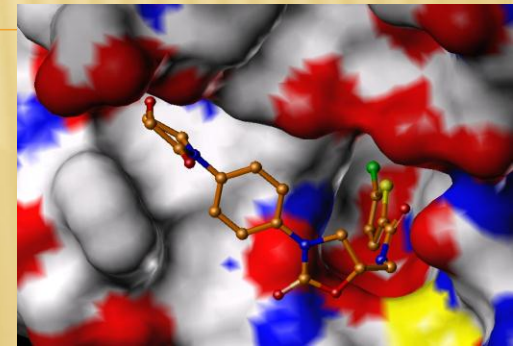


**NEW ORAL ANTICOAGULANTS SHOULD NOT
BE USED AS FIRST-LINE
AGENTS TO PREVENT THROMBOEMBOLISM
IN PATIENTS WITH
ATRIAL FIBRILLATION**

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- ❖ Yes, it should not be used.
 - ✘ Why it should not be used?
 - ✘ One should be satisfied with three questions.
Before using a drug.
-

Three Questions

- ✘ What is the effect?
 - ✘ What is the defect (side effects)?
 - ✘ Whether the drug is perfect?
-

STUDIES AND APPROVED INDICATIONS (EMA)

14 April 2011

CHMP adopted the new indication as follows:

– Prevention of **stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors:**

- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure, New York Heart Association (NYHA) Class 2
- Age 75 years
- Age 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

ATRIAL FIBRILLATION

- ✘ **PETRO Study:** Ezekowitz M. et al, Dabigatran With or Without Concomitant Aspirin Compared with Warfarin Alone in Patients with Nonvalvular Atrial Fibrillation (PETRO Study). Am J Cardiol, 2007, 100, 1419 -1426
- ✘ – **RE-LY study:** Connolly S.J. et al, Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med, 2009, 361, 1139-51.

– RE-LY STUDY

- ✘ N = 18113 patients at risk of stroke
 - Noninferiority trial
 - Fixed doses of dabigatran-110 mg twice daily}Blinded
 - Fixed doses of dabigatran 150 mg twice daily}Blinded
 - **Adjusted-dose warfarin (INR 2.0 – 3.0).}Unblinded**
 - The median duration of the follow-up period was 2.0 years.
 - The primary outcome was stroke or systemic embolism.

- RE-LY STUDY

- ✘ Dabigatran given at a dose of **110 mg** was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.
- ✘ Dabigatran administered at a dose of **150 mg**, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

INTEREST OF BIOLOGICAL MONITORING OF DABIGATRAN

Clinical trials
Safe and Protected
Environment

Real world...

Monitoring not
necessary



INTEREST OF BIOLOGICAL MONITORING OF DABIGATRAN

Clinical trials
Safe and Protected
Environment



Real world...

Monitoring not
necessary

Monitoring to
minimize the risks of
bleedings and identify
non responders (lack
of effectiveness)

SITUATIONS REQUIRING A BIOLOGICAL MONITORING

PK and PD data showing a high variability

- Narrow therapeutic window
- Drug interactions
- Compliance
- Particular clinical situations (elderly, hepatic
- ✘ disorders, renal disorders)



Dabigatran

- Off label use
- Abuse or misuse

INTEREST OF BIOLOGICAL MONITORING OF DABIGATRAN

- ✗ Risk of **overdose**
- ✗ Bleedings

- ✗ – Risk of **underdose**
- ✗ Lack of effectiveness!!!
- ✗ Thrombosis

MONITORING

Situations requiring a biological monitoring

- **Who said no monitoring?**
- Biological monitoring or clinical monitoring?
- How to monitor?

WHO SAID NO MONITORING?

EMA public assessment report:

- ✘ “It is important to underline that the PK characteristics of DAB i.e low bioavailability (6.5%) with a very large interindividual variability, the concentration-effect relationship and the bleeding risks strongly suggest that drug monitoring is needed”.

WHO SAID NO MONITORING?

- ✘ “The possibility of drug monitoring would be valuable, especially for these patients at risk and commercially available TT test kits will be developed for measurement of TT following administration of DTIs”.
- ✘ “A cross-validation of chronometric TT measurements at local laboratories will be performed as part of the FUM . Commercially available TT test kits developed for measurement of TT following administration of DTIs (i.e. hirudin) will be validated for measurement of TT of DAB”.

BIOLOGICAL MONITORING OR CLINICAL MONITORING?

- ✘ P-gp inhibitors (e.g. verapamil, amiodarone). This may increase the risk of bleeding and these patients should be closely clinically monitored (looking for signs of bleeding and anaemia).
- Patients with **moderate renal impairment have an** increased exposure to dabigatran. In these situations, Pradaxa should be used **with caution and a** close clinical surveillance (looking for signs of bleeding or anemia) is required throughout the treatment period.
- ✘ A **close monitoring should be exercised** when dabigatran etexilate is combined with clarithromycin.

HOW TO MONITOR?

