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Implications of the Presence of Frailty Syndrome in Oral Anticoagulation by Atrial Fibrillation: Evaluating the Evidence

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Subject: frailty, geriatrics, primary care.

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ABSTRACT

Introduction: frailty is a geriatric syndrome that identifies individuals with a greater probability of getting sick and suffering secondary events, also in relation to medication. If frail people use anticoagulants may have greater risk of bleeding. We aim to analyze the evidence available on the influence of frailty on anticoagulation in patients with atrial fibrillation.

Materials and methods: a review of the literature was made through a search in Medline Database. Two independent investigators reviewed and selected the articles and resumed the principal topics.

Results: 14 articles were selected. Anticoagulation is safe frail patients with good therapeutic compliance. Most studies support the use of non vitamin K inhibitors due to a lower risk of bleeding.

Conclusions: frail elderly with AF should receive anticoagulation if there isn´t any contraindication. New anticoagulants are preferable to warfarin for their better safety profile. New studies have to be developed to improve level of evidence.

Keywords: atrial fibrilation, anticoagulant theraphy, frailty.

INTRODUCTION:

Atrial fibrillation is one of the most common arrhythmias in the elderly. For every 100000 inhabitants, the prevalence adjusted for age is 596.2 (95% UI, 558.4-636.7) in men and 373.1 (95% UI, 347.9-402.2) in women[1]. Anticoagulant drugs are needed to reduce the risk of stroke, although these medicines can produce an increased risk of hemorrhage, that is greater in elderly patients [2].

The risk of bleeding can be assessed through HASBLED scale, taking into account factors that are very common in the elderly such as hypertension, decreased liver or kidney function or advanced age[3]. This implies a high risk of bleeding in the elderly.

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CHADS2VASC scale calculates patient's risk of stroke. It considers age, hypertension or previous thrombosis among other factors. Therefore elderly´s risk will also be high[4].
Doctors need more criteria for starting anticoagulation therapy or not and frailty can be a overrriding factor[5] as it considers the patient´s general status.
The aim of this study is to review the influence of frailty syndrome oral anticoagulation therapy in the elderly patient with atrial fibrillation (AF)

MATERIALS AND METHODS:

A bibliographic review has been developed about the influence of the presence of frailty in the prescription and side-effects of anticoagulant therapy in atrial fibrillation in the elderly.
Information sources: a Medline search was performed with the terms "oral anticoagulants" and "frailty". Only written in english, spanish o italian articles were selected. No more search parameters were introduced as the number of results obtained was limitated.
Elegibility criteria: a review of the obtained bibliography was made by reading the abstracts, discarding those articles that did not present information on the effects of the prescription of oral anticoagulants in elderly patients with atrial fibrillation, or didn´t met the elegibility criteria.
Study selection: the reading of the title and the abstract of all the results of the search was made, proceeding to read the complete articles that complied the exposed criteria. If the abstract information was not enough to consider the acceptance of the article, it went through a complete examination. The review was made by two independent investigators, resolving the conflicts by consensus. Topics on selected studies were classified as they appeared, in order to summarize the information.
Analysis: a classification and description of the information found was made based on the data that it provides: side effects of the treatment, indications...

RESULTS:

Study selection: the process of study selection is reflected in Figure 1 through a PRISMA diagram. Of the 26 results obtained, only 14 met the eligibility criteria. The criteria for discarding the articles were: one of them was a publication that reproduced the results of another of the articles, one focused on the use of anticoagulants for deep vein thrombosis, one proposed a safety study of an anticoagulant without showing results, eight did not pick up the variable "frailty" and one was not written in any of the selected languages.

