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Clinical conundrums in antithrombotic therapy management: A Delphi Consensus panel

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ABSTRACT

Background: Anticoagulants are recommended for the prevention of stroke/systemic embolism for most patients with atrial fibrillation (AF) and for the treatment of patients with venous thromboembolism (VTE). Regulatory-driven randomized trials, however, typically exclude extreme patient scenarios involving, for instance, severe bleeding, ischaemic risk, frailty or renal impairment, despite their common occurrence in clinical practice. Uncertainty in the management of such cases leads to a high degree of variability in therapeutic approaches. Consensus conferences or panels may provide insights and help bridge the gaps that separate clinical guidelines from real-world practice. In the present study, a description of challenging AF and VTE patients was submitted to a large panel of experts to investigate areas of common or divergent management.
Method: A modified-Delphi method was used to obtain consensus among 178 Italian AF and VTE specialists. A questionnaire was sent on the appropriateness of anticoagulant therapy in AF and VTE cases, including CHA_2DS_2-VASc = 1, comorbid coronary artery disease, frailty, advanced age, risk of falling, prior haemorrhagic stroke, and low- or intermediate-risk pulmonary embolism. Strategies to improve guideline adherence were also investigated.
Results: All participants completed the questionnaire. Consensus was reached on many, but not all cases, leaving uncertainty on some debated topics (conundrums) where decisions are unsupported by clinical studies or driven by controversial results.
Conclusions: The indications emerging from this large panel of experts may help guide the management of challenging AF or VTE cases. Studies are needed addressing treatment options in those cases for whom no consensus was reached.

1. Introduction

Current guidelines recommend anticoagulant therapy for the prevention of stroke/systemic embolism in most patients with atrial fibrillation (AF) and for the treatment and secondary prevention of venous thromboembolism (VTE). In routine clinical practice, however, therapeutic decisions are often challenging because evidence from clinical trials is not always available for selected groups of patients, such as those with high risk of bleeding, multiple comorbidities, or receiving potentially interfering drugs [1,2].

Consensus methods gather the opinion of experts to obtain a formal agreement on debated topics. When evidence-based medicine (EBM) does not provide a clear answer to a clinical problem, consensus methods may enhance decision-making and support expert opinion guidelines [3]. Several methods have been developed, including the nominal group technique, the Delphi technique, and the National

Abbreviations: AF, atrial fibrillation; PE/VTE, pulmonary embolism and venous thromboembolism; EBM, Evidence Based Medicine; RCT, Randomized Controlled Trial; NOAC, Non-vitamin K antagonist oral anticoagulant; ACS/DES, acute coronary syndrome/drug eluting stent; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke-vascular disease, age 65–74 years, sex category; sPESI, pulmonary embolism severity index score; SmPC, summary of product characteristics.

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Institutes of Health consensus development conference methodology. Delphi panels are characterized by a large number of participants without the need for face-to-face contacts [4].

Here, we report the results of a Delphi Consensus panel that was organized to address multiple unanswered questions related to the clinical management of difficult cases of patients with AF or VTE.

2. Methods

2.1. Delphi participants

We used a modified Delphi method [5] to reach consensus in a voting panel of 178 medical doctors from different specializations (Internists, Pneumologists, Geriatricians, Cardiologists and Neurologists) with a large experience in prescribing oral anticoagulation for AF or VTE (see full list of participants provided in Ref [6]).

2.2. Delphi method

The method aims to reach the best estimate of consensus and to provide expert recommendations on controversial topics [5]. Each expert freely, individually, and anonymously delivers his/her opinion, generally through one or more rounds of discussion. After each round, an administrator provides a summary of the experts' answers and their rationale. The process ends when an agreement has been reached on the discussed topic.

