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CLINICAL DISCUSSIONS IN ANTITHROMBOTIC THERAPY MANAGEMENT IN PATIENTS WITH ATRIAL FIBRILLATION: A DELPHI CONSENSUS PANEL

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Abstract

Background: In the recent years, direct-acting oral anticoagulants (DOACs) have entered the clinical practice for stroke prevention in non-valvular atrial fibrillation (NVAF) or prevention and treatment of venous thromboembolism (VTE). However, there is uncertainty on DOAC use in some clinical scenarios not fully explored by clinical trials, but commonly encountered in the real world.

Methods: We report a Delphi Consensus on DOAC use in NVAF patients. The consensus dealt with 9 main topics: (1) DOACs versus vitamin K antagonists (VKAs) in AF patients; (2) Therapeutic options for patients with stable total time in range (TTR) treated with VKA; (3) Therapeutic options for patients aged more than 85 years; (4) Therapeutic management of hyperfiltering patients; (5) Pharmacological interactions; (6) Therapeutic options in the long-term treatment (prevention) of patients with AF and ACS after the triple therapy; (7) Low doses of DOACs in AF patients; (8) Ischemic stroke in patients inappropriately treated with low doses of DOACs; (9) Management of patients taking DOACs with left atrial appendage thrombosis.

Results: One hundred and one physicians (cardiologists, internists, geriatricians and hematologists) from Italy expressed their level of agreement on each statement by using a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: somewhat agree, 4: agree, 5: strongly agree). Namely, votes 1-2 were considered as disagreement while votes 3-5 as agreement. Agreement among the respondents of ≥66% for each statement was considered consensus. A brief discussion about the results for each topic is also reported.

Conclusions: In clinical practice there is still uncertainty on DOACs use, especially in elderly, fragile, comorbid and hyperfiltering patients.

Summary

There is still uncertainty on DOACs use in some clinical scenarios not fully explored by clinical trials, but commonly encountered in the real world. We report a Delphi Consensus involving 101 Italian physicians and about DOACs use in non-valvular atrial fibrillation (NVAF) patients, particularly regarding: elderly patients, hyperfiltering subjects, pharmacological interactions, acute coronary syndrome, ischemic stroke, left atrial appendage thrombosis.

Introduction

In the recent years, direct-acting oral anticoagulants (DOACs) have entered the clinical practice of a large group of specialists such as cardiologists, internists, angiologists, neurologists, hematologists, and geriatricians to reduce the thromboembolic risk associated with atrial fibrillation (AF) or to prevent or treat venous thromboembolism (VTE). They have represented a landmark revolution in these fields.

Efficacy or safety of DOACs compared to vitamin K antagonists (VKAs), both in pharmacoeconomic terms and in management of follow-up have been evaluated. Economic sustainability has been assessed. Rivaroxaban, apixaban, edoxaban (direct factor Xa inhibitors), and dabigatran (a direct thrombin inhibitor) have been tested vs the traditional approach in phase III randomized clinical trials (RCTs) [1-4]. However, some aspects related with the routine use of DOACs are still doubtful, such as the real world security and handling of these drugs, the behavior with patients adequately anticoagulated with VKAs, the choice of a DOAC after an ischemic stroke assuming an inappropriate low dose, the long-term treatment after a period of triple therapy in patients with AF and acute coronary syndrome (ACS), the management of left atrial appendage thrombosis. Moreover, clinical practice constantly faces patients under-represented in RCTs, such as elderly, fragile, comorbid, hyperfiltering patients. Further clinical research and phase IV registries are required to fully explore the handling of DOACs in these subgroups.

A consensus conference focused on these issues from different points of view has been realized with the aim of discussing on these topics.

Materials and methods

The Delphi method is frequently used in scientific and medical settings with the aim of reaching consensus within a group of experts, when scientific evidence is absent or conflicting [5-7]. In this paper, Delphi method was used to evaluate the consensus on clinical management of DOACs in patients with AF. The process has been structured into four phases. In the first phase (May-October 2018) eighteen regional round tables were organized. Participants involved in the treatment of AF (cardiologists, internists, geriatricians and hematologists) were indicated by Medical representatives and discussed on the following

main issues on DOACs: safety and handling, pharmacological interactions, use of low doses and patients adherence and compliance. In the second phase (November 2018), a scientific board of six experts were unanimously identified during the round tables for scientific authoritativeness as representative of clinical specialties involved in the treatment of patients with AF. This scientific board identified a list of statements arose from the six round tables discussions. During the third phase (December 2018-January 2019) the list of statements was administered online to the 101 clinicians participating in the regional round tables. Survey was performed online on a secured survey website (first round), by using a web-based survey platform (http://www.consensusdelphinao.it/). The results were evaluated by the scientific board (February 2019). The responses of participants were collected and analyzed prior to two final consensus meetings held in Milan (29th May 2019) and Naples, Italy (20th June 2019). Results from the first-round vote were presented by the scientific board and a second-round vote was performed (101 participants) in order to estimate consensus on the statements that were controversial in the first round. Both rounds of vote were blinded.

