REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Antiplatelet therapy in secondary ischemic stroke prevention – a short review

CRISTINA FLORESCU[1)], EDME ROXANA MUSTAFA[1)], ELENA-ANCA TÂRTEA[2)], DIANA-RUXANDRA FLORESCU[3)], VALERIA-CARMEN ALBU[2)]

[1)]*Department of Cardiology, University of Medicine and Pharmacy of Craiova, Romania*
[2)]*Department of Neurology, University of Medicine and Pharmacy of Craiova, Romania*
[3)]*"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Abstract

Platelets play an essential role in atherothrombosis and for this reason they are the primary target of antithrombotic therapy in ischemic stroke. We discussed here the evidence for efficacy and safety of current knowledge in antiplatelet therapy for stroke prevention after an acute ischemic stroke or transient ischemic attack. After an acute episode, long-term antithrombotic therapy is essential for the secondary prevention of stroke recurrence and complications. Antiplatelet therapy for acute ischemic stroke (non-cardioembolic) or ischemic stroke consists of three antiplatelet drugs, in accordance with *Food and Drug Administration* (FDA) from the USA and also with the Guidelines published by the *American Heart Association* (AHA) and nevertheless with the Guidelines of the *American Stroke Association* (ASA), in 2014, for preventing vascular events, such as stroke. These are aspirin, clopidogrel and dipyridamole. Moreover, recent randomized clinical trials and the last Guidelines for stroke of *AHA/ASA*, in 2018, also mention ticagrelor. All of these antiplatelet therapies, besides inhibiting acute arterial thrombosis, also interfere with physiological hemostasis. In conclusion, we can say that current recommendations focused primarily on the therapy with aspirin for the secondary prevention of stroke in patients that presented vascular events, such as ischemic stroke of non-cardioembolic cause or transient ischemic attack and, as appropriate, aspirin plus dipyridamol or clopidogrel. The new therapy with ticagrelor in secondary stroke prevention seems to be promising, but more randomized clinical trials are needed to accurately assess the safety and efficacy of this new antiplatelet drug.

Keywords: ischemic stroke secondary prevention, aspirin, clopidogrel, ticagrelor.

Introduction

Stroke, along with coronary artery disease and peripheral arterial disease, is a major health problem that is caused by the formation of a thrombus following the rupture of the atheroma plaque [1].

Taking into account the frequency and importance of stroke, it is situated on the first position in terms of all neurological diseases encountered in adulthood [2]. Stroke is a huge burden if we look at things from a global perspective. In 2013, stroke was the second cause of death (11.8% of all deaths) worldwide after acute myocardial infarction that was responsible of 14.8% of all deaths all over the world and it is the third most common cause of disability (4.5% of total disability-adjusted life years), after ischemic heart disease (6.1%) and oncological disorders [2].

After an acute episode, long-term antithrombotic therapy is essential for the secondary prevention of stroke recurrence and complications [1]. We discussed here the evidence for efficacy and safety of current knowledge in antiplatelet therapy for stroke prevention after an acute cerebral vascular event (including transient ischemic attack and ischemic stroke).

For creating a review of the therapy based on antiplatelet drugs in ischemic stroke, we studied several databases [Medline, Scopus, PubMed, *World Health Organization* (WHO) Library, *WHO* Regional Databases, Google Scholar], in order to identify original articles and reviews published over the past decade on the secondary prevention of ischemic stroke by using antiplatelet therapy, we took into account the recommendations of current guidelines on this issue, but also the latest clinical trials or published cohort studies, according to the current recommendations on reviews and meta-analyses, included in *Meta-Analysis of Observational Studies in Epidemiology* [3–5].

The aim of this study was to bring into light the newest information about the antiplatelet therapy in secondary ischemic stroke prevention.

Antiplatelet therapy

The two major causes of ischemic stroke are cerebral embolism and atherothrombosis or atherosclerotic-thrombotic disease of cerebral or extracerebral vessels [1]. Platelets play an essential role in atherothrombosis and for this reason they are the primary target of antithrombotic therapy in ischemic stroke [6].

