Oral anticoagulation in primary care

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ABSTRACT

Oral anticoagulant therapy is currently widespread in the population and primary care plays an important role in its control in Spain. Younger populations, such as those in prisons, often require this treatment for reasons other than atrial fibrillation, often in relation to valvular or congenital or acquired hypercoagulability situations. The possibility of obtaining the INR by portable coagulometers has allowed primary care physicians to tackle the indication of this therapy and the control of these patients in coordination with haematology services. The emergence of new therapeutic alternatives (Dabigatran, Rivaroxaban, Apixaban and Edoxaban, the so called "ACOD") has permitted the expansion of options for oral anticoagulation in some cases, since they do not require systematic monitoring of their effect and interact with far fewer drugs than their predecessors, although there are still restrictions by the health authorities on their widespread use. This article reviews the different indications of oral anticoagulant therapy according to the new recommendations as well as the clinical scenarios in which it should be used.

Keywords: prisons; atrial fibrillation; thromboembolism; primary health care; therapeutics; Spain; disease prevention; anticoagulants.

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INTRODUCTION

Since the 1950s, oral anticoagulation therapy (OAT) has become the cornerstone of the prevention and treatment of thromboembolic disease in different favoring clinical contexts. The first to be used were those inhibiting the synthesis of Vitamin K -dependent clotting factors (VKCF) since they enabled a delayed formation of the thrombus. The determination of INR with ready and easy-to use coagulometers has lead throughout the last twenty years to the decentralization of controlling these patients towards their nearest environment: primary care (or prison healthcare in this case). Warfarin and acenocoumarol are the two main drugs currently available in our country although there are other VKCF antagonists (VKA) with different pharmacodynamic yet leading to the same effect. More recently, throughout the last decade, the appearance of new anticoagulants, also known as direct action oral anticoagulants (DAOA) since they act on the last part of the coagulation cascade, more specifically as Factor Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban), or directly as thrombin inhibitors (Dabigatran), has enabled a yet simpler treatment and prevention of thromboembolic disease, since they do not require monitoring and interact with less foods and drugs than VK antagonists.

Throughout recent years, progressive ageing of population and an increased number of indications for the prescription of these drugs have lead to a steady expansion of the population susceptible to being treated with them, specially due to an increased prevalence of Atrial Fibrillation (AF) and the undisputed evidence for the effective prevention of cardioembolic stroke and systemic embolism associated to AF (in the presence of other cardiovascular risk factors).

RATIONALE FOR OUTPATIENT MONITORING OF ORAL ANTICOAGULATION TREATMENT

Throughout recent years several factors have contributed to the progressive involvement of primary care (PC) in the control of these patients, who until

recently were monitored on a monthly basis in specialized haemostasis consultancy services in hospitals. This was inconvenient for patients and lead to the overcrowding of these services, which now can prioritize high risk patients since primary care has taken over the management of low thromboembolic risk patients. This measure has improved access to treatment for many patients, which before due to exclusively logistic reasons was very complex. This is the case of elder patients (frequent candidates for treatment), home-based care or patients hosted in correctional facilities. This has enabled a comprehensive care of patients and intercurrent clinical conditions which is taken up by a sole actor: family doctors. The development of primary care, together with an improved training of physicians and the involvement of nurses has gradually made this possible. As it has been mentioned before, standard monitoring of the effect of VK antagonists by means of INR and portable coagulometers has enabled outpatient procurement of this value. Through computer tools to share results between Primary Care and Specialized Care (hospitals) and the use of formulas for the administration of total weekly dose (TWD) family doctors can easily establish VKCF inhibitor doses and coordinate their work with reference hematologists.

INDICATIONS FOR ANTICOAGULANT THERAPY

The main indication for OAT is the prevention and treatment of thromboembolic disease. In Primary Care, due to the high prevalence of atrial fibrillation (AF), the vast majority of patients are anticoagulated to prevent cardioembolic stroke and systemic embolic events (SEE) associated to this arrhythmia. Nevertheless, for younger populations such as those hosted in correctional facilities, the indications for OAT are very diverse, as shown in Table 1. [1]

Prevention of cardiac embolism

Lone (non-valvular) atrial fibrillation

The terms lone AF or non-valvular AF have been used to refer to AF in the absence of moderate to severe mitral stenosis and artificial heart valves in anly localization. [2]

It is associated with a mortality risk twice as high in women and 1.5 times higher in males, regardless of other diseases. Population ageing and an increased identification of so called silent AF have lead the current prevalence rising over 3% in the general popu-

Table 1. Indications to oral anticoagulation.

INDICATION	*DURATION*	*INR(VKCFI)*
VENOUS THROMBOEMBOLISM (DVT/PE)	• Reversible causes: 3-6 m • Idiopathic: 6-12 months • Persistent or recurrent causes: INDEFINITELY	2-3
HEART VALVE DISEASE		
RHEUMATIC MITRAL VALVE DISEASE *(+ AF or previous embolism or LA > 55mm)*	• Indefinitely	2-3
BIOLOGICAL PROSTHESES	•3 months •3-12 months: if EE •Indefinitely if AF or LA thrombus	2-3
MECHANICAL PROSTHESES	Indefinitely	Mitral: 2.5-3.5 AORTIC: 2-3 *
OTHER HEART DISEASE		
ATRIAL FIBRILLATION **	Indefinitely	2-3
DILATED CARDIOMYOPATHY (if AF or EF <25%)	Indefinitely	2-3
ACS (High risk patients)	1 to 6 months depending on the extension of infarction, type of stents and antiplatelet therapy.	2-3

AVK: en pacientes en tratamiento con cumarínicos TVP: trombosis venosa profunda, TEP: tromboembolismo pulmonar, FA: fibrilación auricular AI : aurícula izquierda, FE fracción de eyección, IAM: infarto agudo de miocardio

* INR 2-3 si: prótesis mecánica en posición aórtica, bivalva St. Jude i v. bivalvas Carbomedics o de disco basculante Medtronic-Hall en ausencia de FA y de crecimiento AI

** Si CHADS ≥ 2 o CHA_2DS_2-VAS_c ≥2 (hombres) o CHA_2DS_2-VAS_c ≥3 (mujeres)

lation. [3, 4] One of every four adults in the European Union will develop this condition at some point, with previsions of between 120,000 and 215,000 new AF cases every year. For 2030, a prevalence of around 14 to 17 million patients is expected in Europe. [5] As previously stated, the presence of AF together with certain cardiovascular risk factors, make patients need OAT to reduce the risk of cardioembolic disease. These factors and overall stroke risk are collected in the CHA_2DS_2-VAS_c score (Table 2). [6]