2.1 Delphi statements

The scientific board defined 9 statements: (1) DOACs versus VKAs in AF patients; (2) Therapeutic options for patients with stable TTR treated with VKA; (3) Therapeutic options for patients aged more than 85 years; (4) Therapeutic management of hyperfiltering patients; (5) Pharmacological interactions; (6) Therapeutic options in the long-term treatment (prevention) of patients with AF and ACS after the triple therapy; (7) Low doses of DOACs in AF patients; (8) Ischemic stroke in patients inappropriately treated with low doses of DOACs; (9) Management of patients taking DOACs with left atrial appendage thrombosis. Participants expressed their level of agreement on each statement by using a 5-point Likert scale (1: strongly disagree, 2: disagree, 3: somewhat agree, 4: agree, 5: strongly agree). Agreement among the respondents of ≥66% for each statement was considered consensus. Namely, votes 1-2 were considered as disagreement while votes 3-5 as agreement.

Results

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The overall response rate of Delphi first round was 100% (101 responding participants out of 101 total panelists) and that of second round was 100% (101 out of 101). Of the total of 36 items, 10 reached a positive consensus (agreement), 12 reached a negative consensus (disagreement) and 14 did not reach a consensus. In particular, the statements 2 (item 2.2), 4 (all items), 5 (item 5.2), 6 (item 6.1) and 9 (all items) underwent a second vote, without changing the consensus. The items 7.1 and 8.1 have been deleted because considered wrong.

3.1 Topic 1. DOACs versus VKAs in AF patients

Table 1. Statement 1: I retain that DOACs must be considered as the first choice:

	1	2	3	4	5	TOT
1.1 In patients with CHA2DS2-VASc ≥ 2	1	2	7	30	61	101
	3%		97%			100%
1.2 Only in patients with high hemorrhagic risk	44	36	9	5	7	101
	79%		21%			100%
1.3 Only in patients not compliant to VKA therapy	44	29	9	9	10	101
	72%		28%			100%
1.4 In patients with CHA2DS2-VASc = 1	18	27	36	11	9	101
	45%		55%			100%

The panel fully agreed in considering DOACs as the first choice in patients with

CHA_2DS_2-VASc ≥ 2, and not only in patients with high hemorrhagic risk or only in patients

not compliant to VKA therapy. Vice versa, no consensus was reached about DOACs as the first choice in patients with CHA_2DS_2-VASc 1.

3.2 Topic 2. Therapeutic options for patients with stable TTR treated with VKA

Table 2. Statement 2: Regarding the patient treated with VKA and with stable TTR:

	1	2	3	4	5	TOT
2.1 I propose switching to a DOAC because it is superior in terms of safety	6	11	22	29	33	101
	17%		83%			100%
2.2 I consider to switch to a DOAC only if requested by the patient	18	42	20	11	10	101
	59%		41%			100%
2.3 I consider to switch to a DOAC to further improve the patient's compliance	3	9	22	38	29	101
	12%		88%			100%
2.4 I consider inappropriate to switch to a DOAC	68	21	5	7	0	101
	88%		12%			100%

A positive consensus was reached regarding the switch from VKAs to DOACs in patients with stable total time in range (TTR) because they are safer and to further improve the compliance, despite the recommendation of the current European Society of Cardiology (ESC) guidelines [8]. Accordingly, a negative consensus was reached about the inappropriateness to switch to a DOAC in these patients. Vice versa, no consensus was reached when the switch is requested by the patient.

3.3 Topic 3. Therapeutic options for patients aged more than 85 years

Table 3. Statement 3: To patients aged more than 85 years I administer DOACs:

	1	2	3	4	5	TOT
3.1 At low dose, independently from SmPC criteria, to ensure the safety	60	25	10	4	2	101
	84%		16%			100%
3.2 Choosing the dose according to SmPC criteria	0	3	20	9	69	101
	3%		97%			100%
3.3 In case the VKA has a difficult management and does not ensure an adequate safety in terms of bleeding	8	18	32	24	19	101
	26%		74%			100%
3.4 I do not use DOACs in these patients	88	10	2	0	1	101
	97%		3%			100%

In the setting of elderly patients there was a negative consensus in not using DOACs at all or using them at low dose independently from summary of product characteristics (SmPC) criteria. On the other hand, the panel agreed in choosing the dose according to SmPC criteria or in case the VKA has a difficult management and does not ensure an adequate safety in terms of bleeding.

3.4 Topic 4. Therapeutic management of hyperfiltering patients

Table 4. Statement 4: In hyperfiltering patients the use of DOACs:

	1	2	3	4	5	TOT
4.1 Is always indicated	8	34	39	11	9	101
	42%		58%			100%
4.2 Must require a closer follow-up than in normofiltering patients	6	18	43	18	16	101
	24%		76%			100%
4.3 Depends from patients' BMI	9	35	38	8	11	101
	44%		56%			100%
4.4 Is indicated only for certain DOACs	15	22	44	6	14	101
	37%		63%			100%

Hyperfiltering patients are always a matter in terms of drug doses. Accordingly, the use of DOACs in these patients is doubtful. The panel agreed that hyperfiltering subjects treated with DOACs should undergo a closer follow-up. Vice versa, no consensus was reached about the absolute indication to the use of DOACs in these patients. Similarly, the panel expressed no consensus to the use of DOACs depending from BMI or restricted to certain molecules.