Antiplatelet therapy for acute ischemic stroke (non-cardioembolic) or ischemic stroke consists of three antiplatelet drugs approved in the USA by the *Food and Drug Administration* (FDA), in accordance with the Guidelines of the *American Heart Association* (AHA) and nevertheless in accordance with the Guidelines published by the *American Stroke Association* (ASA), in 2014, for preventing vascular events, such as stroke [7]. These are aspirin, clopidogrel and dipyridamole [7]. In addition, recent randomized

clinical trials and the last Guidelines for stroke of *AHA/ASA*, in 2018, also mention ticagrelor [8]. All of these antiplatelet therapies, besides inhibiting acute arterial thrombosis, also interfere with physiological hemostasis [9].

Aspirin (acetylsalicylic acid) is the first antiplatelet agent used for over a hundred years but has not yet lost its utility [10]. It is an irreversible inhibitor of cyclooxygenase-1 (COX-1), the enzyme involved in the transformation of arachidonic acid into thromboxane A2 (TxA2), which acts as a platelet activator, as well as a vasoconstrictor [10]. It was proved that using aspirin for a long period of time helps reducing by approximately 20–25% the risk of major vascular events consisting of ischemic stroke, myocardial infarction and even death in patients with atherothrombotic disease having an intermediate or a high risk [10]. On the other hand, due to the fact that aspirin inhibits only partial platelet aggregation, but also due to the gastrointestinal side effects, far more specific, more potent and consistent platelets are still being investigated. The *AHA/ASA* Guidelines of 2018 maintains Class I (strength) of recommendation (COR) and level A (quality) of evidence (LOE) for the use of antiplatelet agents in patients with non-cardioembolic acute ischemic stroke for reducing stroke recurrence or other cardiovascular events, rather than oral anticoagulation [8]. For patients who had an acute ischemic stroke during the treatment with aspirin, changing the aspirin dose or using another antiplatelet agent instead of aspirin for secondary stroke prevention has not been well established by clinical trials, so the *AHA/ASA* Guidelines of 2018 giving COR IIb and LOE BR [8]. It should be noted that the benefits of aspirin are similar at doses ranging from 50 to 1500 mg daily, while its adverse effects increase proportionally to doses [7].

Another category of antiplatelet agents is P2Y12 blockers [11–14]. P2Y12 is considered the most important receptor involved in platelet aggregation mediated by adenosine diphosphate (ADP), being the therapeutic target of two major classes of antiplatelet drugs [10]. On one hand, we have the class of thienopyridines (clopidogrel, prasugrel and ticlopidine) that are selective but irreversible P2Y12 inhibitors [10]. Also, on the other hand, direct and reversible P2Y12 blockers include ticagrelor, cangrelor and elinogrel [15, 16]. Of the P2Y12 receptor inhibitors, randomized clinical trials have been performed so far only for clopidogrel and ticagrelor, as we shall see below. Ticlopidine is no longer used due to its high adverse effects compared to clopidogrel, although it was evaluated in three randomized clinical trials in patients with cerebrovascular blisters [17–19].

Dipyridamole is an agent that inhibits phosphodiesterase-5, thus increasing the degree of inhibition of prostacyclin-related platelet aggregation [20]. The 200 mg dose is commonly used with 50 mg aspirin for stroke [such as *European Stroke Prevention Study* 2 (ESPS-2) and *European/Australasian study that presents the Stroke Prevention in a Reversible Ischemia Trial* (ESPRIT) showed] but it is not superior to clopidogrel in secondary stroke prevention according to the *Prevention Regimen for Effectively Avoiding Second Strokes* (PRoFESS) trial.

Triflusal (an aspirin-like agent that irreversibly inhibits COX-1), mainly used in Spain and Latin America, is a new anti-aggregator but with less potency than aspirin, as showed in the *Triflusal Aspirin Cerebral Infarction Prevention* (TACIP) trial for stroke prevention [7]. Also, cilostazol (inhibitor of phosphodiesterase-3) but also sarpogrelate were studied for their beneficial effects in secondary stroke prevention [21–25].

Recent clinical trials on antiplatelet therapy in stroke

Aspirin and dipyridamole

The first trial comparing the efficacy of aspirin and dipyridamole *vs.* placebo was ESPS-1, which included 2500 patients with a recent cerebrovascular event (stroke, transient ischemic attachment or reversible ischemic neurological deficit), patients who were subdivided into two groups [26]. The first group of patients (n=1250) was treated with aspirin 325 mg and dipyridamole 75 mg, while the second group of patients (n=1250) received placebo, the first group 108 (16%) patients died, while in the second group, 156 (25%) deaths were recorded [relative risk (RR): 33%, p<0.001] [26].

