Cardiology Lett. 2022;31(4):221–228
doi:10.4149/Cardiol_2022_4_2

The role of thromboelastometry in monitoring the response to antiplatelet therapy: our experiences and review of literature

Využitie tromboelastometrie pri monitorovaní odpovede na protidoštičkovú liečbu: vlastné skúsenosti a prehľad literatúry

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Samos M, Simonova R, Bolek T, Skornova I, Stanciakova L, Stasko J, Mokan M. **The role of thromboelastometry in monitoring the response to antiplatelet therapy: our experiences and review of literature.** Cardiology Lett. 2022;31(4):211–228

Abstract. *Aim:* Insufficient response to antiplatelet therapy, so called high on-treatment platelet reactivity (HTPR), has been repeatedly associated with increased risk of adverse ischemic events. Rotational thromboelastometry (ROTEM®) is a novel viscoelastic hemostatic assay which could, in theory, overcome some limitations of currently available platelet function testing assays. The aim of the article is to report our experiences with the use of ROTEM® for assessment of HTPR in patients with acute myocardial infarction (MI) and review the current experience with the use of the assay for platelet function testing and for monitoring of the response to antiplatelet therapy.
Methods: A pilot prospective study assessing the use of ROTEM® in monitoring the antiplatelet therapy in consecutively enrolled patients with acute MI was performed. In addition, a narrative review of current knowledge about the use of the assay for identifying HTPR is given.
Results: Patients with MI showed decreased platelet aggregation after the use of specific inducers. The ROTEM® analysis showed significant differences in clotting time for EXTEM® and FIBTEM® test and in maximum clot firmness for FIBTEM® comparing MI patients with controls. No significant differences in other variables were found.
Conclusion: Up to date, there is no study demonstrating the ability of ROTEM® to monitor the treatment response to antiplatelet drugs or to search for patients with HTPR. Fig. 2, Tab. 2, Ref. 22, on -line full text (Free, PDF) www.cardiologyletters.sk

Key words: rotation thromboelastometry – ROTEM® – antiplatelet therapy – acute coronary syndrome

Samoš M, Šimonová R, Bolek T, Škorňová I, Stančiaková L, Staško J, Mokáň M. **Využitie tromboelastometrie pri monitorovaní odpovede na protidoštičkovú liečbu: vlastné skúsenosti a prehľad literatúry.** Cardiology Lett. 2022;31(4):211–228

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Manuscript received 21 June 2022; accepted for publication 27 July 2022

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Abstrakt. *Ciele:* Nedostatočná odpoveď na protidoštičkovú liečbu, tzv. vysoká reaktivita trombocytov na liečbe („high on-treatment platelet reactivity" = HTPR) bola opakovane spojená so zvýšeným rizikom nežiaducich ischemických príhod. Rotačná tromboelastometria (ROTEM®) je novším viskoelastickým testom hemostázy, ktorý môže prekonať niektoré nevýhody doteraz dostupných testov funkcie trombocytov. Cieľom článku je podať naše skúsenosti s použitím ROTEM® na stanovenie HTPR u pacientov s akútnym infarktom myokardu (IM) a sumarizovať súčasne dostupné skúsenosti s využitím testu pri stanovení funkcie trombocytov a pri monitorovaní odpovede na protidoštičkovú liečbu.
Metódy: Bola uskutočnená pilotná prospektívna štúdia overujúca použitie ROTEM® pri monitorovaní protidoštičkovej liečby u pacientov s IM. Ďalej bol vykonaný rešerš dostupnej literatúry venujúcej sa uvedenej problematike.
Výsledky: Pacienti s IM mali zníženú agregabilitu doštičiek po použití špecifických induktorov. ROTEM® analýza preukázala signifikantný rozdiel v čase zrážania pri teste EXTEM® a INTEM® a v maximálnej hrúbke koagula v teste FIBTEM® pri porovnaní pacientov s IM a kontrol. Nebol zistený rozdiel v ostatných skúmaných parametroch.
Závery: V súčasnosti neexistuje štúdia potvrdzujúca použiteľnosť ROTEM® pri monitorovaní odpovede na protidoštičkovú liečbu alebo identifikácii pacientov s HTPR. Obr. 2, Tab. 2, Lit. 22, on -line full text (Free, PDF) www.cardiologyletters.sk
Kľúčové slová: rotačná tromboelastometria – ROTEM® – protidoštičková liečba – akútny koronárny syndróm

