SARAWAK HEART CENTRE

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18th Joint Coronary Revascularisation Meeting, Busan, Dec 2018

Personalised antithrombotic therapies: current and future strategies

Prof Dr Alan Fong

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Disclosures

- Advisory boards
  - Bayer
  - Pfizer
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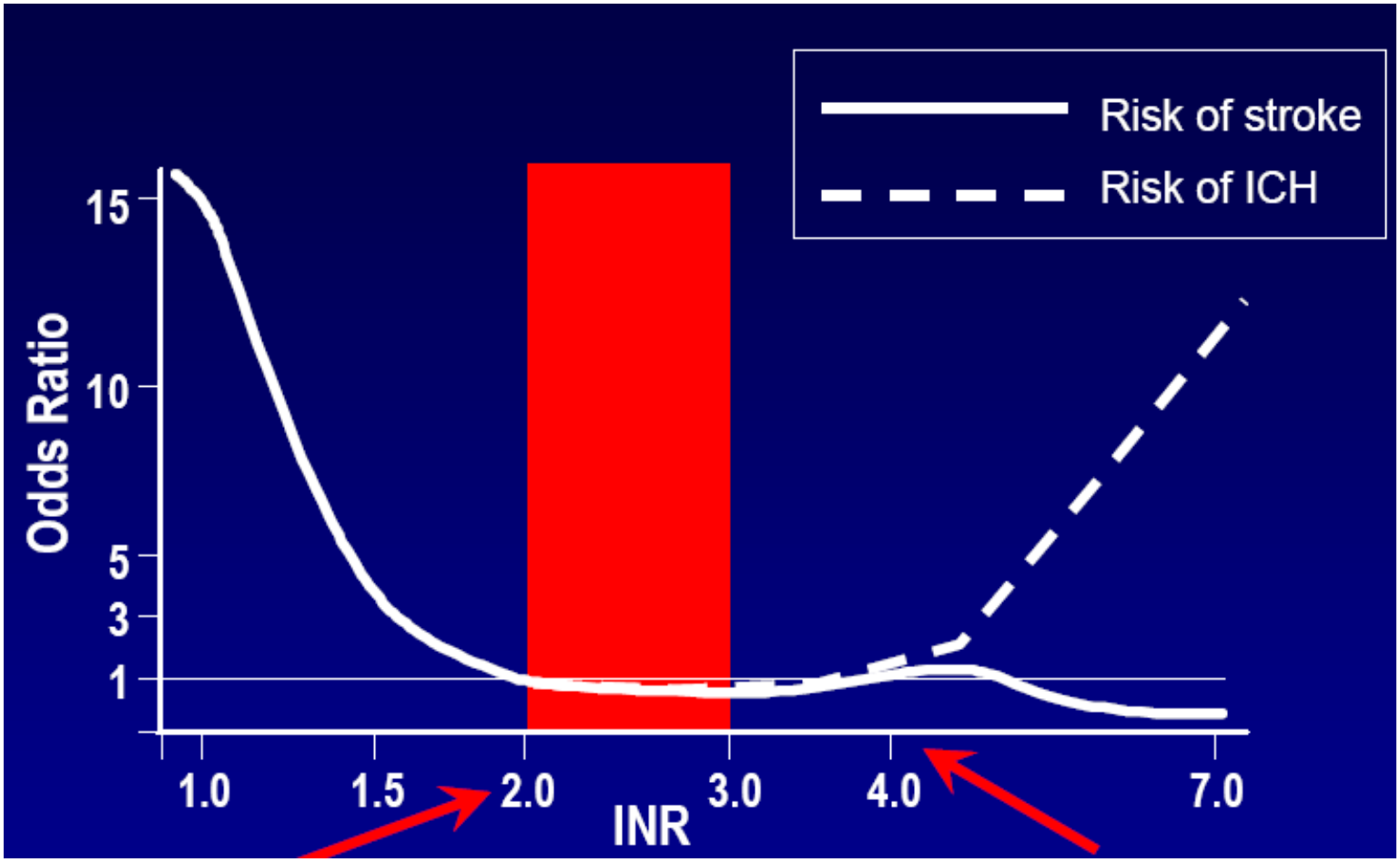
  - Bayer
  - Pfizer
- Research grants
  - Boerhringer Ingelheim
  - Ministry of Health, Malaysia

Lecture outline

- Anticoagulation
  - Warfarin
  - NOACs
- New diagnostic strategies
- Clinical applications