The ESPS-2 was another more comprehensive trial than ESPS-1, which included 6602 patients with pre-stroke or ischemic stroke, patients who were divided into four groups [27]. The first group of patients received twice a day double antiplatelet therapy consisting of 25 mg aspirin and 200 mg dipyridamole, the second group received twice a day 25 mg aspirin, the third group received 400 mg dipyridamole daily, placebo group. Primary endpoints were death, stroke and death and stroke together [27]. The study's final results pointed a decrease of about 24% in stroke occurrence in the group of patients treated with aspirin plus dipyridamole, a 15% reduction in the group of patients that received dipyridamole alone and a 13% reduction in the group of patients that received only aspirin [27].

Another trial, ESPRIT, made a comparison between the double antiplatelet therapy consisting of a dose of aspirin between 30–325 mg and a dose of 200 mg dipyridamole received twice a day (n=1363) and the therapy consisting of aspirin alone (n=1376) [20]. The primary outcome events were: regardless of cause, myocardial infarction and stroke both non-fatal and major bleeding [20]. Patients included in the study were surveilled for three years and a half and so it was revealed a recurrence of primary outcome events for 13% (n=173) of patients treated with aspirin (median dose was 75 mg) plus dipyridamole [hazard ratio (HR): 0.8%, 95% confidence interval (CI): 0.66–0.98] and 16% (n=216) of patients treated with aspirin alone (a risk reduction of approximately 1% per year, 95% CI: 0.1–1.8) [20].

Double antiplatelet therapy consisting of both aspirin and dipyridamole compared to the therapy with clopidogrel alone

The PRoFESS study included 20 332 patients with ischemic stroke and compared the effectiveness of clopidogrel alone or aspirin plus dipyridamole with 80 mg telmisartan or placebo daily [28]. Recurrent stroke was observed in about 9% of the patients that received

aspirin plus dipyridamole (n=916) and in about 9% of patients treated with clopidogrel alone (n=898), with no statistically significant difference between the two groups of pediatricians p=0.38), so clopidogrel treatment was not more effective than treatment with aspirin plus dipyridamole [28].

Aspirin *vs.* clopidogrel

The CAPRIE (study that made a comparison between the treatment with Clopidogrel and the treatment with Aspirin in Patients that presented a Risk for Ischemic Events) was a primary blinded, randomized, study that was meant to evaluate the efficacy of the daily treatment with 75 mg of clopidogrel and 325 mg of aspirin in 19 185 patients [29]. For the group of patients treated with clopidogrel, the risk of primary outcome vascular events (such as ischemic stroke or myocardial infarction and even death) was 5.32% and for the group of patients that received aspirin, the risk for primary outcome vascular events was 5.83%, this data reflecting a statistically significant difference between the two groups of patients (p=0.043), there was also in favor of the treatment with clopidogrel a reduction of the RR of about 8.7% (95% CI: 0.3–16.5) in favor of clopidogrel [29]. This study highlights the greater effectiveness of the treatment with clopidogrel in comparison with the treatment with aspirin in what secondary prevention of cerebral vascular events (stroke) is concerned in patients that had suffered before a stroke or other atherosclerotic vascular disease [29].

A study that evaluated the effectiveness of double antiplatelet therapy (aspirin 75 mg and clopidogrel 75 mg) than clopidogrel alone (75 mg) was MATCH study (that presented the Management of Atherothrombosis based on the treatment with Clopidogrel in patients with High-risk) [30]. This study included 7599 patients with an elevated risk, who had transient ischemic attach or recent ischemic stroke [30]. Of these, approximately 15.7% (n=596), who were treated with aspirin and clopidogrel, reached the primary composite endpoint similar to those who received clopidogrel alone (16.7%, n=636), there was no statistically significant difference, thus double antiplatelet therapy was not superior compared to clopidogrel alone in the secondary prevention of stroke [30].

