OPPORTUNITIES AND CHALLENGES IN THE USE OF COMBINATION ANTIPLATELET AND ANTICOAGULANT THERAPY FOR SECONDARY STROKE PREVENTION

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Abstract

The aim of this review is to summarize current evidence and identify potential settings for the use of combination therapy with low-dose rivaroxaban and aspirin in patients with history of previous stroke. Combined therapy with low-dose rivaroxaban and aspirin seems to be superior in both primary and secondary stroke prevention for patients with history of coronary artery disease or peripheral artery disease. There are several settings in secondary stroke prevention where the combined therapy of low-dose rivaroxaban and aspirin might be a preferred option, including a history of coronary artery disease, peripheral artery disease, complex aortic atherosclerosis, extracranial and intracranial large vessel disease and after carotid revascularization procedures. As questions on the optimal management of patients on combination therapy in the acute stroke setting will arise, we propose an algorithm for treatment decisions for patients receiving combination of low-dose rivaroxaban and aspirin presenting within 4.5 hours from symptom onset.

Keywords: ischemic stroke, prevention, atherosclerosis, antiplatelet, anticoagulation

ΕΥΚΑΙΡΙΕΣ ΚΑΙ ΠΡΟΚΛΗΣΕΙΣ ΣΤΗ ΧΡΗΣΗ ΤΟΥ ΣΥΝΔΥΑΣΜΟΥ ΑΝΤΙΑΙΜΟΠΕΤΑΛΙΑΚΗΣ ΚΑΙ ΑΝΤΙΠΗΚΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΣΤΗ ΔΕΥΤΕΡΟΓΕΝΗ ΠΡΟΛΗΨΗ ΤΩΝ ΑΓΓΕΙΑΚΩΝ ΕΓΚΕΦΑΛΙΚΩΝ ΕΠΕΙΣΟΔΙΩΝ.

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Περίληψη

Ο στόχος αυτής της ανασκόπησης είναι να συνοψίσει τα τρέχοντα στοιχεία και να εντοπίσει πιθανές ενδείξεις για τη χρήση συνδυαστικής θεραπείας με χαμηλή δόση rivaroxaban και ασπιρίνης σε ασθενείς με ιστορικό προηγούμενου εγκεφαλικού επεισοδίου. Η συνδυασμένη θεραπεία με χαμηλή δόση rivaroxaban και ασπιρίνης φαίνεται να είναι ανώτερη τόσο στην πρωτογενή όσο και στη δευτερογενή πρόληψη εγκεφαλικού επεισοδίου για ασθενείς με ιστορικό στεφανιαίας νόσου ή περιφερικής αρτηριακής νόσου. Υπάρχουν πολλές περιπτώσεις στη δευτερογενή πρόληψη εγκεφαλικού όπου η συνδυασμένη θεραπεία χαμηλής δόσης rivaroxaban και ασπιρίνης μπορεί να είναι μια προτιμώμενη επιλογή, συμπεριλαμβανομένου του ιστορικού στεφανιαίας νόσου, περιφερικής αρτηριακής νόσου, σύνθετης αθηροσκλήρωσης της αορτής, εξωκράνιας και ενδοκράνιας νόσου των μεγάλων αγγείων και μετά από επεμβάσεις επαναγγείωσης των καρωτίδων. Καθώς θα προκύψουν ερωτήματα σχετικά με τη βέλτιστη διαχείριση των ασθενών σε θεραπεία συνδυασμού στο πλαίσιο του οξέος εγκεφαλικού επεισοδίου, προτείνουμε έναν θεραπευτικό αλγόριθμο για ασθενείς που λαμβάνουν συνδυασμό χαμηλής δόσης rivaroxaban και ασπιρίνης, και προσέρχονται εντός 4,5 ωρών από την έναρξη των συμπτωμάτων.

Λέξεις-κλειδιά: ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο, πρόληψη, αθηροσκλήρωση, αντιαιμοπεταλιακό, αντιπηκτικό

Introduction

Aspirin is still considered the antiplatelet agent of choice for secondary stroke prevention, as it has been associated with a 21% decrease in the risk of ischemic stroke recurrence and a 19% reduction in the risk of serious vascular events [1, 2]. Randomized controlled trials (RCTs) found no additional benefit on the risk of major cardiovascular events by the use of other antiplatelet agents (clopidogrel, triflusal, ticagrelor, cilostazol) alone (Table 1) [3-15], or in combination, (aspirin with either dipyridamole or clopidogrel) after an ischemic stroke (Table 2) [16-25] with the exception of short term treatment after an event [19-22].

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial was a double-blind RCT testing the hypothesis that low dose rivaroxaban (2.5mg BID) in combination with aspirin (100mg OD) or rivaroxaban alone (5mg BID) is more effective than aspirin alone for the prevention of cardiovascular outcomes in patients with stable atherosclerotic vascular disease [26]. The study was prematurely terminated after a mean follow-up of 23 months due to the superiority of the combination of low-dose rivaroxaban with aspirin [26]. The trial recruited patients with history of peripheral arterial disease, including previous carotid revascularization procedures or asymptomatic carotid artery stenosis ≥50%, and/or history of coronary artery disease over 65 years of age or under 65 years of age with documented atherosclerosis or revascularization involving at least 2 vascular beds, including the aorta or arterial supply to the brain, or two vascular risk factors, including history of non-lacunar ischemic stroke more than a month ago (Table 3). Patients with a history of stroke within 1 month or any history of hemorrhagic or symptomatic lacunar stroke were excluded [26]. Individuals with incidental lacunes on neuroimaging were included. An overview of the exclusion criteria is briefly presented in Table 4. Patients randomized to low-dose rivaroxaban and aspirin were found to have a significantly lower risks

