WCN 2019 Teaching Course
ICH RELATED TO ORAL ANTICOAGULANTS

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Disclosures

I declare that I have no conflicts of interest

Objectives

To determine and understand

1/The mode of action and pharmacocinetic of Anticoagulant therapy

Vitamine K Antagonists

Direct oral anticoagulants

2/ Causes of cerebral hemorrhage

3/ Association ICH and OAC and its complication

4/ Reversal of anticoagulation related to ICH

Introduction

- Intracerebral hemorrhage (ICH) is a non-traumatic brain parenchymal hemorrhage, that may extend into the ventricular system or into the subarachnoid space (1).
- intracerebral hemorrhage (ICH) is responsible for most deaths caused by bleeding complications during long-term anticoagulation. (2)
- These bleedings are due to hypertension and cerebral amyloid angiopathy
- How ever anticoagulant therapy concerns also a part of these causes ,generally in patients taking oral anticoagulant the annual rate of intracranial hemorrhage is 0,3% to 0,6% of these 46% to 86% are intracerebral(3,4)

1/ Anticoagulant therapy

1) Vitamin K antgonists (VKAs)

Oral anticoagulants are a main component of cardiovascular therapy, and for over 60 years vitamin K antagonists (VKAs) were the only available agents for long-term use.

- Overall effect :dose-dependent anticoagulant effect
- Avantages :self-monitoring and self-management programmes.
- Inconvenients : Slow onset of action
  Variable dose requirement
  Multiple drug-drug interactions
  Dietary vitamin K intake

2) Direct oral anticoagulants (DOACs)

4 (DOACs)

- Dabigatran,
- Rivaroxaban,
- Apixaban,
- and Edoxaban are as efficacious and safe as warfarin for stroke prevention in patients with atrial fibrillation (AF).(5)

- Theses molecules have been developped to limit pharmacodynamic and pharmacocynetic variability

Pharmacocynetic parametters

	Mechanism of action	Tmax (h)	Voie d'éliminati on	T ½ (h)	dialyse	Pro-drug	Food effect	Dosing
Dabigatran	Direct F IIa inhibitor	2	Rénale 80% Fécale 20%	14-17	Yes	Yes	No	1x/day (DVT,prevention) 2x/day (DVT,AF)
Rivaroxaban	Direct F Xa inhibitor	2-4	Fécale 65% Rénale 33%	7-13	No	No	No	1x/day (DVT,AF,PE)
Apixaban	Direct F Xa inhibitor	3-4	Fécale 75% Rénale 25%	8-15	No	No	No	2x/day all indications
Edoxaban	Direct F Xa inhibitor	1-2	Renal 40%	9-11	No	No	No	1 x/ day (DVT,AF,PE)

DOACs VS VKA

	Advantages	Inconvenients
VKA	The INR is widely available with rapid turn-around, can be determined at the bedside	Food and drug interactions
DOACs	No food interactions do not generally require regular international normalisation ratio blood test monitoring.(6) They have faster onset and offset of action	Routine coagulation tests are less useful for measuring the anticoagulant effects an absence of or a limited choice of antidotes, some of which are also expensive.(7, 8)

2/Causes of ICH

- Intracerebral hemorrhage is provoked by diseases of large (15%) or small(85%) cerebral vessels .
- Large vessel diseases includes:

arterial aneurysm

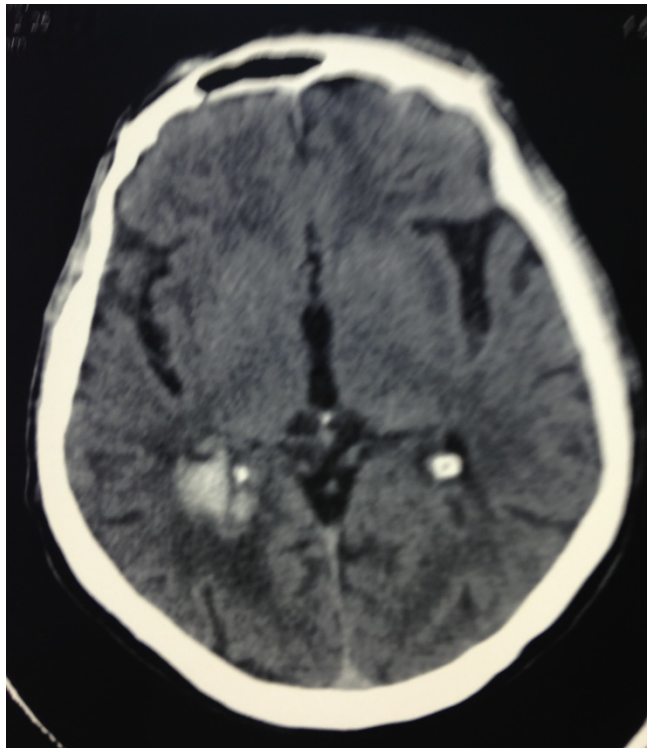
AVM

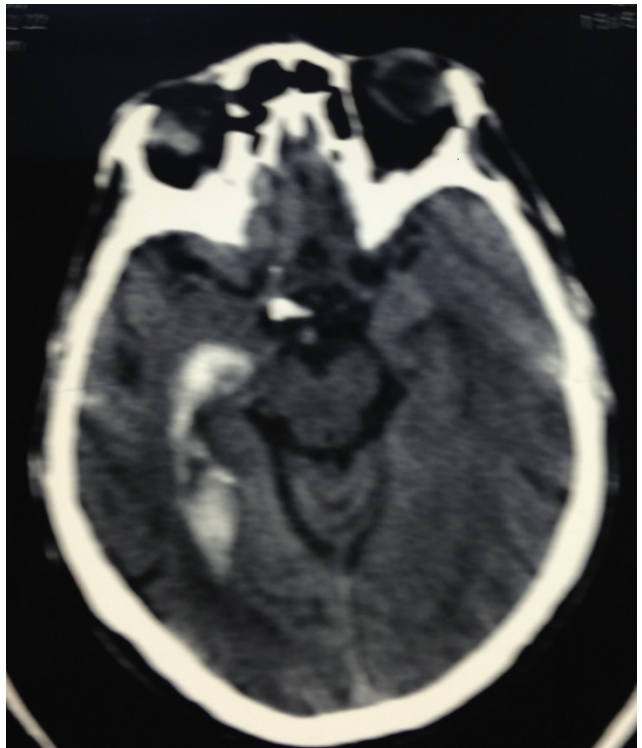
and less frequently dural fistules and venous malformations

- Small vessel disease :deposition of extracellular lipid « lipohyalinose » and β amyloid in « amyloid angiopathy » . (9)

3/ Association ICH and OAC

- Current data suggests that intracerebral hemorrhage in patients taking OAC reflects spontaneous bleeding exacerbated by anticoagulation.
- So OAC sustains intracerebral hematome formation but does not cause it.