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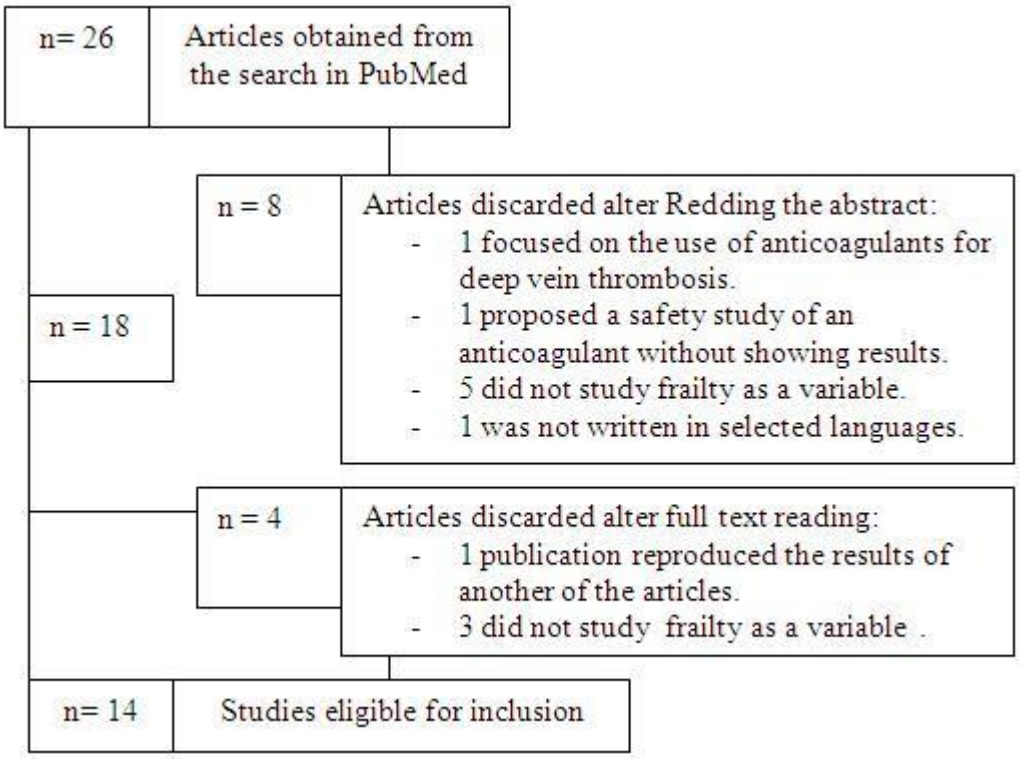

Figure 1.- PRISMA diagram explaining the flow of the studies through the review

Characteristics of the Studies: table 1 summarizes the type of study, the level of evidence provided, the scale of frailty used and the main results of the selected articles. Of the 14 selected studies, 5 of them were written in 2017, 2 were published in 2016 and 4 in 2015.

Author	**Frailty scale**	**Type of study**	**Principal results**	**LI**
Fumagalli et al[6]	Clinical impresion	Experts opinion	- Anticoagulation with non-vitamin K antagonists is preferred. The history of falls was not considered a contraindication.	V
Colonna et al[7]	Not specified	Case series	- In frail patients with FA there is a lower rate of use of anticoagulants.	IV
Wehling et al[8]	Not specified	Bibliographic review	- The evidence supports the use of warfarin or anticoagulants that do not inhibit vitamin K, but highlights the	V

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			absence of specific studies.	
Alboni et al[9]	Not specified	Experts opinión	- In frail patients with AF there is a lower rate of use of anticoagulants.	V
Wilson et al[10]	Not specified	Retrospective	- It does not find differences in the prevalence of adverse events using inhibitors of vitamin K with respect to non-inhibitors.	IV
Annoni et al[11]	Robinson	Case series	- AF is associated with frailty syndrome. Patients with both comorbidities should receive an adjusted anticoagulant treatment	IV
Bo et al[12]	Not specified	Cohort studies	- Anticoagulation in frail patients with AF reduces mortality	IV
Suárez Fernández et al[13]	Clinical impresión / social status	Experts opinion	- Frail patients have an increased risk of bleeding and thrombosis. Frailty does not contraindicate anticoagulation, but it must be monitored. The use of non-vitamin K antagonist drugs is recommended	V
Turagam et al[14]	Fried criteria	Bibliographic review	- Anticoagulation is less used in frail patients, in whom it is recommended to use new anticoagulants. Research on the relationship between frailty and anticoagulation is scarce and should be developed.	V
Lefebvre et al[15]	Clinical Frailty Scale	Cross-sectional	- Frail elderly with AF recieve less anticoagulant drugs. Protocols should be made including frailty.	IV
Granziera et al[16]	Not specified	Experts opinion	- Develops a protocol for anticoagulation in the elderly, taking into account the score on the scales CHADS2VASC and HASBLED. In the case of frail elderly, it recommends (if there are no absolute contraindications) to reduce the anticoagulant dose and / or to closely monitor the anticoagulation process.	V
Denoël et al[17]	Identification of Seniors at Risks	Cross-sectional	- It does not relate a lower rate of anticoagulation rate in AF with frailty, but it does with social conditions and	IV