This score was designed to consider "minor" factors which increased the risk of cardioembolic events and which the previous score ($CHADS_2$) did not include. A score of 2 or higher in male patients and 3 in females corresponds to a greater annual risk and anticoagulation is indicated in these cases, unless contraindicated. [7] It is not recommended to initiate OAT for scores of 0 nor 1 in females, while male patients with scores of 1 and female patients with scores of 2, deserve throughout consideration of risk-benefit balance for anticoagulation. The alternative of initiating platelet antiaggregation therapy in these patients as the previous guidelines proposed has now been ruled out due to the new evidence regarding the safety of antiplatelet drugs and new alternatives to VK antagonists. [8]

The objective of antithrombotic therapy in patients with heart valve disease is a reduced incidence of associated thromboembolic disease. OAT in patients with heart valve disease will be initiated with VK antagonists, acenocoumarol or warfarin in our case. New oral anticoagulants are nor indicated in AF associated to heart valve disease.

Native heart valve disease[9]

MITRAL STENOSIS

Systemic embolic events affect between 10 and 20% of patients with mitral stenosis, with annual incidence rates of 5% and mortality rates as high as 16%. The presence of atrial fibrillation in these patients due to an increased size of the left atrium increases the embolic risk by 3 to 7 and this association is so dramatic that in the month following the appearance of AF up to one third of patient's present embolic events. After the first event, recurrence reaches 10% every year. This has lead to the indication of anticoagulant therapy event in the absence of AF (INR 2-3, except for recurrent cases: 2.3-3.5) in patients with mitral stenosis and left atria over 55 mm diameter or with a previous record of embolic events. The presence of valvular calcification in the absence of the other factors is not a criterion for anticoagulation.

MITRAL REGURGITATION

The incidence of embolic events in mitral regurgitation is lower than in mitral stenosis, under 3% every year. This makes that only concurrent AF in these patients justifies the initiation of OAT with coumarin drugs and target INR between 2 and 3.

MITRAL VALVE PROLAPSE

It is a quite common defect which affects around 3-6% of the general population. In the absence of other risk factors, the incidence rate of embolic events is very low which only accounts for oral anticoagulation (INR 2.5-3.5) if the patient has suffered previous cerebrovascular accident (CVA) or AF.

MITRAL VALVE ANNULOPLASTY

Despite a low incidence of embolic events, it is not unimportant, especially during the first three months after valve repair, thus anticoagulation (INR 2-3) is recommended during that period. In the presence of previous CVA, AF or intracardiac thrombi, long-term anticoagulation is also recommended.

AORTIC VALVE DISEASE

Lone aortic valve disease in normal sinus rhythm presents a very low incidence of embolic events, around 1.1% per year many emboli being calcareous. Therefore there is no indication for anticoagulation. OAT should only be initiated with severe left ventricular dysfunction (EF<35%) or upon the appearance of AF.

Prosthetic heart valves[9]

bIOLOGICAL PROSTHESES

Long-term incidence of embolic events is very low, under 3% per year, especially for aortic replacements (under 1% per year). Nevertheless this incidence increases considerably during the first three months after valve replacement, anticoagulation (INR 2-3) thus being recommended during this period. In the presence of previous CVA, AF or intracardiac thrombi, long-term anticoagulation is also recommended.

MECHANICAL VALVE PROSTHESES

The presence of mechanical valves entails a relevant risk for cardiac embolism, anticoagulation thus being indicated indefinitely. An increased risk is observed during the first three months after valve replacement in the case of mitral prostheses and in the presence of other thromboembolic risk factors. Regardless of OAT an annual incidence rate of embolic events of

Table 2. CHA_2DS_2-VAS_c score.

Evaluation of stroke risk in atrial fibrillation: CHA_2DS_2-VAS_c score

Risk Factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Prior stroke /AIT/embolic event	2
Vascular disease*	1
Age 65-74 yrs	1
ex category (female)	1

* Prior myocardial infarction, peripheral artery disease or aortic plaque.

CHA_2DS_2-VAS_c score	Annual CVA risk:
0	Close to none
1	1.3% (1 in every 77)
2	2.2% (1 in every 45)
3	3.2% (1 in every 31)
4	4% (1 in every 25)

2% has been reported. Therefore, we recommend the modification of INR targets to 2.5-3.5. In low risk patients (no AF, nor other thromboembolic risk factors) with certain aortic prostheses (St Jude Medical, On-X, Carbomedics, Medtronic Hall) lower INR targets are recommended (INR 2-3).

Acute coronary syndrome (ACS)

Around 1% of all ACS patients present cardioembolic strokes during their recovery. Several concurrent factors favor this: age, hypertension, AF, previous stroke or reduced ejection fraction. Myocardial infarction (MI) at any localization can cause thrombus formation but particularly extensive anterior MI with dyskinesia is that most frequently associated with thrombus formation. The release of part or all of the thrombus from left chambers can cause embolic stroke and thus, anticoagulation is indicated in the case of intraventricular thrombi or ventricular aneurysm. INR between 2 and 3 is recommended during 1 to 6 months depending of concurrent bleeding risk factors such as the use or one or more antiplatelet drugs. [10]

Prevention of venous thromboembolism (VTE)

Venous thromboembolism is favored by several factors, some modifiable and some not. Venous thromboembolism (VTE) can lead to deep vein thrombosis (DVT) or pulmonary embolism (PE). The objective of OAT in these patients is primary or secondary prevention of these events.

VTE is a common disorder in Primary Care, with an estimated prevalence or around 3% and an incidence of 120 to 180 new cases per every 100,000 inhabitants/year. It can be due to several reasons: prolonged immobility, congenital or acquired coagulation disorders or even spontaneously with no apparent cause (idiopathic or essential). After the first event, OAT should be maintained for 3 to 6 months or until confirmation of VTE resolution and its cause. Nevertheless, the vast majority of patients under OAT in primary care are not first-event patients since hematology services take up first events due to a higher probability or recurrence during the first year and mainly because once OAT is discontinuated, unless there is a very clear cause, patients are subject to a study to determine hypercoagulable states (antithrombin III deficiency, protein C or S deficiency, antiphospholipid syndrome, presence of Factor V Leiden, prothrombin gene mutation, high homocysteine levels…). Patients with non-modifiable risk factors for VTE should undergo treatment indefinitely and most frequently Primary Care takes up OAT monitoring.