Warfarin



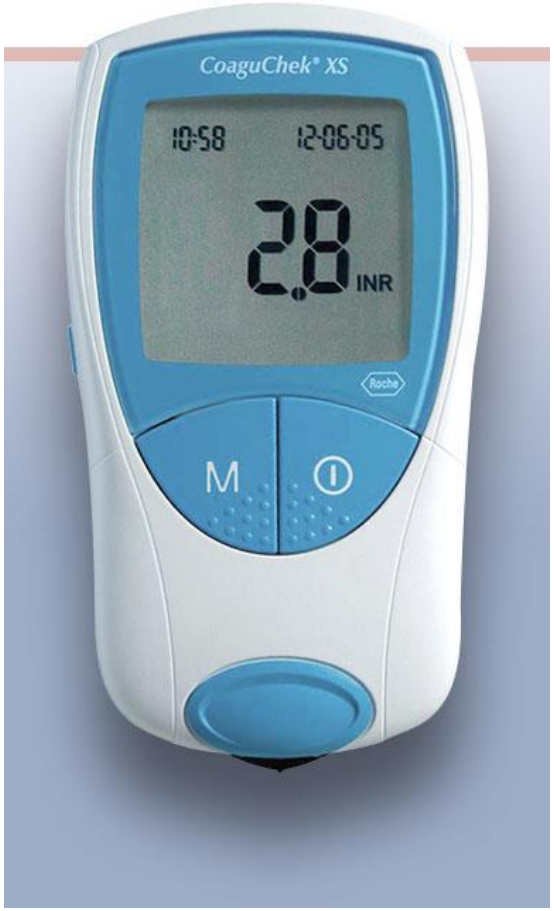
INR below 2.0 results in a higher risk of stroke

The estimated odds ratio of subdural hemorrhage increased 7 fold as INR increased above 4.0

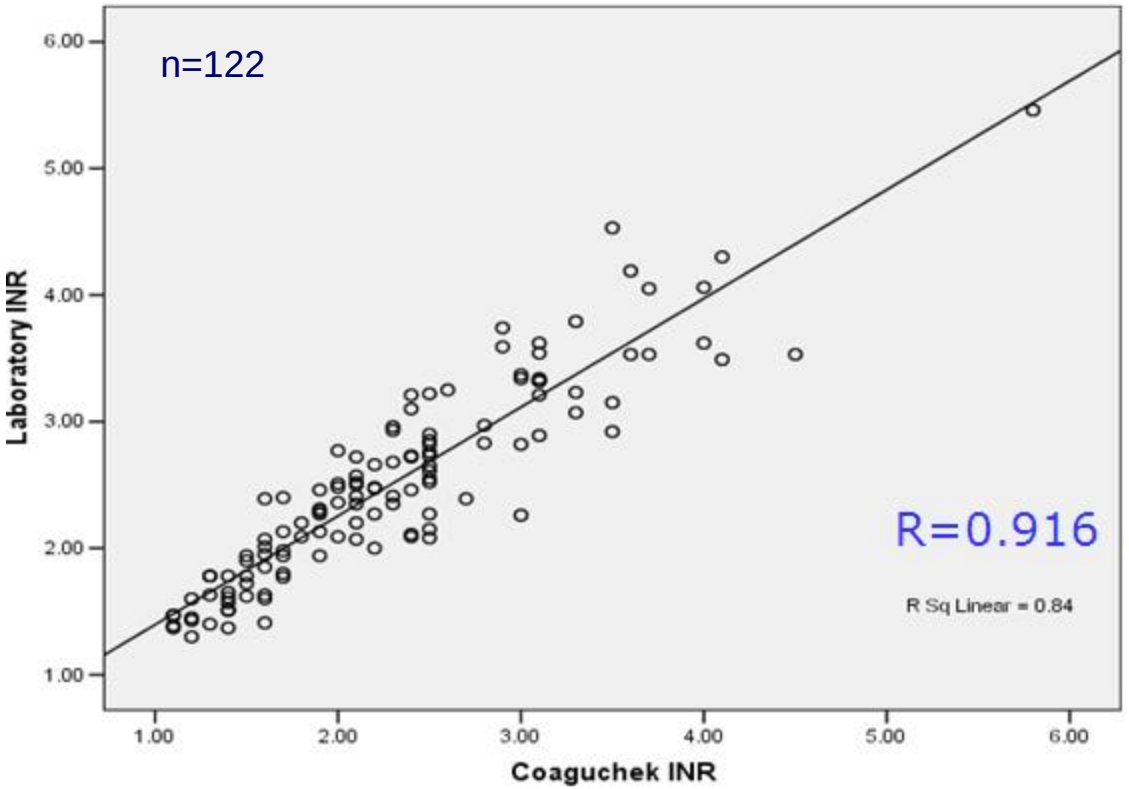
Hylek EM, et al. N Engl J Med 1996;335:540-546.

