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Contemporary use of ticagrelor in Polish medical centres as a reflection of antiplatelet treatment guidelines adherence

Współczesne wykorzystanie tikagreloru w ośrodkach medycznych w Polsce jako odzwierciedlenie przestrzegania wytycznych dotyczących terapii przeciwpłytkowej

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Abstract

Introduction. Ticagrelor is the newest $P2Y_{12}$ inhibitor recommended as the first treatment option for acute myocardial infarction both with and without ST-segment elevation. Recent studies have revealed unsatisfactory use of novel $P2Y_{12}$ inhibitors. The aim of our study was to assess the contemporary use of ticagrelor in major medical centres located in Kuyavian-Pomeranian, Pomeranian, and Warmian-Masurian voivodships.

Materials and methods. Retrospective analysis of hospital records regarding the number of ticagrelor tablets purchased monthly was performed covering a three-year period from January 2015 to December 2017. Data from 15 major medical centres was analysed.

Results. A total of 78,871 tablets of ticagrelor were purchased over the study period, with a monthly median of 2,013.5 and an interquartile range (IQR) of 1,255–2,996. The amount of ticagrelor increased monthly by 7.9%. The lowest monthly value (294, 0.37%) was recorded in the first month, while the highest (4,550, 5.77%) was in October 2017. The median of tablets purchased in 2017 (3,934, IQR 3,010–4,270) was over four times greater than in 2015 (980, IQR 728–1,288, $p < 0.001$) and more than double that in 2016 (1,689, IQR 1,353–2,479, $p = 0.012$). The highest reported amount of the drug in one centre (16,296, 20.6%) was 291 times greater than the amount in the centre with the lowest ticagrelor use (56, 0.07%, $p = 0.27$).

Conclusions. The use of ticagrelor has been significantly increasing in recent years, which reflects the implementation of current guidelines by medical centres. Substantial heterogeneity regarding the use of ticagrelor is observed within particular centres.

Key words: ticagrelor, $P2Y_{12}$ inhibitor, guidelines adherence

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Introduction

Ticagrelor, cyclopentyl-triazolopyrimidine, is the newest oral $P2Y_{12}$ inhibitor; it was approved for use in Europe in 2010 [1]. Unlike thienopyridines, ticagrelor binds to a $P2Y_{12}$ receptor and causes conformational changes providing reversible inhibition of ADP-induced platelet aggregation [2]. Furthermore, this drug does not require liver metabolism as it is already an active drug with additional active metabolite and rapid onset of platelet inhibition. Ticagrelor is less vulnerable to gene polymorphism compared to clopidogrel. However, the effectiveness of platelet inhibition

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still can be affected by external causes e.g. administration of morphine [3, 4] or type of myocardial infarction [5, 6]. Ticagrelor is contraindicated in patients with a history of intracranial haemorrhage or ongoing bleeding. Risk of dyspnoea, ventricular pauses, and increased uric acid should be taken into consideration before starting the treatment [7].

Previous European guidelines for the management of patients with myocardial infarction with ST-segment elevation (STEMI) highlighted the role of newer oral $P2Y_{12}$ inhibitors, and recommended ticagrelor and prasugrel as preferable to clopidogrel for periprocedural antithrombotic treatment in a primary percutaneous intervention (class IB) and for dual antiplatelet therapy with aspirin (class IA) [8]. Recent guidelines on the same subject have supported previous recommendations with improvement to the level of evidence for both indications [9]. Despite the more potent platelet inhibition achieved with ticagrelor and prasugrel, there is still a place for clopidogrel as it is recommended for patients treated with fibrinolysis and triple antiplatelet therapy as an addition to aspirin and oral anticoagulation [9]. Ticagrelor is also preferred for patients with acute coronary syndromes without ST-segment elevation (NSTE-ACS) both for conservative and invasive initial treatment strategy in the absence of contraindications (class IB) [10].

The current guidelines, as already mentioned, underline the importance of ticagrelor in the treatment strategy of patients with acute coronary syndromes (ACS). Previous studies indicated that higher adherence to existing guidelines is associated with better results [11]. Furthermore, adherence to appropriate treatment after ACS could result in decreased costs to healthcare systems [12]. Contemporary use of the novel $P2Y_{12}$ inhibitors has been proven to be unsatisfactory, with a persistently high rate of clopidogrel use [13].