3.5 Topic 5. Pharmacological interactions

Table 5. Statement 5: Regarding pharmacological interactions of DOACs I retain:

	1	2	3	4	5	TOT

5.1 They must be a criterium of choice among DOACs	2	5	20	28	46	101
	7%		93%			100%
5.2 Should be considered in the general evaluation, but are not a criterium of choice	15	37	26	18	5	101
	51%		49%			100%
5.3 Food-drug interactions are not a criterium of choice	14	28	24	15	20	101
	42%		58%			100%

The panel fully agreed that pharmacological interactions are a criterium of choice among DOACs. On the contrary, no consensus was reached about pharmacological interactions to be considered in the general evaluation and not a criterium of choice or about food-drug interactions to not be a criterium of choice.

3.6 Statement 6. Therapeutic options in the long-term treatment (prevention) of patients with AF and ACS after the triple therapy

Table 6. Statement 6: In the long-term treatment (prevention) of patients with AF and ACS after the triple therapy I consider appropriate to administer:

	1	2	3	4	5	TOT
6.1 DOAC + SAPT in patients at high hemorrhagic risk	11	22	21	24	23	101
	33%		67%			100%
6.2 DOAC + SAPT independently from the hemorrhagic risk	18	33	18	12	20	101
	50%		50%			100%

	1	2	3	4	5	TOT
6.3 Triple therapy if the patients are not at high hemorrhagic risk	38	32	14	9	8	101
	69%			31%		100%

The long-term treatment after triple therapy for ACS in patients with AF is a matter of debate. A positive consensus was reached in administrating DOAC + single antiplatelet agent in patients at high hemorrhagic risk. On the contrary, no consensus was reached about this option independently from the hemorrhagic risk. Vice versa, the experts agreed not to use triple therapy if the patients are not at high hemorrhagic risk.

3.7 Topic 7. Low doses of DOACs in AF patients

Table 7. Statement 7: I retain that low doses:

	1	2	3	4	5	TOT
7.1 Are not related to the risk of thromboembolic events	32	38	16	9	6	101
	69%			31%		100%
7.2 Increases the risk of thromboembolic events only if inappropriately prescribed	4	8	19	28	42	101
	12%		88%			100%
7.3 Must be prescribed in all patients with borderline GFR (< 50 mL/min) independently from the criteria reported in SmPC	36	37	17	10	1	101
	72%			28%		100%
7.4 Must be prescribed in all patients aged more than 85 years	39	40	9	8	5	101
	78%			22%		100%

The panel did not retain that low doses of DOACs are not related to the risk of thromboembolic events. Accordingly, they fully agreed that they increase the risk of

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thromboembolic events only if inappropriately prescribed. A negative consensus was reached regarding the indication of low doses to all patients with borderline GFR or aged more than 85 years.

3.8 Topic 8. Ischemic stroke in patients inappropriately treated with low doses of DOACs

Table 8. Statement 8: In patients taking a DOAC reporting an ischemic stroke due to inappropriate low doses I retain correct:

	1	2	3	4	5	TOT
8.1 To continue the treatment increasing the dose of the same DOAC	3	5	26	29	38	101
	8%		92%			100%
8.2 To continue the treatment changing the DOAC	14	38	26	10	13	101
	51%		49%			100%
8.3 To switch to the treatment with VKA	44	45	8	4	0	101
	88%		12%			100%
8.4 To use UFH/LMWH	49	43	6	3	0	101
	91%		9%			100%

Ischemic stroke during DOAC treatment is a rare event. However, when it happens in patients taking an inappropriate low dose the panel fully agreed that they should continue the same drug increasing the dose. In addition, a negative consensus was reached about switching to VKAs or to UFH/LMWH. No consensus was reached about changing the DOAC.

3.9 Topic 9. Management of patients taking DOACs with left atrial appendage thrombosis

Table 9. Statement 9: In patients taking a DOAC with left atrial appendage thrombosis I retain appropriate:

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	1	2	3	4	5	TOT
9.1 To continue the treatment with the same DOAC	29	37	14	11	10	101
	65%		35%			100%
9.2 To continue the treatment changing the DOAC	18	21	25	22	15	101
	39%		61%			100%
9.3 To switch to the treatment with VKA	25	27	18	14	17	101
	51%		49%			100%
9.4 To use UFH/LMWH	37	38	17	5	4	101
	74%		26%			100%

In presence of left atrial appendage thrombosis the panel did not reach a consensus about continuing the treatment with the same DOAC or changing it or switching to a VKA. The experts agreed not to use UFH/LMWH.