Hylek EM, and Singer DE. Ann Intern Med 1994;120:897-902

Point of Care INR testing (and then dosing)



Correlation: Coaguchek XS vs Laboratory INR



Fong AYY, et al. Feasibility of a Portable Prothrombin Time Device (Coaguchek XS) as a Component of a Home-Based Warfarin Anticoagulation Programme. YIA Presentations, NHAM 2007

INR Control and Mechanical Heart Valves

INR Control of Patients with Mechanical Heart Valve on Long-Term Warfarin Therapy

Crystal Sing Yee Tan*,†, Alan Yean Yip Fong†,‡, Yuan Hsun Jong§, Tiong Kiam Ong‡
Sarawak, Malaysia

ABSTRACT

Background: Warfarin is an anticoagulant indicated for patients who had undergone mechanical heart valve(s) replacement (MHVR). In these patients, time in therapeutic range (TTR) is important in predicting the bleeding and thrombotic risks.

Objective: This study aimed to describe the anticoagulation control of warfarin using TTR in patients with MHVR in a tertiary health care referral Center.

Methods: Data were collected retrospectively by reviewing clinical notes of outpatients who attended international normalized ratio (INR) clinics in November 2015. Patients who had MHVR and who took warfarin were included. The data collected were demographics, relevant laboratory investigations, and patients' prior medical history. TTR was calculated using Rosendaal and traditional methods.

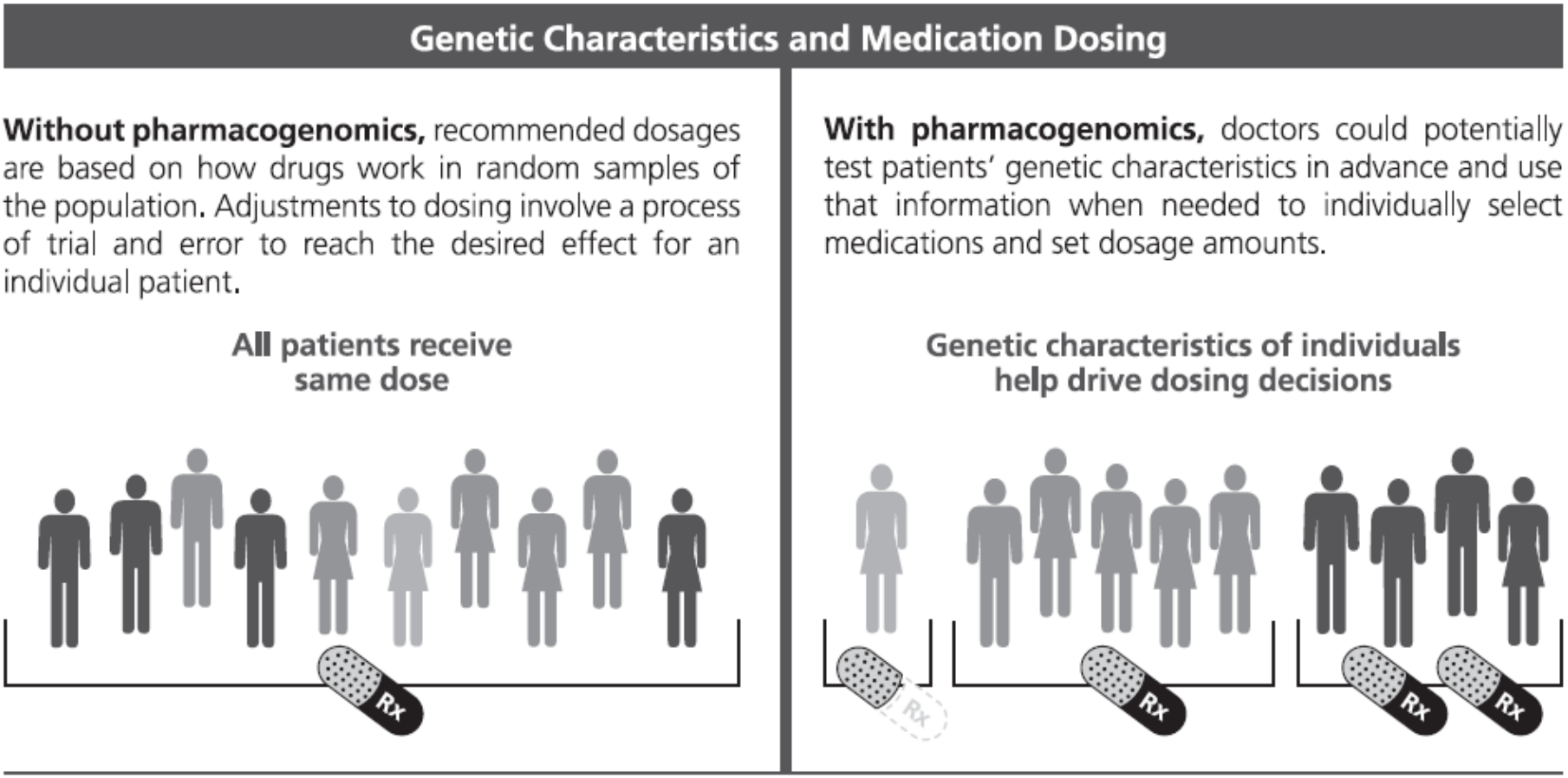
Results: A total of 103 patients with MHVR were recruited. The mean age was 51.72 ± 13.97 years and 46.6% were male. A total of 54.4% had mitral valve replacement (MVR), whereas 26.2% had aortic valve replacement (AVR). The mean TTR calculated using the Rosendaal method was 57.1%. There was no significant difference among patients with AVR, MVR, and both valves (AMVR) in terms of TTR (AVR vs. MVR vs. AMVR, 62.94 ± 23.08, 54.12 ± 21.62, 57.63 ± 17.47; $p = 0.213$). The average dose of warfarin for all groups was approximately 3 mg/day. Moreover, MVR, AVR, and AMVR patients who had TTR (Rosendaal method) ≤60% were 58.9%, 37.0%, and 45.0%, respectively. Only 4.8% had minor bleeding, whereas none had stroke in the period of TTR determination.