The aim of our study was to assess the contemporary use of ticagrelor in major medical centres located in Kuyavian-Pomeranian, Pomeranian, and Warmian-Masurian voivodships.

Material and methods

A retrospective analysis of hospital records regarding the number of ticagrelor tablets purchased monthly was performed covering a three-year period from January 2015 to December 2017. A request to provide data regarding monthly ticagrelor use was sent to 20 major medical centres: 13 located in Kuyavian-Pomeranian Voivodship, six in Pomeranian Voivodship, and one in Warmian-Masurian Voivodship. A total of 5 centres were excluded — three did not respond to the request, one was incapable of disclosing the exact amount of the drug, and in one centre ticagrelor, in general, was not used. Data from the remaining 15 centres was further analysed.

Monthly purchase of ticagrelor was expressed as a total number of ticagrelor tablets. Based on the amount of the drug purchased monthly, we evaluated the variation of ticagrelor use over time. Each year and month of the study period was compared to the others regarding the amount of purchased drug. An analysis of ticagrelor use within particular centres was also performed. Continuous variables were presented as median with interquartile range (IQR), and categorical as absolute counts and percentages. Shapiro-Wilk test was performed to determine normality of the distribution. The Kruskal-Wallis and Mann-Whitney tests were used for comparison of more than two and two variables respectively. The trend line was calculated using the three-period moving average. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS software.

Results

A total of 78,871 tablets of ticagrelor were purchased over the study period. The cost of ticagrelor oscillated around 590,000 PLN. Median of ticagrelor purchased monthly was 2,013.5 with IQR: 1,255–2,996. The amount of ticagrelor noticeably increased over the three years. The dynamic growth during that period is illustrated by the red trend line (Figure 1).

During the first month of the observation, four medical centres purchased a total of 294 tablets (0.37%) of ticagrelor. The highest monthly amount of ticagrelor was recorded in October 2017. In that month,11 centres together acquired 4,550 tablets (5.77%). Thus the amount of the drug increased by over 1,447% between the months with the lowest and the highest values of purchased ticagrelor ($p = 0.006$).

Over the study period, the amount of ticagrelor increased by an average of 7.9% each month. The increased use of the novel $P2Y_{12}$ inhibitor is also noticeable in a year-to-year comparison (Figure 2). The median of ticagrelor tablets purchased in 2017 was over four times greater than in 2015 (3,934, IQR 3,010–4,270 vs 980, IQR 728–1,288, $p < 0.001$) and over two times greater than in 2016 (3,934, IQR 3,010–4,270 vs 1,689, IQR 1,353–2,479, $p = 0.012$). A pairwise comparison between the years 2015 and 2016 did not reach statistical significance ($p = 0.515$).

Our results revealed a significant ($p < 0.001$) diversity in ticagrelor use within the medical centres (Figure 3). Three hospitals purchased more than 11,000 tablets during the study period. The amount of ticagrelor purchased by those centres covered 50.3% of the total value, with the median significantly higher than the median of the remaining 12 centres (11,984, IQR: 11,704–14,140 vs 2,380, IQR 560–5,460, $p = 0.004$). Despite the significant differences within all the centres, post-hoc analysis did not reveal a significant result for pairwise comparison