CONTRAINDICATIONS TO ANTICOAGULATION

The consequences of thromboembolic disease are usually devastating and in many cases, disabling or mortal. Therefore, the reasons for which a patient should not be anticoagulated have to be clearly justified and the risk-benefit balance should be assessed as to initiate or not.

The contraindications are listed in Table 3. [11, 12]

As to assess bleeding risk (not to contraindicate OAT), HASBLED score is recommended (Table 4) which identifies an acts on potential factors increasing the bleeding risk of anticoagulated patients. A score over 3 has been associated with an increased bleeding risk and efforts should be made in this group to avoid bleeding events (intensified INR controls, discontinuation of gastrolesive drugs, etc). [13, 14]

Table 3. Contraindications to oral anticoagulation

ABSOLUTE
- Hypersensitivity/allergy.
- Pregnancy (VKCF in the first trimester, risk of malformations)
- Active bleeding
- Severe bleeding diathesis
- Recent intracranial hemorrhage

RELATIVE
- Lack of patient cooperation or supervision (cognitive impairment, mental disorder, alcoholism…).
- High probability of frequent and/or severe injuries (gait disorders, syncope, seizures, alcoholism…).
- Pregnancy (VKCF in the third trimester, bleeding risk during labor)
- Severe intestinal malabsorption syndrome
- Bleeding diathesis (thrombocytopenia, hemophilia, leukemia, purpura).
- Recent surgery of the CNS or ophtalmologic
- Active gastroduodenal ulcer
- Hemorrhage of the gastroduodenal, urogenital or respiratory tract in the last 6 months.
- Cerebrovascular hemorrhage between 2 weeks and 2 months ago.
- Pericarditis with pericardial effusion.
- Uncontrolled hypertension (SBP>160mmHg)
- Severe hepatic and/or renal failure
- Threatened abortion or incomplete abortion
- Hemorrhagic retinopathy

Table 4. HASBLED score.

Letter	Clinical Characteristic*	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age > 65)	1
D	Drugs or Alcohol	1 or 2
Maximum Score		9

INR: razón normalizada internacional.

* «Hipertensión» se define como presión arterial sistólica > 160 mmHg. «Función renal alterada» se define como la presencia de diálisis crónica o trasplante renal o creatinina sérica ≥ 200 µmol/1. «Función hepática alterada» se define como enfermedad hepática crónica (p. ej. , cirrosis) o evidencia bioquímica de trastorno hepático significativo (p. ej., bilirrubina > 2 veces el límite superior normal, en asociación con aspartato aminotransferasa/alaninaminotransferasa/fosfatasa alcalina > 3 veces el límite superior normal, etc.). «Sangrado» se refiere a historia previa de sangrado y/o predisposición al sangrado, p. ej. , diátesis, anemia, etc. «INR lábil» se refiere a valor de INR inestable/elevado o poco tiempo en el intervalo terapéutico (p. ej., < 60%). «Fármacos o alcohol» se refiere al uso concomitante de fármacos, como antiplaquetarios, antiinflamatorios no esteroideos, abuso de alcohol, etc.

ORAL ANTICOAGULATION THERAPY. DRUGS

In correctional facilities, in order to void their misuse, anticoagulants are included in the group of directly observed therapy (DOT). This ensures correct treatment adherence, something which is poorly controlled in the general population, where missed doses and overdoses are the most common cause of INR alterations.

There are two groups of oral anticoagulants: VCF inhibitors and DAOAs. We hereby review their main features:

Vitamin K-dependent clotting factors (VKCF) inhibitors [11]

VK antagonists act on the synthesis of Vitamin K- dependent clotting factors, more specifically on factors II, VII, IX, X and proteins C and S. Since Vitamin K is responsible for the transformation of these factors into active proteins, their synthesis acts on the cascade of coagulation and jeopardizes the formation of fibrin, and thus, of the thrombus. This makes all of them susceptible to the antagonist effect of phytomeniadone (Vitamin K).

There are several VK antagonists. Dicoumarol is the original molecule from which several drugs are prepared. Warfarin is most commonly used in English-speaking countries and thus the leading drug in oral anticoagulation publications and most widely spread throughout the world. In Spain, it is available under the name Aldocumar® with 1, 3, 5 and 10mg presentations.

Acenocoumarol is the most widespread oral anticoagulant in Spain. It is called Sintrom® and it has a 4mg and a1mg presentation (Sintrom4® and Sintrom Uno®).

Acenocoumarol and warfarin pharmacokinetics are similar and only differ in onset of action and elimination half-life, which are loner for warfarin (4-5 days in comparison with 2-3 days for acenocoumarol).

There are other molecules such as Fluindione (Previscan®) available in France or Femprocuron and Ethyl acetate with a shorter half-life and available in other European countries.

Patients under VKCF antagonists need periodic controls and continuous adjustment of WTD in accordance with INR values and have several interactions with foods and other medications, therefore affecting these patients' quality of life.

Direct action oral anticoagulants (DAOA) [15, 8, 16, 17, 18, 19]

So called "new oral anticoagulants" (NOAs) or more specifically DAOA are direct inhibitors of thrombin (Dabigatran) or of Factor Xa (Rivaroxaban, Apixaban and Edoxaban) and can be administered in fixed doses which do not require systematic monitoring nor adjustments to ensure their efficacy and safety. Their indications include venous thromboembolism prevention in certain orthopedic surgeries, treatment and prevention of venous thrombosis (DVT and PE) and the prevention of stroke in non-valvular AF (AF in the absence of moderate to severe mitral stenosis and mechanical valve prostheses). Available lab tests do not accurately tell the degree of anticoagulation and this varies according to interdose intervals. Therefore it is necessary to take into account potential although scarce pharmacological interactions and patient renal function. In view of its pharmacokinetics, they are contraindicated in kidney failure with creatinine clearance <15 ml /min (<30 ml /min for Dabigatran) and severe hepatic failure (associated to impaired coagulation). This entails

Table 5. Revision of different DAOC dosage.