Conclusions: Despite a majority of patients having <60% TTR, there were low incidences of bleeding and stroke events in this center. There were no factors found to be associated with INR control in this study.

The authors report no relationships that could be constructed as a conflict of interest.
All authors hereby declare that there is no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.
From the *Department of Pharmacy, Sarawak General Hospital, Kuching, Sarawak, Ministry of Health, Malaysia; †Clinical Research

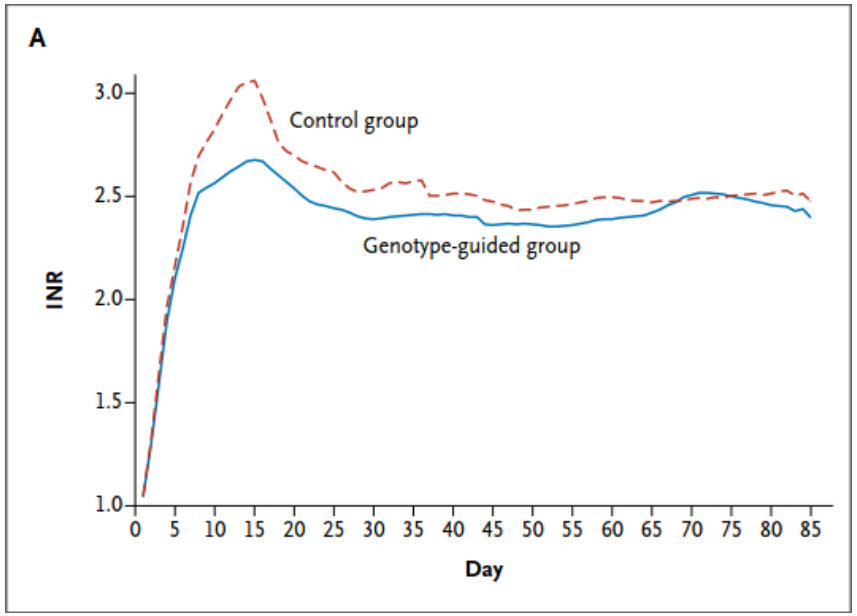
Glob Heart. 2018 Sep 10. pii: S2211-8160(18)30137-6

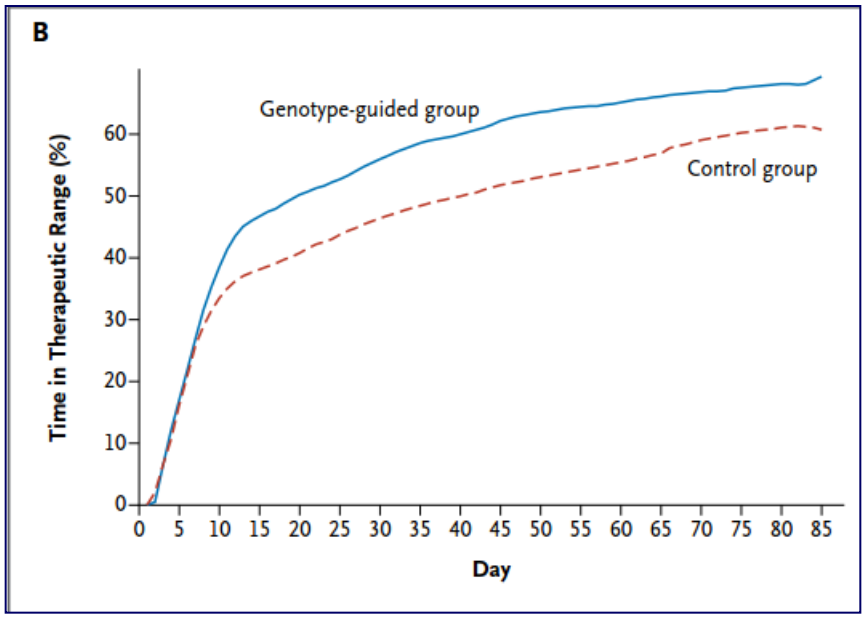
Since everyone is so different….



