Cost-effectiveness of Platelet Function-Guided Strategy with Clopidogrel or Ticagrelor

Nikita Lomakin,1 Anna Rudakova,2 Liudmila Buryachkovskaya3 and Victor Serebrunay4

1. Cardiology Division, Central Clinical Hospital, Presidential Affairs Department, Moscow, Russia; 2. Chemical Pharmaceutical Academy, St Petersburg, Russia; 3. National Medical Cardiology Center, Moscow, Russia; 4. Stroke Unit, Johns Hopkins University, Baltimore, MD, US

Abstract

Some patients treated with dual antiplatelet therapy (DAPT) following acute coronary syndrome (ACS) can still exhibit heightened residual platelet reactivity (HRPR), which is potentially linked to adverse vascular outcomes. Better tailored DAPT strategies are needed to address this medical need. Aim: To assess the cost-effectiveness of guided DAPT with clopidogrel or ticagrelor in addition to aspirin in ACS patients. Methods: The costs were calculated per 1,000 patients aged >55 years. It was assumed that all patients received either generic clopidogrel or ticagrelor for 1 year, and underwent VerifyNow P2Y12 assay testing before DAPT maintenance. Results: Guided DAPT will prevent five more MIs and six more deaths per 1,000 patients than a standard prescription of generic clopidogrel. The total predictive value of costs per patient is 32% lower if a guided strategy is used than if ticagrelor is given to all patients. Conclusion: Assessment of heightened residual platelet reactivity with P2Y12 assay in triaging DAPT post-ACS patients for 1 year is a cost-effective strategy that would reduce financial burden compared to routine administration of more expensive antiplatelet agents.

Keywords
Acute coronary syndrome, antiplatelet therapy, outcomes, clopidogrel, ticagrelor, cost-effectiveness

Methods

Antiplatelet agents are part of secondary prevention following acute coronary syndrome (ACS). Current European and Russian guidelines recommend dual antiplatelet therapy for 1 year after ACS.1,2

Prasugrel is not marketed in Russia, so high-risk patients have been given ticagrelor. The proportion of generic clopidogrel administered has been steadily rising, with the average cost of treatment decreasing annually by 16–17% (Table 1). However, a considerable number of patients on clopidogrel have high residual platelet reactivity (HRPR), potentially leading to inadequate protection and an excess of thrombotic events.3–6 It seems reasonable to switch those patients exhibiting HRPR to ticagrelor. Since the cost of ticagrelor is significantly higher than that of generic clopidogrel, assessing platelet reactivity with the VerifyNow P2Y12 assay may optimise the care of post-ACS patients by identifying those with HRPR, who may benefit from ticagrelor.7

This study’s objective was to evaluate cost-effectiveness of guided DAPT with clopidogrel or ticagrelor with aspirin in patients after ACS in Russia. To identify which patients would benefit from ticagrelor we used the VerifyNow P2Y12 assay to test platelet reactivity.

ACS may cause a temporary increase in HRPR. Therefore, it was assumed in the simulation that the incidence of HRPR in ACS patients is significantly higher than that of generic clopidogrel, assessing platelet reactivity with the VerifyNow P2Y12 assay in triaging DAPT post-ACS patients for 1 year is a cost-effective strategy that would reduce financial burden compared to routine administration of more expensive antiplatelet agents.
performing a PRU test in the course of modelling was set at US$33. working out at US$206 a year and ticagrelor at US$1,222. The cost of generic clopidogrel and ticagrelor conformed with the period, were US$2,440, while the average cost for bleeding events treatment of non-fatal MI, taking into account the early rehabilitation would be 13%. However, since a PRU test is usually performed during admission for ACS, it was estimated that 32% of patients would receive ticagrelor. It was expected that, after 1 year, all patients would discontinue DAPT, and be denied the additional therapeutic effect of these drugs thereafter. The incidence of non-fatal MI and non-fatal stroke, starting from the second year, was consistent with published epidemiological data. Mortality of patients was calculated on the basis of epidemiological data for Russia, with relative risk adjustments made for various cardiovascular events.

Costs for stroke treatment were calculated on the basis of compulsory medical insurance tariffs in St Petersburg for 2014, with consideration for severity of the disease in the Russian population (minor stroke, modified Rankin scale [mRS] 0–2: 51%; moderate stroke, mRS 3–4: 19%; severe stroke, mRS 5: 1%; fatal stroke: 29%). This totalled US$1,468. Death in the acute phase of MI was 16%, in line with Russian national statistics, and stroke death was 29%. Costs for treatment of non-fatal MI, taking into account the early rehabilitation period, were US$2,440, while the average cost for bleeding events amounted to US$245.

