

Special Issue: Atrial Fibrillation

Stroke Prevention in Atrial Fibrillation

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Received: October 30, 2015; Accepted: December 15, 2015; Published: December 27, 2015

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Abstract

Stroke, as a complex, multidimensional cerebrovascular disease, is one of the key issues in the present day's healthcare. Recently, the emerging numbers of studies provide a wide range of future potential solutions in stroke care, implying an imminent change in the aspects of therapy. In this paper, we are going to give a brief insight into the most determinant aspects and factors of the disease, focusing on the very recent findings in research, as well as the practical approach in stroke prevention.

Keywords: Atrial Fibrillation; Ischemic Stroke; Direct Oral Anticoagulants

Introduction

It is not surprising that cerebrovascular diseases, especially stroke is recently in the spotlight. Considering its significant effect on public health and also on healthcare finances, it is proved to be a severe burden on society; therefore, it is an important target of preventive medicine.

The importance of stroke prevention is reflected by sharply characteristic numbers: every forty seconds someone suffers a stroke episode and another one dies from it in every four minutes. Statistics show that stroke is the number five cause of death in the United States and it is responsible for more than 5.5 million deaths a year worldwide [1]. Apart from affecting mortality rates significantly, it is also the leading cause of disability, accounting for, as an average, 44 potentially lost life years and a great decrease in Disability Adjusted Life Years (DALY) [2].

Eighty five to eighty seven percent of cerebrovascular diseases are ischemic, 10-12% is hemorrhagic strokes, and subarachnoid hemorrhages account for only 3% [1].

Risk factors of ischemic stroke have an intense relationship to the ones of other cardiovascular diseases: hypertension, diabetes mellitus, tachyarrhythmias, dyslipidaemia, smoking, physical inactivity, chronic kidney disease and also genetic factors play a relevant role in developing both conditions [2]. Most of these factors have a diminishing effect over time, however, arrhythmia, especially atrial fibrillation is a suddenly threatening condition in the elderly, causing most of the stroke episodes in this age group [3,4].

Atrial Fibrillation and Cardioembolic Stroke

Atrial Fibrillation (AF) is the most common among arrhythmias, affecting the lives of 20.9 million males and 12.6 million females, altogether 33.5 million people worldwide [5]. Its overall prevalence is 1% in the general population, which is risen to 2-4% after the age of 60 and to 10% after the age of 80, reflecting the steeply increasing correlation with age.

AF is caused by a structural or electrophysiological alteration that changes one or more of the functional attributes of the atrial tissue, which eventually leads to decreased pump function and at least a relative stasis of the blood flow, therefore, to a condition of increased prothrombotic state. Among the many potential complications of AF, stroke is the most feared one, caused by emboli originating from the atria and occluding a cerebral artery [6,7]. Both permanent and paroxysmal AF can induce clot forming, therefore causing the same risk for ischemic stroke. The size of the cardiogenic emboli is in constant, clots from the left atrium are usually bigger in size, eighty percent of them ending up in one of the branches of the carotid artery.

Atrial fibrillation is associated with at least a fivefold increase in risk of developing ischemic stroke; [8] and it indicates a doubled risk of cardiovascular and overall mortality [9]. Therefore primary and secondary prevention are continuously highlighted in its management.

Cardioembolic stroke accounts for 14-30% of all cerebral infarctions, and is a most common subtype among the elderly as 50% of atrial fibrillation associated strokes affect patients above 75 of age [10]. The fact that one third of first acute strokes are suffered by elderly over 85 years emphasizes that focusing on the prevention in elderly is a significant issue in stroke care.

Main etiological factors besides AF are categorized into three major groups: atrial (AF and flutter, sick sinus syndrome, left appendage thrombus, myxoma), ventricular (thrombus, myxoma, recent myocardial infarct, dilated cardiomyopathy) and valvular (endocarditis, mitral stenosis, prosthetic valve) [8]. Including a number of cardiac conditions recently proved to have potential to cause embolisation [11]. The most common mechanisms for cardioembolism are stasis due to the enlargement of the atria or the ventricles, detachment of a valvular vegetation and paradox embolism [12].