Source: Adapted from Felix W. Frueh, U.S. Food and Drug Administration, "Personalized Medicine, What Is It? How Will It Affect Healthcare?" slides from the 11th Annual FDA Science Forum, April 26, 2005; available at www.fda.gov/Cder/genomics/scienceForum2005.pdf.

Genotype-guided dosing for Warfarin





RESULTS

A total of 455 patients were recruited, with 227 randomly assigned to the genotype-guided group and 228 assigned to the control group. The mean percentage of time in the therapeutic range was 67.4% in the genotype-guided group as compared with 60.3% in the control group (adjusted difference, 7.0 percentage points; 95% confidence interval, 3.3 to 10.6; P<0.001). There were significantly fewer incidences of excessive anticoagulation (INR ≥4.0) in the genotype-guided group. The median time to reach a therapeutic INR was 21 days in the genotype-guided group as compared with 29 days in the control group (P<0.001).

CONCLUSIONS

Pharmacogenetic-based dosing was associated with a higher percentage of time in the therapeutic INR range than was standard dosing during the initiation of warfarin therapy. (Funded by the European Commission Seventh Framework Programme and others; ClinicalTrials.gov number, NCT01119300.)

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohnke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group*

ABSTRACT

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1311386

Genotype-guided dosing for Warfarin

BJCP British Journal of Clinical Pharmacology

A total of 76 and 94 entries were retrieved were retrieved from PubMed and the Cochrane Library, respectively. A total of 2626 subjects in the genotype-guided dosing (mean age 63.3 ± 5.8 years; 46% male) and 2604 subjects in the conventional dosing (mean age 64.7 ± 6.1 years; 46% male) groups (mean follow-up duration 64 days) from 18 trials were included. Compared with conventional dosing, genotype-guided dosing significantly shortened the time to first therapeutic international normalized ratio (INR) (mean difference 2.6 days, standard error 0.3 days; $P < 0.0001$; I^2 0%) and time to first stable INR (mean difference 5.9 days, standard error 2.0 days; $P < 0.01$; I^2 94%). Genotype-guided dosing also increased the time in therapeutic range (mean difference 3.1%, standard error 1.2%; $P < 0.01$; I^2 80%) and reduced the risks of both excessive anticoagulation, defined as INR ≥4 [risk ratio (RR) 0.87; 95% confidence interval (CI) 0.78, 0.98; $P < 0.05$; I^2: 0%), and bleeding (RR 0.82; 95% CI 0.69, 0.98; $P < 0.05$; I^2 31%). No difference in thromboembolism (RR 0.84; 95% CI 0.56, 1.26; $P = 0.40$; I^2 0%) or mortality (RR 1.16; 95% CI 0.46, 2.91; $P = 0.76$; I^2 0%) was observed between the two groups.

Conclusions

Genotype-guided warfarin dosing offers better safety with less bleeding compared with conventional dosing strategies. No significant benefit on thromboembolism or mortality was evident.

INR control and novel plasma markers

Table 2: Plasma levels of thrombin and Factor Xa in TTR groups

Marker	Overall (n=188)	TTR < 66% (n=102)	TTR ≥ 66% (n=86)	P Value
Thrombin ug/ml, median (IQR)	465(250.9,845.2)	513.65(302.4,1107.5)	374.01(226.8,647.4)	0.002
Factor Xa ng/ml, median (IQR)	0.82(0.5,1.3)	0.84(0.5,1.7)	0.78(0.5,1.1)	0.504

Asean Heart Journal
http://www.aseanheartjournal.org/
Vol. 22, no. 1, 20 – 29 (2014)
ISSN: 2314-4551

Original Article

Thrombin and FXa plasma concentration levels in patients with atrial fibrillation on long term warfarin therapy

Lim MSH[1,2,5], Anchah L[1], Tiong WN[2], Hwang SS[5], Ong TK[3], Sim KH[3,4], Fong AYY[2,3,4]