Platelet activation and subsequent aggregation plays a crucial role in acute vascular atherosclerotic diseases, including myocardial infarction and stroke. Additionally, platelet aggregation is a key target of antiplatelet agents, such as acetylsalicylic acid (ASA, aspirin), P2Y12 ADP receptor blockers (ADPRB) and glycoprotein IIb/IIIa blockers. The insufficient response to these agents, so called high on-treatment platelet reactivity (HTPR), or antiplatelet therapy resistance, has been repeatedly connected with higher risk of vascular events, and increased mortality. This opens the question about the need for platelet function testing to identify individuals with HTPR or impaired response to antiplatelet drugs. Although several methods, such as light transmission or impedance aggregometry, vasodilator-stimulated phosphoprotein (VASP) phosphorylation assessment, PFA-100® assay or Verify Now® assay have been introduced for platelet function/antiplatelet therapy response testing (1 – 3), these methods do have their disadvantages.

Rotational thromboelastometry (ROTEM®) is a viscoelastic hemostatic assay (VHA), which was designed as a whole blood, real-time analyzer of clot formation and lysis (4, 5). The assay is, in theory, capable of overcoming some limitations of currently available platelet function tests, namely longer turnaround times, need for special equipment and skilled staff, and inability to test the platelet function in the settings of point of care. This article reviews our experience and literature data reporting the use of ROTEM® for platelet function testing (PFT) and for monitoring of the response to antiplatelet drugs in patients with acute atherosclerotic vascular diseases.

Methods

ROTEM® assay principle, parameters and standard ROTEM® tests

ROTEM® (4 – 8) is a point of care VHA which assesses the clotting of whole blood in real time. ROTEM® assesses clot formation/dissolution and strength by measuring and displaying the amount of a continuously applied rotational force that is transmitted to an electromechanical transduction system by the developing clot. During ROTEM® analysis, a cylindrical cup with 340 µL of whole blood (300 µL of whole blood, 20 µL of an activator, and 20 µL of CaCl2) is fixed while a pin suspended on a ball-bearing mechanism oscillates through 4°75´ every 6 seconds and applies a constant force. As the viscoelastic strength of the clot increases, the rotation of the pin is obstructed and optically detected using a charge-coupled device image sensor system. The assay graphically records kinetic changes of citrated whole blood samples during clot formation and its lysis, resulting in a compact map of the various phases of clot formation and its lysis in the form of a thromboelastogram (**Figure 1**). As stated previously, the examination is based on a solid, constantly oscillating pin in a fixed cup with a blood sample with reagents. If there is no formation of clot, rotation is not obstructed. If a clot forms, the rotation is