Cardioembolic stroke is potentially the most dangerous type of ischemic strokes as it is responsible for the highest rates (6-27%) of in-hospital mortality [13]. And it has the most disadvantageous long term prognosis [8,11]. It also has 12% chance of developing a second embolism in two weeks [13]. And its overall recurrence rate is as high as 90% [8,11]. Predictive features regarding recurrence are hypertension with valvular disease, AF, nausea and vomiting, as well as history of alcohol abuse [12].

We can expect hemorrhagic transformation in 70% of the patients with cardioembolic stroke, including 20-40% transformation rates on the first week after the stroke episode [8]. Multifocal transformations are usually asymptomatic, while secondary hematomas indicate poor prognosis and worsening condition due to the mass effect. Decreased vigilance, NIHSS >14, involvement of the proximal vessels, delayed recanalization and hypo-density are factors predicting these transformations [8].

Emboli from the heart are responsible for 90% of the hemorrhagic stroke, since the vasospasms, induced by the occluding emboli and the fragmentation of the thrombus, contribute to an instant reperfusion after vessel occlusion, causing the bleeding through the damaged intracerebral vessels [8,12].

There is, so far, no specific approach to diagnose cardioembolic stroke, therefore diagnosis is usually set up by excluding the presence of other possible conditions. It is important to differentiate vascular causes from cardiogenic etiology, however, these are often related, making clinical decision challenging [11,12]. Most typical clinical features of the cardioembolic origin are the sudden onset in less than five minutes, the progressive deterioration of vigilance, early recanalization and hemorrhagic transformation, simultaneous or sequential multiinfarcts, speech disturbance without hemiparesis; although embolism to other systemic organs is occasionally the only sign indicating the cardioembolic etiology [8,11-13].

In addition to the assessment of the clinical symptoms, more specific examinations are necessary: echocardiography reveals structural and functional alterations of the heart, and paroxysmal arrhythmias are caught by 24-48 hour Holter monitoring, the elevated D-dimer and fibrinogen degradation product levels show limited information but are indicative of a prothrombotic state; whereas traceable cerebral lesions are revealed by brain Magnetic Resonance Imaging (MRI) [8,11,12].

Despite the wide range of diagnostic approaches, 25-40% of strokes is of unknown etiology and therefore labeled cryptogenic [14]. Paroxysmal AF is a major cause of cryptogenic stroke; however it often goes undetected due to being intermittent, short, randomly occurring and asymptomatic [14-16]. AF, which is undetectable in standard clinical settings but found by most of the cardiac monitoring systems is called 'silent' [17]. These silent arrhythmias responsible for under-diagnosed cases, suboptimal therapy and the lack of rehabilitation are the foci of recently emerging research to improve decision-making regarding the treatment in patients with cryptogenic stroke.

Standard post-stroke diagnostic schemes include a 12-electrode ECG analysis and a 24 hour Holter monitoring with low sensitivity (1-3%) and detection rates of 2-5% and 2-6%, respectively [15-17]. Other diagnostic methods are proved to be more effective in arrhythmia detection: 7-day or repeated and prolonged (3x10days) Holter monitoring proved to be potentially more effective (with up to 18.5% detection rate) in Find-AF and Find-AF_{RANDOMIZED} trials with benefits of being continuous during the set period but less cost- and time-consuming [14,18]. The EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) study investigated the 30-day event-triggered loop recorder efficacy compared to standard 24-hour Holter monitoring; rates of detecting atrial arrhythmia lasting 2.5 minutes went as high as 9.9% with the loop recorder and only 2.5% with the standard method, while short (30 sec) episodes were detected in 16.1% and 3.2% of all cases, respectively [17,19]. The recent CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation) international, multi-center, randomized, controlled trial emphasizes the advantages of subcutaneously implanted continuous cardiac monitoring systems, which offer a thorough detection of cardiac electrophysiology for as long as three years. The implanted monitoring system detected 8.9% of atrial fibrillation episodes in 6 months and 12.4% in 12 months; compared to the standard short term or intermittent diagnostic methods revealing episodes in only 1.4% and 2% of patients [14,15,17].