The rise of the NOAC – Dabigatran/Apixaban/Rivaroxaban/Edoxaban

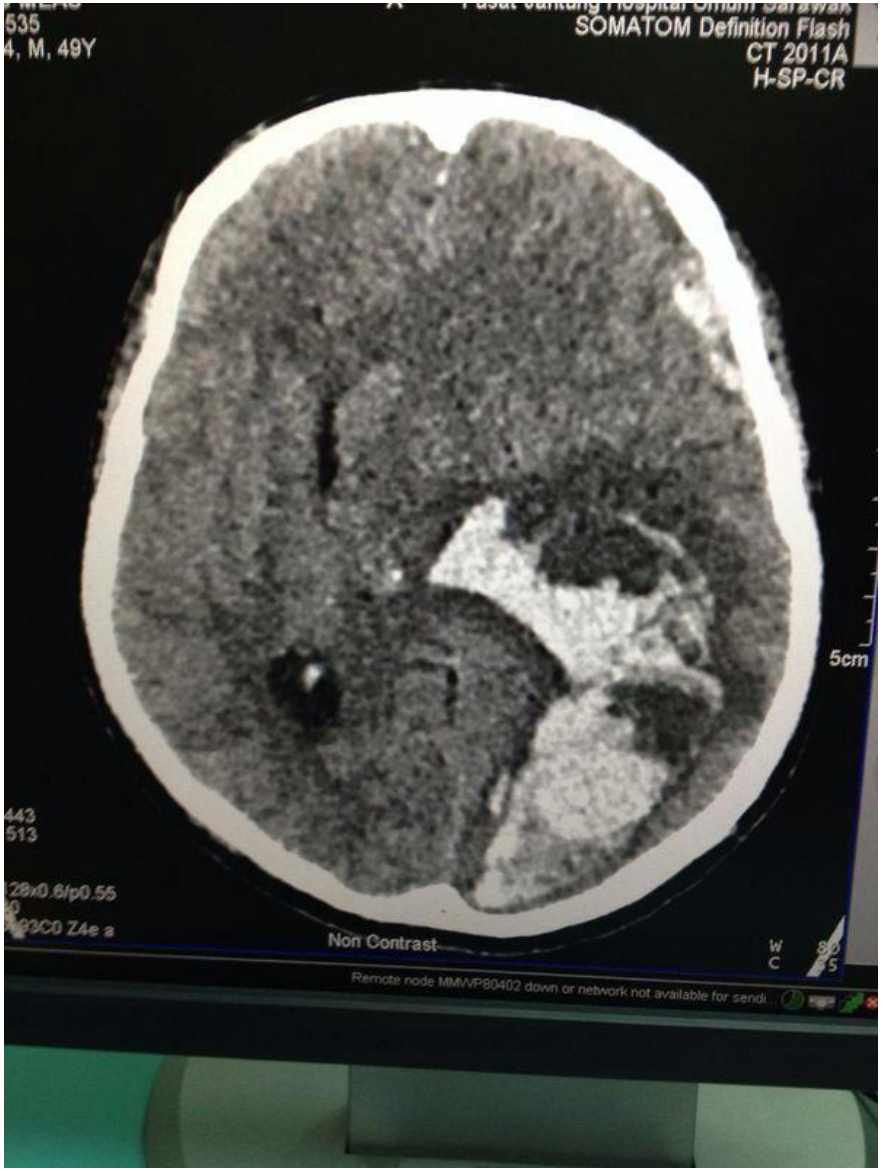
Conclusions: NOACs are superior to warfarin for the prevention of the composite of stroke and systemic embolism in patients with AF and an additional risk factor for stroke. There is a significant reduction in intracranial haemorrhage, which drives the finding of significantly lower mortality. During the poststudy switch from NOACs to warfarin there is an excess of the composite of stroke and systemic embolism as well as major bleeding events, which may be of significance in clinical practice.

Meta-analysis

openheart NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis

Tim Hicks,[1] Fiona Stewart,[2] Anne Eisinga[3]

ICH on a NOAC !! (~1:250 per year)



But at an individual level… (here, dabigatran)

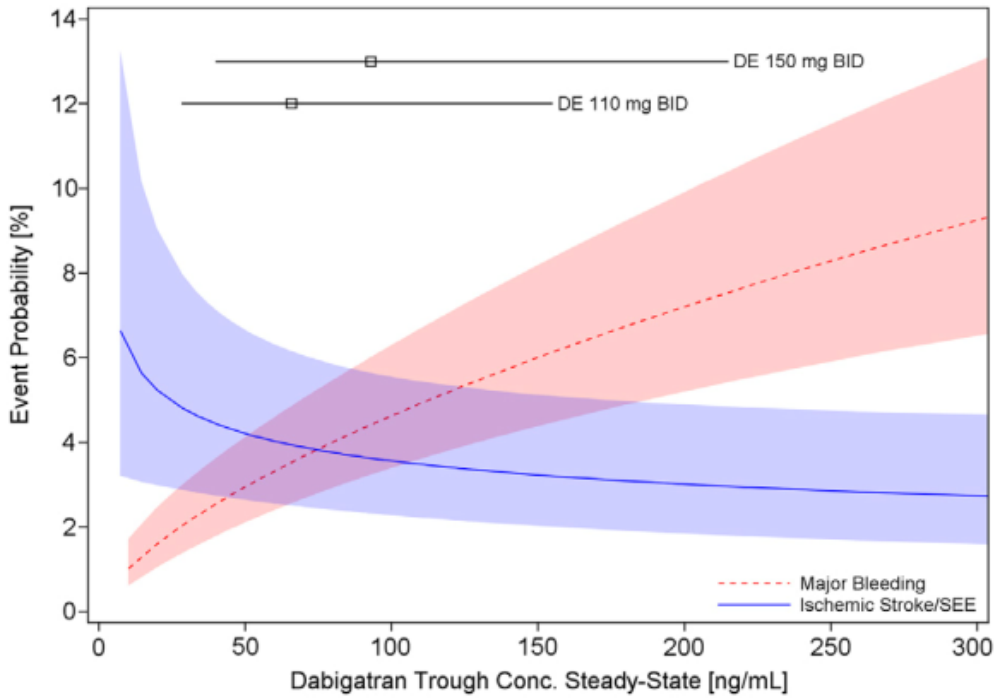
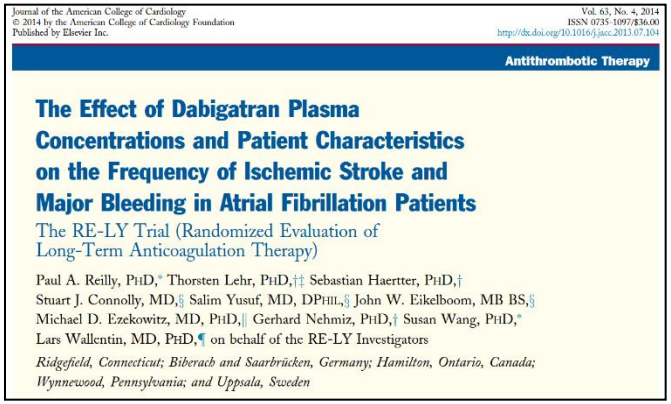