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	(ISAR)		the lability of INR	
O´Brien et al[18]	Risk of falls	Bibliographic review	- Identifies frailty with risk of falls, and indicates that it is a contraindication for anticoagulation.	V
Ferguson et al[19]	Cognitional / functional status	Bibliographic review	- Stroke risk prediction tools should be expanded taking into account complex geriatric syndromes such as frailty	V

Table 1.- *Resume of the evidence found. LI = level of evidence*

Principal topics described:

a) Use of anticoagulants among elderly frail patients.

Alboni et al point out that anticoagulant therapy is less used in frail elderly than in other population groups. They associate this situation to a greater vulnerability to stressors (including pharmacological treatments), due to the higher risk of falls and consequent hemorrhages and to higher complications rates due to the treatments[9]. This lower use of anticoagulants is further confirmed by Turagam[14] et al, as well as by Lefebvre et al[15]. However, Denoël et al do not detect this situation[17].

b) Initiating anticoagulation therapy.

As Granziera et al comment, decision on initiating oral anticoagulation therapy or not depends on the bleeding and stroke risk of the patient, assesored by HASBLED and CHADS2VASC scales. Only if there is high bleeding risk, poor adherence, the patient is affected by dementia, the caregiver cannot control the use of drugs or when life expectancy is less than 6 months oral anticoagulation is not recommended[16].

Wehling et al indicated that evidence supports the use of warfarin and / or non-vitamin K-inhibiting anticoagulants in the elderly with FA[8]. Annoni et al point out that AF is related to frailty, appearing in up to 85% of frail or pre-frail individuals[11]. They show that the use of anticoagulant therapy is widespread among these patients, although it is more complex and requires an adapted approach in them as they present factors that may affect the safety of anticoagulation such as comorbid conditions (heart failure, dementia, COPD, diabetes, chronic kidney disease, etc.), risk of falls, malnutrition, and polypharmacy. Frailty does not contraindicate anticoagulant therapy, but is a syndrome that forces the patient to follow a more watchful tracing. Frail patients have a higher risk of haemorraghe, but also a higher stroke risk[13].

Bo et al highlight that vulnerable elderly with anticoagulation therapy after AF diagnosis have lower mortality rates than the ones who don´t receive this therapy[12].

c) Use of inhibitors of vitamin K against the use of other anticoagulants

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The studies found mostly talk about the preference of using anticoagulants that do not act through mechanisms dependent on vitamin K due to the lower risk of bleeding, but the level of evidence they provide is low (IV or V), as Suárez Fernández et al stand[13].

However, the data they give may be contradictory. Fumagalli et al do not consider the risk of falls as a factor that should influence the decision on anticoagulation in the frail patient[6]. In contrast, Colonna et al recommend edoxaban in these patients due to studies with this drug have demostrated a lower bleeding risk[7].

Wehling et recommend the use of warfarine or anticoagulants that do not inhibit vitamin K, rejecting therapy with other anticoagulants due to the scarce available evidence. At the same time, they highlight the need to carry out future studies to clarify whether some drugs or others have a better safety profile[8].

Turagam et al. indicate the favorable aspects of the new anticoagulants against vitamin K inhibitors in aspects such as the evolution of cognitive deterioration, pharmacokinetics, fixed dosing, dosage and interactions with diet[14].

d) Side effects of anticoagulant therapy in elderly frail patients.