Indication	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Prevention of venous thromboembolism in orthopedic surgery: hip/ knee joint replacement	First 110mg /24h Then 220mg /24h DR: First 75mg Then 150mg /24h	10 mg /24h	2.5mg /12h	30 mg /24h
Treatment of DVT/PE and prevention of recurrence	150 /12h	First:15mg/12h Then: 20 c/24h DR: 15 c/24h	First: 10mg/12h Then: 5mg/12h (>6 months :2.5mg /12)	60 mg /24h DR: 30 mg /24h
Prevention of cardioembolic stroke/ systemic EE in patients with AF	150 MG c/12h DR: 110 MG c/12h (75 mg in USA.)	20mg /24h DR: 15mg /24h	t5mg /12h DR: 2,5mg /12h	60 mg /24h DR: 30 mg /24h

DR: Dosis reducida (según riesgo hemorrágico para cada producto)

that depending on the clinical condition of patients more or less regular control tests are needed. All of them count upon at least two different dosage presentations to adapt to each patient's bleeding risk, which will be mainly determined by renal function and for some, by age, weight or the presence of potentiating drugs (Table 5).

Non-inferiority assessments in comparison with Warfarin proved that only Dabigatran 150mg and Apixaban reduced the risk for ischemic stroke while Dabigatran 110mg, Apixaban and Edoxaban reduced the risk for major bleeding. All DAOA significantly reduce hemorrhagic CVA although for the specific case of digestive bleeding, patients under Dabigatran 150mg, Rivaroxaban or Edoxaban 60mg seem to suffer more events than those under warfarin.

DABIGATRAN (Pradaxa®):[16]

It acts very specifically on thrombin, both as a free protein and in the thrombus. It is orally administered, as a fixed dose, once or twice a day according to the indication (for AF always twice a day). It has a rapid onset of action, between 3 and 6 hours. It has an elimination half-life of around 14 to 17 hours and it is 80% renally excreted. In Europe there are two available doses: 110 and 150mg, which are used in accordance with the indication, the presence of potentiating drugs (such as verapamil), age, bleeding risk and renal function. It is contraindicated in severe renal insufficiency (creatinine clearance <30ml/min) and it has not proven interference with other common drugs. Recently, a reversing agent for hospital use has been approved in Europe. Unlike other DAOA, it can be dialyzed.

RIVAROXABAN (Xarelto®)[17]

It is a powerful and selective inhibitor of Factor Xa. It is orally administered at fixed doses once a day (or twice a day in the case of the first weeks of PE and DVT treatment). There are four available doses: 2.5, 10, 15 and 20mg (the two last only authorized for AF) which, as in the previous case, will be used according to the indication and bleeding risk. It contains lactose, it is recommended to take the drug with food and it can be crushed. Peak action is reached 2-4 hours after intake; it has a half-life of 5-9 hours. One third is renally excreted unaltered (the rest is biliary and renally metabolized). It is contraindicated in end-stage renal disease (CrCl<15 ml / min) and it should be carefully used for CrCl between 15 and 30ml/min. Alike other DAOA its anticoagulant effect cannot be accurately quantified but it has proven to prolong activated partial thromboplastin time (aPTT). Currently, there is no available reversing agent but severe bleeding can be subject to treatment with prothrombin complex concentrate (PCC).

APIXABAN (Eliquis®)[18,21]

It is a selective and reversible inhibitor of Factor Xa. It is orally absorbed, it contains lactose and food intake alters its absorption. Peak blood levels are reached 3 hours after and its half-life can range between 8 and 15 hours. It is administered twice a day and there are two available doses: 2.5 and 5 mg, used according to patient bleeding risk. It is contraindicated in end-stage renal disease (CrCl<15 ml / min) and it should be carefully used for CrCl between 15 and 30ml/min. Approximately 25% is renally excreted while the rest is excreted through the digestive tract. The effect on hematological tests is similar as that of Rivaroxaban. It lacks reversing agent: the administration of PCC can be useful in the event of severe bleeding.

EDOXABAN (Lixiana®)[19]

Its mechanism of action also entails direct rapid (1-2 hours) reversible inhibition of Factor Xa and 50% is renally excreted. It does not contain lactose. There are three available doses: 15, 30 and 60mg and it are always administered once a day. The 30mg dose is left for higher bleeding risk patients or those under potentiating treatments (Dronedarone, cyclosporine, and erythromycin). It has been assessed and approved for the prevention of venous thromboembolism and the prevention of cardioembolic stroke in AF. The alteration of hematological tests is apparently similar to that of other Factor Xa inhibitors and it also lacks reversing agent.

Chosing anticoagulants for patients with non-valvular af requiring oral anticoagulation [24]

In view of available data on DAOA efficacy and safety by European regulatory authorities and their potential advantages and disadvantages, the National Health System (NHS) has published the following recommendations regarding the choice of anticoagulant therapy:

Situations where VKCF antagonists are recommended in the NHS setting

- Patients previously treated with VK antagonists and optimal control of INR. For these patients it is not recommended to initiate DAOA.
- New non-valvular AF patients for whom anticoagulation is indicated. For these patients,

it is recommended to initiate VK antagonists except if there is a clear justification for DAOA therapy.
— Valvular atrial fibrillation; VKCK inhibitors are the treatment of choice.

Situations where DAOA can be considered a therapeutic option in the NHS setting

— Patients with known hypersensitivity or specific contraindication for acenocoumarol or warfarin.
— Patients with a record of intracranial hemorrhage (ICH)
— Patients with ischemic stroke and clinical and/or neuroimaging criteria of a high risk of ICH.
— Patients under VK antagonists who suffer from severe thromboembolic events despite optimal control of INR.
— Patients who have initiated treatment with VK antagonists and who do not achieve target INR levels (2-3) despite optimal adherence. Suboptimal control is considered for therapeutic ranges under 65% target levels, as calculated by the Rosendaal method in the last 6 months.
— Impossible access to conventional INR control.

MANAGEMENT OF ORAL ANTICOAGULATION WITH VITAMIN K-DEPENDENT CLOTTING FACTORS INHIBITORS [11, 12]

Initiation of treatment

Upon treatment initiation with coumarin-type drugs, no loading dose is needed and according to the type of drug: acenocoumarol or warfarin, patient age and nutritional status one dose or the other will be used. First INR control will be 4 to 6 days after initiation of treatment:

1.1. When initiating acenocoumarol, 3mg/day (21 mg/w) will be used in patients under 80 years old or 2mg/day (14mg/w) for over 80 years old or malnourished patients, for three days. The first control will be made 4 days after and the second will depend on INR results. If it did not achieve target values it would be 3 or 4 days later and if it did, 6 to 8 days later.

1.2. When initiating warfarin, 5mg/d (35mg/w) will be used in patients under 80 years old or 3mg/day (21mg/w) for over 80 years old or malnourished patients for five days with the first control on the sixth day. The next control will be 5 days later if target values were not achieved and between 6 and 8 days later if it did.