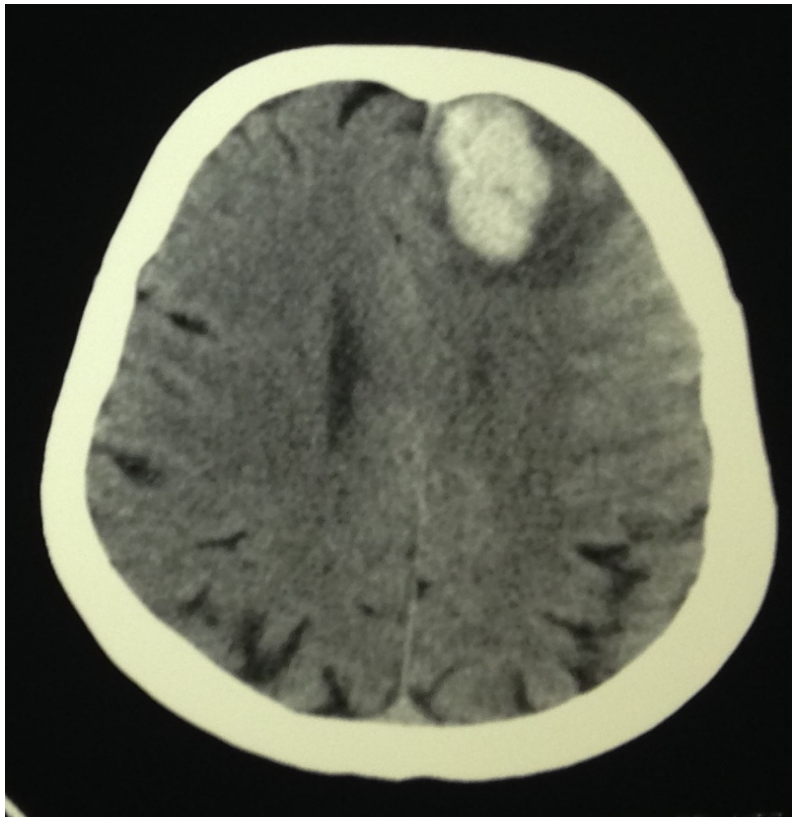


Case fatality

- Fatality = hematoma expansion
- Hematoma expansion results of vessel tissue pressure gradient and shear forces. (10)
- This pressure is highest in the early stages after vessel rupture and then gradually decreases .

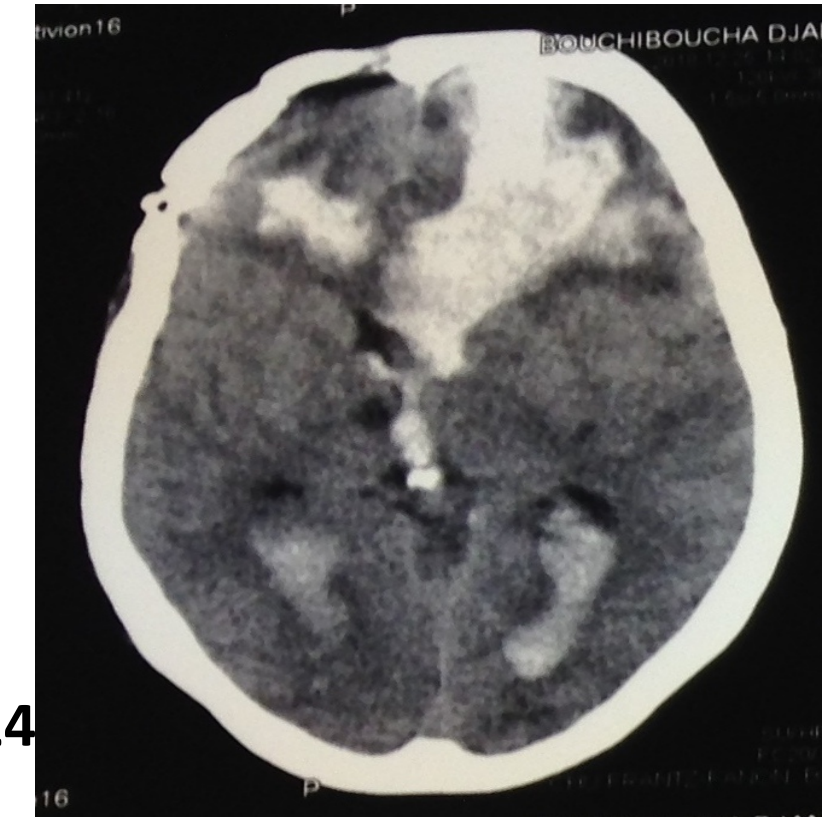
Case fatality =Hematoma expansion

- In patients not on OAC , hematoma expansion occurs in 30% to 40% of patients within 3to 6 hours after onset .
- In patients taking VKAs hematoma expansion is approxymately 54% first hours but often it is delayed .