2.3. Selection of Delphi questionnaire statements

After a careful review of the literature, a restricted steering committee formed by the five authors representing multiple specializations as job setting and professional education, selected 7 controversial topics in AF and VTE antithrombotic management, as follows:

1. AF in a recent acute coronary syndrome-drug eluting stent (ACS-DES) patient at moderate-high bleeding risk;
2. Recurrent AF in an elderly patient with impaired renal function;
3. A challenging CHA_2DS_2 VASc (congestive heart failure, hypertension, age ≥ 75, diabetes, prior stroke, vascular disease, age 65–74, sex category) = 1 case;
4. AF with prior hypertension-associated haemorrhagic stroke;
5. AF in a patient at high risk of falling;
6. Hemodynamically stable patient with pulmonary embolism;
7. Moderate risk pulmonary embolism in a frail lady;

Each statement was declined in 4 or more items, and each expert expressed his/her level of agreement according to the following 5-point Likert scale: 1 = absolutely disagree, 2 = disagree, 3 = agree, 4 = more than agree, 5 = absolutely agree. Consensus was reached when the sum of items 1 and 2 (Disagree) or 3, 4 and 5 (Agree) reached 66%. Where no consensus was reached the results were shown as Neither Disagree/Nor Agree (ND/NA), with ND standing for the sum of items 1 and 2 and NA as the sum of items 3, 4 and 5.

2.4. Delphi rounds

An information letter by the steering committee was sent to the 178 participants outlining the aims and the study procedure. Panel members were then contacted to perform an online questionnaire through a web platform. To limit the chance of bias or influence by the other specialists' opinions, the answers were anonymous. Based on a summary of the scores received, all items were ranked by the steering committee in a single Delphi round.

Then, the experts participated in a plenary session held in Mestre, Italy, on October 5th 2016, where the results were presented and discussed; this part of the process was supported by an unrestricted grant supplied by Daiichi Sankyo Italy. Agreement was reached on most - but not all - items. In case of no agreement, a second round of voting was purposely not performed in order to highlight the inconsistencies of opinion or the insufficient information of evidence-based literature on the therapeutic options for certain AF/VTE patients.

3. Results

As first round of the survey all 178 participants completed the questionnaire for all 7 statements.

Statement 1: AF in recent ACS-DES at moderate-high bleeding risk (Table 1). The 178 members of the panel were asked which therapy to prescribe "in an 80 year old AF patient, with ACS and DES 6 months ago, and HAS-BLED = 3 (current therapy: aspirin and NOAC)". The panel considered continuing aspirin and NOAC as the most appropriate therapeutic approach (84% positive consensus, item 3). They disagreed with stopping the NOAC and continuing aspirin alone (98% disagreement, item 1) or with replacing the NOAC with warfarin (86% disagreed, item 4). No consensus was achieved on the hypothesis of reducing the NOAC dose and continuing aspirin, regardless of the summary of product characteristics (SmPC) indications (44% ND/56% NA, item 2). See Fig. 1A and Table 1 in Ref [6].

Table 1
In an 80 year old AF patient, with recent ACS-DES and HAS-BLED = 3 (current therapy: aspirin and NOAC), I would:

	1	2	3	4	5	Tot.
1. Discontinue NOAC and continue aspirin.	154	20	3	0	1	**178**
	98%		**2%**			
2. Regardless of the SmPC indications, reduce the NOAC dose and continue aspirin.	26	52	34	42	24	**178**
	44%		**56%**			
3. Continue both aspirin and NOAC.	9	20	36	48	65	**178**
	16%		**84%**			
4. Continue aspirin and replace the NOAC with warfarin.	94	59	15	6	4	**178**
	86%		**14%**			

Statement 2: Recurrent AF in an elderly patient with impaired renal function (Table 2). The panel, when asked how to manage "recurrent AF in an elderly patient with renal impairment", agreed on using warfarin for creatinine clearance of 30 ml/min glomerular filtration rate (74% agreement, item 4). It reached a negative consensus (that is, it fully disagreed) for all the other items concerning the use of a NOAC without information on renal function (83% disagreed), of a NOAC at low doses independently of clinical variables (86% disagreed), of warfarin independently of renal function (86% disagreed), preferring either warfarin for creatinine clearance >40 ml/min (87% disagreed), or aspirin in the presence of comorbidities (95% disagreed) or reduced mobility (91% disagreed) or HAS-BLED >3 (94% disagreed). See Fig. 1B in Ref [6].