Table 1: Overview of randomized controlled trials assessing antithrombotic treatments with antiplatelets and/or anticoagulants for secondary stroke prevention

Study Name	Publishing Year	Population	N	Treatment (daily dose)	Control (daily dose)	Efficacy Outcome	Safety outcome
Ischemic Stroke or TIA							
CAST [3]	1997	-IS within 48h of symptom onset	21,106	ASA (160mg)	Placebo	↓ Death ↓ non-fatal stroke ↓stroke recurrence	↑extracranial bleeding
CASISP [4]	2008	-IS 1 to 6 months, from diagnosis mRS<4	720	Cilostazol (200mg)	ASA (100mg)	↔ recurrent stroke	↓intracranial bleeding
CSPS [5]	2000	- IS 1 to 6 months, from diagnosis - age<80 years	1,052	Cilostazol (200mg)	Placebo	↓recurrent stroke	↔ major bleeding
TACIP [6]	2003	- TIA/IS within 6 months - Oxford Neurological Scale score ≤2 - age ≥40 years	2,113	Triflusal (600mg)	ASA (325mg)	↔ recurrent stroke	↓major bleeding
TIA/minor IS							
DUTCH TIA [7]	1991	- TIA/ minor IS (mRS≤3) within 3 months	3,131	ASA (30 mg)	ASA (283 mg daily)	↔ MACE	↔ major bleeding
SPIRIT [8]	1997	- TIA/ minor IS (mRS≤3) within 6 months	1,316	Warfarin (INR target 3.0-4.5)	ASA (30mg)	↑MACE	↑major bleeding
UK TIA [9]	1991	-TIA/ minor IS within 3 months - age ≥40 years	2,435	ASA (1200 mg)/ ASA (300mg)	Placebo	↔ MACE	↑ GI bleeding

Non-Cardio-embolic IS							
NAVIGATE ESUS [10*]	2018	- ESUS 7 days to 6 months - age ≥49 years (if 18 to 59 at least one additional vascular risk factor)	7213	Rivaroxaban (15mg)	ASA (100mg)	↔ MACE	↑major bleeding
RE-SPECT ESUS [11*]	2019	-ESUS within 3/ 6 months - age ≥18 years (if 18 to 59 at least one additional vascular risk factor)	5390	Dabigatran (150/110mg)	ASA (100mg)	↔ recurrent stroke	↔ major bleeding
WARSS [12]	2001	- IS within 1 month - Glasgow outcome scale≥3 -age 30-85 years	2,206	Warfarin (INR target 1.4-2.8)	ASA (325mg)	↔ recurrent stroke	↔ major bleeding
Large vessel disease							
Amarenco et al [13]	2014	- TIA/ IS (mRS≤4)/ PE within 3 months - Aortic atheromatosis - age ≥18 years	349	Warfarin (INR target 2.0-3.0)	ASA (75-150 mg) + Clopidogrel (75 mg)	↔ MACE	↑vascular mortality
SAMMPRIS [14]	2011	-TIA/ non-disabling IS (mRS≤3) within 30 days - intracranial stenosis 70-99%	451	PTAS	ASA (325 mg) + clopidogrel (75 mg)	↑recurrent stroke/ death	↑major bleeding
WASID [15]	2005	- TIA/ non-disabling IS (mRS≤3) within 3 months -intracranial stenosis 50-99%	569	Warfarin (INR target 2.0-3.0)	ASA (1300 mg)	↔ MACE	↑major bleeding ↑death

IS: ischemic stroke, h: hours, ASA: acetylsalicylic acid, mRS: modified Rankin Scale, TIA: transient ischemic attack, MACE: Major adverse cardiovascular events (as indicated in each study), NIHSS: National Institutes of Health Stroke Scale, INR: international normalized ratio, ESUS: embolic stroke of undetermined source, PE: peripheral embolism,GI: gastrointestinal, TCD: transcranial doppler, PTAS: percutaneous transluminal artery stenting

Table 2: Overview of randomized controlled trials assessing antithrombotic treatments with antiplatelets treatment combination for secondary stroke prevention.