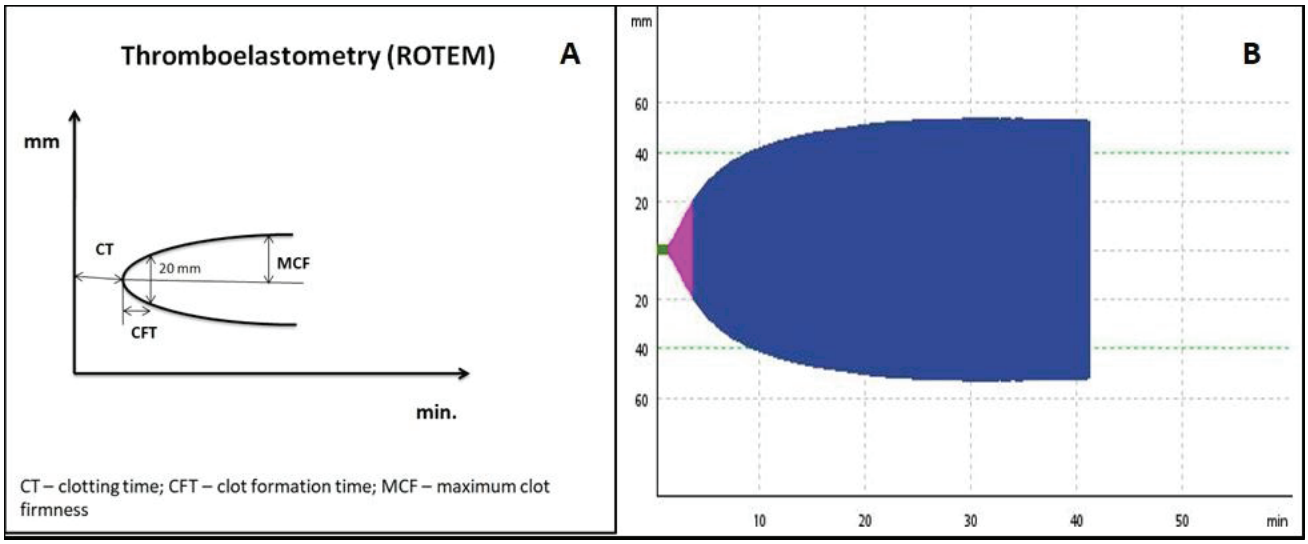

Figure 1 ROTEM® thromboelastogram (A – scheme, B – practical example)

obstructed due to a link between the cup wall and the pin. The rotation of the pin is graphically transformed to amplitude, where free rotation meets an amplitude of 0 mm (non-coagulated sample) and no rotation meets an amplitude of 100 mm (the most possible strength of the clot in a sample). Four samples simultaneously can be analyzed on a standard ROTEM® device.

The most important advantages of the assay are complexity, rapid evaluation and the ability to test a whole blood sample in a point-of-care testing setting. However, ROTEM® may have several limitations. Clot formation and lysis is connected with a wide range of normal values due to the high variability of the components of the hemostatic system, including platelets (function and count), and coagulation factors concentration (including fibrinogen). Ideally therefore, each patient should have baseline ROTEM® measurements before undergoing treatment or a procedure to ensure that there is an internal, individualized reference against which change can be assessed. Additionally, there are problems with assay standardization and validation. This problem has been, to some extent, overcome by the use of computer software analysis, the use of disposable cups and pins, individual temperature control and the use of activators such as kaolin (to standardize the initiation of the clotting process) and the use of standardized reagents in the form of commercially available ROTEM® tests. The most widely used ROTEM tests are INTEM®, EXTEM® and FIBTEM®:

The INTEM® test is initiated by activating the intrinsic pathway with ellagic acid;

the EXTEM® test is initiated by activating the extrinsic pathway with tissue factor;

and the FIBTEM® corresponds to an EXTEM® with the inhibition of platelets by cytochalasin.

In addition, several parameters can be measured with ROTEM. The most important ones in clinical research and clinical practice are:

clotting time (CT) – the time elapsed from the coagulation trigger until the formation of a clot of 2 mm;

clot forming time (CFT) – the time elapsed from 2 to 20 mm;

and maximum clot firmness (MCF) – the maximum amplitude of the signal reflecting the maximum clot strength.

Study rationale and aims

HTPR predicts future ischemia in patients undergoing percutaneous coronary interventions (PCI) for acute coronary syndromes (ACS) (9), as well as in those after-coronary stenting for stable coronary artery disease (SCAD) (10), and platelet activation after PCI could independently predict worse clinical outcome and may be helpful in risk stratification (11). Going further, HTPR on P2Y12 ADPRB (10 – 13), and aspirin (13) (with lower level of evidence) is associated with an unfavorable clinical course, and predicts independently future thrombotic adverse events in those undergoing coronary stent implantation (both for ACS and SCAD). For example, in a sub-analysis

of randomized GRAVITAS (Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety) study (12), HTPR (defined as > 208 P2Y12 reaction units when examined with point-of--care Verify Now® assay at 12 to 24 hours after PCI) was connected with a higher risk of adverse ischemia at 60 days and at 6 months (at 60 days: hazard ratio (HR): 0.18; 95% confidence interval (CI): 0.04 – 0.79; p = 0.02; at 6 months: HR: 0.43; 95% CI: 0.23 – 0.82; p = 0.01). Additionally, HTPR remains independently associated with adverse vascular events (including stent thrombosis) also in individuals treated with novel P2Y12 ADP receptor blockers with stronger platelet inhibition, such as prasugrel and ticagrelor (14 – 16). Summarizing the data HTPR, despite oral antiplatelet agents, has been consistently connected with the risk of adverse ischemia; thus identifying individuals with insufficient antiplatelet therapy response might help in preventing these possibly fatal events.

