Anticoagulation therapy in older patients at risk for syncopal and not-syncopal fall and/or frailty. An AcEMC-GIMSI multidisciplinary consensus document

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Abstract

In aged patients, the most frequent indications for anticoagulation are atrial fibrillation (AF) and venous thromboembolism for stroke and systemic embolism prevention. Despite systemic anticoagulation recommended by current guidelines for patients over 65 years, in clinical practice up to 50 % of elderly patients do not receive maintenance anticoagulation therapy. This is particularly evident in frail subjects at risk of syncopal and not-syncopal fall, fearing intracranial bleeding following a fall. As the risk of bleeding associated with falls is still debated, the boards of the Academy of Emergency Medicine and Care (AcEMC) and the Italian Multidisciplinary Working Group on Syncope (GIMSI), in order to write a consensus document, submitted to a panel of experts eight statement which could represent as many controversial topics for anticoagulant prescription in patients over 75 years. The Delphi method was used to obtain consensus between 15 physicians from different medical specialties; some of them were expert in syncope management and worked in a Syncope Unit. All had experience in prescribing oral anticoagulation. A questionnaire was sent on the appropriateness of oral anticoagulation in eight clinical situations where the risk of fall is present (frailty, cognitive impairment, previous falls, absence of caregiver, chronic renal impairment, non-valvular AF with HAS-BLED score ≥3 or CHA_2DS_2-VASc score ≥3). All experts completed the questionnaire within three rounds and the consensus was reached on many but not all statements, leaving room for debate on some clinical situations. The consensus document gives useful advice for elderly patients' management, who need oral anticoagulant therapy but are at risk of syncopal or not-syncopal fall. Nonetheless, there are some unresolved issues where an individual decision should be taken by the physician in agreement with the patient.

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Introduction

The prevalence of medical conditions at risk of venous or arterial thrombosis increases with age. In elderly patients, the most frequent indications for anticoagulation are atrial fibrillation (AF) and venous thromboembolism (VTE).[1] Current AF guidelines recommend systemic anticoagulation for almost all patients >65 years,[2] but in practice up to 50% of older patients do not receive maintenance anticoagulation therapy.[3] Even if explicitly recommended by the American College of Chest Physicians Evidence-Clinical Practice Guidelines in prevention and treatment of VTE,[4] prophylactic and long-term anticoagulation is under-used in elderly patients. This behavior seems to be based more on the physicians' fear of higher bleeding risk than on objective data.[1] Admittedly, AF and VTE current practice guidelines commonly extrapolate study results from younger and healthier patients rather than from older comorbid patients[5,6] and this greatly affects physicians' reluctance, because evidence from clinical trials in the elderly are unavailable.[7] Hesitancy to prescribe anticoagulants increases in elderly population at risk of syncopal and not-syncopal, fearing intracranial bleeding following a fall. As the risk of bleeding associated with falls on oral anticoagulants is still debated and given the lack of clinical trials involving patients over 75 years, the boards of the Academy of Emergency Medicine and Care (AcEMC) and the Italian Multidisciplinary Working Group on Syncope (GIMSI) appointed a panel of experts and asked them to write a consensus document with the aim to give a way out to unanswered questions on this debated topic. Methodology consisted in obtaining a formal consensus among experts using the Delphi technique.[8]

Materials and Methods

Consensus method

Delphi method was used to reach a consensus, submitting to a panel of experts a questionnaire prepared by the Steering Committee.

Panel of experts

Fifteen physicians from different specialties (internal medicine, emergency medicine, hematology (hemostasis and thrombosis), geriatrics, cardiology, neurology, toxicology and family medicine) formed the panel. Four physicians were expert in syncope and part of a Syncope Unit. All medical doctors had experience in prescribing oral anticoagulation.

Selection of Delphi questionnaire statements

The Steering Committee was formed by experts in syncope and fall, as well as in Delphi method. After literature review, the Steering Committee selected eight statements that could represent as many controversial topics for anticoagulant prescription in patients over 75: i) medium cognitive impairment; ii) severe cognitive impairment; iii) absence of caregiver and with poor therapy compliance; iv) frail subjects with non-valvular atrial fibrillation and with CHA_2DS_2-VASc score ≥3; v) previous falls in the last year; vi) non-valve atrial fibrillation with HAS-BLED ≥3; vii) chronic impaired renal function [around 30 mL/min creatinine clearance (CrCl)]; viii) difficult-to-control isolated systolic hypertension. Each statement was declined in seven items and 5-point of the Likert scale. Each expert expressed the level of agreement as follows: 1= absolutely disagree, 2 = disagree, 3= agree, 4= more than agree, 5 = absolutely agree. The consensus was reached when the sum of the items 1 and 2 (disagree) reached 75% or 3, 4 and 5 (agree) reached 75%.