Elaborate assessment of these patients is crucial, since prior to most ischemic stroke or Transient Ischemic Attack (TIA), asymptomatic episodes and paroxysmal arrhythmia are already present for years [20]. SPAF (Stroke Prevention in Atrial Fibrillation) investigations also confirm its importance by stating that paroxysmal arrhythmia has similar risks of stroke as sustained AF, accounting for combined stroke and systemic embolism end-point rates of 2/100 patient years and 2.2/100 patient years, respectively [21]. It has also been documented that atrial arrhythmias lasting longer than 6 minutes have a significantly increased risk of thromboembolism including stroke (maintaining a hazard ratio of 1.76 when AF lasts 6 minutes, 2.0 if duration is 6 hours and 1.978 when one-day long arrhythmia occurs). It has been also demonstrated that all subclinical atrial tachyarrhythmias are independently indicate a 2.5 fold increase of stroke episodes [22].

Risk Assessment in AF

Due to the high risk of stroke, therefore, potential disability and elevated mortality rates, risk stratification is essential in terms of adequate decision-making on available prevention and treatment options.

The most widely used method is the CHA₂DS₂-VASc score, which is a more reliable and comprehensive method of evaluation than the previous CHADS₂ score. The score is clinically more relevant by offering better predictive values for thrombo embolic episodes as well as recognizing low risk patients and allowing a more suitable choice on treatment in high risk patients but not in moderate or low risk ones [23-26].

Possible improvement of currently used risk assessment methods have been investigated by combining scores used in routine diagnosis with data of presence or duration of AF from continuous arrhythmia monitoring. These systems provide accurate and reliable data, which contribute to an enhancement in specificity and sensitivity of risk stratification. By using the combination method, specificity of the CHA₂DS₂-VASC score is increased from 7% to 42%, [27]. Making it a capable and more appropriate tool to differentiate between high moderate (4%) and low moderate (0.6%) risk of developing thromboembolic events in the same population [28].

Scores for the evaluation of bleeding risk regarding the anticoagulant therapy are also essential parts of the decision-making process. HAS-BLED score remains the most relevant method of bleeding risk assessment, in contrast to the less reliable ATRIA and overly difficult HEMORR2HAGES score [23-25]. A score higher than three reveals an increased risk of bleeding; however, this risk is modifiable, and it does not necessarily mean an indication for the cessation of anticoagulation but a need for closer monitoring.

Preventive Anticoagulation

One of the most important agenda in the therapy of AF in addition to the adequate rhythm and frequency control is stroke prevention with anticoagulation. Anticoagulation is individualized based on risk assessment and current guidelines, however, the personal cost-benefit ratio of thromboembolism and hemorrhage should always be evaluated.

Preventive treatment is considerable when non-valvular AF is present and the CHA₂DS₂-VASC score is 1, and oral anticoagulation is necessary when CHA₂DS₂-VASC score ≥ 2 [6]. It is very likely that the patient benefits from oral anticoagulation, since 70% of all ischemic strokes lead to disability or death, while most hemorrhagic events are of less significance [8]. Effective anticoagulation results in 26% less mortality and a stroke risk reduced by 67% [29].

An ideal anticoagulant would be easily administered, it would have fix dosage, predictable effect, have no interactions or risk of bleeding and thrombocytopenia. Although no current agent fits these conditions, warfarin still has an A level of evidence for preventive oral anticoagulation in AF, whereas the direct oral anticoagulants (DOAC) have a B level of evidence [6].