As already mentioned, ROTEM® is a relatively novel hemostatic assay for the complex evaluation of changes in hemostasis in a sample of whole blood. In 2012 we were awarded a research project of the Slovak Society of Cardiology which aimed to assess the utility of ROTEM® in monitoring the response to dual antiplatelet therapy in patients with acute STEMI. At this time, no other study focused on this issue was available.

Study design, patients and methods

We performed a single-centre pilot prospective observational study (17). The study period started in 2012 and ended in 2015. This study enrolled patients with acute STEMI treated with primary PCI of culprit coronary lesion. All patients were treated with the then--recommended dual antiplatelet therapy (200 – 400 mg aspirin loading dose, followed by a maintenance dose of 100 mg/daily and 600 mg clopidogrel loading dose, followed by a maintenance dose of 75 mg/daily or 60 mg prasugrel loading dose, followed by a maintenance dose of 10 mg/daily or 180 mg ticagrelor loading dose, followed by a maintenance dose of 90 mg/twice daily) and weight-adjusted unfractionated heparin (100 IU/kg) administrated prior to urgent coronary angiography. No other antiplatelet or anticoagulant therapy (including oral anticoagulants) was administerted. Exclusion criteria for patient enrollment included insufficient initial dosage of antiplatelet therapy, "rescue" PCI after thrombolysis, inability to perform PCI, primary PCI failure, cardiac arrest with the need of resuscitation, severe cardiac failure (Killip class IV), abnormal blood count (thrombocytopenia, platelet count less than 100x109/l), active bleeding, hemorrhagic stroke in the patient past history, creatinine clearance less than 25 ml/min. and the history of non-compliance.

The control group was enrolled from healthy blood donors. Exclusion criteria for the control group were the following: history of previous PCI, heart failure, anticoagulant or antiplatelet therapy, abnormal blood count (thrombocytopenia), smoking, active bleeding, or history of hemorrhagic stroke.

All included persons agreed with study participation and signed written informed consent prior to blood sampling. This prospective study was approved by our local ethical committee.

Blood samples were taken before the urgent coronary angiography (for the monitoring of the loading doses given in the pre-hospital setting, sample 1) and one day after primary PCI (for the monitoring of the maintenance doses given during the in-patient stay, sample 2). Light transmission aggregometry (LTA) with the use of adenosinediphosphate /ADP/ (concentration 10 μmol/l) and arachidonic acid /AA/ (concentration (0.5 mmol/l) as the agonists of platelet aggregation and ROTEM® using EXTEM® and FIBTEM® reagent were chosen for the laboratory monitoring of hemostasis. ROTEM analysis was performed on ROTEM® Gamma (Pentapharm GmbH, Munich, Germany) according to instructions from the manufacturer. Reference range for adequate ADP receptor inhibition was the rate of platelet aggregation less than 50% and for adequate aspirin therapy a rate of AA induced platelet aggregation less than 20%.

Statistical analysis

Data were in the first step tested for normality with the Shapiro-Walk test. Results are expressed as a number or a percentage (%) of cases, normally distributed continuous or interval-scaled variables are presented as mean ± standard deviation (SD); otherwise median (M) and quartile ranges from the lower quartile to the upper quartile were used. Data were tested with t-test or ANOVA in the case of normally distributed data or with Mann-Whitney U test or Kruskal-Walis test when data distribution was asymmetrical. Differences between proportions were tested with binominal tests. Categorical variables grouped in 2-way contingency tables were analyzed using chi-square tests. The significance of $p < 0.05$ was considered as a criterion for comparison between data sets with equal and unequal variances. The statistical analysis was performed with

Table 1 Demographic data, concomitant medication in studied acute STEMI patients and controls

	Studied patient population		
	Patients	**Controls**	**Significance**
Number of patients (men/women)	56 (34/22)	21 (17/4)	N/A
Age	67.75 (38 – 88)	50.38 (40 – 74)	p = 0.12
Arterial hypertension	71.4%	0.0%	p < 0.001
Type 2 Diabetes (T2D)	30.3%	0.0%	p < 0.001
Dyslipidaemia	55.4%	28.5%	p = 0.09
Family history of cardiovascular diseases	21.4%	9.5%	p < 0.05
Smoking	19.6%	0.0%	N/A
Beta blockers	88.9%	0.0%	N/A
ACE inhibitors or AT1R blockers	66.7%	0.0%	N/A
Statins	98.2%	0.0%	N/A
Diuretics	37.0%	0.0%	N/A
Clopidogrel	53.6%	0.0%	N/A
Prasugrel	37.5%	0.0%	N/A
Ticagrelor	8.9%	0.0%	N/A
Pantoprazole	28.6%	0.0%	N/A
Calcium channel blockers	7.4%	0.0%	N/A

ACE – angiotensin converting enzyme; AT1R – angiotensin 1 receptor; N/A – not applicable.