Statement 3: A challenging CHA_2DS_2-VASc = 1, male patient (Table 3). This case was the most controversial. For no more than one episode of AF per year, the panel did not reach consensus for any of the following three items: prescribing no antithrombotic

Table 2
In an elderly patient with recurrent AF and impaired renal function, I would:

	1	2	3	4	5	Tot.
1. Treat with a NOAC, regardless of risk factors and renal function.	92	55	16	9	6	**178**
	83%		**17%**			
2. Treat with a reduced dose of NOAC, regardless of risk factors and renal function.	83	70	11	10	4	**178**
	86%		**14%**			
3. Treat with warfarin, regardless of risk factors and renal function.	92	61	21	1	3	**178**
	86%		**14%**			
4. Treat with warfarin with creatinine clearance of 30 ml/min.	13	33	54	43	35	**178**
	26%		**74%**			
5. Treat with warfarin with creatinine clearance of 40 ml/min.	64	90	15	6	3	**178**
	87%		**13%**			
6. Treat with aspirin, in the presence of comorbidities.	122	47	7	0	2	**178**
	95%		**5%**			
7. Treat with aspirin, in the presence of poor physical autonomy.	115	47	13	1	2	**178**
	91%		**9%**			
8. Treat with aspirin, in the presence HAS-BLED > 3.	120	48	6	3	1	**178**
	94%		**6%**			

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Table 3
In a young patient with paroxysmal AF and CHA2DS2-VASc = 1, I would:

	1	2	3	4	5	Tot.
1. Not prescribe any antithrombotic therapy, if no more than one episode per year.	26	40	46	35	31	**178**
	37%		**63%**			
2. Treat with warfarin, with no more than one episode/year.	109	62	4	3	0	**178**
	96%		**4%**			
3. Treat with a NOAC, if no more than one episode/year.	50	64	37	15	12	**178**
	64%		**36%**			
4. Prescribe antithrombotic therapy only with atrial dysfunction, with no more than one episode/year.	42	66	48	14	8	**178**
	61%		**39%**			
5. Not prescribe any antithrombotic therapy.	40	44	39	27	28	**178**
	47%		**53%**			

treatment (37% ND/63% NA, item 1); prescribing a NOAC (64% ND/36% NA, item 3); prescribing antithrombotic treatment only in the presence of atrial dysfunction (61% ND/39% NA, item 4) intended as transthoracic echocardiographic findings of left atrial dilation, appendage dysfunction or reduction of A wave velocity [7]. There was also no agreement on not prescribing any antithrombotic therapy, regardless of the number of AF episodes/year (47% ND/53% NA, item 5). The option of warfarin treatment, in case of no more than one episode/year, obtained a negative consensus (96% disagreement, item 2). See Fig. 1C and Table 2 in Ref [6].

Statement 4: AF with prior hypertension-associated hemorrhagic stroke (Table 4). In "a patient with a prior hypertension-associated, hemorrhagic stroke 2 years ago, with recently documented AF, with CHA_2DS_2-VASc = 4, and stable blood pressure", the panel agreed to use a NOAC according to the SmPC (89% agreement, item 4). The panel disagreed (negative consensus) with the hypothesis of excluding any antithrombotic treatment (92% disagreement, item 1), or of administering aspirin 100 mg/die (97% disagreement, item 2) or warfarin (84% disagreement, item 3). No consensus was obtained on the options of low dose NOAC therapy, regardless of the SmPC indications (52% ND/48% NA, item 5), or left atrial appendage (LAA) closure without any anticoagulation (39% ND/61% NA, item 6). See Fig. 1D and Table 3 in Ref [6].