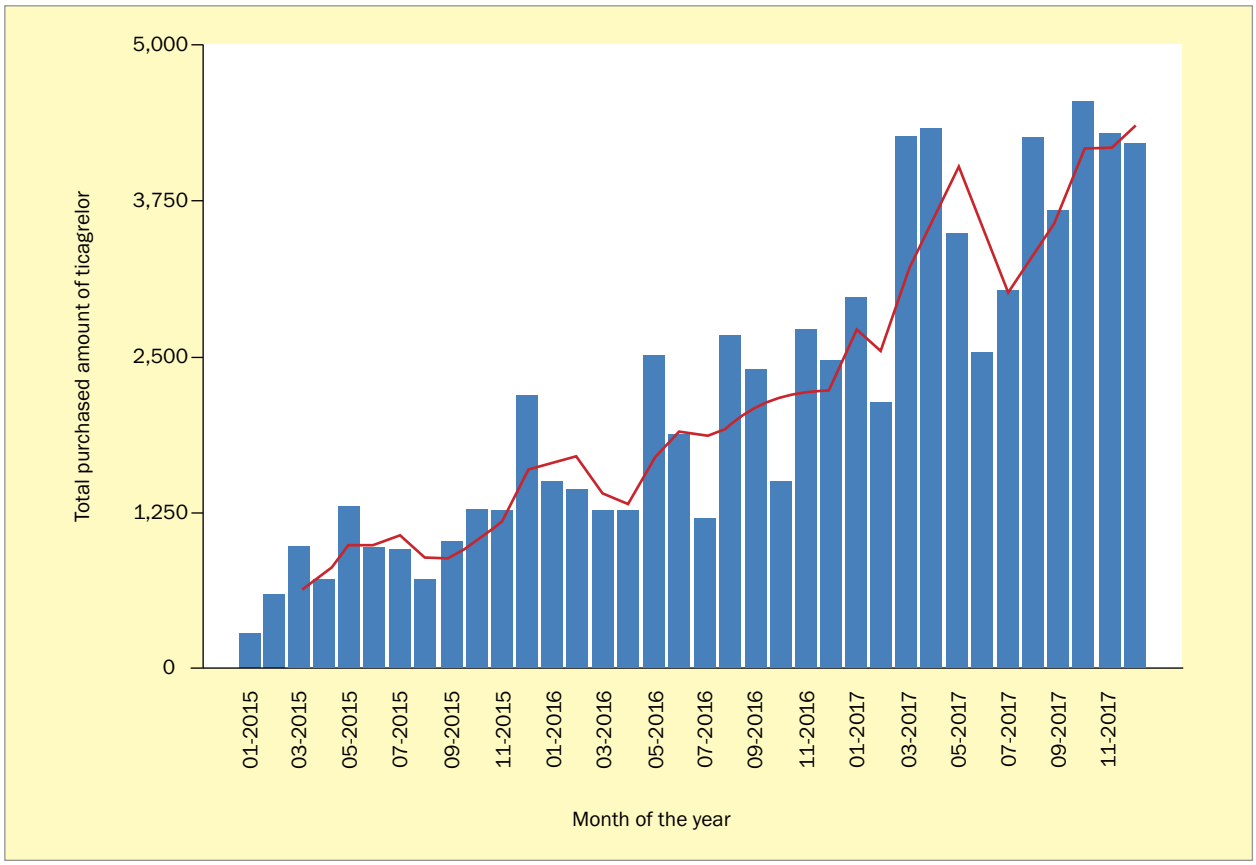

Figure 1. Total amount of ticagrelor purchased each month between January 2015 and December 2017 with marked trend line (red), p = 0.35

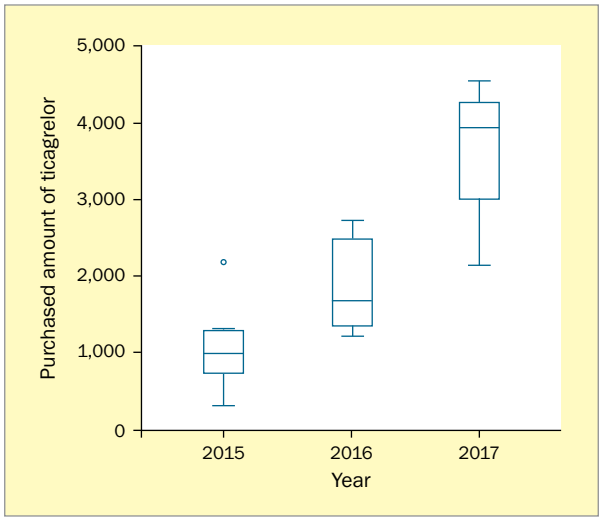

Figure 2. Comparison of ticagrelor use between each year of observation. The median value is represented by the line inside the box, the interquartile range is denoted by the top and the bottom edge of the rectangle, and whiskers represent the minimum and the maximum value. One outlier observed in 2015 is marked with a circle; overall p < 0.01; 2015 vs 2016, p = 0.515; 2015 vs 2017, p < 0.001; 2016 vs 2017, p = 0.012

between the unit with the highest reported amount of the drug (16,296 tablets, 20.6%) and the lowest (56 tablets, 0.07%, p = 0.27). However, the first-mentioned absolute value was 291 times greater than the latter.