Figure 2 **Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles.
Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).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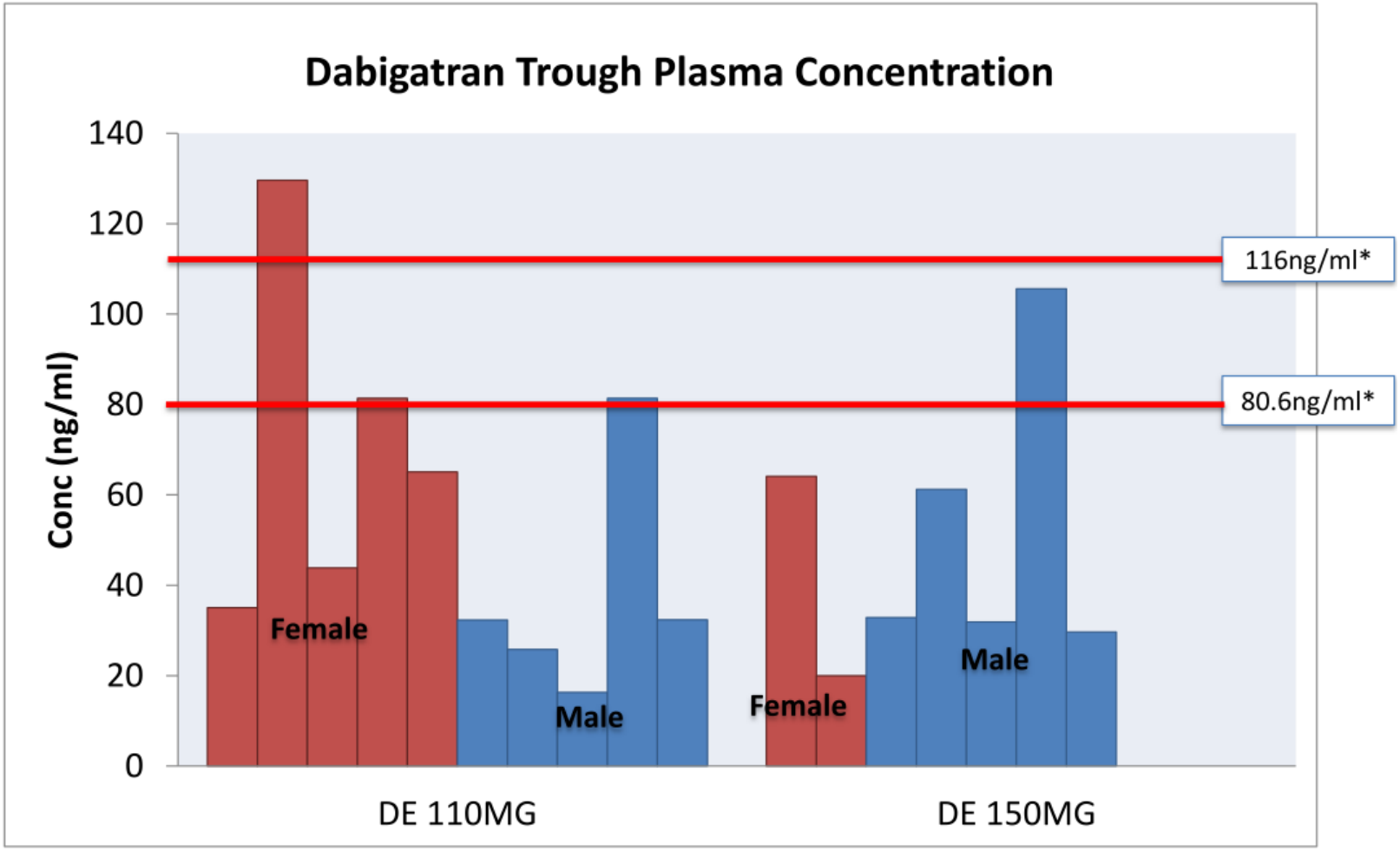
http://dx.doi.org/10.1016/j.jacc.2013.07.104
Antithrombotic Therapy