Study Name	Publishing Year	Population	N	Treatment (daily dose)	Control (daily dose)	Efficacy Outcome	Safety outcome
Ischemic Stroke or TIA							
CSPS.com [16]	2019	- IS within 6 months -≥50% stenosis of a major intracranial or extracranial artery or ≥ 2 vascular risk factors.	1879	cilostazol (100 mg BID) + aspirin (81/ 100 mg) or clopidogrel (50/ 75 mg)	aspirin (81/ 100 mg) or clopidogrel (50/ 75 mg)	↓recurrent stroke	↔ major bleeding
MATCH [17]	2004	-TIA/IS within 3 months - previous IS/ MI/ angina/ PAD/ DM	7,599	ASA (75 mg) + clopidogrel (75 mg)	Clopidogrel (75 mg)	↔ MACE	↑major bleeding
PROFESS [18]	2008	- IS within 3 months - >55 years	20,332	Dipyridamole (400mg) + ASA (25mg)	Clopidogrel (75 mg)	↔ recurrent stroke	↑major bleeding
TIA/minor IS							
CHANCE [19]	2013	- TIA (ABCD2≥4)/ minor IS (NIHSS≤3) within 24 hours - age ≥40 years	5170	ASA (75 mg) + Clopidogrel (75 mg)*	ASA (75 mg)	↓recurrent stroke	↔major bleeding
ESPRIT [20]	2006	- TIA/ minor IS (mRS≤3) within 6 months - age ≥30 years	2,739	Dipyridamole (400mg) + ASA (50-325mg)	ASA (50-325mg)	↓MACE	↔major bleeding
PRINCE [21]	2019	- TIA (ABCD2≥4 or ≥50% symptomatic vessel stenosis) within 24 hours/ minor stroke (NIHSS≤3) - age ≥40 years	675	Ticagrelor (180mg)+ASA (100mg)	Clopidogrel (75mg)+ASA (100mg)	↔ stroke recurrence	↔ major/ minor bleeding
POINT [22]	2018	- TIA (ABCD2≥4)/ minor IS (NIHSS≤3) within 12 hours - age ≥18 years	4,881	Clopidogrel (75mg)+ASA (50-325mg)**	ASA (50-325mg)	↓MACE	↑major bleeding
SOCRATES [23]	2016	- TIA (ABCD2≥4)/ minor IS (NIHSS≤5) within 12 hours - age ≥40 years	13,199	Ticagrelor (180mg)+ASA (100mg)	ASA (100mg)	↔ MACE	↔major bleeding
Large vessel disease							
CARESS [24]	2005	- TIA/ IS within 3 months - symptomatic ICA stenosis ≥50%	230	Clopidogrel (75mg)* + ASA (75mg)	ASA (75mg)	↓MES on TCD	↔ adverse events
CLAIR [25]	2010	- TIA/ minor IS within 7 days - age ≥18 years symptomatic ICA/ MCA stenosis ≥50%	100	Clopidogrel (75mg)* + ASA (75–160 mg)	ASA (75–160 mg)	↓MES on TCD	↔ adverse events

*after a loading dose of 300mg in day 1
**after a loading dose of 600mg in day 1
IS: ischemic stroke, TIA: transient ischemic attack, MI: myocardial infarction, PAD: peripheral arterial disease, DM: diabetes mellitus, MACE: major adverse cardiovascular events, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale score, ICA: internal carotid artery, MES: microembolic signals, TCD: transcranial Doppler, MCA: middle cerebral artery

for the composite endpoint of cardiovascular death, stroke and myocardial infarction, with no increase in the risk of hemorrhagic stroke compared to those patients randomized to aspirin alone. [26]. The benefit on the primary composite outcome of cardiovascular death, stroke, or myocardial infarction [Hazard Ratio (HR) = 0.76, 95%CI: 0.66–0.86] was driven by a large decrease in the occurrence of ischemic stroke (HR=0.51, 95%CI: 0.38–0.68), with no increase on the risk of hemorrhagic stroke (HR=1.49, 95%CI: 0.67–3.31). In patients randomized to rivaroxaban 5 mg BID there was a reduction in ischemic stroke (HR=0.69, 95%CI: 0.53–0.90) that was offset by hemorrhagic stroke making this dose unfavorable (HR=2.70, 95%CI: 1.31–5.58) [26].

In a predefined subgroup analysis of the COMPASS trial, the preventive effect of low-dose rivaroxaban and aspirin combination was found to be particularly marked for patients with history of previous stroke, with the rate of ischemic/unknown and disabling strokes being reduced by 67% and 57% with the combination treatment compared to single antiplatelet therapy, respectively [27]. Prior stroke was the strongest predictor of incident stroke and [27] the combination of low-dose rivaroxaban plus aspirin emerges as a novel and potent antithrombotic option for the secondary prevention of patients with clinical atherosclerosis and history of previous stroke (Table 5). This presents an opportunity for more effective stroke reduction while raising potential challenges in the immediate post stroke setting.

Opportunities in secondary stroke prevention

Coronary artery disease – peripheral artery disease

In the COMPASS trial coronary artery disease was defined as history of myocardial infarction within the last 20 years, or multi-vessel coronary disease with symptoms or history of stable or unstable angina, or history of multi-vessel percutaneous coronary intervention, or history of multi-vessel CABG surgery [26]. Peripheral artery disease was defined as previous peripheral artery surgical intervention, or percutaneous transluminal angioplasty revascularization, or previous limb or foot amputation for arterial vascular disease, or history of intermittent claudication and ankle/arm blood pressure (BP) ratio < 0.90, or peripheral artery stenosis (≥50%), or previous carotid revascularization, or asymptomatic carotid artery stenosis ≥50% [26]. Importantly, carotid artery stenosis or previous intervention met the definition of peripheral artery disease. This combination of vascular involvement represents a significant proportion of stroke patients. In the international Reduction of

Table 3: Inclusion criteria of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial

Inclusion criteria	**Definition**
1) Coronary artery disease and	• Myocardial infarction within the last 20 years, or • multi-vessel coronary disease with symptoms or with history of stable or unstable angina, or multi-vessel PCI, or CABG surgery
Age≥65 years, or	
Age <65 and documented atherosclerosis or revascularization involving at least 1 additional vascular bed or at least 2 additional risk factors:	Risk factors - Current smoker - Diabetes mellitus - Renal dysfunction (eGFR<60 ml/min) - Heart failure - Non-lacunar ischemic stroke ≥1 month
2) Peripheral arterial disease	• Previous peripheral artery surgical intervention or percutaneous transluminal angioplasty revascularization, or • previous limb or foot amputation for arterial vascular disease, or • History of intermittent claudication and ankle/arm blood pressure (BP) ratio < 0.90, or peripheral artery stenosis (≥50%) • Previous carotid revascularization, or • asymptomatic carotid artery stenosis ≥50%

PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, eGFR: estimated glomerular filtration rate,