The cost of generic clopidogrel and ticagrelor conformed with the average-weighted cost of public procurement in 2013, with clopidogrel working out at US$206 a year and ticagrelor at US$1,222. The cost of performing a PRU test in the course of modelling was set at US$33.

Table 1: Russian Public Procurement of Generic Clopidogrel in 2010–2013

| Parameters                                      | 2010      | 2011      | 2012      | 2013      |
|------------------------------------------------|-----------|-----------|-----------|-----------|
| Annual courses of treatment with generic clopidogrel (n) | 38,695    | 73,059    | 118,486   | 160,777   |
| Increase in the number of courses of treatment with clopidogrel per annum (%) | –         | 88.9      | 62.2      | 35.7      |
| Increase in the average cost of annual course of generic clopidogrel (US$) | 354       | 297       | 245       | 206       |
| Decrease in the average cost of annual course of treatment with clopidogrel (%) | –         | 16        | 17        | 16        |

Source: Based on Pharmexpert Marketing Research Centre data.

Figure 1: Cost-effectiveness of Platelet Function-guided Strategy with Clopidogrel or Ticagrelor: Study Flow Chart

The impact of cardiovascular events on quality of life was set from published reports. The cost and life expectancy were discounted at 3.5% per year. With regards to cost-effectiveness, WHO recommendations applied. In short, an acceptable level of additional costs per 1 year of life with consideration for quality (quality-adjusted life year [QALY]) should not exceed three times the gross domestic product (GDP) per capita. When the value of additional costs per 1 QALY does not exceed national GDP per capita, the proposed intervention is considered to be economically highly effective and should be widely used in clinical practice. The study design is shown in Figure 1 and main modelling parameters in Table 2.

Results

Providing early, guided DAPT will prevent five MIs and six deaths per 1,000 patients compared to uniform prescription of generic clopidogrel (Table 3). The costs per one additional year of survival with a tailored strategy (US$12,550) was only slightly higher (US$12,440) than when taking the uniform approach. The costs for one additional QALY were US$14,460, and US$16,993 respectively. The total predictive value of costs per patient was 32% lower with guided strategy than with uniformed ticagrelor in all patients. Blindly prescribing ticagrelor without a platelet test increases the affiliated cost more than twice compared to generic clopidogrel. Since the GDP per capita for Russia in 2013 was US$15,500, performing a PRU test in patients post ACS and prescribing DAPT, dependent on the assay results, can be considered as a highly effective economic strategy (Table 4).

Discussion

This analysis revealed that assessment of HRPR with P2Y₁₂ assay in triaging DAPT for post-ACS patients for 1 year is a cost-effective strategy, with a lower financial burden than the routine administration of more expensive antiplatelet agents. This is important since inexpensive generic clopidogrel, including local formulations, are consistently growing and dominate Russian pharmaceutical market. In contrast, branded ticagrelor cost about six times more, so would incur an obvious financial burden.

There are certain limitations. Firstly, many considerations are based on the results of the PLATO trial. Since low-risk patients and medically managed patients were not included in our model, economic considerations may be attributed to ST-segment elevation ACS only if they were planned to undergo primary percutaneous coronary intervention. Therefore, it is difficult to apply this model to the entire ACS cohort.

In addition, in PLATO, 46% of the patients in the ticagrelor group received clopidogrel before randomisation and, within 24 hours before or after randomisation, 34% of the patients in this group received a
Table 2: Modelling Parameters Used to Assess Cost-effectiveness

