Combined association of key risk factors on ischaemic outcomes and bleeding in patients with myocardial infarction. Heart 2019; 105: 1175-81.

12. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39: 213-60.

13. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021; 42: 1289-367.

14. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-15.

15. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57.

16. Navarese E, Khan S, Kołodziejczak M, et al. Comparative efficacy and safety of oral P2Y12 inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. Circulation 2020; 142: 150-60.

17. Bonaca MP, Bhatt DL, Cohen M, et al. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372: 1791-800.

18. Dellborg M, Bonaca MP, Storey RF, et al. Efficacy and safety with ticagrelor in patients with prior myocardial infarction in the approved European label: insights from PEGASUS-TIMI 54. Eur Heart J Cardiovasc Pharmacother 2019; 5: 200-6.