In the first control dosage modification will be applied as exposed in Table 7, by doubling the suggested percentage.

Low molecular weight heparin (LMWH) should be used until target INR values are achieved.

(Table 6)

Continuation of oral anticoagulation with VK antagonists [12]

Target INR values depend on the indication of anticoagulation (as aforementioned between 2 and 3 or between 2.5 and 3.5).

Anyway, acceptable values can be those +/- 10% target values (1.8-3.3). These values will not entail dosage modifications when isolated, yet if repetead they will.

Upon out of range INR values, before modificating the dose, missed doses, doubled doses or changes in common medications, concurrent diseases or diet modifications and alcohol intake should be assessed.

Table 7 resumes the attittude towards different INR values:

Table 7. Attitude towards INR values.

INR value	Strategy	Next control
<1.5	Increase by 20 %	7 days
1.5 – 1.7	Increase by 10 %	14 days
1.8 – 3.2	Same dosage	28 days
3.3 – 4.9	Reduce by 10%	14 days
5.0 – 7.0	Reduce by 20 % dosis Discontinue today's dose	7 days

Table 6. Initiation of Dicoumarol-type treatment.

	<80 yrs	>80 yrs or malnutrition	Days	Control day
Acenocoumarol	3 mg/d (21 mg/w)	2 mg/d (14 mg/w)	3 d	4th d
Warfarin	5 mg/d (35 mg/w)	3 mg/d (21 mg/w)	5 d	6th d

If the INR value is over 7 we should consider whether treatment is with acenocoumarol or warfarin due to different half-life:

2.1.1. Acenocoumarol: Discontinue anticoagulation and new control after 24-48 hours. In the presence of active bleeding administer oral Vitamin K (0.3 to 0.5 cc), if slight with a new control 24 hours later and if moderate or severe pursue urgent assistance.

2.1.2. Warfarin: Always administer Vitamin K (0.3 to 0.5 cc) and pursue urgent consultation in the presence of bleeding. If moderate or severe the patient should be assessed in the ER department and in the case of a slight bleeding a new control will be made 24-48 hours later.

COMPLICATIONS AND SPECIAL SITUATIONS

Missed dose [11, 25, 26]

When a patient misses a dose, it can be taken the same day but later and if forgotten, it will be noted and the next day usual treatment will be continued. If the break day is missed, a break will be taken the next day.

Patients who do not take the same dose every day, when they miss a dose they will correct it the day after.

Pharmacologic and dietetic interactions

VJ antagonists

PHARMACOLOGIC [11]

This group of drugs presents many pharmacologic interactions. Most of the studies are made with warfarin, many conclusions being extrapolated to acenocoumarol.

There are many mechanisms of action: catabolism of clotting factors by thyroid hormones, interference in the synthesis of clotting factors by contraceptives and thyazides, increased hepatic conjugation by thyroid hormones, increased affinity of receptors for thyroid hormones, plasma protein displacement by Sulfonylureas or effect on intestinal vitamin K-producer flora or on its absorption by amynoglucosides.

Anticoagulants can also interfere with the action of other drugs such as sulfonylureas, by increasing the risk of hypoglycemia with its concurrent use.

Generally speaking, before the possibility of any relevant interaction, INR controls should be made every time new medications are initiated, discontinued or modified.

We should consider two different situations: treatment for chronic and acute conditions.

Chronic diseases: we could consider that there are no interactions since before INR alterations we will adjust VKCF inhibitor doses. Due to this, it is recommended to introduce the new drug 3-4 days before the next control so that the dose can be modified if needed. The same will be done upon discontinuation of other medications.

Acute diseases: we will try to administer drugs without any interactions or with as few interactions as possible. Anyway, additional INR controls can be made and doses modified if necessary.

The following Table depicts those drugs without significant interactions.

DIET [11]

The mechanism of action of coumarin-type drugs is to inhibit the activation of Vitamin K-depending clotting factors. This vitamin is obtained from the diet and the production by intestinal flora. If intake changes the efficacy of treatment is modified.

There are studies which prove that vitamin K rich diets (intake over 250 mcg/day) in comparison with controlled intake, substantially decreases INR, therefore increasing thromboembolic risk. This is why patients under VKCF inhibitor therapy are recommended to have a stable intake of vitamin K (65 to 80 mcg/day). Substantial variations of intake can lead to modifications of INR values and thus adjusted doses may be needed.

Chronic alcohol use decreases the effects of warfarin. Upon hepatic disease, this acts as a potentiating factor.

Variations of alcohol intake can jeopardize treatment control. Anyway, there is no basis for eliminating moderate use of alcohol.

HERBAL REMEDIES [11]

Generally speaking herbal remedies are not recommended due to an increased risk of interference, which is most commonly difficult to establish.

Direct action anticoagulants [15, 23]

Unlike VK antagonists, direct action anticoagulants have few pharmacologic and dietetic interactions. Anyhow, we must take into account that these drugs are vulnerable to gp-P and antiXa drugs are

Table 8. Medications recommended with VK antagonists.

Drugs recommended with VKA		
Anti-inflammatory drugs Diclofenac Ibuprofen, fenoprofen Nabumetone Celecoxib, rofecoxib Glucocorticoids	**Antibiotics and antiparasitic drugs** Amoxicillin Amoxicillin+clavulanic acid Cloxacillin Josamycin Ofloxacin Norfloxacin Mebendazole Pipemidic acid	**Antihypertensives** Nifedipine Nitrates (all) Verapamil Atenolol, propanolol Methyldopa Prazosin Captopril, enalapril Irbesartan, losartan Bisoprolol, carvedilol
Analgesics Acetaminophen Dextropropoxyphene Codeine and dihydrocodeine Tramadol	**Antigout drugs** Allopurinol Colchicine	**Cardiotonic drugs, diuretics and others** Cardiac glycosides (all) Diuretics (all) Potassium
Anxiolytics Benzodiazepines	**Antihistamines** All	**Laxatives** Lactulose Glycerine suppositories
Antidepressants Mianserin Amitriptilin Venlafaxin Duloxetin	**Antimigraine agents** Ergotamine Triptans	**Hypoglycemic drugs** Insulins Oral antidiabetics (all except sulfonlylureas)
Antacids: Almagate Magaldrate Pantoprazol	**Antiparkinsonian drugs:** Levodopa Biperiden	**Others:** Biphosphonates Sildenafil Contraceptives
Antitussives Codeine Dextromethorphan	**Antitussives** Codeine	
	Mucolytics Alone, all	
	Bronchodilators All	

partially metabolized by cytochrome P450 3A4. Most interactions are due to this. Gp-P inductors can decrease DAOA plasma concentrations and thus concurrent use of rifampicin, carbamazepine or phenytoin is not recommended.