H2

A 64 YO woman
History of AF on VKA
Admission INR =6



H24

- DOACs +ICH

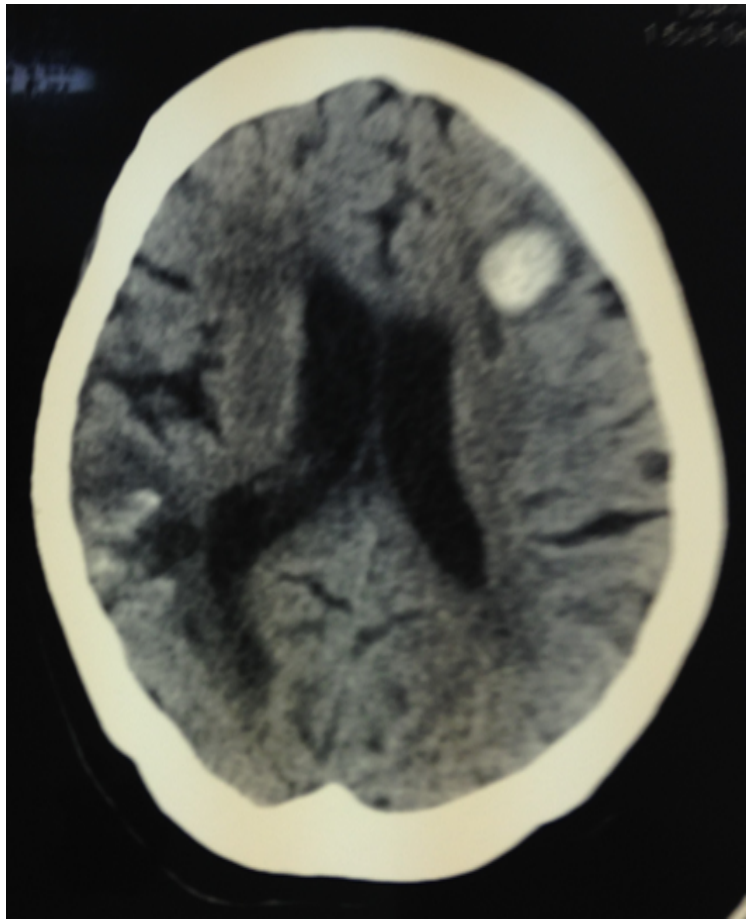
✓There is limited data on the frequency of hematoma expansion on DOACs .

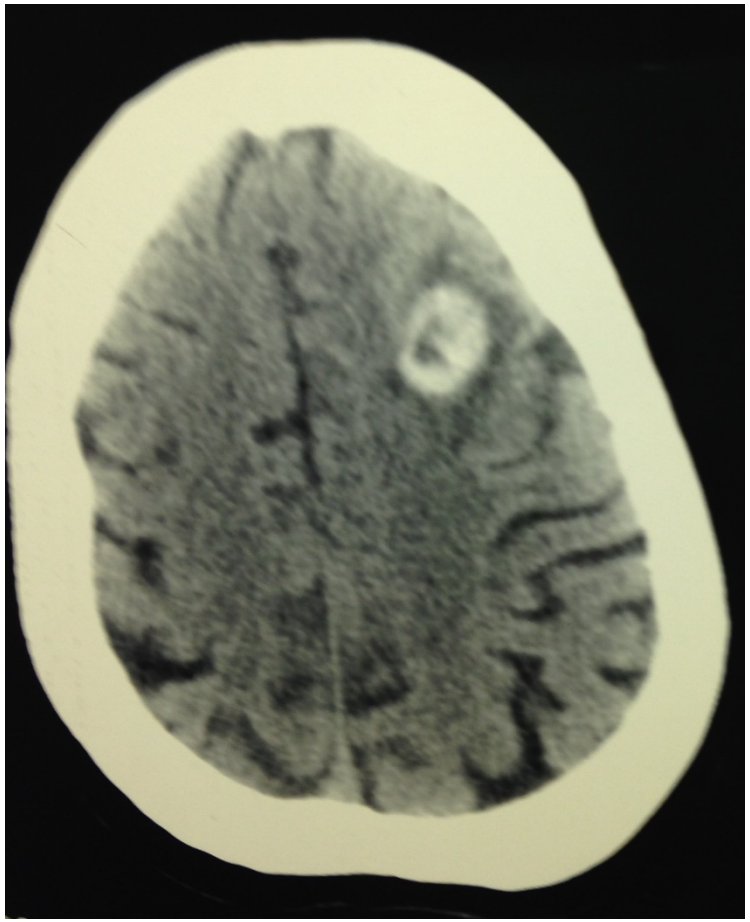
✓It has been reported that hematoma expansion in ICH is the same even for patients on VKAs or on DOACs.

