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

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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 when using VerifyNow $P2Y_{12}$ testing in post-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 $P2Y_{12}$ 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 $P2Y_{12}$ 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

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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 $P2Y_{12}$ 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 $P2Y_{12}$ assay to test platelet reactivity.

Methods

A two-step simulation analysis was carried out by extrapolating the TreeAge™ Pro software program algorithm into the Russian healthcare system, based on the results of the PLATelet Inhibition and Patient Outcomes (PLATO) trial.[8] The index modelling was 5 years. The average age of patients starting therapy was 55 years. The model included a decision tree to assess the costs and clinical effectiveness of therapy for 1 year after ACS, after which patients entered the Markov model, whereby the outcomes of therapy were analysed over the next 4 years.

It was assumed that patients treated with generic clopidogrel or branded ticagrelor underwent a VerifyNow $P2Y_{12}$-based assay before the maintenance phase, with a cut-off of >230 platelet reactivity units (PRU) for ticagrelor, while the remaining patients continue with generic clopidogrel.

For this modelling, we applied conventional daily doses of clopidogrel (75 mg), or ticagrelor (180 mg), both on top of aspirin (100 mg). The magnitude of platelet inhibition was consistent with clinical trial data.[8–10] We deliberately avoided loading antiplatelet strategies, focusing exclusively on maintenance regimen modelling. It was assumed that effectiveness and safety in patients with high reactivity of platelets were comparable to those observed in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.[11]

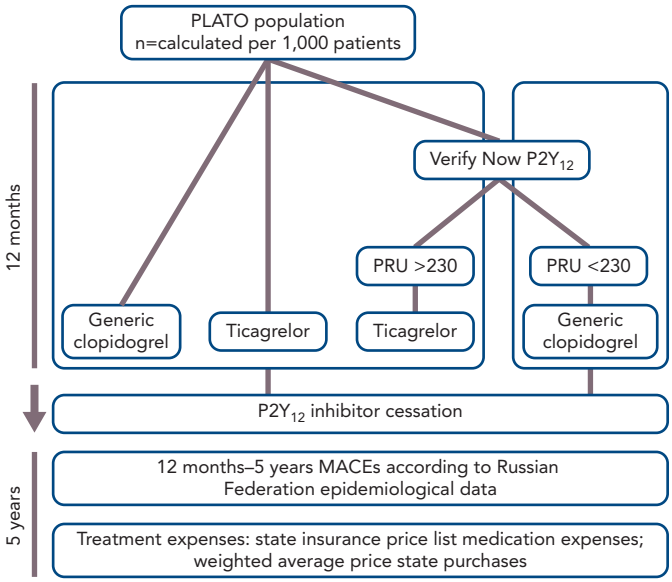
ACS may cause a temporary increase in HRPR. Therefore, it was assumed in the simulation that the incidence of HRPR in ACS patients

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

Parameters	Year			
	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



MACEs = major adverse cardiovascular events; PRU = platelet reactivity units.

would be 13%.[8,9,12] However, since a PRU test is usually performed during admission for ACS, it was estimated that 32% of patients would receive ticagrelor.[10] 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.[13,14] Mortality of patients was calculated on the basis of epidemiological data for Russia, with relative risk adjustments made for various cardiovascular events.[15]

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.[16,17] Death in the acute phase of MI was 16%, in line with Russian national statistics, and stroke death was 29%.[17–19] 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.

The impact of cardiovascular events on quality of life was set from published reports.[20,21] 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.[22,23] 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 $P2Y_{12}$ 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	0.013	0.0045–0.0403
Non-fatal stroke against the background of clopidogrel 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 any causes against the background of aspirin therapy	0.0619	0.0562–0.0681
Relative risk of complications against the background of clopidogrel 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 clopidogrel 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	5.84	3.72–7,97
Risk of death after MI compared with the general population	2.21	0.18–4.24
Risk of death after non-fatal stroke compared with the general population	7.43	6,50–8.50
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 $P2Y_{12}$. ACS = acute coronary syndrome.

Table 3: Cardiovascular Events

Cardiovascular Complication	Clopidogrel	Ticagrelor	PRU test→clopidogrel/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.

Table 4: Cost-effectiveness

Parameters	Clopidogrel	Ticagrelor	PRU-test→Clopidogrel/ ticagrelor
Cost, US$ (000s)	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 (000s)		0.97	0.38
Additional life expectancy compared with clopidogrel, years		0.0784	0.031
Additional life expectancy with allowance for quality compared with clopidogrel (QALY)		0.0574	0.0269
Effectiveness of additional costs compared with clopidogrel $US (000s)/year		12.44	12.55
Effectiveness of additional costs compared with clopidogrel $US (000s)/QALY		16.99	14.46

Cost-effectiveness of platelet reactivity assay based on VerifyNow P2Y$_{12}$ in Patients after ACS. PRU test = P2Y$_{12}$ reaction test; QALY = quality-adjusted life year.

loading dose of clopidogrel (300–675 mg), which could also affect the effectiveness and safety of the variants of DAPT applied here.[8]

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.[24]

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 P2Y$_{12}$ assay in patients with ACS followed by DAPT modification is a more cost-effective approach to reducing treatment costs then the routine use of newer antiplatelet agents. ■