Gp-P inhibitors can increase DAOA concentrations and should therefore be administered carefully. Imidazole antimycotics (ketoconazole, itraconazole) are contraindicated. Dabigatran is contraindicated in the presence of cyclosporine and tacrolimus.

Patients under protease inhibitors (ritonavir) should not use Dabigatran, Rivaroxaban or Apixaban.

Dabigatran doses will be reduced upon concurrent use of verapamil. Dronedarone increases up to 100% the activity of Dabigatran and its concurrent use is not recommended, as for Rivaroxaban.

Attitude towards bleeding [8, 11, 27, 28]

When initiating OAT although the bleeding risk has already been assessed by means of the HASBLED score, it is important to take measures against factors favoring bleeding.

The attitude towards hemorrhage will depend on the severity and localization of bleeding.

We will consider different types of hemorrhage:

Not significant hemorrhage, small and minor hemorrhage.

3.1.1. Small hemorrhage includes gingival bleeding, nosebleed, cutaneous hematoma, and extensive menstruation. In these cases, close follow up and optional INR control are recommended.

3.2.2. Minor hemorrhage includes non-severe epistaxis, subconjunctival hemorrhage, and spontaneous ecchymosis at non-dangerous localizations. Depending on the severity and localization OAT will be discontinued (VK antagonists or DAOA) one or two days until INR levels drop under 2 and then re-initiated prior INR control.

When discontinuation of treatment is over one day the use of LMWH should be considered.

3.2. Important hemorrhage, non dangerous to life or moderate. Among these we include repeated epistaxis or gingival bleeding, haematuria, big spontaneous ecchymosis, In these cases, INR determination is compulsory for patients under VKCF inhibitor therapy. Support therapy will be administered, fluid replacement, blood transfusion, treatment of the cause (for example by means of gastroscopy) and Vitamin K in the case of VK antagonists or activated carbon if DAOA intake is recent.

3.3. Severe hemorrhage or dangerous to life. Sudden headache or neurological deficits which could be a sign of intracranial hemorrhage, severe digestive hemorrhage (hematemesis or melena), respiratory bleeding (hemoptysis), They are hospital emergencies and symptomatic treatment will be initiated when necessary: IV vitamin K, prothrombin complex concentrates, fresh plasma infusion and platelet replacement.

In the case of DAOA we should consider the use of specific antidotes: Idaricizumab, already available in our country, for Dabigatran or Andexanet alpha for direct Factor Xa inhibitors, still in pre-commercialization phases.

Injectable and vaccines [11, 12, 30]

The route of administration of choice will always be subcutaneous. The intramuscular (IM) route will be avoided if possible. If necessary, the middle of the deltoid muscle or the exterior region of the quadriceps is recommended, not the buttock. The maximum volume will be 3 ml and when further volumes are needed both deltoid muscles will be used.

Previous optimal control of INR is recommended (3 days before) and compressing the injection site for 8 to 10 minutes.

With regard to vaccine administration, the subcutaneous (SC) route is recommended (45 degrees) or the IM route in the deltoid muscle. Anti-flu vaccine can be administered IM with less side effects than when administered SC in a reduced number of patients. [30]

When special medications such as hormones with large needles are needed, prior INR control is recommended and post compression for 15 to 20 minutes should be performed at the site of injection.

Teeth extractions and other dental procedures [11, 12, 32, 33, 34]

As recommended by most of guidelines regarding the management of oral anticoagulants and in the meta-analysis by Yang et al, there is not an increased bleeding risk in patients who are to undergo teeth extractions regardless of the discontinuation of OAT. [31]

In the case of VK antagonists it is necessary to control INR levels 24 hours before the procedure.

For patients under DAOA therapy there is currently not enough data to establish high level evidence-based recommendations. After reviewing available bibliography on the issue, they recommend a maximum of 2 to 3 extractions without OAT discontinuation. They also recommend performing the procedure at least 12 hours after the last dose and taking the next dose around 6 hours later, after ensuring correct hemostasis.

To reduce bleeding at the site of extraction compression should be performed for longer than usual and tranexamic acid will be used. Sometimes hemostatic suture may be needed and compression with tranexamic soaked gauze for 30 minutes.

After the procedure patients are encouraged to rinse their mouths for 2 minutes with tranexamic acid every 6 hours and follow a soft diet and avoid hot food or drinks for at least 48 hours.

OAT with complementary tests and surgery [12, 22, 35]

OAT discontinuation and LMWH bridging therapy was the previously recommended strategy, but latest guidelines only consider this for high thrombotic risk and bleeding risk of the test or surgery. Yet, when the latter is low or moderate, this strategy is less recommended, especially after the publication in August 2015 of the study *Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation* which proved that LMWH bridging therapy in the perioperative setting is not associated with a reduction of stroke and/or systemic embolic events and yet is associated with a significant increased risk of hemorrhage. [36]

To decide what strategy to follow an individual assessment of the thrombotic risk and the bleeding risk should be carried out.

Thrombotic risk can be assessed through the following Table according to the indication for OAT: mechanical valve replacement, non valvular atrial fibrillation or venous thromboembolism.

Table 9. Thrombotic risk stratification.

RISK	Mechanical heart valve	Atrial Fibrillation	Venous thromboembolism
HIGH	Mitral prostheses Aortic ball valves or tilting disc valves Stroke or TIA < 6 m	CHADS > 5 Recent stroke or TIA (< 3 m) Rheumatic heart valve disease	Recent VTE (DVT and/or PE) (< 3 m) High risk thrombophilia
MODERATE	Bileaflet aortic valve associated to 1 or more: -Atrial fibrillation -Heart failure -Stroke/TIA -Diabetes -HTA -> 75 yrs	CHADS>3	VTE < 1 yr Recurrent VTE Other thrombophilias Active cancer (6 last months or palliative treatment)
LOW	Bileaflet aortic valve with no other risk factors	CHADS ≤ 2 (without CVA)	1 sole VTE event >1 yr

Tabla extraída del Protocol de maneig de la TAO amb Fàrmacs antivitamina K, Área Inegral de Salut Barcelona Esquerra, Consorci Sanitari de Barcelona

Bleeding risk associated with surgical procedures is depicted in the following Table.