Discussion

The crucial finding of our research is that the use of ticagrelor is constantly increasing, although noticeable differences were observed between particular medical centres. The positive trend observed in our study could reflect the implementation of the newest guidelines by medical centers to improve the results. The adaptation to the new treatment strategies could probably be more effective, but it is worth mentioning that novel $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) are not reimbursed in Poland for patients with acute coronary syndromes. Thus, medical centres are forced to choose between cheaper and older clopidogrel or more expensive newer drugs.

A recently published Polish study on a large group of patients (n = 19,437) diagnosed with STEMI and treated with primary PCI reported clopidogrel to be the most commonly used $P2Y_{12}$ inhibitor (69%), with still low overall use

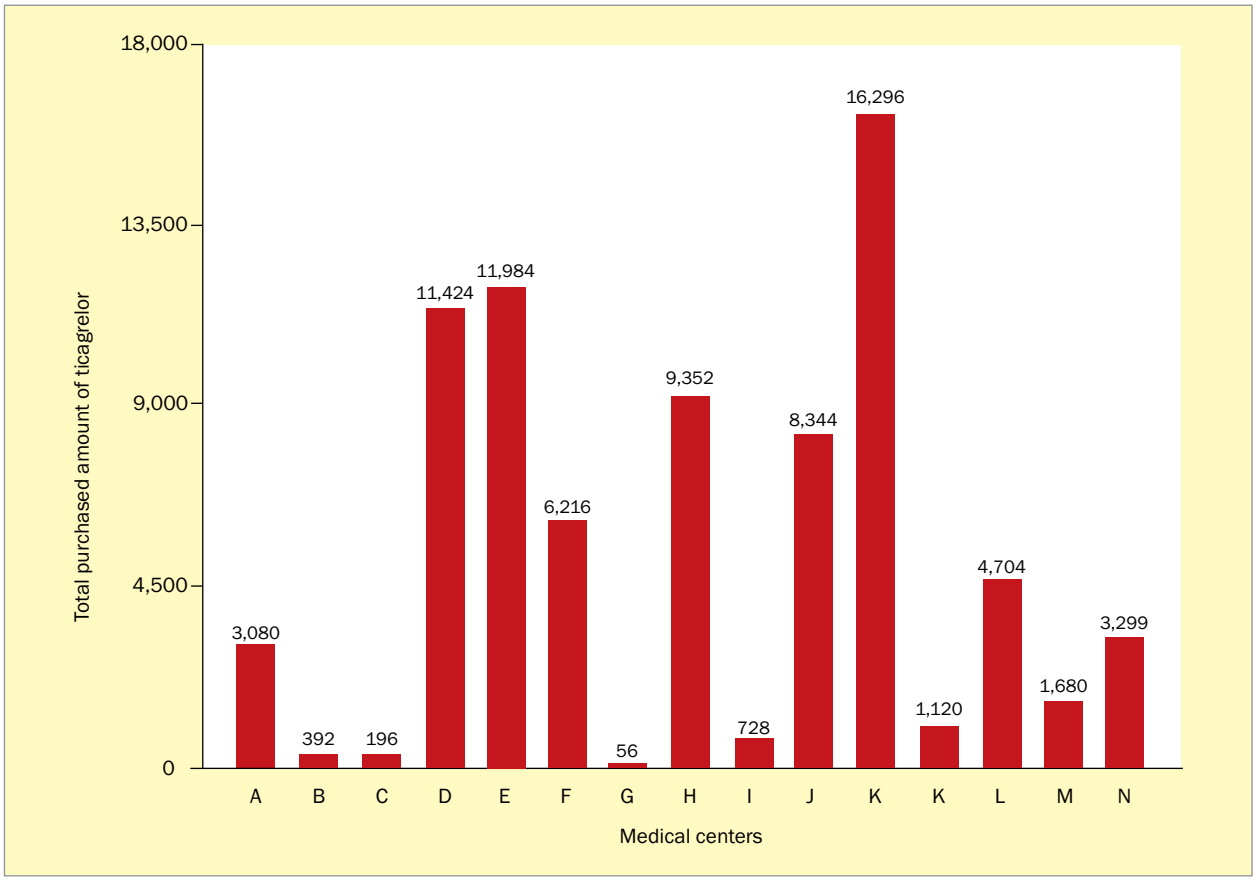

Figure 3. Total amount of ticagrelor tablets purchased by particular medical centres. Each letter (A–N) refers to one particular medical centre included in the analysis; overall $p < 0.001$