Another study comparing double antiplatelet therapy (aspirin and clopidogrel) *vs.* aspirin alone was the trial entitled CHARISMA (meaning treatment with Clopidogrel for patients presenting a High Atherothrombotic Risk and also Ischemic Stabilization, emphasizing both the Management, and Avoidance) [31]. A number of 15 603 patients presenting numerous risk factors or a cardio-vascular disease that is clinically manifested were included in this study [31–37]. These patients were divided into two groups: one group that daily received a treatment with 75 mg of clopidogrel and 75 to 162 mg of aspirin and a group that received placebo plus aspirin. In this trial, there was no statistically significant difference between the effectiveness of dual antiplatelet therapy (6%), compared to the effectiveness (7.3%) of the therapy consisting only in aspirin (95% CI: 0.83–1.05, RR: 0.93, p=0.22) [31].

A recent study, SPS3 (trial that presents the Secondary Prevention of the Small Subcortical Strokes), which included 838 patients who were diagnosed with another type of stroke (lacunar stroke), while under treatment with aspirin, studied the effectiveness of adding clopidogrel to aspirin therapy [38]. The results of the study did not reveal a significant reduction in stroke recurrence by dual antiplatelet therapy in these patients [38].

Triple antiplatelet therapy

Regarding triple antiplatelet therapy, most important are the results of the *Triple Antiplatelets for Reducing Dependency after Ischemic Stroke* (TARDIS) trial; the study presents the triple antiplatelet therapy consisting of aspirin, clopidogrel, and dipyridamole, compared to the therapy only with clopidogrel or with both aspirin and dipyridamole in patients that presented acute cerebral ischemia (randomized, open-label, phase 3 superiority trial) [33]. In this trial, 3096 patients were included (1556 of whom received twice a day triple antiplatelet therapy with a dose of 75 mg of clopidogrel, a dose of 75 mg of aspirin and a dose of 200 mg of dipyridamole, and 1540 patients who were treated with either clopidogrel alone or aspirin plus dipyridamole) [39]. The results of this study revealed that for patients who presented a cerebral vascular event, such as ischemic stroke or transient ischemic attack, triple antiplatelet therapy is not recommended because it does not reduce the incidence or severity of stroke recurrence and they present a very high risk of major bleeding [39].

Ticagrelor

Last but not least, we need to recall here a recent meta-analysis on the treatment with ticagrelor 90 mg, twice a day, published in 2018 [40, 41]. In this meta-analysis, 13 randomized clinical trials were identified and analyzed, with a total of 64 360 patients [40, 41]. Compared to the control group, ticagrelor was shown to reduce the risk of ischemic stroke (95% CI: 0.78–0.95, RR: 0.86, p=0.003), combined risk for hemorrhagic and ischemic strokes (95% CI: 0.81–1, RR: 0.9, p=0.05), but also primary endpoint composite (95% CI: 0.84–1.07, RR: 0.95, p=0.03) [34]. It should be noted that this meta-analysis of ticagrelor has not increased the risk of major bleeding events (95% CI: 0.92–1.5, RR: 1.18, p=0.19) or mortality (95% CI: 0.84–1.07, RR: 0.95, p=0.4) [41].

Conclusions

We can say that current recommendations focused primarily on the therapy with aspirin for the secondary prevention of stroke in patients that presented a cerebral vascular event, such as an ischemic stroke of non-cardioembolic cause or a transient ischemic attack and, as appropriate, aspirin plus dipyridamol or clopidogrel. The new therapy with ticagrelor in secondary stroke prevention seems to be promising, but more randomized clinical trials are needed to accurately assess the safety and efficacy of this new platelet antiagregant.

Conflict of interests

The authors declare that they have no conflict of interest.

Authors' contribution

Cristina Florescu and Edme Roxana Mustafa equally contributed to the manuscript.

References

[1] Ropper AH, Samuels MA (eds). Adams & Victor principles of neurology. 9th edition, McGraw–Hill Medical Companies, Inc., New York, 2009, 778–885.

[2] Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circ Res, 2017, 120(3):439–448.

[3] Feigin V, Hoorn SV. How to study stroke incidence. Lancet, 2004, 363(9425):1920.

[4] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA, 2000, 283(15):2008–2012.

[5] Hankey GJ. The global and regional burden of stroke. Lancet Glob Health, 2013, 1(5):e239–e240.

[6] Jennings LK. Role of platelets in atherothrombosis. Am J Cardiol, 2009, 103(3 Suppl):4A–10A.