Statistical v. 7.0 (Stat Soft Inc., Dell Software, and Tulsa, Oklahoma, USA).

Results

Patients

The study group consisted of 56 acute STEMI patients (34 men, 22 women, mean age 67.75 years, age range 34 – 88 years). Among them, clopidogrel was used in 30 patients, prasugrel in 21 patients and ticagrelor in 5 patients, respectively. Average length of the hospitalization was 3.96 days. The demographic data and concomitant medication used in the studied population is reported in **Table 1**. In addition, 21 healthy individuals (17 men, 4 women, mean age 50.38 years, age range 40 – 74 years), all enrolled in a blood donor programme, were recruited as the control group (Table 1).

Light transmission aggregometry and ROTEM® analysis

Patients with STEMI showed decreased platelet aggregation after the use of both inducers (arachidonic acid: 33.2% versus 74.6% in sample 1 and 21.1% versus 74.6% in sample 2, respectively; ADP: 51.4% versus

Table 2 ROTEM® parameters and LTA in STEMI patients and controls

	Studied patient population				
	Patients Sample 1	**Patients Sample 2**	**Controls**	**Significance Sample 1**	**Significance Sample 2**
Clotting time (EXTEM)	62 (57 – 70) sec	54.5 (50 – 62.3) sec	55 (50 – 58) sec	p < 0.01	p = 0.06
Clotting time (FIBTEM)	58 (51.5 – 68) sec	45 (43 – 54.5) sec	49 (48 – 55) sec	p < 0.05	p = 0.14
Maximum clot firmness (EXTEM)	66 (55 – 73) mm	66 (58 – 74) mm	63.5 (53 – 69) mm	p = 0.15	p = 0.20
Maximum clot firmness (FIBTEM)	19 (15 – 25) mm	19 (15.5 – 26) mm	14 (13 – 17) mm	p < 0.05	p < 0.05
Clot formation time (EXTEM)	80.0 ± 23.8 sec	69.5 ± 31.2 sec	71.6 ± 32.0 sec	p = 0.21	p = 0.43
Clot formation time (FIBTEM)	253.6 ± 60.4 sec	232 ± 48.2 sec	221.0 ± 54.7 sec	p = 0.32	p = 0.58
LTA – arachidonic acid induction	33.2 ± 26.1%	21.1 ± 8.5 %	74.6 ± 18.6%	p < 0.001	p < 0.001
LTA – ADP induction	51.4 ± 18.3%	37.1 ± 12.1 %	72.7 ± 13.7%	p < 0.001	p < 0.001

ADP – adenosine diphosphate; LTA – light transmission aggregometry; ROTEM – rotational thromboelastometry; sec – second

72.7% in sample 1 and 37.1% versus 72.7% in sample 2, respectively). The ROTEM® analysis (**Table 2**) showed significant differences in CT for EXTEM® test comparing sample 1 of STEMI patients with controls (62 seconds versus 55 seconds, $p < 0.01$). No significant differences in other variables (CFT, MCF) were found. ROTEM® analysis with FIBTEM® test showed significant differences in CT between sample 1 of STEMI patients and control sample (58 seconds versus 49 seconds, $p < 0.05$), and in MCF when samples 1 and 2 of STEMI patients were compared with controls ($p < 0.05$). None of the examined ROTEM® parameters showed sensitivity for identification of HTPR in STEMI patients. Full results of our study can be found in our previously published manuscript (17).