| Parameters | Reference Case | Range of Values, Used Insensitivity Analysis |
|------------|----------------|---------------------------------------------|
| Quality of life of patients within 1 year after ACS, independent of the development of cardiovascular events | | |
| Non-fatal MI | 0.77 | 0.75–0.80 |
| Non-fatal stroke | 0.70 | 0.63–0.76 |
| No cardiovascular events | 0.84 | 0.84–0.85 |
| Haemorrhage | −0.02 | −0.04–0 |
| Dyspnoea | −0.01 | −0.02–0 |
| Probability of adverse events within 1 year after ACS | | |
| Non-fatal MI against the background of aspirin therapy | 0.1223 | 0.1191–0.1255 |
| Non-fatal stroke against the background of aspirin therapy | 0.0713 | 0.0604–0.0823 |
| Non-fatal stroke against the background of cilostatol and aspirin therapy | 0.0112 | 0.0039–0.0347 |
| Any haemorrhage against the background of aspirin therapy | 0.1745 | 0.1712–0.1781 |
| Death of all causes against the background of aspirin therapy | 0.0619 | 0.0562–0.0681 |
| Relative risk of complications against the background of cilostatol plus aspirin therapy compared with aspirin monotherapy | | |
| Non-fatal MI | 0.77 | 0.67–0.89 |
| Non-fatal stroke | 0.86 | 0.63–1.18 |
| Haemorrhage | 1.69 | 1.47–1.94 |
| Death | 0.91 | 0.78–1.06 |
| Odds ratio of complications against the background of ticagrelor plus aspirin compared with cilostatol plus aspirin therapy | | |
| Non-fatal MI | 0.84 | 0.75–0.95 |
| Non-fatal stroke | 1.17 | 0.91–1.52 |
| Haemorrhage | 1.05 | 0.96–1.15 |
| Dyspnoea | 1.84 | 1.68–2.02 |
| Death | 0.78 | 0.69–0.89 |
| Quality of life of patients, starting from the second year after ACS | | |
| Non-fatal MI | 0.78 | 0.76–0.80 |
| Non-fatal stroke | 0.7 | 0.52–0.87 |
| No cardiovascular events | 0.84 | 0.84–0.85 |
| Condition after MI | 0.82 | 0.80–0.84 |
| Condition after stroke | 0.70 | 0.63–0.78 |
| Probability of cardiovascular events, starting from the second year after ACS | | |
| Annual incidence of MI | 0.0428 | 0.0403–0.0454 |
| Annual incidence of stroke | 0.0102 | 0.0072–0.0145 |
| Risk of death in the absence of cardiovascular events after ACS compared with the general population | 2.21 | 0.18–4.24 |
| Risk of death after non-fatal MI compared with the general population | 3.84 | 3.72–7.97 |
| Risk of death after MI compared with the general population | 0.0102 | 0.0072–0.0145 |
| Risk of death after non-fatal stroke compared with the general population | 2.21 | 0.18–4.24 |
| Risk of death after stroke compared with the general population | 2.07 | 1.30–3.32 |

Main modelling parameters used for cost-effectiveness evaluation of platelet reactivity assay based on VerifyNow P2Y12 ACS = acute coronary syndrome.

Table 3: Cardiovascular Events

| Cardiovascular Complication | Clopidogrel | Ticagrelor | PRU test—cilostatol/ticagrelor |
|-----------------------------|-------------|-------------|-------------------------------|
| MI (%)                      | 22.0        | 20.6        | 21.5                          |
| Stroke (%)                  | 4.0         | 4.2         | 4.0                           |
| Fatality rate (%)           | 22.2        | 21.2        | 21.8                          |

Statistics are for cardiovascular events for the 5-year period following acute coronary syndrome, according to various approaches to antiplatelet drug selection. PRU = platelet reactivity units.
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Table 4: Cost-effectiveness

| Parameters                                      | Clopidogrel | Ticagrelor | PRU-test—Clopidogrel/ ticagrelor |
|------------------------------------------------|-------------|------------|----------------------------------|
| Cost, US $1000s                                | 0.86        | 1.84       | 1.25                              |
| Median life expectancy(years)                  | 4.1561      | 4.2345     | 4.2035                            |
| Median life expectancy with allowance for quality (QALY)  | 3.4525      | 3.5099     | 3.4830                            |
| Additional costs compared with clopidogrel, US $1000s/year | 0.97        | 0.38       |                                   |
| Additional life expectancy with allowance for quality compared with clopidogrel (QALY) | 0.0784      | 0.031      |                                   |
| Effectiveness of additional costs compared with clopidogrel US $1000s/QALY | 12.44       | 12.55      |                                   |
| Effectiveness of additional costs compared with clopidogrel US $1000s/year | 16.99       | 14.46      |                                   |

Cost-effectiveness of platelet reactivity assay based on VerifyNow P2Y12® in Patients after ACS. PRU test = P2Y12 reaction test; QALY = quality-adjusted life year.

Another shortcoming is that the current analysis covered generic clopidogrel, specifically the Russian pharmaceutical market, while branded clopidogrel was used in PLATO.

Conclusion

Within the Russian healthcare system assessment of platelet reactivity with VerifyNow P2Y12® assay in patients with ACS followed by DAPT modification is a more cost-effective approach to reducing treatment costs than the routine use of newer antiplatelet agents.

loading dose of clopidogrel (300–675 mg), which could also affect the effectiveness and safety of the variants of DAPT applied here.6

In addition, some randomised evidence, in particular the negative Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) trial, did not include the benefits of monitoring HRPR during DAPT and to guide dosing strategy.23

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