Table 4: Patient categories that were excluded from the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial

Reason for exclusion	Definition
1. High risk of bleeding	
2. Any stroke within 1 month	Presence of acute focal neurological deficit thought to be of vascular origin with signs and symptoms lasting ≥ 24 hours or to time of death.
3. Patients with lacunar strokes	<1.5 cm on CT or <2 cm on DWI-MRI
4. Severe heart failure	EF <30% or NYHA class III/IV symptoms
5. End stage renal disease	eGFR<15ml/h
6. Indication for dual antiplatelet therapy	
7. Indication for anticoagulation therapy	
8. Poor prognosis due to non-cardiovascular disease	e.g. metastatic cancer
9. Treatment with drugs affecting CYP3A4 and/or p-glycoprotein	Ketoconazole, HIV-protease inhibitors, rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine
10. Hypersentivity or contraindications to aspirin and/or rivaroxaban	

CT: computed tomography, DWI-MRI: diffusion weighted imaging sequence on magnetic resonance imaging, EF: ejection fraction, NYHA: New York Heart Association, eGFR: estimated glomerular filtration rate, HIV: human immunodeficiency virus

Atherothrombosis for Continued Health (REACH) Registry approximately 40% of stroke patients were found to have coexisting coronary artery disease and/or peripheral arterial disease [28]. Coronary artery plaque and carotid artery stenosis ≥50% can be seen in 62% and 20-30% of patients with recent ischemic stroke, respectively [29-31]. Almost one in four patients with a recent stroke have a history of symptomatic coronary artery disease, and these patients are at an increased risk for both ischemic stroke and coronary artery disease recurrence [32]. In addition, stroke patients have an approximately 2% annual risk of myocardial infarction, suggesting a 10% risk in the first 5 years following stroke [33, 34]. A significant portion of stroke patients have atherosclerosis – a progressive multifocal vascular disease [35-37]. It is this high risk population that has a substantially greater risk reduction for stroke with the use of a combination of low-dose rivaroxaban and aspirin, over aspirin alone. [26].

Complex aortic atheroma

Atherosclerotic disease of the ascending aorta and aortic arch is known to be independent ischemic stroke risk factors, especially in the presence of complex plaques protruding more that 4mm from the artery lumen and/or with ulcerations or superimposed thrombus [38, 39]. Ascending aorta atherosclerosis is a known marker of diffuse atherosclerotic disease and is associated with a higher prevalence of coronary artery disease, carotid artery disease and peripheral vascular disease [40]. Complex plaques in the proximal descending aorta, apart from being associated to a higher general vascular risk and atherosclerotic burden in other vascular territories [41], have recently been proposed as a potential mechanism of cerebral ischemia through end-diastolic retrograde embolism [42]. Anticoagulation with warfarin in patients with ischemic stroke and severe atherosclerosis of the aortic arch was found to be associated with increased risk of vascular mortality compared to dual antiplatelet treatment with aspirin and clopidogrel [13]. While not specifically studied in COMPASS, patients with extensive atherosclerotic plaque in the aorta may well benefit from low-dose rivaroxaban combined with aspirin, especially in case of recurrent ischemic events despite antiplatelet treatment, and always after the exclusion of other stroke etiologies.

Extracranial large vessel disease

Carotid stenosis of any degree is observed in up to 45% of patients with stroke [43]. In patients with symptomatic carotid artery disease the risk of stroke recurrence decreases steadily reaching a level similar to that of patients with asymptomatic carotid disease after 2 years from onset, whereas

Table 5: Overview on the effects of combination treatment on patients with history of prior stroke randomized in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial.

Outcome	Rivaroxaban plus Aspirin (N=351)	Aspirin Alone (N=335)	HR (95%CI)	p-value
CV death, stroke or MI	3.7%/ year	7.0%/ year	0.57 (0.34-0.96)	0.04
All strokes	0.7%/ year	3.4%/ year	0.42 (0.19-0.92)	0.03
Ischemic or uncertain stroke	1.1%/ year	3.4%/ year	0.33 (0.14-0.77)	0.01
Hemorrhagic stroke	0.3%/ year	0%/ year	-	-
Major bleeding	1.9%/ year	0.5%/ year	3.79 (1.07-13.4)	0.04
Minor bleeding	3.0%/ year	3.3%/ year	0.91 (0.48-1.73)	0.76

CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio, 95%CI: 95% confidence intervals

the risk of coronary artery disease seems to increase continuously over time [44]. Population-based studies suggest that patients with ischemic stroke due to large artery atherosclerosis have the highest risk of stroke recurrence from all subtypes, reaching up to 10% in the first month after index event onset [45]. According to current guidelines from the American Heart Association/ American Stroke Association (AHA/ASA) carotid revascularization procedures with endarterectomy or stenting are suggested in the ipsilateral internal carotid artery within 14 days from the ischemic event and are indicated for all patients with severe ipsilateral stenosis (equal or more than 70%) and in selected patients with moderate ipsilateral stenosis (50-69%) [46]. Even though carotid revascularization procedures are not indicated in patients with stroke and ipsilateral stenosis less than 50%, numerous observational data suggest that large non-stenotic atheromatous plaques, especially in the presence of ulcers or micro-hemorrhages are directly associated with a higher risk for cerebral ischemia [47-49]. Taking into account the aforementioned evidence and the AHA/ASA recommendations [46] we consider that patients with ischemic stroke attributed to a moderate carotid artery stenosis (50-59%) that are not candidates for carotid revascularization procedures could potentially benefit from combined antiplatelet-low dose anticoagulant treatment. Although not included in COMPASS, it could be postulated that patients with complex plaques (increased width, ulceration, micro-hemorrhage) associated with less than 50% stenosis and ipsilateral ischemic stroke/transient ischemic attack (TIA) could also benefit from combined low-dose rivaroxaban and aspirin treatment. Likewise, even though patients with extracranial vertebral artery stenosis were not included per se in COMPASS and this subgroup carries a lower risk for stroke recurrence compared to carotid stenosis [50], combined low-dose rivaroxaban and aspirin treatment could also be postulated to provide benefit for patients with acute ischemic stroke attributed to extracranial vertebral artery atherosclerosis, with or without significant stenosis, and particularly in those patients with recurrent events despite antiplatelet monotherapy. Finally, as per the COMPASS trial inclusion criteria [26] combination treatment with low-dose rivaroxaban and aspirin can be used for the long-term management of patients with symptomatic carotid artery stenosis receiving treatment with endarterectomy or stenting, given that carotid intervention reduces the risk of ipsilateral stroke but does not affect the ongoing risk of coronary events or stroke in another vascular distribution, which must be addressed by medical optimization.