[7] Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2014, 45(7):2160–2236.

[8] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: a Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke, 2018, 49(3):e46–e110.

[9] Marczewski MM, Postula M, Kosior D. Novel antiplatelet agents in the prevention of cardiovascular complications – focus on ticagrelor. Vasc Health Risk Manag, 2010, 6:419–429.

[10] Awtry EH, Loscalzo J. Aspirin. Circulation, 2000, 101(10): 1206–1218.

[11] Shankar H, Kunapuli SP. Is the $P2Y_1$ receptor a better target for antithrombotic drugs? Drug Discov Today, 2005, 2(3):285–290.

[12] Michelson AD. P2Y12 antagonism: promises and challenges. Arterioscler Thromb Vasc Biol, 2008, 28(3):s33–s38.

[13] Jin J, Quinton TM, Zhang J, Rittenhouse SE, Kunapuli SP. Adenosine diphosphate (ADP)-induced thromboxane A(2) generation in human platelets requires coordinated signaling through integrin alpha(IIb)beta(3) and ADP receptors. Blood, 2002, 99(1):193–198.

[14] Tudoraşcu DR, Bătăiosu C, Paraschiv A, Târtea EA, Donoiu I, Florescu C. The effectiveness of cardiac resynchronization in a patient with ischemic cardiomyopathy. J Mind Med Sci, 2018, 5(1):145–150.

[15] Tantry US, Bliden KP, Gurbel PA. AZD6140. Expert Opin Investig Drugs, 2007, 16(2):225–229.

[16] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor *versus* clopidogrel in patients with acute coronary syndromes. N Engl J Med, 2009, 361(11):1045–1057.

[17] Gent M, Blakely JA, Easton JD, Ellis DJ, Hachinski VC, Harbison JW, Panak E, Roberts RS, Sicurella J, Turpie AG. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet, 1989, 1(8649):1215–1220.

[18] Hass WK, Easton JD, Adams HP Jr, Pryse-Phillips W, Molony BA, Anderson S, Kamm B. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med, 1989, 321(8):501–507.

[19] Gorelick PB, Richardson D, Kelly M, Ruland S, Hung E, Harris Y, Kittner S, Leurgans S; African American Antiplatelet Stroke Prevention Study Investigators. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. JAMA, 2003, 289(22):2947–2957.

[20] ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Medium intensity oral anticoagulants *versus* aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol, 2007, 6(2):115–124.

[21] Culebras A, Rotta-Escalante R, Vila J, Domínguez R, Abiusi G, Famulari A, Rey R, Bauso-Tosselli L, Gori H, Ferrari J, Reich E; TAPIRSS investigators. Triflusal *vs* aspirin for prevention of cerebral infarction: a randomized stroke study. Neurology, 2004, 62(7):1073–1080.

[22] Huang Y, Cheng Y, Wu J, Li Y, Xu E, Hong Z, Li Z, Zhang W, Ding M, Gao X, Fan D, Zeng J, Wong K, Lu C, Xiao J, Yao C; Cilostazol *versus* Aspirin for Secondary Ischaemic Stroke Prevention cooperation investigators. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomized, double-blind, pilot study [*erratum* in Lancet Neurol, 2008, 7(8):675]. Lancet Neurol, 2008, 7(6):494–499.

[23] Shinohara Y, Nishimaru K, Sawada T, Terashi A, Handa S, Hirai S, Hayashi K, Tohgi H, Fukuuchi Y, Uchiyama S, Yamaguchi T, Kobayashi S, Kondo K, Otomo E, Gotoh F; S-ACCESS Study Group. Sarpogrelate–Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS): a randomized, double-blind, aspirin-controlled trial. Stroke, 2008, 39(6):1827–1833.

[24] Mustafa ER, Firulescu SC, Parvanescu CD, Chisalau BA, Tartea GC, Efrem IC, Barbulescu AL, Dinescu SC, Ciurea PL, Lucretiu R, Vreju AF. Triple valve infective endocarditis – a late diagnosis. J Mind Med Sci, 2018, 5(1):141–144.

[25] Puiu I, Albu CV, Tartea EA, Calborean V, Gheorman V, Dinescu SN, Vasile RC, Dinescu VC, Bica EC, Romanescu FM, Tudorascu DR. Relationships between glial enteric cells, beta-cell signaling and tumor proliferative activity in patients with colorectal neoplasia. Rev Chim (Bucharest), 2018, 69(10): 2744–2748.