of novel drugs: 10.1% and 1.1% treated with ticagrelor and prasugrel respectively [13]. The authors found also a much higher percentage of pre-procedural than periprocedural administration of clopidogrel, while these proportions were inverted for ticagrelor. Other European registries also report a still high rate of patients diagnosed with STEMI or NSTE-ACS and treated with clopidogrel. In the APATHY registry [14], over half of the patients with ACS received clopidogrel (52%), a quarter prasugrel (25.5%), and less than a quarter ticagrelor (22.5%). De Luca et al. [15] reported that clopidogrel was prescribed at discharge for almost half of the patients (47.5%) diagnosed with NSTE-ACS and treated with PCI, while 42.8% received ticagrelor and only 8.3% prasugrel. For STEMI patients treated with PCI those proportions were different in favour of novel $P2Y_{12}$ inhibitors — ticagrelor, prasugrel, and clopidogrel were prescribed for 38.2%, 29.1%, and 32.1% respectively. More recent data from an Austrian registry revealed an improvement in the use of newer drugs in ACS patients treated with PCI [16]. Ticagrelor was prescribed for over 38% of patients at discharge (24.2% with STEMI, 52.3% with NSTE-ACS), prasugrel for one-third of patients (54.8% with STEMI, 11.2% with NSTE-ACS), and clopidogrel for 27.2% (18.7% with STEMI, 35.9% with NSTE-ACS). Alexopoulos et al. [17] reported that clopidogrel was appropriately prescribed at discharge only in 23.8% of cases, whereas in over three--quarters it was a less preferable option. On the other hand, novel $P2Y_{12}$ inhibitors, when selected, were in most cases prescribed appropriately (almost 90% for both ticagrelor and prasugrel).

The role of newer $P2Y_{12}$ inhibitors is crucial during prehospital, inhospital, and after-discharge treatment of patients. In recently published recommendations for medical emergency teams [18], it was underlined that ticagrelor should be the preferred $P2Y_{12}$ inhibitor in patients without contraindications and diagnosed with STEMI or very high-risk NSTE-ACS. Ticagrelor seems to have several advantages over prasugrel regarding the prehospital phase of antiplatelet treatment. Firstly, it can be administered to a wider spectrum of patients, as it has fewer contraindications. Furthermore, prasugrel is not recommended for NSTE-ACS patients with an unknown coronary anatomy. In everyday practice, a knowledge of the coronary anatomy is usually inaccessible for medical emergency teams.

Thirdly, ticagrelor is preferred over prasugrel in prehospital treatment due to Polish legal regulations. Paramedics in Poland after sending ECG and consulting the cardiologist are allowed to administer on their own only clopidogrel and ticagrelor.

Clopidogrel compared to newer $P2Y_{12}$ inhibitors has fewer contraindications e.g. it can be administered to patients already treated with an oral anticoagulation or with a history of previous intracranial bleeding [18]. However, the presence of contraindications along with the higher purchase cost of the novel drugs may not explain the higher usage of clopidogrel in medical centres in Poland. Patients treated with ticagrelor or prasugrel were more likely to be younger males with a lower prevalence of chronic obstructive pulmonary disease [13]. Prescription of ticagrelor at discharge was also associated with lower GRACE score and lower bleeding risk [19]. Probably, more efficient education regarding $P2Y_{12}$ inhibitors for physicians along with other medical professions (paramedics, nurses *etc.*) could improve the use of ticagrelor or prasugrel and in so doing improve adherence to the newest guidelines.