- APTT: Activated Partial Thromboplastin Time
- PT: Prothrombin Time
- dPT: Dilute Prothrombin Time
- TT: Thrombin Time
- PiCT: Prothrombinase induced Clotting Time
- ECT: Ecarin Clotting Time
- ECA-T: Ecarin Chromogen Assay
- ACT: Activated Clotting Time
- Hemoclot® Thrombin Inhibitor assay (Hyphen BioMed)
- HepTest
- antiXa chromogenic assays (StaChrom and Rotachrom/ Liquid anti Xa)
- Thrombin Generation test (TGT)
- Thromboelastogram (TEG)

APTT AND PT

- ✘ qualitative indication of anticoagulant activity, but it may not be suitable for the precise quantification of anticoagulant effect
- ✘ => INR is not considered a suitable tool for monitoring the anticoagulant effects of DE
- ✘ -Linear relationship between plasma concentration and INR (<2.0)
- ✘ -**BUT: modest INR increase** at supratherapeutic doses
 - => low sensibility!
 - => high variability!

ECARING CLOTTING TIME (ECT)

- ✘ ECT may provide a more accurate measurement of DAB banticoagulation than the other PD parameters.
- ✘ **BUT:**
 - Not standardized!
 - Not current practice
- ✘ Routine use not recommended

THROMBIN TIME AND THROMBIN GENERATION ASSAY

- ✘ TT assay is only presented as a sensitive method for determining if any DAB is present.
- ✘ Should be adapted : **Hemoclot**
- ✘ **Still it is non specific**

WHICH TEST IN CLINICAL PRACTICE ?

	Dabigatran	Rivaroxaban
Non-specific - -	-ECT -Dilute TT - Thrombin generation test	-PT - Thrombin generation test
Specific	Anti-IIa activity	Anti-Xa activity

All these tests are still not routinely standardized and recommended

FINALLY

- ✘ **New oral anticoagulants: potential role to play a role in a small range of clinical settings.**
- **Developed with the intent not to require monitoring due to their predictable pharmacologic effects.**
- **However this will be (is?) required in many clinical settings (liver, kidney, drug interactions, compliance, bleeding, recurrence).**

DO WE HAVE TOOL TO MONITOR

Monitoring to minimize the risks for both overdose and underdosage is crucial but unfortunately we don't have that monitoring tool

Effect of Old and New Anticoagulants

OLD	NEW
<ul style="list-style-type: none">❖ Well established efficacy❖ Well circumscribed❖ Full confidence of prescriber	<ul style="list-style-type: none">❖ Well established efficacy but❖ No full confidence of prescriber

Defects (Side Effects) of Old and New Anticoagulants

OLD

- ❑ Well known
- ❑ Their remedy also well known to the prescribers.

NEW

- ❑ Some are known
- ❑ Many are unknown like the horizon which seems to be in touch with ground but in fact, its far away from the sky...

Is New Anticoagulant Perfect?

A NEW DRUG WHICH IS PERFECT OR NOT IS
STILL IN IMAGINATION.

-
- ❖ So its time to establish a drug's EFFECT, SIDE EFFECTS and PERFECTION.
 - ❖ AND, ALL THESE THINGS ARE MEASURED WITH THE PASSAGE OF TIME.

OLD - NEW Conversation

NEW says OLD,

“People no more desire you,
Except a few”

OLD says,

“If desire is lost, nothing is lost.”

Again NEW continues,

“Oh old, someone loosing hope-
You have no scope (to be used),”

OLD - NEW Conversation (cont...)

OLD says, “Ok, if hope is lost, something is lost.
But people are not confident on you,
As because you are new.”

(NEW keeps silence)

Then OLD says, “When confidence is lost,
Everything is lost.... ...”

Moral of This Conversation

If desire is lost, nothing is lost.

If hope is lost, something is lost.

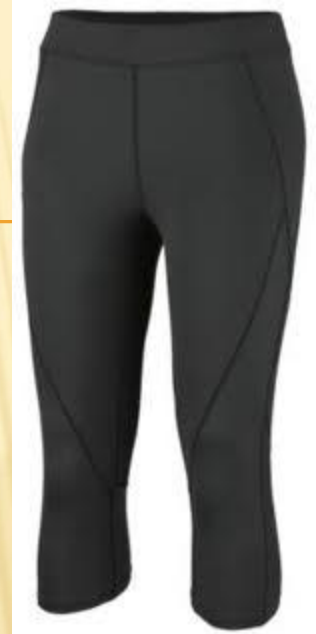
But when confidence is lost, everything is lost.

- ❖ So when confidence is lost, use of a drug is not possible.

For the NEWS'
There are some views,
Cheer to learn,
Fear to practice
Confidence is shallow,
Incidence may follow.



Pant of 50,s



Pant of 60's



Pant of 70's



Pant of new era

Conclusion

In conclusion, what wise man says,

WISE MAN OF OLD	WISE MAN OF RECENT
Wise man of old, All along told, The old is gold.	Wise man of recent, Says, it is decent, be careful about nascent.

THANK YOU