1. National guidelines on the diagnosis and treatment of patients with acute myocardial infarction with ST-segment elevation. *Kardiovaskulyarnaya Terapiya i Profilaktika* 2007;6(8 suppl 1):1–28 [in Russian].
2. National guidelines for the treatment of acute coronary syndromes without ST-segment elevation. *Kardiovaskulyarnaya Terapiya i Profilaktika* 2006;8(5 suppl 1):1–34 [in Russian]. https://doi.org/10.15829/1728-8800-2006-0.
3. Aradi D, Komócsi A, Vorobcsuk A, et al. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. *Am Heart J* 2010;160:543–51. https://doi.org/10.1016/j.ahj.2010.06.004; PMID: 20826265.
4. Brar S, ten Berg J, Marcucci R, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention: a collaborative meta-analysis of individual participant data. *J Am Coll Cardiol* 2011;58:1945–54. https://doi.org/10.1016/j.jacc.2011.06.059; PMID: 22032704.
5. Combescure C, Fontana P, Mallouk N, et al. Clinical implications of clopidogrel non-response in cardiovascular patients: a systematic review and meta-analysis. *J Thromb Haemost* 2010;8:923–33. https://doi.org/10.1111/j.1538-7836.2010.03809.x; PMID: 20156305.
6. Reny JL, Fontana P, Hochholzer W, et al. Vascular risk levels affect the predictive value of platelet reactivity for the occurrence of MACE in patients on clopidogrel. Systematic review and meta-analysis of individual patient data. *Thromb Haemost* 2016;115:844–55. https://doi.org/10.1160/TH15-09-0742; PMID: 26607655.
7. Gurbel P, Bliden K, Butler K, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND Study. *Circulation* 2010;121: 1188–99. https://doi.org/10.1161/CIRCULATIONAHA.109.919456; PMID: 20194878.
8. Wallentin L, Becker R, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57. https://doi.org/10.1056/NEJMoa0904327; PMID:19717846.
9. Storey R, Becker R, Harrington R, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J* 2011;32:2945–53. https://doi.org/10.1093/eurheartj/ehr231; PMID: 21804104.
10. Bonello L, Tantry U, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol* 2010;56:919–33. https://doi.org/10.1016/j.jacc.2010.04.047; PMID: 20828644.
11. Fileti L, Campo G, Valgimigli M. Latest clinical data on testing for high on-treatment platelet reactivity. *Rev Cardiovasc Med* 2011;12:S14–S22; PMID:22080983.
12. Campo G, Parrinello G, Ferraresi P, et al. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention relationship with gene polymorphisms and clinical outcome. *J Am Coll Cardiol* 2011;57:2474–83. https://doi.org/10.1016/j.jacc.2010.12.047; PMID:21679849.
13. Marcucci R, Gori AM, Paniccia R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet re-activity to ADP detected by a point-of-care assay: a 12-month follow-up. *Circulation* 2009;119:237–42. https://doi.org/10.1161/CIRCULATIONAHA.108.812636; PMID:19118249.
14. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502. https://doi.org/10.1056/NEJMoa010746; PMID:11519503.
15. Crespin DJ, Federspiel JJ, Biddle AK, et al. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. *Value Health* 2011;14:483–91. https://doi.org/10.1016/j.jval.2010.11.012; PMID: 21669373.
16. WHO. *Life tables by country. Russian Federation*. Geneva: WHO; 2018. Available at: http://apps.who.int/gho/data/?theme=main&vid=61360 (accessed 4 July 2019).
17. Secrieru EM, Moravian SV, Zakharova AB. Some features of formation of statistical data on hospital morbidity using the federal reporting data. *Social Aspects of Population Health* 2009;3: [in Russian].
18. Applications to the General Agreement on Tariffs tariff for medical care (medical services) and the terms of payment for medical care provided in the framework of the existing territorial program of compulsory health insurance for citizens of the Russian Federation in St Petersburg in 2014. Available at: http://www.spboms.ru/kiop/main?page_id=338.
19. Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics* 2003;21:191–200. https://doi.org/10.2165/00019053-200321030-00004; PMID: 12558469.
20. Rudakova AV, Parfenov VA. Pharmacoeconomic aspects of prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: the use of apixaban compared with warfarin and acetyl-salicylic acid. *Rational Pharmacotherapy in Cardiology* 2014;10:275–82. https://doi.org/10.20996/1819-6446-2014-10-3-275-282.
21. Bagust A, Boland A, Blundell M, et al. *Ticagrelor for the treatment of acute coronary syndromes: a single technology appraisal.* Liverpool: Liverpool Reviews and Implementation Group, University of Liverpool, 2011. Available at: http://tinyurl.com/y4nzruya (accessed 1 May 2019).
22. Coleman C, Limone B. Cost-effectiveness of universal and platelet reactivity assay-driven antiplatelet therapy in acute coronary syndrome. *Am J Cardiol* 2013;112:355–62. https://doi.org/10.1016/j.amjcard.2013.03.036; PMID: 23631863.
23. WHO. *Investing In health for economic development. Report of the Commission on Macroeconomics and Health.* Geneva: WHO, 2001.
24. Collet JP, Cayla G, Elhabad S, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100–9. https://doi.org/10.1056/NEJMoa1209979; PMID:23121439.