Vitamin K antagonist drugs like warfarin have been the only available medications for stroke prevention in the past decades. Warfarin reduces levels of activated factors II, VII, IX, X as well as those of protein S and C via inhibiting the vitamin K oxide reductase, therefore inhibiting the reduction of vitamin K and consequently preventing the γ -carboxylation of these vitamin K dependent factors. Warfarin requires increased attention since it is solely effective between International Normalized Ratio (INR) levels of 2.0 and 3.0—lower INR values are associated with thromboembolic events, while INR above 3.0 has a high risk for bleeding.

The main reasons for failure in preventing stroke with

warfarin is that the time spent in the therapeutic range accounts for only 65-58% of full treatment time, reflecting poor control on coagulation in the ORBIT-AF (US Outcome Registry for Better Informed Treatment of Atrial Fibrillation) [30,31]; a European study emphasizes the need for better treatment and follow up, since they report less than half of the patients being in therapeutic range for the 70% of the time on warfarin, causing an increasing in thromboembolic risk but having no effect on hemorrhagic events [32].

Warfarin is suitable for long-term anticoagulation but it is not recommended for acute treatment since it has a delayed onset of action, an additional overshooting effect and potentially transient hypercoagulability during the early period of use [33]. Patients on warfarin need regular monitoring of INR and they are subject of frequent dose adjustments; further disadvantages include interactions with other drugs and diet, narrow therapeutic range and high individual variety due to genetically determined resistance factors expressed on chromosome 16 [29,34].

Compared to the warfarin, the recent introduction of Direct Oral Anticoagulants (DOAC) offer an easily manageable, instant and predictable anticoagulation via directly inhibiting factor II or X, with no need of regular monitoring or dose adjustments. DOAC agents are proved to have a 20% lower risk of developing ischemic stroke and systemic embolism and a reduced rate of hemorrhagic events by 14%, resulting in significant reduction of the all-cause mortality [35]. DOAC are contraindicated in patients with impaired creatinine clearance (≤ 15 ml/min), with high hemorrhagic risks or active bleeding, as well as during pregnancy or lactation [34].

Dabigatran-etexilate is a prodrug for dabigatran, the first DOAC, which has been approved in the EU (2008) and later in the USA (2010), as well. It is an oral, reversible, direct thrombin inhibitor agent that comes in two doses: 150 mg BID and 110 mg (or 75 mg in the USA) BID, the latter used in the elderly, for patients with high bleeding risks or deteriorated kidney function [34,36]. Dabigatran-etexilate has a bioavailability of 6%, its effect peaks in 2-3 hours and it has a 12-17 hour half-life time; it is activated in the liver and eliminated via the kidneys (80%). The study RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) showed not only non-inferiority but it has provided evidence on superior efficacy for thromboembolic episodes compared to warfarin, and similar rates (3.11% vs. 3.36% with dabigatran) of preventing hemorrhagic events with 150 mg dose dabigatran (110 mg regimen was more effective in reducing bleeding risks of 2.71% vs. 3.36% with warfarin, but had similar effect on stroke prevention as warfarin treatment). The reliability of RE-LY is characterized by the fact that it also draws attention to adverse effects, such as dyspepsia and higher rates of gastrointestinal hemorrhage and myocardial infarction (0.81%) [34-42].

Direct inhibitors of factor Xa represent an important group of oral anticoagulants, including rivaroxaban, apixaban and edoxaban. These agents have higher bioavailability and similar peak effect times. The half-life of rivaroxaban is 5-9 hours; it is mainly excreted by the liver and to a less extent by the kidneys.

