Warfarin as a new anticoagulant – improving stability and outcome of warfarin by monitoring factors II and X only

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Dr Önundarson discussed the results of his Fiix-PT trial which aimed to assess non-inferiority of anticoagulation stabilisation with a warfarin monitoring method affected only by factors II and X (Fiix-prothrombin time [Fiix-PT]) compared with standard PT-INR monitoring that includes factor VII measurement as well (and factors I and V).

Whilst warfarin is very efficacious, the efficacy of VKA depends heavily on the quality of warfarin management. Between 1985 and 2014 there has been a marked improvement in warfarin control in the Western world, from the introduction of international standardisation of prothrombin time (PT) reporting (the INR) to anticoagulation management centres with specialised staff; computer assisted dosing; and self-monitoring.

Despite its effectiveness, warfarin still has a number of pros and cons:

Pros	Cons

• Well studied and efficacious
• Controllable anticoagulation intensity by monitoring
  • Therapeutic window is well delineated
  • Adjustable to personal needs (titratability)
• Compliance is measurable
• Immediately reversible
  • Immediately with PPC
  • Hours (FFP)
  • 12-16 hours vitamin K
• Cheap
	• Slow onset of effect
	• Hard to predict initial dose
	  • Mutations affect metabolism and dose size
	  • VKORC
	  • CYP450
	• PT-INR fluctuates
	  • In many patients leading to need for frequent testing and dose adjustments
	• Serious bleeding complications
	• Needlestick
	• Work!

So can warfarin treatment be improved further in 2015? Managing warfarin is not easy as doses vary between patients and more importantly, the measured effect fluctuates. This measured fluctuation is often due to food interactions, drug interactions or compliance problems; but could test problems (the PT itself) misrepresent the anticoagulation in a patient and lead to a fluctuating effect?

A number of studies have suggested that the PT-INR is not a great indicator of the antithrombotic effect of VKA and that the antithrombotic effect depends mainly on reductions in FII and FX:

- **Thrombin generation correlates with FII and less with FX but poorly with factors VII and IX activity**. *Xi M, Béguin S, Hemker HC. Thromb Haemost. 1989 Sep 29;62:788-91;*
- **Induced DIC in rabbits is prevented by reduced FII and FX but not by reduced FVII**. *A Zivelin, LV Rao and SI Rapaport. J. Clin. Invest. 92: 2131-2140 (1993);*

- **Monitoring warfarin with NPA. Monitoring native FII lead to 85% reduction in major events compared to PT monitoring.** ***Furie B, Diuguid CF, Jacobs*** *M, Diuguid DL, Furie BC. Blood. 1990; 75:344-9;*
- ***ROTEM experiments with low TF*** **concentration.** *Gudmundsdottir BR, Francis CW, Bjornsdottir A, Nellbring M, Onundarson PT. Thromb Res 2012;130:674–81.*

*Based on these results a hy*pothesis was formed:

'During VKA anticoagulation, measuring the combined influence of only the stable FII and FX reflects clottability better than does the PT-INR which is affected also by the short half-life FVII that has little influence on thrombus prevention but confounds VKA dosing'

Fiix-PT: "Fiixing" the prothrombin time

A modified PT was developed that is only influenced by factors II and X (FIIX). Subsequently a randomized blinded clinical trial was designed and conducted at the Landspitali in Reykjavik.

Design

- Single Center Prospective RCT
  - investigator initiated
  - randomized double blind study
  - non-inferiority trial 2012-2014
  - Landspitali AMS in Reykjavik
- All patients on warfarin with INR target 2-3 > 18 yo invited to participate
  - only exclusions: nursing home patients, cardioversion patients
  - ¾ had atrial fibrillation
- Randomized to monitoring with:
  - Fiix-PT/INR ("Fiix-warfarin")

    - active arm
  - PT/INR ("PT-warfarin")
    - control arm
- A blinded research INR was reported
- Warfarin management
  - specialized nursing staff
  - DAWN anticoagulation software
  - dosing protocol designed for the PT-INR *(with maximum recommended interval 42 days)*

Endpoints

- Efficacy
  - Total thromboembolism
    - Ischemic stroke *(not haemorrhagic stroke)*
    - TIA
    - Systemic arterial embolism
    - Myocardial infarction
    - VTE
- Safety
  - Major bleeding *(ISTH criteria)*
  - Other clinically relevant bleeding
  - Non-vascular death
- Composite major vascular events
- Surrogate efficacy/convenience parameters
  - Number of tests and tests in range
  - Dose change frequency
  - TTR *(Time within target range)*
  - VGR *(variance growth rate; INR fluctuation)*

1,148 patients were randomised for inclusion in the trial, with 573 assigned to the Fiix-PT/INR monitoring arm and 575 to the PT/INR arm. The median observation time was 1.7 years.