Statement 5: AF in a patient at high risk of falling (Table 5). For "AF in a patient with previous episodes of falling" and CHA_2DS_2-VASc = 4, the panel did not consider the risk of falling as a contraindication to an antithrombotic therapy (94% disagreement, item 1). It agreed on

Table 4
In a patient with a prior hypertension-associated, haemorrhagic stroke 2 years ago, with recently documented AF, CHA2DS2-VASc = 4, and stable blood pressure, I would:

	1	2	3	4	5	Tot.
1. Not prescribe any antithrombotic.	119	45	9	2	3	**178**
	92%		**8%**			
2. Prescribe aspirin 100 mg/die.	125	47	6	0	0	**178**
	97%		**3%**			
3. Prescribe warfarin.	81	69	25	3	0	**178**
	84%		**16%**			
4. Prescribe a NOAC, according to the SmPC.	12	7	59	41	59	**178**
	11%		**89%**			
5. Prescribe a NOAC, reducing the dose.	22	71	38	35	12	**178**
	52%		**48%**			
6. Not prescribe any antithrombotic therapy, but recommend LAA closure.	25	45	62	25	21	**178**
	39%		**61%**			

Table 5
In an AF patient with previous episodes of falling and CHA2DS2-VASc = 4, I would:

	1	2	3	4	5	Tot.
1. Not prescribe any antithrombotic therapy, fearing bleeds from further falls.	98	70	8	2	0	**178**
	94%		**6%**			
2. Prescribe aspirin.	116	58	4	0	0	**178**
	98%		**2%**			
3. Treat with warfarin, at INR = 2.0–3.0.	53	65	50	8	2	**178**
	66%		**34%**			
4. Treat with a NOAC, according to the SmPC.	2	23	53	51	49	**178**
	14%		**86%**			
5. Treat with a NOAC, at a lower dose than recommended in the SmPC.	29	67	44	22	16	**178**
	54%		**46%**			

NOAC treatment at full or adjusted dose according to the SmPC (86% agreement, item 4) and excluded aspirin (98% disagreement, item 2) or warfarin (66% disagreement, item 3) as therapeutic options. The hypothesis of a reduced NOAC dose, independently of the SmPC indications, did not reach consensus (54% ND/46% NA, item 5). See Fig. 1E and Table 4 in Ref [6].

Statement 6: Hemodynamically stable, 55 year old patient with pulmonary embolism (Table 6). For a "haemodynamically stable patient with pulmonary embolism", the experts preferred NOAC prescription, both for low (88% of agreement, item 5) and moderate risk patients (85% of agreement, item 6). They agreed on the importance of the simplified pulmonary embolism severity index (sPESI) score (82% agreement, item 1) and of echocardiography in sPESI > 0 cases (66% agreement, item 2) as requirements for any therapeutic decision (the sPESI score attributes 1 point to each of: age > 80 years, oxygen saturation < 90%, systolic blood pressure < 100 mm Hg, heart rate > 110 bpm, history of cancer and chronic cardiopulmonary disease in patients with diagnosed PE). No consensus was reached on the role of brain natriuretic peptide (BNP) and troponin dosing in sPESI > 0 patients (47% ND/53% NA, item 3) to drive the therapeutic decision and on the use of parenteral anticoagulant therapy, regardless of the profile risk (59% ND/41% NA, item 4). See Fig. 1F in Ref [6].

Statement 7: Moderate risk pulmonary embolism in a little, old, frail lady (Table 7). For a "moderate risk pulmonary embolism in a frail old lady" with renal impairment, the majority of experts expressed disagreement on two of the proposed therapeutic strategies, one

Table 6
In a haemodynamically stable, 55 year old patient with pulmonary embolism, I would:

	1	2	3	4	5	Tot.
1. Evaluate the PESI score for any therapeutic decision.	7	25	78	33	35	**178**
	18%		**82%**			
2. Perform an echocardiography in sPESI > 0 cases.	105	69	30	19		**178**
	34%		**66%**			
3. Evaluate BNP and troponin doses to evaluate any therapeutic decision for sPESI > 0 cases.	21	63	60	14	20	**178**
	47%		**53%**			
4. Give parenteral anticoagulant therapy, regardless of the risk profile.	29	76	41	17	15	**178**
	59%		**41%**			
5. Treat with a NOAC, even in low risk patients.	5	16	60	40	57	**178**
	12%		**88%**			
6. Treat with a NOAC in moderate risk patients.	6	20	68	37	47	**178**
	15%		**85%**			

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Table 7
In an 80 year old lady, with low body weight, moderate risk pulmonary embolism, and renal impairment, I would:

	1	2	3	4	5	Tot.
1. Treat with parenteral therapy and warfarin.	24	49	71	25	9	**178**
	41%		**59%**			
2. Treat with parenteral therapy and a NOAC, at full therapeutic dose.	46	85	28	16	3	**178**
	74%		**26%**			
3. Treat with parenteral therapy and a NOAC, at reduced dose, if previously tested.	22	40	59	35	22	**178**
	35%		**65%**			
4. Directly treat with a NOAC, with initial loading dose followed by full therapeutic dose.	31	91	29	18	9	**178**
	69%		**31%**			
5. Directly treat with a NOAC, with initial loading dose followed by reduced dose.	20	59	54	28	17	**178**
	44%		**56%**			

with parenteral anticoagulant therapy followed by full dose NOAC (74% disagreement, item 2), and one with NOAC treatment as a single drug approach, starting with an initial loading dose followed by the full therapeutic maintenance dosage (69% disagreement, item 4). Conversely, the panel did not reach a consensus on the three alternative proposed strategies, that included the use of parenteral anticoagulant therapy followed by warfarin (41% ND/59% NA, item 1) or by a NOAC administered at the lower therapeutic dose (35% ND/65% NA, item 3), and NOAC treatment as a single drug approach with an initial loading dose followed by a reduced maintenance dose (44% ND/56% NA, item 5). See Fig. 1G and Table 5 in Ref [6].

4. Discussion

In 2016, the European Society of Cardiology (ESC) strongly recommended NOACs over vitamin K antagonists (VKA; Class I, level of evidence A) as the preferred oral anticoagulation therapy in AF patients eligible for a NOAC [8]. However, the trials that support EBM often do not provide indications on how to manage peculiar clinical scenarios. In particular, comorbidities such as uncontrolled hypertension, complex haemorrhagic risks, drug interactions, and certain confounding factors, are often exclusion criteria for enrolment in RCTs [9]. This limits the applicability of evidence-based guidelines, leading to underuse of antithrombotic therapy in some AF patients.

The gaps left by EBM may only be bridged by consensus methods. For this reason, the contribution of clinicians, based on their daily practice, is relevant to attenuate guidelines deficiencies. Unlike position papers, consensus methods provide quantitative results on a given topic and gather the opinion of a large group of specialists. The most common consensus methods are the nominal group techniques, the Delphi technique, and the National Institutes of Health consensus development conference. Among these, the consensus development conference lacks formal feedback and has not been used, so far, to generate new criteria sets [10]. The nominal group and the Delphi techniques represent the most reliable consensus methods in healthcare [4].

The Delphi method, in particular, has been widely used to develop therapeutic management indicators for various diseases [3,11], including cardiovascular [12,13]. In the present Delphi analysis, after a careful literature review, cases of AF or VTE of uncertain management were submitted to a panel of 178 specialised clinicians who answered a questionnaire on the appropriateness of antithrombotic strategies. This is the first study of its kind, aimed at obtaining a consensus on complex, real-life AF and VTE cases, where definitive guidelines are not applicable. The results reported here are empowered by the number and variety of participating specialists, providing robust information, from a wide range of clinical perspectives.