The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial proved that the 20 mg dose of rivaroxaban is non-inferior to warfarin in prevention of stroke (risk of 1.7% vs. 2.2% with warfarin) and similar rates of hemorrhagic events (14.9% vs. 14.5% with warfarin), however, rivaroxaban reduced both fatal bleedings (0.2% vs. 0.5% with warfarin) and intracerebral hemorrhages (0.5% vs. 0.7% with warfarin). The study population of this trial had a higher stroke risk than the patient group of the RE-LY trial with warfarin patients spending only in 55% of the time in the therapeutic range of INR. The meta-analysis of the available studies revealed that the incidence of myocardial infarction is significantly less during rivaroxaban treatment [34-41,43].

ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial proved that the apixaban (5 mg) is the best agent regarding safety (decreasing major bleeding rates by 31%). The risk of all major bleedings was significantly decreased, except for gastrointestinal hemorrhage, where the results were neutral. Irrespectively of previous cerebrovascular episodes, apixaban, compared to warfarin, reduced significantly the number of strokes and systemic embolisms, as well as the overall mortality rates.

The AVERROES study included AF patients with contraindication to Vitamin K antagonists therapy. Apixaban was compared to acetylsalicylic acid in a patient group with the CHADS₂ score [2]. The trial was stopped after 1.1 years due to the significant superiority of apixaban, decreasing ischemic events by 55% but with no differences in preventing intracerebral and other major hemorrhagic events [34-41,44,45].

The most lately discovered edoxaban was investigated in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial. The multi-centric study including 20,000 patients with atrial fibrillation investigated two doses of edoxaban for a period of 2.8 years. The results showed that its peak plasma concentration and half-life are similar to the other DOAC agents, and it has also found to be non-inferior to warfarin in efficacy with less hemorrhagic complications and reduced cardiovascular mortality [46].

DOAC in Practice

Thrombolysis in DOAC taking patients

Patients on DOAC require a comprehensive assessment when acute ischemic stroke care is needed. Safe thrombolysis with warfarin has already been proven [47-49], and success with several experimental models, as well as case studies, has been reported with DOAC agents [50-53]. Current guidelines are cautious about thrombolysis in these patients, therefore the use of intravenous thrombolysis with recombinant tissue plasminogen activators are limited to cases where the absence of DOAC effect is proven by negative coagulation studies or when last dose was taken more than two half-lives before intervention [54]. The NOACISP-ACUTE (Novel Oral Anticoagulants in Stroke Patients), a recent, retrospective, multi-center cohort study;

showed that compared to the Vitamin K antagonist agents and individuals without any anticoagulation, DOAC has similar safety profile in acute thrombolysis. All selected patients went through intravenous thrombolysis with recombinant tissue plasminogen activator or intraarterial treatment (intra-arterial thrombolysis or mechanical revascularization) and the number of intracranial bleedings, mortality rates and 3-month favorable outcome were measured. No statistical significance was noted, however, intracranial bleedings found to be less (18.4%) in DOAC patients versus in the warfarin group (26.8%). Mortality and 3-month favorable outcome rates also reflect safety accounting for 23.0% and 40.5% in patients taking DOAC agents and 26.9% and 39.5% in those, who take warfarin, respectively [55].

Timing of DOAC treatment

The emerging trend of switching preventive anticoagulation from vitamin K antagonist therapy to DOAC treatment proposes the need for specific timing guidelines [47]. DOAC can be administered immediately when INR ≤ 2 ; between 2-3, warfarin should be stopped and DOAC administered in 48 hours; patients with INR rates above 3 should be re-evaluated in 48 hours [29,36].

Restarting anticoagulation after stroke or TIA reduces recurrent stroke rates but increases symptomatic intracerebral bleeds (the damaged tissue and vessels are prone to re-bleeding when anticoagulation is restarted too early). Guidelines advice to start DOAC treatment immediately after TIA if no bleeding is detected on CT scan, 3 days after minor, 6 days after moderate and 14-21 days after severe strokes. Personalized treatment is achievable when extension of stroke and patient risk factors are carefully evaluated. Adverse effects due to early anticoagulation are expansion of hematoma and recurrent intracerebral bleeding in the acute phase, while increased risk of thromboembolism in the post-acute period [33,54,56,57].