Intracranial stenosis

RCTs suggest decrease in the microembolic signal burden detected by transcranial Doppler in patients with extracranial or intracranial large vessel stenosis more than 50% treated with a combination of aspirin with clopidogrel [24, 25]. However, these studies were underpowered to uncover a significant clinical benefit of dual antiplatelet treatment in the given clinical setting. SAMMPRIS was the only study providing evidence of superiority for best medical treatment with aspirin and clopidogrel over percutaneous transluminal artery stenting for patients with ischemic stroke due to an intracranial vessel stenosis equal or more than 70% [14]. In ischemic stroke patients with intracranial artery stenosis more or equal to 50% anticoagulation with warfarin and a therapeutic

Table 6: Current and possible indications of combination treatment with low dose rivaroxaban and aspirin in secondary stroke prevention

Current
1. Coexisting coronary artery disease
2. Coexisting peripheral artery disease (including asymptomatic carotid stenosis)
3. After carotid endarderectomy
4. After carotid artery stenting
Possible
1. Complex atheromatosis of the aorta
2. Symptomatic carotid artery plaque causing 50-69% stenosis and high surgical/ interventional risk
3. Symptomatic non-stenotic complex carotid artery plaque (wide, ulceration, microhemorrhage)
4. Extracranial vertebral artery stenosis with recurrent events despite antiplatelet treatment
5. Intracranial stenosis with recurrent events despite antiplatelet treatment

INR target between 2.0 and 3.0 was found to be associated with increased major bleeding events and mortality, with no additional benefit on cardiovascular outcomes compared to high dose aspirin [15]. Given the disappointing results of both percutaneous transluminal artery stenting and full dose anticoagulation with warfarin in ischemic stroke patients with intracranial stenosis [15, 51], we consider that even though this population has not been formally assessed within the COMPASS trial the use of low-dose rivaroxaban and aspirin could potentially be of benefit for cases of recurrent episodes despite dual antiplatelet treatment (Table 6).

Embolic Strokes of Undetermined Source

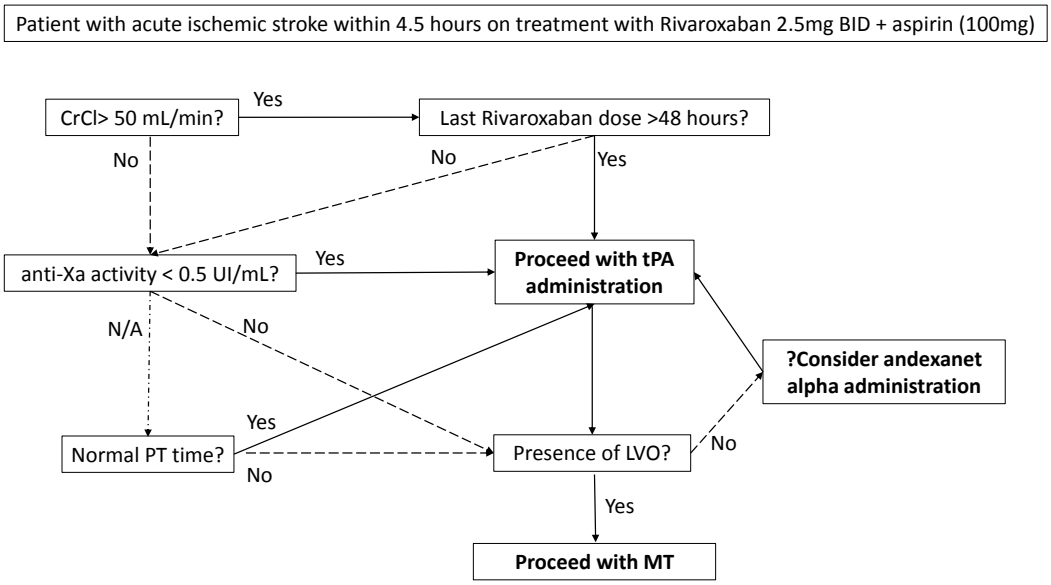
In 2014 the definition of embolic strokes of undetermined source (ESUS) emerged as a new clinical construct to characterize patients with non-lacunar (>1.5cm on CT or >2 cm on MRI), non-atherosclerotic (absence of significant ipsilateral vessel stenosis ≥50%) strokes of undetermined embolic source, in the absence of a high-risk for embolism cardiac disease or any other specific cause [52]. Single anticoagulant pathway inhibition with the use of rivaroxaban (15mg OD) in the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial was not found to ameliorate the risk of recurrence compared to aspirin, while was found to increase the intracerebral hemorrhage risk (HR=6.50, 95%CI: 1.47–28.8) compared to aspirin [10]. Likewise, in the Randomized, Double-blind, Evaluation in Secondary Stroke Prevention Comparing the EfficaCy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate (110 mg or 150 mg, Oral b.i.d.) Versus Acetylsalicylic Acid (100 mg Oral q.d.) in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial dabigatran monotherapy was again not found to be superior to aspirin in the prevention of thromboembolism in ESUS patients [11]. Considering the lack of efficacy and the safety concerns of full-dose anticoagulation in patients with ESUS, and that the ESUS construct encompasses multiple potential embolic sources [53], we expect that combined therapy of low-dose rivaroxaban and aspirin would provide benefit for selected ESUS patients with presumed artery-to-artery embolism, and after a thorough diagnostic work-up [54]. A very recent subgroup analysis from the COMPASS trial suggested that combination treatment was associated with reduced risk of both cardioembolic strokes (HR=0.40, 95% CI: 0.20-0.7) and ESUS (HR=0.30, 95% CI: 0.12-0.74) compared to aspirin monotherapy, while rivaroxaban 5mg BID monotherapy was not associated with reduction of any stroke subtype [55].