Delphi rounds

A detailed information letter was sent to every expert, describing scope, method and giving details for every single statement. Attached to the letter was also sent the relevant literature on the topic. Their answers were collected anonymously and data were inserted in an electronic form. The Steering Committee evaluated the items in three Delphi rounds. When a consensus on a single item was reached, it was not repeated in the following rounds.

Abbreviations used for each statement were: oral anticoagulant therapy (OAT); vitamin K antagonist (VKA); direct oral anticoagulants (DOACs). Key: in the tables the red color means agreement reached, while the blue one means agreement not reached

Results

Panel experts participated in all three rounds, the entire questionnaires were completed and the scheduled times were perfectly respected. All statements dealt with common situations involving elderly subjects at risk of syncopal and not-syncopal fall and/or frailty.

Statement 1

Patients over 75 with medium cognitive impairment who need anticoagulation therapy (Figure 1). There was consensus to prescribe anticoagulants; the consensus was very high (93%). The panel considered also DOACs the best approach. There was 100% agreement not to prescribe aspirin as alternative to anticoagulants

Statement 2

Patients over 75 with severe cognitive impairment who need anticoagulation therapy (Figure 2). There was not sufficient consensus (67%) to prescribe anticoagulants, but, if prescribed, there was good agreement on prescribing DOACs (80%) instead of VKA (93%). There was 93% agreement not to prescribe aspirin as alternative to anticoagulants.

Statement 3

Patients over 75 without caregiver and with a poor therapy compliance (Figure 3). In four items (1, 2, 3, 6) no consensus (neither positive nor negative) was achieved by the panel. In particular, only the item 2 approached the 75% cut-off value. There is large agreement not to prescribe low-dose DOACs or aspirin.

			1=absolutely disagree	2	3	4	5=absolutely agree
1.	Not prescribe OAT	n°v	10	4	1	0	0
		%	93*			7	
2.	Prescribe VKA	n°v	3	7	4	1	0
		%	67			33	
3.	Prescribe DOACs	n°v	1	0	4	5	5
		%	7			93*	
4.	Prescribe low-dose DOACs	n°v	8	2	3	2	0
		%	67			33	
5.	Prescribe aspirin	n°v	11	4	0	0	0
		%	100*			0	
6.	No therapy	n°v	9	5	0	0	1
		%	93*			7	
7.	I don't know	n°v	0	0	0	0	0

Figure 1. Consensus level on each item of statement 1. The red color means agreement while the blue one means not agreement. *Consensus obtained in first round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

			1= absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OAT	n°v	4	6	2		3
		%	67			33	
2.	Prescribe VKA	n°v	5	9	1	0	0
		%	93***			7	
3.	Prescribe DOAC	n°v	3	0	5	7	0
		%	20			80***	
4.	Prescribe low-dose DOACs	n°v	6	5	3	1	0
		%	73			27	
5.	Prescribe aspirin	n°v	10	4	0	1	0
		%	93*			7	
6.	No therapy	n°v	1	2	9	1	2
		%	20			80***	
7.	I don't know	n°v	0	0	0	0	0

Figure 2. Consensus level on each item of statement 2. The red color means agreement while the blue one means not agreement. *Consensus obtained in first round; ***Consensus obtained in third round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

			1 = absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OA	n°v	1	9	4	1	0
		%	67			33	
2.	Prescribe VKA	n°v	7	4	3	1	0
		%	73			27	
3.	Prescribe DOACs	n°v	2	4	7	2	0
		%	40			60	
4.	Prescribe low-dose DOACs	n°v	8	6	1	0	0
		%	93*			7	
5.	Prescribe aspirin	n°v	10	4	1	0	0
		%	93**			7	
6.	No therapy	n°v	2	5	6	2	0
		%	47			53	
7.	I don't know	n°v	0	0	0	0	0

Figure 3. Consensus level on each item of statement 3. The red color means agreement while the blue one means not agreement. *Consensus obtained in first round; **Consensus obtained in second round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

Statement 4

'Frail' patients over 75 with non-valvular AF and CHA_2DS_2-VASc score ≥3 (Figure 4). The experts agreed on prescribing anticoagulants. In this subset of patients, the consensus of the panel on using DOACs (obtained in the second round) was very high (93%).