Discussion

The ESC guidelines (2016) about AF suggest stroke prevention with either DOACs or VKAs in patients with a CHA$_2$DS$_2$-VASc score of at least 2 (3 for females) without mechanical heart valves or mitral stenosis more than mild, preferring the firsts in naïve subjects (IA recommendation) [8]. A meta-analysis [9] focusing on the four phase III RCTs about DOACs in AF [1-4] suggests a higher efficacy of DOACs than VKAs as regards the prevention of stroke or systemic embolism (RR 0.81, 95%CI 0.73-0.91, p<0.0001), and a greater/equal safety considering several bleeding endpoints. Accordingly, the panel agreed on considering DOACs as the first choice in these patients, independently from the bleeding risk. Moreover, by the fact that the compliance to VKA treatment is about 50%, DOACs should be considered the first choice also for the adherence to therapy [10], in particular for once-a-day administration [11]. On the contrary, twice daily dosing may lead to wrong pills

intake [12]. An easier handling (e.g., once-a-day administration) has been demonstrated pivotal in patients starting an anticoagulant therapy [13]. Patients with CHA_2DS_2-VASc 1 (2 for females) constitute a grey zone where anticoagulation should be considered (recommendation IIaB) [8], because of the lack of extensive data about this topic. In a nationwide Danish population, these cases are considered at a moderate annual risk of thromboembolism: 2.01 (1.70 to 2.36) per 100 person-years [14]. A post-hoc analysis of ORBIT-AF I & II registries found that the majority (60-70%) of CHA_2DS_2-VASc=0-1 patients are treated with oral anticoagulation. In addition, the absolute risks of death, stroke/transient ischemic attack (TIA) and major bleeding were low among male and females with a CHA_2DS_2-VASc of 0-1 as well as among females with a CHA_2DS_2-VASc score of 2 [15]. Several factors have to be considered and weighted in this setting in order to identify the antithrombotic approach of choice, including the expected incidence of both thromboembolic stroke and bleeding side effects, their impact in terms of morbidity and mortality, the patient's bleeding risk profile, an accurate stratification of the thromboembolic risk beyond the CHA_2DS_2-VASc score (e.g., renal failure, left atrial enlargement, left atrial and its appendage morphology and flow, AF burden), and socioeconomic issues [16]. Accordingly, the panel reached no consensus about this topic.

In patients already taking a VKA, ESC guidelines consider the switch to a DOAC (recommendation IIbA) if TTR is inadequate (despite good adherence) or according to patient's preference (if eligible for DOAC) [8]. Given the assumption about greater safety and compliance discussed above [9-13], the panel agreed on considering the switch to DOACs when the TTR is optimal. Vice versa, the patient's preference reached no consensus among the panel (in other words the patient opinion should be considered, but cannot represent the only criterium of choice).

Thromboembolic and bleeding events are increased in the very elderly [17], with the first prevailing on the second [18]. Accordingly, anticoagulation reduces them in the same group [17], but it is administered less frequently [19]. In patients treated with a VKA the hemorrhagic risk increases with age more than the thromboembolic risk [20]. Vice versa, age per se is a dose reduction criterium only for dabigatran and apixaban [21]. Edoxaban shows stable efficacy and safety also in the elderly subgroup [20]. Every DOAC reduces the risk of intracranial hemorrhage than VKAs in the elderly [22]. The inappropriate use of low doses of DOACs is associated to a greater risk of ischemic stroke and systemic thromboembolism, a higher mortality and cardiovascular hospitalization rate, with no safety benefits [23-26]. The panel strongly disagreed with a default use of low doses in the elderly, confirming the

administration of doses according to SmPC indications and the switch from VKA to DOAC if VKA does not ensure an adequate safety.

All DOACs are at least partly eliminated by the kidneys, principally dabigatran (80%), so that renal function may affect systemic drug exposure, efficacy, and safety. Consequently, renal function needs to be monitored diligently, at least once a year, to detect functional changes in order to adapt the dose [8,27]. In contrast, there is less focus on DOAC efficacy in patients with normal renal function, in whom it could be hypothesized that normal or supranormal filtration may lead to suboptimal effective dosing and so suboptimal prevention of thromboembolism. Of note, hyperfiltration or augmented/enhanced renal clearance is a condition characterized by CrCl > 130 ml/min and typical of critically ill patients [28,29]. In this context, real world data suggest that dabigatran is less efficacious than warfarin in patients with CrCl >90 mL/min [30], rivaroxaban shows a trend toward higher relative rates of stroke or systemic embolism in subjects with CrCl >95 mL/ min [31] and apixaban carries a higher HR for first ischemic stroke when CrCl >80 mL/min [32,33]. In addition, a box warning from FDA and an alert from EMA have been provided about the use of edoxaban in patients with CrCl >95 mL/min. Nevertheless, real-world data do not confirm this caution [34-36]. Several exploratory analyses suggested lower relative efficacy for the prevention of stroke/systemic embolism with high-dose edoxaban compared with warfarin at higher levels of renal function (CrCl ≤50 mL/min: HR, 0.87; 95% CI, 0.65-1.18; CrCl >50-95 mL/min: HR, 0.78; 95% CI, 0.64-0.96; CrCl >95 mL/min: HR, 1.36; 95% CI, 0.88-2.10; P for interaction=0.08) [37]. However, bleeding rates were lower at all levels of CrCl with edoxaban, so that the net clinical outcome was more favorable [37]. Consequently, the panel agreed that caution should be paid in this subgroup of patients, reaching a consensus about the adoption of a closer follow-up. In particular, in very obese patients a VKA should be considered.