Challenges in acute stroke treatment

It is expected that a large number of individuals with high atherosclerotic burden will be treated with low-dose rivaroxaban plus aspirin for either primary or secondary stroke prevention [56, 57]. Individuals on dual therapy have a significantly reduced risk of ischemic stroke compared with aspirin but some patients on this treatment will experience events and neurologists must be prepared to make acute treatment decisions in this setting. Inevitably questions on the optimal management of these patients in the acute setting will arise, mainly regarding the safety of intravenous thrombolysis.

In a patient with history of low-dose rivaroxaban plus aspirin intake presenting with a measurable neurological deficit within 4.5 hours from symptom onset, it is probably safe to proceed with intravenous alteplase treatment if the patient has no history of renal disease (creatinine clearance >50 ml/min) and

Figure Proposed algorithm on treatment of acute ischemic stroke patients receiving combination of low-dose rivaroxaban and aspirin presenting within 4.5 hours from symptom onset.



CrCl: creatinine clearance, tPA: tissue plasminogen activator, PT: prothrombin time, LVO: large vessel occlusion, MT: mechanical thrombectomy

the last rivaroxaban dose was more than 48 hours [58]. In case that the last rivaroxaban dose was less than 48 hours and/or the patient has renal disease, coagulation tests to estimate either directly or indirectly rivaroxaban activity should be considered (Figure).

Rivaroxaban is a selective factor Xa inhibitor, with a half-life of 5 to 9 hours in healthy subjects and a dose-dependent bioavailability and prolongation of prothrombin time (PT), the activated partial thromboplastin time (aPTT) and the heparin clotting assay [59]. Even though prolongation of the PT is known to be linearly correlated with the rivaroxaban plasma concentrations [60], PT cannot provide precise information on the level and thus anticoagulant effect of rivaroxaban; however a normal PT would suggest that hemostatic function is not impaired because of the drug [61]. Although anti-Xa activity test is very sensitive with values less than 0.5 U/mL corresponding to low factor Xa inhibitor concentrations (<50-100 ng/mL) [62], is not readily available in most settings while also results in significant treatment delays. Andexanet alfa, a recombinant modified factor Xa protein which was recently approved by the FDA for the reversal of factor Xa inhibitors, can potentially be considered in cases of elevated PT prior to the administration of alteplase [63].

Although the safety of intravenous alteplase treatment in patients on active NOAC treatment has only been suggested by limited case series [64], consideration of stroke severity and weighting against the hemorrhage risk should be the cornerstone on the decision pathway to proceed with intravenous alteplase treatment for any given individual [65]. Taking into account that mechanical thrombectomy can improve functional outcomes independent of pretreatment with intravenous thrombolysis [66], patients on combination therapy with acute large vessel occlusion amendable to endovascular intervention should be treated with direct mechanical thrombectomy (Figure).

Discussion

COMPASS provides evidence on the superiority of combined therapy with low-dose rivaroxaban and aspirin in both primary and secondary stroke prevention for patients with history of coronary artery disease or peripheral artery disease [26, 27]. There are several settings in secondary stroke prevention where the combined therapy of low-dose rivaroxaban and aspirin might be a valid option, and particularly for patients with signs of significant atherosclerosis and recurrent events despite antiplatelet treatment (Table 2). In any case scenario it seems that the higher the atherosclerotic burden and the more the vascular risk factors the greater seems to be the benefit of addition of low-dose rivaroxaban to aspirin [67].

The amelioration of atherothrombotic embolism into the cerebral vasculature could be attributed to the concurrent inhibition of factor Xa by the anticoagulant regimen and the inhibition of cyclo-

oxygenase by the antiplatelet agent, resulting in a dual pathway action in both the coagulation and platelet aggregation cascade. Taking into consideration that one out of four stroke patients is reported to present resistance in the action of either aspirin or clopidogrel and that 7% of stroke patients are reported to have resistance in the action of both antiplatelet agents [68], the addition of an antithrombotic agent that exerts its action through a different pathway seems legitimate.