DOAC treatment in impaired kidney function

One in five patients with Chronic Kidney Disease (CKD) has AF as it is three times more common in impaired kidney function due to their similar risk factors [58,59]. In addition to the twofold increased risk of ischemic episodes and bleeding, the coexistence of AF and CKD increases mortality rates by 3% compared to those without AF [60,61].

CKD interferes with renally eliminated agents, such as dabigatran; therefore DOAC trials offer dose adjustments for patients with impaired kidney function and they exclude patients with Glomerular Filtration Rates (GFR) less than 30% in dabigatran and rivaroxaban trials, and less than 25% in apixaban studies to avoid overexposure to anticoagulant effect, therefore causing hemorrhagic episodes [57,60,62].

The lower dose of 110 mg of the dabigatran was used between the GFR values of 30-49%, and proved to be safer (2.71% vs. 3.36% bleeding risk) and non inferior to warfarin in the RE-LY trial [42,57,63]. The rivaroxaban 15 mg dose was evaluated in patients with GFR 30-49% in the ROCKET-AF study, where the adjusted dose of rivaroxaban resulted in less thromboembolic

episodes (1.7% vs. 2.2%) and similar hemorrhagic risk (4.49% and 4.7%) to warfarin therapy [43]. The AVERROES and ARISTOTLE trials recommend the adjusted doses of apixaban 2.5 mg if two of the three conditions are present: ≥ 80 years of age, ≤ 60 kgs of weight or serum creatinine ≥ 1.5 mg/dl [44,45,57].

The annual evaluation of renal function is essential in patients with normal and mildly impaired renal function and more frequent assessment is necessary when GFR is below 50%.

DOAC agents are not recommended in severe renal impairment (GFR $<30\%$) according to the European Society of Cardiology (ESC), in contrast to the American Heart Association/American Stroke Association (AHA/ASA) guidelines that offer DOAC treatment in severe CKD based on pharmacological studies [64,65]. Warfarin treatment is also available in severely impaired kidney function or in hemodialysis patients if anticoagulation control is strict and INR is maintained between 2 and 2.5; however anti-platelet therapy should be considered in high bleeding risk, particularly when vascular risk factors are present [62].

Stroke Prevention in Acute Coronary Syndrome

Coronary artery disease is present in 20-30% of patients with AF and new onset atrial arrhythmia occurs in 6-8% of patients after Acute Coronary Syndrome (ACS) or Percutaneous Coronary Intervention (PCI) [66,67].

Standard management of ACS is the Dual Anti-Platelet Therapy (DAPT), including aspirin and a thienopyridine agent (clopidogrel, ticlopidine, prasugrel) or ticagrelor. Prasugrel and ticagrelor are new P2Y₁₂ inhibitor agents, that proved to be superior to clopidogrel in PLATO (Platelet Inhibition and Patient Outcomes) and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) trials. These agents, however, showed increased risk of bleeding, therefore are not recommended for stroke or TIA patients, unless the patient demonstrates individual resistance to clopidogrel [67,68]. Patients with coexisting AF are in need of oral anticoagulant therapy for secondary preventative measures of stroke and systemic thromboembolism, therefore treated with triple anti-thrombotic therapy. Triple therapy has similar stroke-preventing effects as DAPT with a twofold increased risk for hemorrhagic events [67,69].

Oral anti-thrombotic therapy should be continued to 12 months after ACS or one to twelve months after PCI to decrease peri-procedural complications and stent thrombosis and the use of proton-pump inhibitors should also be considered to decrease gastrointestinal bleeding risks caused by oral anti-thrombotic treatment [66-68].