The efficacy of Fiix-PT monitoring (or thromboembolic rate) was non-inferior to PT monitoring with an annual rate of thromboembolism of 1.2% in the Fiix-PT arm versus 2.3% in the PT arm.

Whilst the major vascular event rate was similar in the first 6 months, after this time period the difference between the two monitoring arms became much more substantial, in favour of Fiix-PT monitoring with a 50% reduction in thromboembolism rate and the long-term improvement statistically significant.

The primary analysis of clinical outcomes is shown in the table below:

	Fiix-PT group		PT group		Relative risk (95% CI)	p value for total events†
	n	Percentage per patient observation year*	n	Percentage per patient observation year*		
Primary endpoints						
Efficacy						
Primary outcome population	573	..	575	..		
Total observation years	828	100%	825	100%		
Fatal and first non-fatal thromboembolism including myocardial infarction	10 (1)	1·21% (0·12)	19 (3)	2·28% (0·36%)	0·52 (0·25–1·13)	<0·0001
Cerebral infarction or transient ischaemic attacks	9 (0)	1·09%	14 (1)	1·68% (0·12%)	0·65 (0·28–1·48)	0·0002
Cerebral infarction	7 (0)	0·85%	11 (0)	1·31%	0·64 (0·25–1·64)	0·0002
Transient ischaemic attack	2 (0)	0·24%	3 (0)	0·36%	0·67 (0·11–3·99)	0·0001
Myocardial infarction	1 (1)	0·12%	3 (2)	0·36% (0·24)	0·33 (0·03–3·21)	<0·0001
Peripheral arterial occlusion	0	0	1 (0)	0·12% (0)	..	..
Venous thromboembolism	0	0	1 (0)	0·12% (0)	..	..
Safety endpoints						
Per-protocol population	571	..	573	..	..	..
Total observation years	771	100%	786	100%	..	..
First major bleeding	17 (1)	2·20% (0·13%)	20 (3)	2·5% (0·38%)	0·85 (0·45–1·61)	0·0034
Gastrointestinal	12 (1)	1·56% (0·13%)	10 (0)	1·27% (0)	1·2 (0·52–2·76)	0·0093
Intracranial	2 (0)	0·26% (0)	5 (1)	0·64% (0·13%)	0·4 (0·08–2·06)	<0·0001
Intracerebral	1 (0)	0·13% (0)	3 (1)	0·38% (0·13%)	0·33 (0·03–3·21)	<0·0001
Other major bleeding	3 (0)	0·39% (0)	4 (2)	0·51% (0·25%)	0·75 (0·17–3·35)	0·0002
Non-major clinically relevant bleeding						
All (including repeated)	118	14·25%	135	16·16%	0·88 (0·71–1·09)	0·0140
First non-major clinically relevant bleeding	87	10·51%	95	11·38%	0·92 (0·7–1·2)	0·0379
Minor bleeding	279	36·70%	301	36·05%	0·93 (0·83–1·04)	0·0185
Secondary endpoints						
Death from any cause	12	1·45%	16	1·92%	0·75 (0·36–1·58)	0·0008
Non-vascular death	10	1·21%	10	1·20%	1 (0·42–2·39)	0·0027
Composite major vascular events	27 (2)	3·50% (0·26%)	39 (6)	4·96% (0·76%)	0·69 (0·43–1·12)	0·0006

Non-inferiority analysis of total major events occurring during days 1–720 from randomisation. Fatal events are shown in parentheses. Efficacy of the monitoring method is assessed based on intention-to-monitor analysis, but safety of monitoring method is based on actual time on warfarin including a 5-day washout period after warfarin discontinuation (per-protocol population). Fiix-PT=Fiix-prothrombin time. PT=prothrombin time. *Percentage with event per patient observation year. †p value by Farrington-Manning test of non-inferiority with a non-inferiority margin of 0·025.

Table 2: **Primary analysis of clinical outcome**

Surrogate efficacy endpoints showed that anticoagulation monitored with Fiix-PT was more stable as evident by a lower variance growth rate (VGR; a fluctuation indicator), higher TTR and fewer dose changes than in patients monitored with the traditional PT.

Conclusions:

Compared to high quality (TTR 80%) PT-warfarin, Fiix-warfarin:

- **Is more stable**
- **Is clinically at least non-inferior** (primary analysis)
- **Is clinically superior in the long-term** (secondary analysis)
    - Long-term reduction in thromboembolic events
- **Does not increase bleeding**

Overall conclusion:

- A fluctuating PT-INR during warfarin treatment is partly a confounding side effect of the PT itself.
- The data suggests that if the PT is replaced with a monitoring test that is not affected by FVII such as the Fiix-PT, warfarin becomes more stable than previously assumed; a new oral anticoagulant!