The era of NOACs
(non-Vitamin K oral anticoagulants)
in Clinical Pharmacy :

Patrick Tilleul

Head Pharmacist, Pitié Salpêtrière hospital
Associate professor Paris Sorbonne University

Disclosure Patrick Tilleul

Abbvie, Amgen, Astellas, Biogen, Baxter, BMS, Chiesi, Novartis, Roche, Takeda

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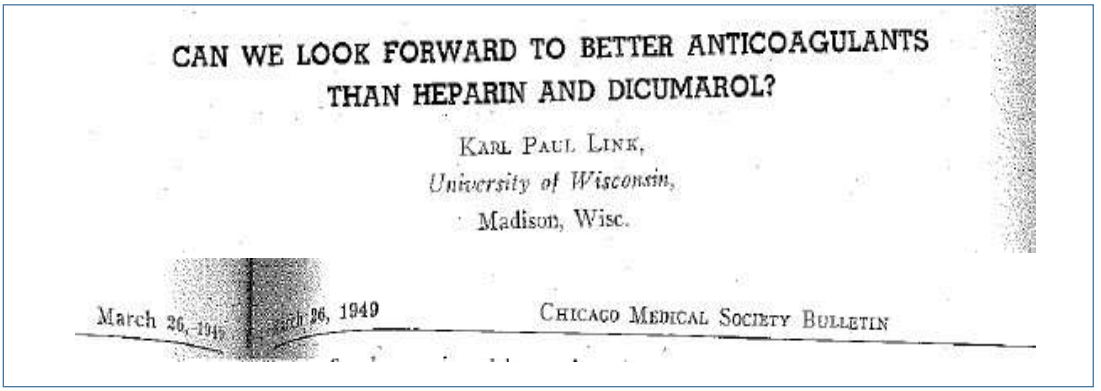
Improve anticoagulants…
… a quest that is not new



CAN WE LOOK FORWARD TO BETTER ANTICOAGULANTS THAN HEPARIN AND DICUMAROL?

KARL PAUL LINK,
University of Wisconsin,
Madison, Wisc.

March 26, 1949 CHICAGO MEDICAL SOCIETY BULLETIN

VKA around 50 years of experience …

Limits		Consequences
• **Low onset of action**	⟷	• Bridging with parenteral anticoagulant
• **Genetic variability for its metabolism**	⟷	• Variability for the doses
• **High interactions with foods and other drugs**	⟷	• Regular Monitoring (INR)
• **Narrow therapeutic window**	⟷	• Regular Monitoring (INR)

Mavrakanas T, Bounameaux H. The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. Pharmacol Ther. 2011;130(1):46-58.

The era of NOACs

NOACs available [1]

- **2008 : dabigatran, rivaroxaban**
- **2011 : apixaban**
- **2015 : edoxaban**

« Drugs that are closer than ever to the 'ideal anticoagulant'[2] »

Characteristics required for an 'ideal anticoagulant' [2]

- Oral administration
- No requirement for routine coagulation monitoring and dose adjustment
- Wide therapeutic window
- Rapid onset of action
- Predictable pharmacokinetics and pharmacodynamics
- Minimal interactions with foods and other drugs
- Ability to inhibit free and clot-bound coagulation factors
- Low non-specific binding
- Availability of an antidote
- No unexpected toxicities
- Acceptable costs

(1) Date of issue of marketing authorisation valid throughout the European Union. http://www.ema.europa.eu
(2) Mavrakanas T, Bounameaux H. The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. Pharmacol Ther. 2011;130(1):46-58.

Are NOACs more convenient ?

Are all NOACs the same?

Clinical pharmacology of oral anticoagulants

	Apixaban[1,2]	Dabigatran[1,3]	Edoxaban[4,5]	Rivaroxaban[1,6]
Mechanism of action	Direct factor Xa inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Oral bioavailability	~50%	~6.5%	62%	80–100%
Pro-drug	No	Yes	No	No
Food effect	No	No	No	Yes (20 mg and 15 mg doses need to be taken with food)
Renal clearance	~27%	85%	49%	~33 %*
T_{max}	3–4 hours	0.5–2 hours	1–2 hours	2–4 hours
Mean half-life ($t_{1/2}$)	12 hours	12–17 hours†	6–11 hours	5–9 h (young) 11–13 h (elderly)

* Direct renal excretion as unchanged active substance
† Prolonged in patients with impaired renal function
T_{max} time to maximum concentration

The information in this table for apixaban, dabigatran, rivaroxaban, edoxaban , and warfarin is based on the SmPCs..

1. Ansell *Hematology Am Soc Hematol Educ Program* 2010:221-8; 2. Apixaban SmPC 2014; 3. Dabigatran SmPC 2013; 4. Rosanio *et al. Int J Cardiol* 2014; Apr 26 [Epub ahead of print]; 5. Heidbuchel *et al. Europace* 2013;15:625-51. 6. Rivaroxaban SmPC 2013; 7. Warfarin SmPC 2013.

Are all NOACs the same?

HAS
HAUTE AUTORITÉ DE SANTÉ

Summary of Pivotal Clinical Trials (phase III) with NOACs in Non Valvular Atrial Fibrillation (NVAF)

Product	Study Design	Protection	Stroke/SE	Major Bleedings	Mortality	Net Clinical Benefit
Dabigatran 110	Open	Open	Non-inferiority 0.91 [0.74 to 1.11]	Superiority 0.80 [0.69 ; 0.93]	0.9 [0.80 ; 1.03]	0.9 [0.84 ; 1.02]
Dabigatran 150	Open	Open	Superiority 0.66 [0.53 ; 0.82]	Non-inferiority 0.93 [0.81 ; 1.07]	0.88 [0.77 ; 1.00]	0.91 [0.82 ; 1.00]
Rivaroxaban	Double blinded	Double blinded	Non-inferiority§ 0.88 [0.75 ; 1.03]	No Superority§§ 1.04 [0.90 à 1.20]	0.85 [0.70 ; 1.02]	NA
Apixaban	Double blinded	Double blinded	Superiority 0.79 [0.66 ; 0.95]	Superiority 0.69 [0.60 ; 0.80]	Superiority 0.89 [0.80 ; 0.998]	0.77 [0.69 ; 0.86]

§ Population ITT ; §§ No limit for non-inferiority defined

"… when one of these three drugs is prescribed and when the choice between these three drugs Is possible (absence of contraindications such as renal insufficiency for example), in terms of level of proof, **apixaban has demonstrated its best interest in comparison to warfarin** " (1,2)

(1) HAS, Avis de la Commission de la transparence ELIQUIS – 17 decembre 2014
(2) HAS Avis de la Commission de la transparence LIXIANA – 6 juillet 2016

What are the current perspectives of NOACs for hospital pharmacists ?

- Treatment Management ?
  - in Non Valvular Atrial Fibrillation (NVAF)
  - in Venous Thromboembolism (VTE)
- Patients Adherence ?
- Cost-effectiveness ?

The era of NOACs (non-Vitamin K oral anticoagulants) in Clinical Pharmacy :

09:00-09:10	**Introduction**	
09:10-09:30	**Clinical data in treatment and secondary prophylaxis of VTE**	Menno Huisman (NL)
09:30-09:45	**Clinical data for stroke prevention in patients with non-valvular atrial fibrillation**	Juan Cosin Sales (ES)
09:45-10:00	**Consideration for BID regimen : potential impact on adherence and persistence**	Bernard Vrijens (BE)
10:00-10:15	**Cost-effectiveness learnings with NOACs: the European perspectives**	Patrick Tilleul (FR)
10:15-10:30	**Q&A**	All