The decision to treat any patient with a combination of low-dose rivaroxaban and aspirin should be individualized and after considering the inclusion and exclusion criteria of the COMPASS trial (Table 3). Further research on the patient subgroups that were excluded from the COMPASS trial (patients requiring anticoagulation, patients with stroke within 1 month or with previous lacunar stroke or intracerebral hemorrhage) and in the subgroup of patients with significant carotid stenosis ≥50% or previous carotid intervention (present in 7% of the COMPASS trial population) is needed to provide definite answers on the potential utility of combined anticoagulant-antiplatelet treatment for these high-risk patient populations.

Acknowledgements

None

References

[1] Anderson DC, Goldstein LB. Aspirin: it's hard to beat. Neurology. 2004;62:1036-7.
[2] Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al.; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.Lancet. 2009; 373:1849–1860.
[3] CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997;349:1641-9.
[4] Huang Y, Cheng Y, Wu J, Li Y, Xu E, Hong Z, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. Lancet Neurol. 2008;7:494–9.
[5] Gotoh F, Tohgi H, Hirai S, Terashi A, Fukuuchi Y, Otomo E, et al. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis. 2000;9:147–57.
[6] Matías-Guiu J, Ferro JM, Álvarez-Sabín J, Torres F, Jiménez MD, Lago A, Melo T; TACIP Investigators. Comparison of triflusal and aspirin in prevention of vascular events in patients after cerebral infarction: the TACIP Study: A randomized, double-blind multicenter trial. Stroke 2003;34:840–848.
[7] van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med. 1991;325:1261–6.
[8] A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. Ann Neurol. 1997;42:857-65.
[9] Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry. 1991;54:1044-54.
[10] Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med. 2018;378:2191-2201.
[11] Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med. 2019;380:1906-1917.
[12] Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345:1444-51.
[13] Amarenco P, Davis S, Jones EF, Cohen AA, Heiss WD, Kaste M, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. Stroke. 2014;45:1248-57.
[14] Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993-1003.
[15] Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005;352:1305-16.
[16] Toyoda K, Uchiyama S, Yamaguchi T, Easton JD, Kimura K, Hoshino H, et al. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial. Lancet Neurol. 2019;18:539-548.
[17] Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient isch-

aemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:331-7.
[18] Sacco RL, Diener H-C, Yusuf S, Cotton D, Ôunpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008;359:1238–51.
[19] Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369:11-9.
[20] Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet. 2006;367:1665–73.
[21] Wang Y, Chen W, Lin Y, Meng X, Chen G, Wang Z, et al. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. BMJ. 2019;365:l2211.
[22] Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med. 2018;379:215-225.
[23] Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med. 2016;375:35-43.
[24] Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005;111:2233-40.
[25] Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9:489-97.
[26] Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017;377:1319-1330.
[27] Sharma M, Hart RG, Connolly SJ, Bosch J, Shestakovska O, Ng KKH, et al. Stroke Outcomes in the COMPASS Trial. Circulation. 2019;139:1134–1145.
[28] Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis.JAMA 2006; 295: 180-189.
[29] Calvet D, Touzé E, Varenne O, Sablayrolles JL, Weber S, Mas JL. Prevalence of asymptomatic coronary artery disease in ischemic stroke.patients: the PRECORIS study. Stroke 2010;121:1623-1629.
[30] Amarenco P, Lavallée PC, Labereuche L, Ducrocq G, Juliard JM, Feldman L, et al. Prevalence of coronary atherosclerosis in patients with cerebral infarction. Stroke 2011;42:22-29.
[31] Yoon YE, Chang HJ, Cho I, Jeon KH, Chun EJ, Choi SI, et al. Incidence of subclinical coronary atherosclerosis in patients with suspected embolic stroke using cardiac computed tomography. Int J Cardiovasc Imaging 2011;27:1035-1044.
[32] Arima H, Tzourio C, Butcher K, Anderson C, Bousser MG, Lees KR, et al. Prior events predict cerebrovascular and coronary outcomes in the PROGRESS trial. Stroke 2006; 37: 1497-1502.
[33] Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke. A systematic review and meta-analysis. Stroke 2005; 36: 2748-2755.
[34] Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. Neurology 2006;66:641-646.
[35] Adams RJ, Chimowitz MI, Alpers JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the stroke council and the council on clinical cardiology of the American Heart Association/American Stroke Association. Stroke 2003;34:2310-2322.
[36] Kallikazaros I, Tsioufis C, Sideris S, Stefanadis C, Toutouzas P. Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain. Stroke. 1999;30:1002-7.
[37] Seo WK, Yong HS, Koh SB, Suh SI, Kim JH, Yu SW, Lee JY. Correlation of coronary artery atherosclerosis with atherosclerosis of the intracranial cerebral artery and the extracranial carotid artery. Eur Neurol. 2008;59:292-8.
[38] Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. N Engl J Med 1994; 331:1474-1479
[39] Tunick PA, Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. J Am Coll Cardiol. 2000;35:545–554.
[40] Nihoyannopoulos P, Joshi J, Athanasopoulos G, Oakley CM. Detection of atherosclerotic lesions