[26] ***. The European Stroke Prevention Study (ESPS). Principal end-points. The ESPS Group. Lancet, 1987, 2(8572):1351–1354.

[27] Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci, 1996, 143(1–2):1–13.

[28] Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW; Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study group. Effects of aspirin plus extended-release dipyridamole *versus* clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study [*erratum* in Lancet Neurol, 2008, 7(11):985]. Lancet Neurol, 2008, 7(10):875–884.

[29] CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel *versus* aspirin in patients at risk of ischaemic events (CAPRIE). Lancet, 1996, 348(9038):1329–1339.

[30] Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet, 2004, 364(9431):331–337.

[31] Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ; CHARISMA Investigators. Clopidogrel and aspirin *versus* aspirin alone for the prevention of atherothrombotic events. N Engl J Med, 2006, 354(16):1706–1717.

[32] Pleşa CF, Nicolae C, Sîrbu CA, Nemeş R, Păunescu A, Ţânţu MM. Use of anticoagulants in cerebral vascular pathology. Farmacia, 2019, 67(1):27–33.

[33] Ţânţu MM, Man GM, Rogozea LM, Domnariu CD, Pleşa FC, Traşcă DM, Cotoi BV, Stoica LE, Nicolae C, Nemeş RM. Diabetic foot – epidemiological and histopathological aspects. Rom J Morphol Embryol, 2018, 59(3):895–902.
[34] Iurciuc S, Cimpean AM, Mitu F, Heredea R, Iurciuc M. Vascular aging and subclinical atherosclerosis: why such a "never ending" and challenging story in cardiology? Clin Interv Aging, 2017, 12:1339–1345.
[35] Iurciuc S, Avram C, Turi V, Militaru A, Avram A, Cimpean AM, Iurciuc M. Physical training, hemodynamic parameters and arterial stiffness: friends or foes of the hypertensive patient? *In Vivo*, 2016, 30(4):521–528.
[36] Florescu C, Rotaru LT, Varut RM, Grigorasi G, Kostici R, Ciobanu D, Cimpoesu D. Determination of the inhibitory capacity on HMG-CoA reductase enzyme by statins using molecular docking method. Rev Chim (Bucharest), 2018, 69(4):837–839.
[37] Novac MV, Niculescu M, Manolea MM, Dijmărescu AL, Iliescu DG, Novac MB, Rotaru LT, Stoenescu MF, Tabacu MC, Tudorache Ş, Busuioc CJ, Gheonea IA. Placental findings in pregnancies complicated with IUGR – histopathological and immunohistochemical analysis. Rom J Morphol Embryol, 2018, 59(3):715–720.
[38] Côté R, Zhang Y, Hart RG, McClure LA, Anderson DC, Talbert RL, Benavente OR. ASA failure: does the combination ASA/ clopidogrel confer better long-term vascular protection? Neurology, 2014, 82(5):382–389.
[39] Bath PM, Woodhouse LJ, Appleton JP, Beridze M, Christensen H, Dineen RA, Duley L, England TJ, Flaherty K, Havard D, Heptinstall S, James M, Krishnan K, Markus HS, Montgomery AA, Pocock SJ, Randall M, Ranta A, Robinson TG, Scutt P, Venables GS, Sprigg N; TARDIS Investigators. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole *versus* clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Lancet, 2018, 391(10123): 850–859.
[40] Florescu C, Rogoveanu I, Vere CC, Târtea GC, Târtea EA, Mogoantă L. From molecular mechanism to morphological changes in cardiomyopathy. Rom J Morphol Embryol, 2016, 57(4):1207–1214.
[41] Malhotra K, Goyal N, Kasunich AS, Sheth SA, Katsanos AH, Alexandrov AV, Tsivgoulis G. Ticagrelor for stroke prevention in patients with vascular risk factors: a systematic review and meta-analysis. J Neurol Sci, 2018, 390:212–218.

Corresponding author
Elena-Anca Târtea, MD, PhD, Department of Neurology, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone +40746–027 471, e-mail: puiu.elenaanca@yahoo.ro

Received: March 30, 2019

Accepted: August 28, 2019