In an elderly AF patient, 6 months after ACS-DES, at moderate-high bleeding risk, independently of the antiplatelet agents used in the acute phase of ACS, the panel agreed to continue therapy with a NOAC and aspirin (Table 1), as recommended by the ESC guidelines [8] and by the European Hearth Rhythm Association (EHRA) practical guide [14]. No data are available to justify a switch to a VKA, given the overall higher bleeding and thromboembolic risks compared to NOACs [14]. In the ENGAGE AF-TIMI48 trial, AF patients receiving single antiplatelet therapy in addition to an anticoagulant (VKA or edoxaban) had a similar risk of stroke or systemic embolic event but higher rates of bleeding than those not receiving an antiplatelet [15]. The NOAC edoxaban showed similar efficacy and reduced bleeding compared to warfarin, with or without concomitant single antiplatelet therapy [16]. Moreover, the recent multicentre, randomized, open-label PIONEER AF-PCI trial demonstrated that either a low-dose or a very-low-dose of the NOAC rivaroxaban, combined with one or two antiplatelet agents, was associated with a lower risk of bleeding compared to standard triple therapy with a VKA and two antiplatelet agents. However, although comparable efficacy was found, the trial was undersized to demonstrate noninferior efficacy of the new strategy with a NOAC [17]. The panel's uncertainty on reducing the NOAC dose may be explained by the SmPC indications that differ from the EHRA indication to use NOACs at a low dose [14].

For the elderly AF patient described in the second statement (Table 2), the panel considered all risk factors and renal function as requirements for prescribing antithrombotic therapy. The EHRA practical guide does not recommend NOACs when the estimated creatinine clearance is below 30 ml/min, especially dabigratan [14], although adjusted doses are allowed as per SmPC. Interestingly, the panel showed a clear preference toward warfarin, based on the patient's renal impairment. This is in contrast with a recent meta-analysis, supporting the use of NOACs compared to warfarin, even in old patients, without increasing the risk of bleeding [17]. Another concordant point is the panel's preference for anticoagulation instead of aspirin even in presence of comorbidities, lack of autonomy, or high bleeding risk. This is explained by the results of a RCT showing that, in nonvalvular AF patients, aspirin doubled the risk of stroke/systemic embolism compared to the NOAC apixaban [18]. Interestingly, the 2012 and 2016 ESC AF guidelines exclude the risk of bleeding as a decisive parameter for the choice of antithrombotic therapy [8].

A challenging and controversial topic is whether to prescribe anticoagulation to young male AF patients at low risk of stroke (Table 3). Considering the low ischemic risk for these patients, and the paucity of experimental data, the current guideline recommendations for anticoagulation are graded IIaB [8]. On this basis, the panel expressed a lack of consensus for the items proposed, including NOAC anticoagulation, but clearly excluded warfarin as a treatment option. Some authors recommend anticoagulation for these challenging patients, as suggested by Fauchier's study [19]. However, the panel did not unanimously considered antithrombotic therapy as beneficial, supporting the conclusion of a recent retrospective study of AF patients with CHA_2DS_2-VASc score of 1 [20].

For the case of AF with prior hypertension-associated haemorrhagic stroke (Table 4), the panel unanimously agreed on NOAC treatment, ruling out any other therapeutic option (VKA, aspirin or no treatment). The agreement on these items reflects clinical judgment for this type of patient, which is supported by a Danish registry on restarting anticoagulant treatment after intracranial haemorrhage in AF [21], by the reduction in haemorrhagic stroke rate obtained in all recent RCTs that compared NOACs to warfarin [21,22] and by the real life data of a recent nationwide cohort study [23]. The uncertainty expressed in the last two items of this clinical case (Table 4) reflects the dearth of trials and literature supporting the reduction of NOAC dose (including recent real life prescription database in nationwide cohort studies) [24,25] or LAA closure with no antithrombotic treatment.