Statement 5

Patients over 75 with previous falls in the last year (Figure 5). The panel agreed on prescribing OAT, not VKA (87%) but rather a DOAC (87%). When the panel was asked about no therapy, no agreement was reached nor negative neither positive. Interestingly, the consensus was obtained in the third round for item 1, 2, 4.

Statement 6

Patients over 75 with non-valvular AF and HAS-BLED ≥3 (Figure 6). The panel reached a high consensus (87%) on prescribing anticoagulant therapy in this group of patients and the indicated drugs were DOACs, according to the Italian Drug Agency (AIFA) indications.

Statement 7

Patients over 75 with chronic impaired renal function (around 30 mL/min CrCl) and need for anticoagulant therapy (Figure 7). Most of the panel experts (93%) believed that the best pharmacological approach should be low-dose DOACs, while the use of VKAs did not achieve full consensus. All responders (100 %) disagree on using aspirin and in any case, there was no agreement on not prescribing any anticoagulant therapy.

			1 = absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OAT	n°v	7	7	1	0	0
		%	93*			7	
2.	Prescribe VKA	n°v	0	11	3	1	0
		%	73			27	
3.	Prescribe DOACs	n°v	0	1	4	7	3
		%	7			93**	
4.	Prescribe low-dose DOACs	n°v	2	6	3	4	0
		%	53			47	
5.	Prescribe aspirin	n°v	11	3	1	0	0
		%	93*			7	
6.	No therapy	n°v	8	7	0	0	0
		%	100*			0	
7.	I don't know	n°v	0	0	0	0	0

Figure 4. Consensus level on each item of statement 4. The red color means agreement while the blue one means not agreement. *Consensus obtained in first round; **Consensus obtained in second round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

			1= absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OAT	n°v	5	7	2	1	0
		%	80***			20	
2.	Prescribe VKA	n°v	4	9	2	0	0
		%	87***			13	
3.	Prescribe DOACs	n°v	1	1	8	5	0
		%	13			87**	
4.	Prescribe low-dose DOACs	n°v	2	11	1	1	
		%	87***			13	
5.	Prescribe aspirin	n°v	12	2	0	1	0
		%	93**			7	
6.	No therapy	n°v	3	6	5	1	0
		%	60			40	
7.	I don't know	n°v	0	0	0	0	0

Figure 5. Consensus level on each item of statement 5. The red color means agreement while the blue one means not agreement. **Consensus obtained in second round; ***Consensus obtained in third round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

Statement 8

'*Frail' patients over 75 who need anticoagulant therapy with difficult-to-control isolated systolic hypertension* (Figure 8). The panel did not achieve the consensus on item 1 (73%), but the treatment with DOACs is however the indication that had the greatest agreement.

			1 = absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OAT	n°v	5	9	0	1	0
		%	93*			7	
2.	Prescribe VKA	n°v	3	11	1	0	0
		%	93**			7	
3.	Prescribe DOACs	n°v	1	1	7	4	2
		%	13			87**	
4.	Prescribe low-dose DOACs	n°v	3	8	3	0	1
		%	73			27	
5.	Prescribe aspirin	n°v	12	2	1		0
		%	93**			7	
6.	No therapy	n°v	5	8	1	0	1
		%	87**			13	
7.	I don't know	n°v	0	0	0	0	0

Figure 6. Consensus level on each item of statement 6. The red color means agreement while the blue one means not agreement. *Consensus obtained in first round; **Consensus obtained in second round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

			1= absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OAT	n°v	10	4	0	1	0
		%	93**			7	
2.	Prescribe VKA	n°v	1	3	9	1	1
		%	27			73	
3.	Prescribe DOACs	n°v	2	9	2	2	0
		%	73			27	
4.	Prescribe low-dose DOACs	n°v	1	0	7	6	1
		%	7			93**	
5.	Prescribe aspirin	n°v	11	4	0	0	0
		%	100**			0	
6.	No therapy	n°v	10	4	0	1	0
		%	93*			7	
7.	I don't know	n°v	0	0	0	0	0