A strictly controlled warfarin regime (INR 2-2.5) remains the standard for anticoagulation; however DOAC agents are considerable alternatives [67]. There are few data available of the suitability of DOACs due to the exclusion criteria of the AF trials; nonetheless subgroup analyses and ACS studies are available for further assessment. Dabigatran raises concern due to its increased risk for myocardial ischemia revealed in

RE-LY study and its dose-related hemorrhagic risk in RE-DEEM trial [60,68]. Apixaban also proved to be unprofitable in trials APPRAISE (Apixaban for Prevention of Acute Ischemic Events) and APPRAISE-2 and it has also been demonstrated that the concomitant use of anti-platelet drugs with these agents increases risk without benefit. ATLAS ACS 2-TIMI 46 and 52 investigated reduced doses of rivaroxaban and revealed its association with lower ischemic and bleeding risks, as well as a decrease in both stent thrombosis and mortality rates; therefore suggesting rivaroxaban to be a potential choice for anticoagulation in triple therapy in the future [68,70-72].

The careful evaluation of procedural risks is essential in patients undergoing invasive revascularization. The choice of radial access prevented complications in STEMI-RADIAL trial and STENTICO (Stenting and oral anticoagulants) registry by 5.8% and 6.5%, respectively, compared to femoral site access. Bare Metal Stents (BMS) only require a one-month long administration of anti-thrombotic therapy, as well as the new Drug Eluting Stents (DES) using everolimus or zotarolimus. However, six to twelve months of triple anti-thrombotic therapy is needed if first or second generation DESs are implanted [67,68].

AFCAS (Prospective Multi-center Registry of Patients with Atrial Fibrillation Undergoing Coronary Artery Stenting) registry demonstrated superiority of DES to BMS regarding stent thrombosis risks. This trial also supports uninterrupted intra-procedural anticoagulation as an alternative to bridging heparin therapy [67]. WOEST (What is the Optimal anti-platelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) uncovered reduction of bleeding risks and overall mortality with the same thrombotic rate in DAPT with warfarin and clopidogrel, compared to triple anti-thrombotic therapy [67,72].

Ongoing trials like ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation), MUSICA-2 and LASER are sources of further information for the optimization of current management in PCI in patients with AF [68,72].

DOAC Safety

Monitoring of DOAC levels are only required in renal insufficiency, hemostatic emergency, drug interactions and before imminent surgery [34]. Qualitative information is available via APTT (Activated Partial Thromboplastin Time) for dabigatran and via Prothrombin Time (PT) for factor X inhibitors. Thrombin Time (TT), Hemoclot assay, Ecarin Clotting Time (ECT), liquid chromatography and tandem mass spectrometry provide qualitative assessment of dabigatran levels [36,54]. If bleeding occurs while on dabigatran, treatment discontinuation and general supportive therapy is required. If last dose was taken in 2 hours, active charcoal can be administered for adsorption; prothrombin complex concentrates, recombinant factor VII are effective in severe bleedings, while fresh frozen plasma is profitable in dilutional coagulopathy. Unlike the other DOAC agents, dabigatran can be eliminated successfully by hemodialysis in emergency [34,36,57,73].

The lack of antidote has been the main concern regarding DOAC, however, intensive investigations in this field are promising. Idarucizumab (Praxbind), a humanized antibody that binds to dabigatran with high affinity, is the first antidote for dabigatran, approved in October of 2015 [74]. It is worth noting that factor Xa competitive agonists are also in final stage of testing [39].

Conclusion

There is still limited knowledge on direct anticoagulant effects and limitations, especially timing of restarting the anticoagulation after stroke and the concomitant use of anti-thrombotic agents. However, the emerging research for antidotes seem to provide a solution for the instant reversal of anticoagulation, as well as the potential to rise to the first line preventive agents for ischemic stroke in non-valvular atrial fibrillation. The intense ongoing innovations offer comprehensive, extended opportunities that contribute to an individualized stroke prevention for thousands of patients with non-valvular atrial fibrillation.

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