Table 11 depicts the bleeding risk of the more common endoscopic procedures.

In accordance with the assessment of the corresponding risks we can take the following decisions:

Patients under VKCF inhibitor therapy [12]

Non discontinuation: INR control 24 hours before the procedure to ensure optimal control levels.

Discontinuation and re-initiation: acenocoumarol will be discontinued 3 days before the procedure or 5 days before for warfarin without initiating LMWH. Treatment will be re-initiated the day after the procedure when the bleeding risk is moderate or when appropriate for high bleeding risk procedures. Usual doses will be used and upon day 4 or 6 depending on whether treatment is with acenocoumarol or warfarin, INR controls will be performed. VTE prevention will always be considered 6 to 12 hours after the procedure.

Bridging therapy: Acenocoumarol will be discontinued 3 days before the procedure (5 days before in the case of warfarin) and LMWH will be initiated.

Acenocoumarol will be discontinued on day -5 and on day -3 therapeutic doses of LMWH will be initiated until 24 hours before the procedure and on day +1, if appropriate, acenocoumarol will be re-initiated together with LMWH until optimal INR values are reached from day 4 onwards. Patients under warfarin will discontinue their treatment on day -6 and LMW will be initiated on day -3. The first post-intervention control will be on day +6.

Patients under DAOA therapy [20, 22, 24, 32, 33]

In this case, it is not possible to establish evidence based recommendations. Current recommendations are based on expert recommendations, guidelines published by task force groups or scientific societies.

In the case of direct action oral anticoagulants discontinuation will be associated with the balance between thrombotic and bleeding risks as well as with the patient's renal function.

Non-discontinuation: the procedure can be performed around 12 hours after the last dose and the next will be taken around 6 hours after the procedure.

Discontinuation and re-initiation: for moderate to high bleeding risk procedures, discontinuation is recommended. The time for discontinuation depends on the bleeding risk, the specific drug and the patient's renal function. OAT will be reinitiated once hemostasis has been ensured, 12 to 24 hours after the procedure or even 48 to 72 hours later for very high bleeding risk interventions. Anticoagulation under normal circumstances is established 2 hours after the administration of DAOA. VTE prevention will always be considered 6 to 12 hours after the procedure.

Bridging therapy: Generally speaking, since their elimination half-life is short and the anticoagulant effect rapidly decreases upon discontinuation, LMWH will not be necessary; except for very high thrombotic risk indications (most of DAOA are indicated for low thrombotic risk conditions, since they are contraindicated for valve replacement and not financed in Spain for VTE and PE).

Table 10. Bleeding risk of surgical procedures.

HIGH	Cardiac surgery Neurosurgery Orthopedic surgery Major abdominal surgery Major oncological surgery Lumbar puncture Hepatic biopsy Renal biopsy	Percutaneous nephrostomy Percutaneous nephrolithotomy Major vascular surgery Bladder and prostate surgery Reconstructive surgery Thoracic surgery AF ablation
MODERATE	Pacemaker insertion SVPT ablation Electrophysiological procedures Conization Surgery for urinary incontinence Urethral repair surgery Thoracocentesis, Paracentesis Multiple dental extractions, implants, periodontal surgery, oral surgery	
LOW	Excision of cutaneous lesions Minor penile and scrotal surgery Cataract surgery (with no retrobulbar anesthesia) Dental higiene, gingival curettage, conservative odontology, simple extractions Insertion of central venous catheters Infiltration of soft tissues and peripheral joints FNAB of the thyroid and nodes	

Tabla extraída del Protocol de maneig de la TAO amb Fàrmacs antivitamina K, Área Inegral de Salut Barcelona Esquerra, Consorci Sanitari de Barcelona.

Table 11. Bleeding risk of endoscopic procedures.

HIGH	Colon or gastric polypectomy > 5 mm Laser coagulation or ablation Endoscopic papillotomy Pneumatic dilation of both benign and malign strictures Percutaneous endoscopic gastrostomy (PEG) Ultrasound guided FNAB TUR of the prostate (TURP) TUR of bladder tumors
MODERATE	Transbronchial biopsy Transrectal prostate biopsy Ureteroscopy Laser lithotripsy
LOW	Gastroscopy and colonoscopy Endoscopic biopsy Endoscopic polypectomy < 5 mm (colon or gastric) Diagnostic ERCP and biliary stent implantation (no papillotomy) Endoscopic ultrasounds Diagnostic cytoendoscopy

Tabla extraída del Protocol de maneig de la TAO amb Fàrmacs antivitamina K, Área Inegral de Salut Barcelona Esquerra, Consorci Sanitari de Barcelona.

Table 12. anticoagulation before complementary tests and surgery.

	PROCEDURE		
PATIENT	Low bleeding risk	Moderate bleeding risk	High bleeding risk
Low thrombotic risk	Non discontinuation	Discontinuation and re-initiation	Discontinuation and re-initiation
Moderate thrombotic risk	Non discontinuation	Discontinuation and re-initiation	Discontinuation and re-initiation
High thrombotic risk	Non discontinuation	Bridging therapy	Bridging therapy

Tabla extraída del Protocol de maneig de la TAO amb Fàrmacs antivitamina K, Área Inegral de Salut Barcelona Esquerra, Consorci Sanitari de Barcelona.

Table 13. perioperative DAOA discontinuation intervals depending on drug, bleeding risk and renal function.

Drug	Renal function	CrCl >80		CrCl 50-80		CrCl 50-30		CrCl 30-15	
	Bleeding risk	Low	High	Low	High	Low	High	Low	High
Dabigatran		24 h	48 h	36 h	72 h	48 h	96 h	Contraindicated	
Rivaroxaban, Apixaban, Edoxaban		24 h	48 h	24 h	48 h	24 h	48 h	36 h	48 h

The following Table depicts discontinuation periods for DAOA before procedures depending on bleeding risk, renal function and specific drug. (Table 13)

Switching from VK antagonists to DAOA[15, 33]

Generally speaking, when we need to switch from VK antagonists to DAOA, DAOA will only be initiated with INR levels of 2 or under.

ON the other hand, when we need to switch to VK antagonists, it will depend on whether we are switching from Dabigatran or Factor Xa inhibitors. For Dabigatran we must take into account creatinine clearance: if ≥ 50ml/min acenocoumarol will be initiated 2 days before discontinuation and 3 days before in the case of warfarin. When creatinine clearance ranges between 31 and 50ml/min acenocoumarol will be initiated 1 day before discontinuation (2 days for warfarin). For clearance under 30ml/min Dabigatran will be discontinued and when aPTT is under 2, VK antagonists will be initiated.