Several studies foreground the importante of a lower haemorrage risk with the use of new anticoagulants as dabigatran, apixaban, edoxaban[6, 11, 13, 16]… although Wilson et al explain that mortality secondary to bleeding events is similar between the frail old patients that use this drugs and the ones that use vitamina K antagonists[10].

There is no evidence that frailty adds a higher rate of side-effects within this therapy. Nevertheless, almost all the papers studied highlight that more research much be made in order to obtain better scientific evidence[16, 19].

e) Administration guideline of anticoagulant therapy in frail elderly

Some articles attempt to discern if it is necessary to make some adjustment in the administration regimen of anticoagulants in relation to the presence of frailty syndrome[13].

The recommendations present in the available scientific literature are not specific. For example, Annoni et al point out the need to determine the treatment taking into account frailty[11], while other authors recommend monitoring the occurrence of adverse events in a more intensive manner among frail people[19].

By the moment, anticoagulant therapy must be prescribed without any adjustment but the ones specified by the laboratories that commercialize it, taking into account dosage, renal function or other conditions. Granziera et al suggest considering lower doses of this drugs in some frail patients after global geratric assesment[16]. However, frailty must be further studied as a factor that can modify this drug´s prescription[15].

DISCUSION.

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The adequate prescription of drugs in the elderly is one of the most relevant topics at present. Multimorbidity is one of the most important factors that contribute to polipharmacy, and might be influenced also by geriatric syndromes and other conditions. The iatrogenic effects of treatments are responsible for a significant number of health events[20]. The severity of bleeding secondary to the use of anticoagulant therapies allows us to warn the relevance of considering whether they are adequately prescribed in the frail elderly, that is, if the potential benefits outweigh the risks assumed when applying them[18].

Currently several tools are used to improve deprescription in the elderly. These include the STOPP / START criteria and the Beers criteria.

They indicate the contraindication of anticoagulant therapy in cases of high risk of bleeding[21]. The literature reviewed makes us affirm that frailty does not seem to be associated with an increased risk of hemorrhage due to the use of these drugs[10]. This statement has some nuances. First, the level of evidence from the studies is low in the absence of randomized clinical trials. Secondarily, there are several studies that recommend the use of new anticoagulants in frail elderly because these drugs have a lower risk of bleeding than vitamin K antagonists[6, 13], as has been demonstrated in clinical trials[22, 23].

Actually there are two predominant strategies when facing the elderly patient with chronic comorbidities such as AF. On the one hand, we can isolate the pathologies and examine the risks and benefits of the treatments for each of them. This is the case of the use of the HASBLED or CHADS2VASC scales, which have proved to be useful tools to identify the risk of bleeding and stroke and to collaborate in the decision on whether or not to initiate anticoagulant therapy[16]. On the other hand, there is a growing tendency to consider the individual as a whole, assuming the presence of transversal conditions that influence all the processes he presents. This is the case of frailty[5]. Both strategies might be complementary.

Limited evidence indicates that frailty syndrome is not a contraindication for anticoagulation in the case of AF[11]. However, increased sensitivity of frail elderly to the side effects of medication can be a condition for adjusting these therapies. Some of the ideas proposed for this adjustment are dose reduction or simplification of dosage[13]. However, although there is some proposal for the protocolization of antiacoagulation in the frail patient with AF, no clinical guidelines have been developed for this purpose[15].

CONCLUSION.

Frailty syndrome is not a contraindication in the establishment of anticoagulation in elderly patients with AF[11]. In fact, this therapy decreases mortality in these patients[12]. However, the level of available evidence is low and it is necessary to develop studies that evaluate the possible impact of the syndrome[19]. Dosage adaptation has been proposed in anticoagulant treatment in frail elderly patients, in order to control the risk of bleeding. Some of the proposals include adjusting the dose and simplifying the administration guidelines[13]. The approach provided by frailty includes a holistic view of the patient instead of dividing the management into various pathologies[5].

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