Treatment with VKAs requires careful consideration of multiple food and drug–drug interactions. Fewer interactions with DOACs have been reported instead, even if it is important to be aware that plasma levels of DOACs are affected by drugs that alter the cell efflux transporter P-glycoprotein (P-gp) and/or cytochrome P450 [27,38]. The only DOAC presenting a reduction criteria according to P-gp inhibitors is edoxaban [4]. European practical guidelines provide different kinds of alert depending on the specific DOAC-drug interaction, with some contraindications [27]. Accordingly, the panel reaches a positive consensus regarding drug-drug interactions that should be considered a driver of choice

among DOACs. Vice versa, no consensus was reached in considering drug-drug interactions in the general evaluation without being a driver of choice, and in food-drug interactions to be a driver of choice. This is probably related to the fact that not all interactions deserve a mandatory choice.

5-8% of patients undergoing PCI suffer from AF and approximately one third of those affected by AF have also coronary artery disease, so that the necessity of a triple therapy is frequent in the real world [39]. Antiplatelet therapy is needed to prevent stent thrombosis and oral anticoagulants are required to prevent stroke: combining both treatments increases bleeding [40]. Triple therapy provides a 3.7-fold risk of fatal and non-fatal bleeding than warfarin alone [40]. Importantly, in this field, bleeding is associated with an increased mortality, not only in hospital but also after discharge, regardless of bleeding site [41-44]. The challenge of balancing the risk of thromboembolism (i.e., stroke) and atherothrombotic events (i.e., stent thrombosis), and the risk of bleeding lead to the need to clarify the optimal combination regimen in terms of choice of agents, dose and duration of therapy. After the positive results in terms of safety of the WOEST trial comparing triple therapy with warfarin vs clopidogrel + warfarin for one year [45], four RCTs [46-49] and two meta-analyses [49,50] comparing triple therapy with warfarin to dual therapy with DOAC, confirmed that the combination of DOAC plus $P2Y_{12}$ inhibitor was associated with less bleeding compared with VKA plus DAPT, and that strategies omitting aspirin caused less bleeding, including intracranial hemorrhage, without significant difference in major adverse cardiac events, compared with strategies including aspirin. However, none of these RCTs were designed to be large enough to detect small but potentially meaningful differences in the incidence of ischemic events. The recent European practical guide on DOACs suggest the possibility to shorten triple therapy from three months after ACS to discharge, or to lengthen it to one year or beyond accordingly to the individual balance between bleeding and atherothrombotic risk [27]. An initial period of triple therapy is still considered fundamental to avoid early stent thrombosis, followed by a personalized therapy according to patient's characteristics. The panel agreed to continue the therapy with DOAC plus single antiplatelet agent in patients at high hemorrhagic risk and not to extend this strategy to all patients; however, no consensus exists about choosing DOAC plus single antiplatelet agent independently for the hemorrhagic risk.

The prescription of a reduced dose of DOACs is regulated by precise criteria, which are different for each drug and for AF and venous thromboembolism contexts [27]. The

reduced dose according to the proper criteria aims at providing a similar plasmatic concentration and thus clinical results than the full dose. Otherwise, an inappropriately reduced dose translates into an insufficient plasmatic concentration of the drug, with a lower effect. Interestingly, a low plasmatic concentration in patients taking a reduced-dose DOAC is associated to a high risk of thromboembolism [51]. Consequently, real world data confirm that undertreated patients experience a high risk of ischemic stroke, particularly for apixaban [52-55], and cardiovascular hospitalization [55]. The panel agreed that only inappropriately reduced doses of DOACs are related to thromboembolic events and that the precise criteria of dose reduction must be always followed.

In patients with cardioembolic stroke associated with AF, the risk of early stroke recurrence (within 2 weeks), is between 0.1% and 1.3% per day [56,57], meaning 4.8% within 48 hours [58] and 7.6-10% within 90 days (including TIA and systemic embolism) [59,60]. Interestingly, only half of them recurs as the same subtype (e.g., cardioembolism, large arteries atherosclerosis, small vessel occlusion) [61] and the cardioembolic recurrence is associated with the best survival rate [61]. In the real world about 32% of patients with AF are treated with an inappropriate dose of DOACs, particularly undertreated [62]. Older and riskier patients more frequently receive a wrong low-dose DOAC without a renal indication for dose reduction [63]. Initiation of an anticoagulant in the first few days after stroke could prevent ischemic stroke recurrence but might increase the risk of symptomatic intracranial hemorrhage, including hemorrhagic transformation of the infarct (estimated at about 9% in the first 7 days) [64], leading to clinical uncertainty about when to start anticoagulation. Optimal timing of anticoagulation following an acute ischemic stroke or TIA is unknown [8]. To date, differently from aspirin, RCTs have failed to produce any evidence supporting the administration of heparin, heparinoids or low-molecular-weight heparin in patients with acute ischemic stroke and AF within 48 hours from stroke onset [65-67]. Accordingly, the panel strongly disagreed with switching from low-dose DOAC to heparin. Comparing DOACs to VKAs in this context, explorative data suggest similar efficacy and better safety of DOACs [68,69]. Thus, the experts disagreed with switching from low-dose DOAC to VKA. There is no evidence from RCTs to prefer one DOAC over the other or to switch from one DOAC to another in patients with a history of ischemic stroke under DOAC therapy [8,27]. Recently, Kato et al analyzing a small cohort of patients suffering from ischemic stroke while assuming a DOAC, found that dabigatran 110 mg tended to be changed to other DOAC, rivaroxaban 15 mg tended to remain unchanged, apixaban 2.5 mg tended to be changed to the standard dose

from before the event to discharge [70]. The panel expressed a positive consensus to administer the same DOAC at the standard dose if the lower was inappropriate, but reached no consensus to switch to another DOAC, according to the absence of evidence highlighted by the guidelines [8,27].