Regarding the case of an elderly patient at high risk of falling, with CHA_2DS_2-VASc = 4 (Table 5), given as an example of moderate-to-high stroke risk and to focus the answers of the experts, the panel did not consider the risk of falling as an exclusion criterion for

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antithrombotic therapy; a lower stroke risk score could have induced to be less oriented toward oral anticoagulation. Indeed, a Markov's model sensitivity analysis estimated that a person should fall about 295 times in 1 year for the risks of warfarin therapy to outweigh its benefits, thereby suggesting that older AF patients' propensity to fall is not an important factor in therapeutic decision-making [26]. Despite this, observational data reported the risk of falling and the fear for intracranial haemorrhage (in particular, subdural hematoma) as the most common reasons for not prescribing anticoagulants to AF patients older than 80 years [27]. Since older AF patients at high risk of falling have a greater prevalence of comorbidities such as diabetes which, in turn, contribute to increase their risk of both cardioembolic and bleeding events [28], the panel considered a NOAC preferable to warfarin in this population. In fact, a sub-analysis of the ENGAGE AF-TIMI-48 trial demonstrated that, compared to warfarin, edoxaban reduced the incidence of both strokes/systemic emboli and major haemorrhages to a greater extent in patients at high, than in those at low, risk of falling [29].

The panel also focused the attention on two cases of PE.

The first case of VTE (Table 6) described a hemodynamically stable patient with PE and showed consensus on the relevance of the sPESI score to identify low risk patients and to drive management strategies, especially in low risk patients [2]. Conversely, no consensus was reached on the role of two biomarkers, BNP and troponin, for patient stratification. The recent PEITHO RCT failed to show a net clinical benefit of thrombolytic therapy in patients with intermediate-high risk PE [30]. In these patients, the panel was favourable to prescribe a NOAC as first line anticoagulant therapy, as suggested by ESC guidelines, with grade IB [8]. The other case, of a frail, old lady with moderate PE risk (Table 7), showed a clear heterogeneity in the selected treatment options, with a slight tendency to prefer the use of a NOAC at the reduced therapeutic dose. These agents are recommended for the treatment and the secondary prevention of VTE [8], and in the recently updated guidelines of the American College of Cardiology their use is preferred over the use of VKAs [31,32]. Nevertheless, the fragility of the patient is a challenging factor for clinicians when deciding the appropriate agent and dosage. However, in the meta-analysis of randomized clinical trials by Van Es et al., the clinical benefit of treatment with NOACs was confirmed also in elderly patients and in those with moderate renal failure [33].

Many other points regarding specific subsets of patients situations for NOACs indications remain controversial and evidence based clues on antithrombotic treatment are missing, such as in cancer patients with AF/PE; data from ongoing trials can better indicate the right behaviour in these difficult scenarios.

5. Conclusions

The indications that emerge from the present investigation provide potential therapeutic strategies for difficult AF/VTE cases, based on clinician experience and literature knowledge. The number and variety of contributing specialists empower the results obtained.

Specifically, consensus was achieved on the following points:

In patients with AF, 6 months after ACS/DES, at high risk of bleeding, the preferred therapy is aspirin with a NOAC, according to the SmPC.

In patients with AF and a history of hypertension-related haemorrhagic stroke, at high risk of bleeding and well-controlled blood pressure, a NOAC-based therapeutic option is preferred.

In case of PE diagnosis, management strategies are guided by the sPESI score and echocardiography. Treatment with NOAC is considered as the first choice for patients either at low or at intermediate risk.

In frail elderly patients, NOAC therapy administered according to SmPC is preferred, over VKA, aspirin or no antithrombotic therapy.

Some topics did not reach consensus, such as the use of low NOAC dosages in patients at high risk, the behaviour in patients at CHA2DS2-VASc = 1 and in a "moderate risk pulmonary embolism in a little, old, frail lady". This is not a limitation, but highlights the real conundrums in AF/VTE antithrombotic therapy, as a consequence of the absence of reliable evidence based data. Further studies are necessary to fill the gaps left by RCTs and clinical guidelines for low thromboembolic risk, or fragile and complex AF or VTE patients.

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