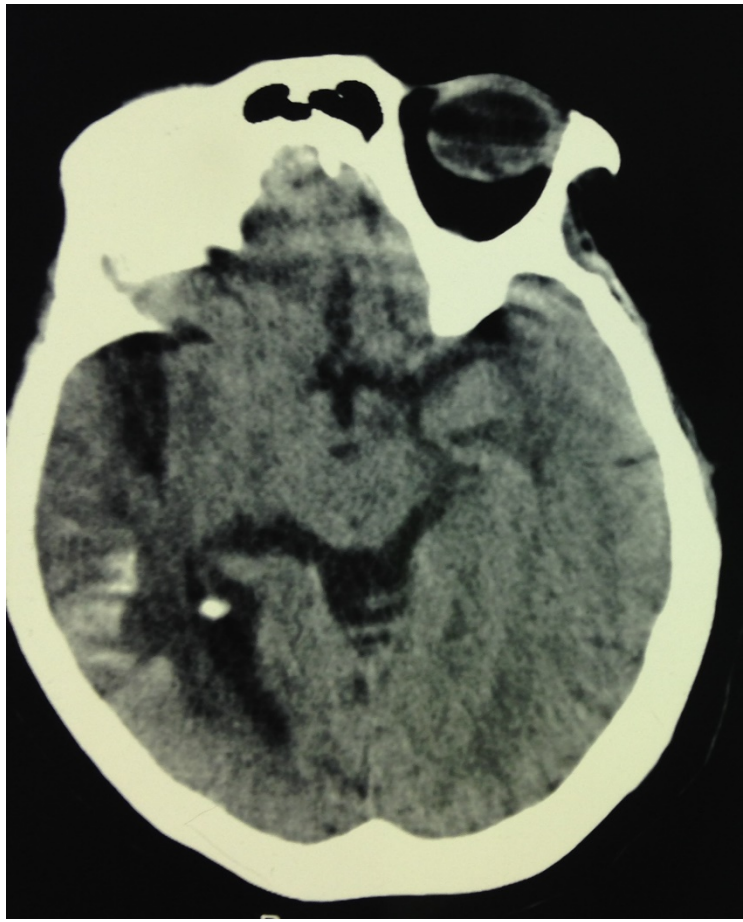
✓Anticoagulant reversal should be undertaken as soon as possible

Particular case :
59 YO man
History of FA+ diabetes
TRT : Xarelto 15mg

Hematoma + hemorrhagic transformation
of acute ischemic stroke







3/Reversal of anticoagulation related to ICH

1) Selection of the appropriate coagulation test

- VKAs are monitored by using the international normalized ratio (INR) wich is based on prothrombine time (PT)

INR= patients PT/ laboratory reference PT

- DOACs

✓Dabigatran : the thrombine time is the most sensitive

A normal test in case of ICH excludes the presence of clinically relevant dabigatran.

✓Rivaroxaban, apixaban and edoxaban have a greater effect on the PT

Anti factor Xa is not widely used .

2) Reversal of OACs

- VKAs : VitK
  PCC
  FPP

Vit K : VitK IV within 20 to 30 mn to avoid anaphylactoid reactions

PCC : Prothrombin Complex Concentrate which countains 4 or 3 factor format (VII,IX,X and prothrombine or IX,X and prothrombine) 25 -50 UI/kg IV

FFP

- PCC is superior than FPP :
  rapid normalisation of INR
  Reduction of hematoma expansion
  VIIa : avoided

❑ DOACs

- Dabigatran :Idarucizumab (praxbind) is a fragment of humanized antibody (5g IV bolus)
- Rivaroxaband,Apixaband and Edoxaban

Andexanet(Andexxya): recombinant variant of humanfactor Xa

Recommendations

- Plasma concentration of Dabigatran ≤ 30ng/ml
  Or APTT ratio ≤ 1,2 — No reversal

- Plasma concentration of Rivaroxaban ≤30 ng/ml
- Or PT ratio ≤ 1,2 — No reversal

In practice

1)In patients with ICH +OAC

Vit K: 5-10 ng IV

PCC: 30-50 UI/kg if INR >1,2

2) In patients with ICH +DOACs

It is difficult to determine the drug levels because of their relatively short half lives

Idarucizumab(5g):

PCC(50 UI/kg): reversal of rivaroxaban,apixaban and edoxaban

Pending availability of andexanet .

Take home messages

- Intracerebral hemorrhage is the most serious complication in patients taking oral anticoagulation
- The severity is related to hematoma expansion
- Generally hematoma expansion occurs more frequently in patients taking VKAs and can be delayed from onset bleeding
- At today there is limited data on the frequency of ICH and its complications related to the use of DOACs
- Anticoagulant reversal should be undertaken as soon as possible for both (VKAs and DOACs)

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