Transesophageal echocardiography is the technique of choice before electric cardioversion to search for atrial thrombi if AF lasts for at least 48 hours and the patient is not taking anticoagulants since at least 3 weeks [8]. VKAs are the anticoagulation of choice in this context [8], since no randomized data exist about DOAC therapy in the presence of a left atrial appendage (LAA) thrombus. Some case series deal about thrombus resolution in >95% of cases, with a low but not negligible percentage of persistence and without difference among DOACs [71-75]. Interestingly, more than 40% of patients with LAA thrombosis show persistent clot despite additional extended uninterrupted anticoagulation, independently from the therapy chosen (i.e., DOAC, VKA, change from DOAC to warfarin or vice versa, change among DOACs) [76]. On the other hand, some cases are reported about thrombus resolution changing DOAC [77,78]. Accordingly, the panel did not reach a consensus about the best strategy in the presence of LAA thrombus during DOAC therapy: continue the same DOAC, change therapy to another DOAC or switch to VKA. However, they strongly disagreed with switching to heparin.

Author statement

N Mumoli and G Mascioli were responsible for the study concept and design; N Mumoli, C Amellone, G Antonelli, G Augello, C Cloro, A D'Alleva, L Di Ascenzo, E Imbalzano, R Masala, G Riccioni, E Romeo, L Rossi, G Santoro, E Sciatti, A Tondo, E Toso, E Venturini, E Vizzardi and G Mascioli were responsible for the acquisition of data; N. Mumoli and G Mascioli were responsible for the database handling and updating; N. Mumoli and G Mascioli were responsible for statistical analysis; N. Mumoli and G Mascioli were responsible for the drafting of the manuscript; N. Mumoli and G Mascioli were responsible for interpretation of results; N Mumoli, C Amellone, G Antonelli, G Augello, C Cloro, A D'Alleva, L Di Ascenzo, E Imbalzano, R Masala, G Riccioni, E Romeo, L Rossi, G Santoro, E Sciatti, A Tondo, E Toso, E Venturini, E Vizzardi and G Mascioli were responsible for critical revision of the manuscript for important intellectual content. All authors had full access to the data and the accuracy of the data analysis.

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.

2. Patel MR, Mahaffey KW, Garg J, Pan G, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365: 883-891.

3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.

4. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-104.

5. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67: 401-9.

6. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32:1008-15.

7. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic cri-teria and guideline development. Semin Arthritis Rheum. 2011; 41: 95-105.

8. Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-962.

9. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.

10. Raparelli V, Proietti M, Cangemi R, et al. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thromb Haemost. 2017;117(2):209-218.

11. Caldeira D, Vaz-Carneiro A, Costa J. The impact of dosing frequency on medication adherence in chronic cardiovascular disease: systematic review and meta-analysis. Rev Port Cardiol. 2014;33(7-8):431-7.

12. Andrade JG, Krahn AD, Skanes AC, et al. Values and Preferences of Physicians and Patients With Nonvalvular Atrial Fibrillation Who Receive Oral Anticoagulation Therapy for Stroke Prevention. Can J Cardiol. 2016;32(6):747-53.

13. Prins MH, Guillemin I, Gilet H, et al. Scoring and psychometric validation of the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). Health Qual Life Outcomes. 2009;7:30.

14. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124.

15. Jackson LR 2nd, Kim S, Fonarow GC, Freeman JV, et al; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Patients and Investigators. Stroke Risk and Treatment in Patients with Atrial Fibrillation and Low CHA_2DS_2-VASc Scores: Findings From the ORBIT-AF I and II Registries. J Am Heart Assoc. 2018;7(16):e008764.

16. Patti G, Cavallari I. Patients with atrial fibrillation and CHA_2DS_2-VASc score 1: "To anticoagulate or not to anticoagulate? That is the question!". Heart Rhythm. 2015;12(12):2515-20.

17. Patti G, Lucerna M, Pecen L, et al. Thromboembolic Risk, Bleeding Outcomes and Effect of Different Antithrombotic Strategies in Very Elderly Patients With Atrial Fibrillation: A Sub-Analysis From the PREFER in AF (*PRE*vention o*F* Thromboembolic Events-*E*uropean *R*egistry in *A*trial *F*ibrillation). J Am Heart Assoc. 2017;6(7).

18. Kato ET, Goto S, Giugliano RP. Overview of oral antithrombotic treatment in elderly patients with atrial fibrillation. Ageing Res Rev. 2019;49:115-124.

19. Fumagalli S, Said SAM, Laroche C, et al; EORP-AF Investigators. Age-Related Differences in Presentation, Treatment, and Outcome of Patients With Atrial Fibrillation in Europe: The EORP-AF General Pilot Registry (EURObservational Research Programme-Atrial Fibrillation). JACC Clin Electrophysiol. 2015;1(4):326-334.

20. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and Safety of Edoxaban in Elderly Patients With Atrial Fibrillation in the ENGAGE AF-TIMI 48 Trial. J Am Heart Assoc. 2016;5(5).