Discussion and review of literature

Looking at the available data, in fact, there are quite limited experiences in platelet function testing with ROTEM®. Primarily, the assay has been tested for evaluation of treatment response to antiplatelet therapy. Apart from our previously mentioned study (17), in which we were not able to discriminate between HTPR and normal response to antiplatelet therapy, there are only two other studies dealing with this issue. In one of these studies, Scharbert et al. (18) reported their first experiences with modified ROTEM® with platelet mapping assay. In this study, platelet aggregability was determined from blood samples taken from 22 adult healthy individuals and patients without or with antiplatelet drugs (clopidogrel with or without aspirin) using three different assays: multiple electrode aggregometry, thromboelastography with platelet mapping assay using both inducers – ADP and arachidonic acid, and its adapted version on ROTEM®. The authors of this study reported that the specificity for detection of ADP receptor blocker-induced platelet inhibition was low in both assays; however, the differences in frequency distribution between the results obtained in thromboelastography and ROTEM® were not statistically significant. Subsequently, Braun at al. (19) studied the antiplatelet and anticoagulant action of clopidogrel plus heparin (26 patients) versus prasugrel plus bivalirudin (25 patients) versus untreated controls (20 individuals) with multiple electrode aggregometry and ROTEM® in patients with STEMI. In this study, in ROTEM® analysis, there were no differences in reducing CFT between studied antiplatelet/anticoagulation agent regimens, and both regimens did not affect MCF compared to the control group. This observation confirmed our observation of the low sensitivity of standard ROTEM® assays in detecting P2Y12 ADP receptor blockers-induced changes in platelet reactivity. Unfortunately, to date, there is no specific platelet mapping assay for ROTEM®, and no other larger study evaluating the ability of ROTEM® with Platelet Mapping Assay (which was originally developed for thromboelastography) to assess the response on antiplatelet agents in patients with acute vascular diseases or patients undergoing invasive vascular procedures.

Going further, several studies tried to evaluate the use of ROTEM® for procedural bleeding risk assessment and blood replacement therapy in patients undergoing cardiac surgeries. Looking more closely at these trials, Ogawa et al. (20) observed significant correlations between thromboelastometry test FIBTEM®-amplitude at 10 minutes (A10) and fibrinogen levels ($r = 0.87$; $p < 0.001$), and between test EXTEM® and INTEM®-A10 values and platelet count ($r = 0.72$ and 0.67; $p<0.001$) in patients undergoing procedures with cardiopulmonary bypass. The authors suggested the ability of ROTEM® testing with FIBTEM® assay to quickly detect decreasing levels of fibrinogen in patients who underwent cardiopulmonary bypass. In another study enrolling patients undergoing CABG surgery on antiplatelet agents (aspirin alone or aspirin plus clopidogrel), Tarzia et al. (21) reported an observation of comparable pre-operative classic coagulation tests and traditional ROTEM® parameters in those with major bleeding and those without a bleeding event. Nevertheless, the authors reported that the area-under-curve in the EXTEM® test was significantly lower in patients with major hemorrhage than non-bleeders. Finally, Azarfarin et al. (22) studied the relation between MCF in ROTEM® and bleeding after CABG surgery in patients on clopidogrel and found that needs for chest tube drainage and for blood product transfusion were significantly higher in those with MCF below 50 mm. Furthermore, in patients who experienced postoperative bleeding of 1 liter of blood or more, several ROTEM® parameters including MCF (tested with INTEM®, EXTEM® and HEPTEM® reagents) were significantly lower than in those with postoperative bleeding < 1 liter. This observation suggested that ROTEM® might be more useful for the prediction of increased risk of hemorrhage after CABG in patients on clopidogrel prior to the procedure.

Conclusion

To date, there is no study demonstrating the ability of ROTEM® to monitor the treatment response to antiplatelet drugs or to search for patients with HTPR. Thus,

until specific platelet mapping assays for ROTEM@ are available and validated, ROTEM® should not be used for this indication. However, several studies (although on limited samples) have suggested that it can be used for procedural management of bleeding events in the settings of cardiac surgery.

Acknowledgments

This study was supported by the research project of the Slovak Society of Cardiology 2012 – 2015 and by the project of the Slovak Research and Development Agency (APVV) 16-0020.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflicts of interest that might be relevant to the content of this manuscript.

Funding

This study was supported by the research project of the Slovak Society of Cardiology 2012 – 2015 and by the project of the Slovak Research and Development Agency (APVV) 16-0020.

Ethical approval and informed consent

This research was undertaken according to ethical standards. All persons included in reported prospective study agreed with study participation and signed written informed consent prior to blood sampling. The prospective study was approved by the local ethical committee (Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava). Formal approval is not needed for a review article.

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