Figure 7. Consensus level on each item of statement 7. The red color means agreement while the blue one means not agreement. *Consensus obtained in first round; **Consensus obtained in second round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

			1 = absolutely disagree	2	3	4	5 = absolutely agree
1.	Not prescribe OAT	n°v	9	2	2	1	1
		%	73			27	
2.	Prescribe VKA	n°v	3	9	3	0	0
		%	80**			20	
3.	Prescribe DOACs	n°v	1	1	6	5	2
		%	13			87**	
4.	Prescribe low-dose DOACs	n°v	5	5	4	1	0
		%	67			33	
5.	Prescribe aspirin	n°v	11	3	1	0	0
		%	93**			7	
6.	No therapy	n°v	8	6	0	0	1
		%	93**			7	
7.	I don't know	n°v	0	0	0	0	0

Figure 8. Consensus level on each item of statement 8. The red color means agreement while the blue one means not agreement. **Consensus obtained in second round; n°v = number of votes; % = % of votes. The yellow labeled columns indicate disagreement, the green ones agreement.

Discussion

Despite the proven benefits of oral anticoagulants in preventing stroke or other thrombotic diseases, many old patients do not receive OAT. The risk of intracranial bleeding as consequence of fall is probably the main reason why patients with indications for anticoagulation do not receive it.[9-14] It was estimated that an individual should have to fall 295 times in 1 year so that the risk of fall-related major bleeding would outweigh the benefit of warfarin in reducing the risk of stroke[15] and therefore, although anticoagulation is associated with a higher risk of bleeding in patients who fall, the absolute risk seems to be small. Despite being at an increased risk of thromboembolic events because of non-valvular AF, frail patients appear less likely to receive adequate OAT compared with non-frail patients.[16-18] Frailty is associated with a higher cardio- and cerebrovascular risk,[19] and net clinical benefit of OAT is higher in frail older patients than in non-frail elderly patients.[20] For this reason, despite the common clinical practice, frail patients have a clear indication to OAT. The same concept may be expressed for older patients with previous fall, who are often frail.[21] For both $CHADS_2$ and CHA_2DS_2-VASc, systemic anticoagulation is recommended for patients with a score of 2 or higher.[22] Numerous large randomized trials have shown that anticoagulation with warfarin reduces the risk of stroke by about two-thirds in patients with AF, and that this benefit extends to the elderly.[23,24] More recently, the oral anticoagulants dabigatran, rivaroxaban, apixaban and edoxaban have been shown to be at least as effective as warfarin with respect to both stroke prevention and major bleeding complications.[10,25,26] In elderly patients, compared to warfarin, DOACs were associated with a lower risk of intracranial hemorrhage and among oral anticoagulants, they seem to be the more favorable choice.[27-30] Nevertheless, the prescription of DOACs is still low.[31] In the management of AF, current USA guidelines recommend a very limited role for aspirin as a single agent while Europeans ones firmly discourage its prescription.[2]

Conclusions

According to the agreements achieved among the panel of experts, the following are the proposed consensus recommendations: i) OAT is strongly recommended in patients >75 years with medium grade cognitive deficit and risk of fall or syncope who have indication for OAT. DOACs are the preferred recommended drugs. When indicated, DOACs should also be the recommended drugs in patients >75 years with severe cognitive deficit; ii) it is reasonable not to administer OAT in case of particularly poor clinical conditions or short life expectancy; iii) OAT is strongly recommended in *frail* patients >75 years with non-valvular AF and CHA_2DS_2-VASc ≥3. DOACs are the preferred recommended drugs; iv) DOACs should be preferred in patients >75 years with non-valvular AF and HAS-BLED ≥3; v) OAT is recommended for antithrombotic prophylaxis in patients >75 years who had falls in the last year. DOACs are the preferred recommended drugs. According to some experts, OAT should not be administered if falls are particularly frequent; vi) no agreement was reached on treatment with OAT or not in case of patients with poor therapy compliance. Thus, in such circumstance, the decision to treat or not is left to physician and patient's wishes; vii) aspirin is not recommended in managing patients who need OAT.

In addition, some of the panel members suggest that, in these frail patients, DOACs anticoagulant level should be measured within the first month of treatment and in case of clinical worsening, comorbidity or possible pharmacological interference.

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