in the aorta by transesophageal echocardiography. Am J Cardiol. 1993;71:1208-12.
[41] Katsanos AH, Giannopoulos S, Kosmidou M, Voumvourakis K, Parissis JT, Kyritsis AP, et al. Complex atheromatous plaques in the descending aorta and the risk of stroke: a systematic review and meta-analysis. Stroke. 2014;45:1764-70.
[42] Harloff A, Strecker C, Dudler P, Nussbaumer A, Frydrychowicz A, Olschewski M, et al. Retrograde embolism from the descending aorta: visualization by multidirectional 3D velocity mapping in cryptogenic stroke. Stroke. 2009;40:1505-8.
[43] Touboul PJ, Elbaz A, Koller C, Lucas C, Adraï V, Chédru F, et al. Common carotid artery intima-media thickness and ischemic stroke: the GÉNIC case-control study, Circulation 2000;102:313-318
[44] Rothwell PM, Gibson R, Warlow CP; on behalf of the European Carotid Surgery Trial Investigators. Interrelation between plaque surface morphology and degree of stenosis on carotid angiograms and the risk of ischemic stroke in patients with carotid stenosis. Stroke; 2000; 31:615-621.
[45] Tsivgoulis G, Katsanos AH, Patousi A, Pikilidou M, Birbilis T, Mantatzis M, et al. Stroke recurrence and mortality in northeastern Greece: the Evros Stroke Registry. J Neurol. 2018;265:2379-2387.
[46] Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. 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;45:2160-236.
[47] Coutinho JM, Derkatch S, Potvin AR, Tomlinson G, Kiehl TR, Silver FL, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. Neurology. 2016;87:665-72.
[48] Komatsu T, Iguchi Y, Arai A, Sakuta K, Sakai K, Terasawa Y, et al. Large but Nonstenotic Carotid Artery Plaque in Patients With a History of Embolic Stroke of Undetermined Source. Stroke. 2018;49:3054-3056.
[49] Singh N, Moody AR, Panzov V, Gladstone DJ. Carotid Intraplaque Hemorrhage in Patients with Embolic Stroke of Undetermined Source. J Stroke Cerebrovasc Dis. 2018;27:1956-1959.
[50] Kim YJ, Lee JH, Choi JW, Roh HG, Chun YI, Lee JS, Kim HY. Long-term outcome of vertebral artery origin stenosis in patients with acute ischemic stroke. BMC Neurol. 2013;13:171.
[51] Tsivgoulis G, Katsanos AH, Magoufis G, Kargiotis O, Papadimitropoulos G, Vadikolias K, et al. Percutaneous transluminal angioplasty and stenting for symptomatic intracranial arterial stenosis: a systematic review and meta-analysis. Ther Adv Neurol Disord. 2016;9:351-8.
[52] Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429-38.
[53] Kamel H, Merkler AE, Iadecola C, Gupta A, Navi BB. Tailoring the Approach to Embolic Stroke of Undetermined Source: A Review. JAMA Neurol. 2019;76:855-861.
[54] Tsivgoulis G, Katsanos AH, Köhrmann M, Caso V, Lemmens R, Tsioufis K, et al. Embolic strokes of undetermined source: theoretical construct or useful clinical tool? Ther Adv Neurol Disord. 2019;12:1756286419851381.
[55] Perera KS, Ng KKH, Nayar S, Catanese L, Dyal L, Sharma M, et al. Association Between Low-Dose Rivaroxaban With or Without Aspirin and Ischemic Stroke Subtypes: A Secondary Analysis of the COMPASS Trial. JAMA Neurol. 2019 Sep 16. doi: 10.1001/jamaneurol.2019.2984. [Epub ahead of print]
[56] Zomer E, Si S, Hird TR, Liew D, Owen AJ, Tonkin A, et al. Cost-effectiveness of low-dose rivaroxaban and aspirin versus aspirin alone in people with peripheral or carotid artery disease: An Australian healthcare perspective. Eur J Prev Cardiol. 2019;26:858-868.
[57] Tsilimigras DI, Moris D, Karaolanis G, Kakkos SK, Filis K, Sigala F. Rivaroxaban versus Clopidogrel for Peripheral Artery Disease: A Clinico-Economic Approach of the COMPASS Trial. Curr Pharm Des. 2018;24:4516-4517.
[58] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Oct 30:STR0000000000000211. doi: 10.1161/STR.0000000000000211. [Epub ahead of print]
[59] Samama MM, Contant G, Spiro TE, Perzborn E, Le Flem L, Guinet C, et al. Laboratory assessment of rivaroxaban: a review. Thromb J. 2013;11:11.
[60] Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53:1-16.
[61] Pollack CV Jr. Coagulation assessment with the new generation of oral anticoagulants. Emerg Med J. 2016;33:423-30.

[62] Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012;119:3016-23.
[63] Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019;380:1326-1335.
[64] Shahjouei S, Tsivgoulis G, Bavarsad Shahripour R, Jones GM, Alexandrov AV, Zand R. Safety of Intravenous Thrombolysis among Stroke Patients Taking New Oral Anticoagulants--Case Series and Systematic Review of Reported Cases. J Stroke Cerebrovasc Dis. 2015;24:2685-93.
[65] Touzé E, Gruel Y, Gouin-Thibault I, De Maistre E, Susen S, Sie P, et al. Intravenous thrombolysis for acute ischaemic stroke in patients on direct oral anticoagulants. Eur J Neurol. 2018;25:747-e52.
[66] Tsivgoulis G, Katsanos AH, Mavridis D, Magoufis G, Arthur A, Alexandrov AV. Mechanical Thrombectomy Improves Functional Outcomes Independent of Pretreatment With Intravenous Thrombolysis. Stroke. 2016;47:1661-4.
[67] Darmon A, Sorbets E, Ducrocq G, Elbez Y, Abtan J, Popovic B, et al. Association of Multiple Enrichment Criteria With Ischemic and Bleeding Risks Among COMPASS-Eligible Patients. J Am Coll Cardiol. 2019;73:3281-3291.
[68] Fiolaki A, Katsanos AH, Kyritsis AP, Papadaki S, Kosmidou M, Moschonas IC, et al. High on treatment platelet reactivity to aspirin and clopidogrel in ischemic stroke: A systematic review and meta-analysis. J Neurol Sci. 2017;376:112-116.