21. Andreotti F, Rocca B, Husted S, et al; ESC Thrombosis Working Group. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2015;36(46):3238-49.

22. Capranzano P, Miccichè E, D'Urso L, et al. Personalizing oral anticoagulant treatment in patients with atrial fibrillation. Expert Rev Cardiovasc Ther. 2013;11(8):959-73.

23. Coleman CI, Antz M. Real-world evidence with apixaban for stroke prevention in patients with nonvalvular atrial fibrillation in Germany: a retrospective study (REASSESS). Intern Emerg Med. 2017;12(3):419-422.

24. Nielsen PB, Skjøth F, Søgaard M, et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2017;356:j510.

25. Yao X, Shah ND, Sangaralingham LR, et al. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol. 2017;69(23):2779-2790.

26. Steinberg BA, Shrader P, Thomas L, et al; ORBIT-AF Investigators and Patients. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol. 2016;68(24):2597-2604.

27. Steffel J, Verhamme P, Potpara TS, et al; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330-1393.

28. Mahmoud SH, Shen C. Augmented Renal Clearance in Critical Illness: An Important Consideration in Drug Dosing. Pharmaceutics. 2017;9(3).

29. Tomasa Irriguible TM. Augmented renal clearance: Much more is better? Med Intensiva. 2018;42(8):500-503.

30. Del-Carpio Munoz F, Yao X, Abraham NS, et al. Dabigatran Versus Warfarin in Relation to Renal Function in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2016;68(1):129-31.

31. Lindner SM, Fordyce CB, Hellkamp AS, et al; ROCKET AF Steering Committee and Investigators. Treatment Consistency Across Levels of Baseline Renal Function With Rivaroxaban or Warfarin: A 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) Analysis. Circulation. 2017;135(10):1001-1003.

32. Fanikos J, Burnett AE, Mahan CE, Dobesh PP. Renal Function Considerations for Stroke Prevention in Atrial Fibrillation. Am J Med. 2017;130(9):1015-1023.

33. Weir MR, Kreutz R. Influence of Renal Function on the Pharmacokinetics, Pharmacodynamics, Efficacy, and Safety of Non-Vitamin K Antagonist Oral Anticoagulants. Mayo Clin Proc 2018;93(10):1503-1519.

34. Lee SR, Choi EK, Han KD, et al. Edoxaban in Asian Patients With Atrial Fibrillation: Effectiveness and Safety. J Am Coll Cardiol. 2018;72(8):838-853.

35. Yu HT, Yang PS, Kim TH, et al. Impact of Renal Function on Outcomes With Edoxaban in Real-World Patients With Atrial Fibrillation. Stroke. 2018;49(10):2421-2429.

36. Lee SR, Choi EK, Han KD, et al. Comparison of Once-Daily Administration of Edoxaban and Rivaroxaban in Asian Patients with Atrial Fibrillation. Sci Rep. 2019;9(1):6690.

37. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. Circulation. 2016;134(1):24-36.

38. Vranckx P, Valgimigli M, Heidbuchel H. The Significance of Drug-Drug and Drug-Food Interactions of Oral Anticoagulation. Arrhythm Electrophysiol Rev. 2018;7(1):55-61.

39. Lip GY, Huber K, Andreotti F, et al; European Society of Cardiology Working Group on Thrombosis. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/ stenting. Thromb Haemost. 2010;103(1):13-28.

40. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010;170(16):1433-41.

41. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol. 2007;49(12):1362-8.

42. Chhatriwalla AK, Amin AP, Kennedy KF, et al; National Cardiovascular Data Registry. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. JAMA. 2013;309(10):1022-9.

43. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J. 2011;32(15):1854-64.

44. Capodanno D, Angiolillo DJ. Management of antiplatelet and anticoagulant therapy in patients with atrial fibrillation in the setting of acute coronary syndromes or percutaneous coronary interventions. Circ Cardiovasc Interv. 2014;7(1):113-24.

45. Dewilde WJ, Oirbans T, Verheugt FW, et al; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381(9872):1107-15.

46. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016;375(25):2423-2434.

47. Cannon CP, Bhatt DL, Oldgren J, et al; RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017;377(16):1513-1524.

48. Lopes RD, Heizer G, Aronson R, et al; AUGUSTUS Investigators. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med. 2019;380(16):1509-1524.

49. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet. 2019 Sep 2. pii: S0140-6736(19)31872-0. doi: 10.1016/S0140-6736(19)31872-0. [Epub ahead of print]

50. Lopes RD, Hong H, Harskamp RE, et al. Safety and Efficacy of Antithrombotic Strategies in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A Network Meta-analysis of Randomized Controlled Trials. JAMA Cardiol. 2019 Jun 19. doi: 10.1001/jamacardio.2019.1880. [Epub ahead of print]

51. Testa S, Paoletti O, Legnani C, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. J Thromb Haemost. 2018;16(5):842-848.

52. Coleman CI, Antz M. Real-world evidence with apixaban for stroke prevention in patients with nonvalvular atrial fibrillation in Germany: a retrospective study (REASSESS). Intern Emerg Med. 2017;12(3):419-422.

53. Yao X, Shah ND, Sangaralingham LR, et al. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol. 2017;69(23):2779-2790.