For Factor Xa inhibitors, they will be simultaneously administered with VK antagonists, performing INR control two days later. Concurrent administration will be continued until INR is over 2.

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REFERENCES

1. Hirsh J, Guyatt G, Albers G, Harrington R, Schünemann H. American College of Chest Physicians Evidence-Based Cliical Practice Guidelines. CHESt. 2008; 133: p. 71S-109S.
2. Camn A, LIP G, de Caterina R, Savelieval R, Atar D, Hohnloser S, et al. Focused update of the ESC Guidelines for the manegement of atrial fibrilation. European heart Journal. 2012; 33: p. 2719-47.
3. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and autcome of a large contemporary cohort of patients with incident non-valvular atrial fibrilation. J Am Heart Assoc. 2015; 4(e001486).
4. Kishore A, Vail A, Majid A, Dawson J, Lees K, Tyrrell P, et al. Detection of atrial fibrilation after ischemic stroke or transient ischemic attack; a systematic rewew and meta-analysis. Stroke. 2014; 45: p. 520-5.
5. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrilation in the European Union fron 2000 to 2060. Eur Heart J. 2013; 34: p. 2746-51.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refinig clinical risk stratification for predicting stroke an thromboembolism in atrial fibrilation using a novel risk factor-based approach: The Euro Herat Survey on Atrial Fibrilation. Chest. 2010; 137: p. 263-72.

7. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study 2012. Eur Heat J; 33(12).
8. Kirchhooff P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS 2016. Europace. 2016 Nov; 18(11): p. 1609-78.
9. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. A report of American College of Cardiology/American Association Task Forc on Practice Guidelines. J Am Coll Cardiol. 2014; 63(22): p. e-57-e185.
10. Gordon HG, Akl EA, Crowther M, Gutterman D, Schünemann HJ. Antithrombotic Therapy and Prevention of Thrombosis 9th Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2): p. 7s-47s.
11. Enfedaque B, Mourelo M, Sant E, Altirriba J, Aparico P, Ballester MM, et al. Prevenció de la malaltia tromoembòlica en Atenció Primària. Barcelona: SCMFiC; 2014.
12. Area Integral de Salut Barcelona Esquerra, Consorci Sanitari de Barcelona. Protocol de Maneig de la teràpia Anticoagulant Oral amb fàrmacs antivitamina K. Barcelona: Consorci Sanitari de Barcelona; 2016.
13. Pisters R, Lane D, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLES) to assess one-year risk of major bleeding en atrial fibrillation patients: The Euro Heart Survey. Chest. 2010 Nov; 138(5): p. 1093-1100.
14. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLEd score. J Am Coll Cardiol. 2011; (57): p. 173-80.
15. Arellano E, Escolar G. Anticoagulants orals directes en la prevenció de l'ictus i l'embòlia sistèmica en pacients amb fibril·lació auricular no valvular. Butlletí d'Informació Terapèutica. 2015; 26(9).
16. Connolly S, RE-LY Steering Commite and investigators. Dabigatran versus warfarin en patients with atrial fibrilation. N Engl J Med. 2009; 361(12): p. 1139-51.
17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, ROCKET AF investigators, et al. Rivaroxaban versus warfarin in non valvular atrial fibrillation. N Engl J med. 2011; 365(10): p. 833-91.
18. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11): p. 981-92.
19. Giugliano R, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013; 369(22): p. 2093-2104.
20. Heidbuchel H, Verhamme P, Alins M, Antz M, Diener H, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. European Society of Cardiology. 2015 Ago; doi:10.1093/europace/euv309.
21. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for Extended Treatement of Venous Thrombolism. N Engl J Med. 2013;(368): p. 699-708.
22. Alonso Roca R. Terapia puente en Anticoagulación Oral. Actualización en Medicina de Familia. 2016 Marzo; 12(3): p. 147-51.
23. Escolar G, García-Frade J, López-Fernández M, Roldán-Schilling V. Guía sobre los nuevos anticoagulantes orales. Madrid: Sociedad Española de Hematología y Hemoterapia; 2013.
24. Criterios y recomendaciones generales para el uso de los anticoagulantes directos (ACOD) en la prevención del ictus y la embolia sistémica enpacientes con fibrilación auricular no valvular. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad, Agencia Española de Medicamentos y Productos Sanitarios; 2016.
25. Protocol per al control dels anticoagulants orals antagonistes de la vitamina K. Barcelona: Departament de Salut, Generalitat de Catalunya; 2010.
26. Servei d'Atenció Primària Muntanya-Dreta Àmbit d'atenció Pimària Barcelona Ciutat i Vall Hebron Hospitals, ICS. Protocol per al control dels pacients amb tractament d'anticoagulants orals. Barcelona: Generalitat de Catalunya; 2014.
27. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idaruzimab for dabigatran Reversal. N Engl J Med. 2015; (373): p. 2600-08.
28. Siegal DM, Curmutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Eng J Med. 2015;(373): p. 2413-24.
29. Ballester MM, Aballí-Acosta M, Maudos-Pérez MT, Iglesias-Pérez B, Casajuana-Brunet J, Losada-Doval G, et al. Intramuscular route for the administration of the anti-flu vaccine in patients

receiving oral anticoagulation therapy. Med Clin. 2005; (124): p. 291-4.
30. Guyatt H, Akl E, Crowter M, Gutterman D, Schünemann H. Antitrobotic Therapy and Prevention of Thrombosis 9th Ed American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 142(2): p. 7s-47s.
31. Yang S, Shi Q, Liu J, Li J, Xu J. Should oral anticoagulant therapy be continued during dental extraction? A meta-analysis. BMC oral Health. 2016; DOI 10.1186/s12903-016-0278-9.
32. Criterios y recomendaciones generales para el uso de los Anticoagulantes Orales directos (ACOD). Oviedo: Servico de Salud del Principado de Asturias; 2016.
33. Nuevos anticoagulantes orales. Guía de manejo ante diversas situaciones clínicas. Complejo Asistencial Universitario de León, Sacyl. León: Junta de Castilla y León; ca2015.
34. Beltran C, Morelo M. Atenció primària basada en l'evidència. Barcelona: 3 Clics; 2016.
35. Douketis JD, Spyropoulus AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015 Agosto; 373(9): p. 823-33.