The use of ticagrelor, as the reflection of the guidelines adherence, should increase because of its beneficial effect, especially in the prehospital phase. Ticagrelor, as a novel $P2Y_{12}$ inhibitor, has been investigated in many previous studies regarding for instance the administration of crushed tablets to overcome previously described drug-to-drug interactions with morphine [20]. Furthermore, it is necessary to determine the appropriate dose of ticagrelor in patients with acute myocardial infarction to optimise treatment and reduce adverse events [21]. It is indisputably necessary to further investigate ticagrelor, as well as other innovative drugs like cangrelor (intravenous $P2Y_{12}$ inhibitor), in order to improve the results of treatment strategies in ACS patients [22].

We are aware of several limitations of this study. Firstly, we describe only an absolute value of ticagrelor purchased in various medical centres without adjustment for the number of patients treated in a particular centre and their diagnosis (*i.e.* STEMI vs NSTE-ACS). Furthermore, we provide no information regarding other $P2Y_{12}$ inhibitors. However, the aim of our study was to present the contemporary use of ticagrelor and its change over a three-year time period. Assuming that the number of patients treated in analysed centres did not increase drastically during the observation period, we do believe that our results could fairly reflect adherence to the newest guidelines regarding ticagrelor use in patients with STEMI or NSTE-ACS.

Conclusions

The use of the newest oral $P2Y_{12}$ inhibitor (ticagrelor) has been systematically increasing in the past few years. Observed trends could reflect the implementation of current guidelines by medical centres. Substantial heterogeneity within particular centres can still be observed regarding the use of ticagrelor, with differences reaching 291 times more ticagrelor purchased by one centre compared to another. Such differences indicate the need for a greater effort to improve the adherence to antiplatelet treatment guidelines, and to eliminate the existing differences between regional medical centres.

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Conflict(s) of interest

The authors report no conflict of interest.

Streszczenie

Wstęp. Tikagrelor to najnowszy doustny inhibitor receptora $P2Y_{12}$ zalecany w leczeniu pierwszego rzutu w zawale serca zarówno z uniesieniem, jak i bez uniesienia odcinka ST. Ostatnie doniesienia wskazują na niezadowalające wykorzystanie w terapii nowych inhibitorów receptora $P2Y_{12}$. Celem niniejszego badania była ocena współczesnego wykorzystania tikagreloru w głównych ośrodkach medycznych zlokalizowanych na terenie województw kujawsko-pomorskiego, pomorskiego oraz warmińsko-mazurskiego.

Materiały i metody. Przeprowadzono retrospektywną analizę danych pochodzących ze szpitalnych rejestrów, które dotyczyły miesięcznej liczby zakupionych tabletek tikagreloru. Badanie obejmowało okres 3 lat — od stycznia 2015 do grudnia 2017 roku. Przeanalizowano dane pochodzące z 15 ośrodków medycznych.

Wyniki. W trakcie okresu obserwacji kupiono w sumie 78 871 tabletek tikagreloru, a miesięczna mediana wyniosła 2013,5 z przedziałem międzykwartylowym (IQR) 1255–2996. Ilość wykorzystywanego tikagreloru wzrastała miesięcznie o 7,9%. Najmniejszą ilość leku zarejestrowano w pierwszym miesiącu obserwacji (294; 0,37%), natomiast najwięcej tabletek (4550; 5,77%) kupiono w październiku 2017 roku. Mediana ilości tikagreloru w roku 2017 (3934, IQR 3010–4270) była ponad 4-krotnie większa od mediany w roku 2015 (980; IQR 728–1288; p < 0,001) i ponad 2-krotnie większa od zaobserwowanej w 2016 roku (1689; IQR 1353–2479; p = 0,012). Ośrodek, w którym odnotowano największą sumaryczną ilość zastosowanego tikagreloru (16 296; 20,6%), kupił w całym okresie obserwacji 291 razy więcej tabletek niż ośrodek z najmniejszą zarejestrowaną ilością leku (56; 0,07%; p = 0,27).

Wnioski. Wykorzystanie tikagreloru istotnie się zwiększyło w ostatnich latach, co odzwierciedla wprowadzanie do codziennej praktyki klinicznej zaleceń obecnych w aktualnych wytycznych dotyczących leczenia przeciwpłytkowego. Obserwuje się znaczne zróżnicowanie pod względem użycia tikagreloru w poszczególnych ośrodkach.

Słowa kluczowe: tikagrelor, inhibitory receptora $P2Y_{12}$, stosowanie wytycznych

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