54. Barra ME, Fanikos J, Connors JM, et al. Evaluation of Dose-Reduced Direct Oral Anticoagulant Therapy. Am J Med. 2016;129(11):1198-1204.

55. Steinberg BA, Shrader P, Thomas L, et al; ORBIT-AF Investigators and Patients. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol. 2016;68(24):2597-2604.

56. Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. Stroke. 1983;14(5):688-93.

57. Kelley RE, Berger JR, Alter M, Kovacs AG. Cerebral ischemia and atrial fibrillation: prospective study. Neurology. 1984;34(10):1285-91.

58. Saxena R, Lewis S, Berge E, et al. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. Stroke. 2001;32(10):2333-7.

59. Paciaroni M, Agnelli G, Falocci N, et al. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. Stroke. 2015;46(8):2175-82.

60. Abdul-Rahim AH, Fulton RL, Frank B, et al; VISTA collaborators. Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: analysis from VISTA. Eur J Neurol. 2015;22(7):1048-55.

61. Toni D, Di Angelantonio E, Di Mascio MT, et al; PRoFESS Study Group. Types of stroke recurrence in patients with ischemic stroke: a substudy from the PRoFESS trial. Int J Stroke 2014;9(7):873-8.

62. Ruiz Ortiz M, Muñiz J, Raña Míguez P, et al; FANTASIIA study investigators. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. Europace. 2018;20(10):1577-1583.

63. Yao X, Shah ND, Sangaralingham LR, et al. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol 2017;69(23):2779-2790.

64. Wilson D, Ambler G, Banerjee G, et al; Clinical relevance of Microbleeds in Stroke (CROMIS-2) collaborators. Early versus late anticoagulation for ischaemic stroke associated with atrial fibrillation: multicentre cohort study. J Neurol Neurosurg Psychiatry. 2019;90(3):320-325.

65. [No authors listed] The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997;349(9065):1569-81.

66. Whiteley WN, Adams HP Jr, Bath PM, et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. Lancet Neurol. 2013;12(6):539-45.

67. Paciaroni M, Agnelli G, Falocci N, et al. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) Study. J Am Heart Assoc. 2017;6(12).

68. Yoshimura S, Koga M, Sato S, Todo K, et al; SAMURAI Study Investigators. Two-Year Outcomes of Anticoagulation for Acute Ischemic Stroke With Nonvalvular Atrial Fibrillation - SAMURAI-NVAF Study. Circ J. 2018;82(7):1935-1942.

69. Seiffge DJ, Paciaroni M, Wilson D, et al; CROMIS-2, RAF, RAF-DOAC, SAMURAI, NOACISP LONGTERM, Erlangen and Verona registry collaborators. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. Ann Neurol. 2019;85(6):823-834.

70. Kato Y, Hayashi T, Tanahashi N, Takao M. The Dose of Direct Oral Anticoagulants and Stroke Severity in Patients with Acute Ischemic Stroke and Nonvalvular Atrial Fibrillation. J Stroke Cerebrovasc Dis. 2018;27(6):1490-1496.

71. Saito S, Shindo S, Tsudaka S, et al. Resolving Thrombus in the Left Atrial Appendage by Edoxaban Treatment after Acute Ischemic Stroke: Report of 2 Cases. J Stroke Cerebrovasc Dis. 2016;25(10):e188-91.

72. Frenkel D, D'Amato SA, Al-Kazaz M, et al. Prevalence of Left Atrial Thrombus Detection by Transesophageal Echocardiography: A Comparison of Continuous Non-Vitamin K Antagonist Oral Anticoagulant Versus Warfarin Therapy in Patients Undergoing Catheter Ablation for Atrial Fibrillation. JACC Clin Electrophysiol. 2016;2(3):295-303.

73. Whiteside HL, Nagabandi A, Brown K, et al. Prevalence and clinical characteristics associated with left atrial thrombus detection: Apixaban. World J Cardiol. 2019;11(2):84-93.

74. Wu M, Gabriels J, Khan M, et al. Left atrial thrombus and dense spontaneous echocardiographic contrast in patients on continuous direct oral anticoagulant therapy undergoing catheter ablation of atrial fibrillation: Comparison of dabigatran, rivaroxaban, and apixaban. Heart Rhythm. 2018;15(4):496-502.

75. Bertaglia E, Anselmino M, Zorzi A, et al. NOACs and atrial fibrillation: Incidence and predictors of left atrial thrombus in the real world. Int J Cardiol. 2017;249:179-183.

76. Wu MS, Gabriels J, Khan M, et al. Left atrial thrombus despite continuous direct oral anticoagulant or warfarin therapy in patients with atrial fibrillation: insights into rates and timing of thrombus resolution. J Interv Card Electrophysiol. 2018;53(2):159-167.

77. Sun H, Zhao Q, Wang Y, et al. Dabigatran as an alternative for atrial thrombosis resistant to rivaroxaban: A case report. Medicine (Baltimore). 2018;97(51):e13623.

78. Koyama T, Otsuka Y, Kawahara M, et al. A left atrial appendage thrombus that developed during prophylactic low-dose dabigatran treatment resolved after switching to apixaban. Clin Case Rep. 2017;5(5):711-713.