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PHD,* Thorsten Lehr, PHD,†‡ Sebastian Haertter, PHD,†
Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPHIL,§ John W. Eikelboom, MB BS,§
Michael D. Ezekowitz, MD, PHD,‖ Gerhard Nehmiz, PHD,† Susan Wang, PHD,*
Lars Wallentin, MD, PHD,¶ on behalf of the RE-LY Investigators
Ridgefield, Connecticut; Biberach and Saarbrücken, Germany; Hamilton, Ontario, Canada; Wynnewood, Pennsylvania; and Uppsala, Sweden

Dabigatran levels in SGH patients



*Data extracted from Reilly PA, et al. *Journal of the American College of Cardiology* 2014;4:321-328

Lim, MSH, Fong AY, et al. Free Paper Presentations, NHAM ASM 2015,

Rivaroxaban in Obese/Asian patients

Journal of Thrombosis and Thrombolysis
https://doi.org/10.1007/s11239-018-1726-y

Comparison of rivaroxaban concentrations between Asians and Caucasians and their correlation with PT/INR

Hobart Owen Ng Tsai[1] · Janice Jia Ni Goh[1] · Jernice Wan Xin Aw[1] · Yingying Lin[1] · Alan Yean Yip Fong[2,3] · Lee Len Tiong[3] · Doreen Su-Yin Tan[1]

Abstract

The objectives of this study are to compare steady-state trough (Cmin,ss) and peak (Cmax,ss) concentrations of rivaroxaban between Asians and Caucasians and to evaluate the relationship between rivaroxaban concentrations and prothrombin time/international normalized ratio (PT/INR). Recruited patients were advised on the time to take rivaroxaban. Cmin,ss and PT/INR were taken when patients arrived. Cmax,ss and PT/INR were drawn between 2 and 4 h later after the patient took rivaroxaban with food. Thirty patients were included in the analyses: 57% (n = 17) males and 43% (n = 13) females, 77% (n = 23) on 20 mg and 23% (n = 7) on 15 mg. Median PT_{trough} and PT_{peak} are moderately correlated with Cmin,ss ($r^2 = 0.43$) and Cmax,ss ($r^2 = 0.49$), respectively. Patients on 15 mg have lower Cmin,ss and Cmax,ss versus Caucasians [12 ng/ml vs. 57 ng/ml (Cmin,ss); 87 ng/ml vs. 229 ng/ml (Cmax,ss), $p < 0.01$ for both]. Patients on 20 mg also have lower Cmin,ss and Cmax,ss versus Caucasians [14 ng/ml vs. 44 ng/ml (Cmin,ss); 101 ng/ml vs. 249 ng/ml (Cmax,ss), $p < 0.01$ for both]. Subgroup analysis shows patients with BMI ≥ 30 have lower Cmax,ss than patients with BMI < 30 [80.47 ng/ml vs. 124 ($p = 0.014$)]. Cmin,ss and Cmax,ss were lower in Singaporeans than Caucasians. This may have an impact on the effectiveness of rivaroxaban in Singaporeans. Patients with higher BMI may not benefit similarly as patients with lower BMI. Lastly, the Dade Innovin reagent's measure of PT/INR is not sensitive towards changes in rivaroxaban concentrations.

Keywords Rivaroxaban · Plasma concentration · PT · INR · Asian

Even for NOAC, we should measure something….

A number of alternatives…

TABLE 1 List of assays used for dabigatran measurement with respective reagents, platforms, calibrators, and controls

Assay	ECA-STA	HTI-HY	DTI-IL	DTI-SI	DTI-TC
Reagent	STA-ECA II (Diagnostica Stago)	Hemoclot Thrombin Inhibitors (Hyphen BioMed)	Direct Thrombin Inhibitor Assay (Instrumentation Laboratory)	Direct Thrombin Inhibitor Assay (Siemens Healthcare Diagnostics)	Technoclot DTI (Technoclone GmbH)
Instrument	STA-R (Diagnostica Stago)	CS-2100 (Sysmex)	ACL TOP (Instrumentation Laboratory)	BCS (Siemens Healthcare Diagnostics)	ACL TOP (Instrumentation Laboratory)
Calibrators	STA-dabigatran calibrators (Diagnostica Stago)	Biophen dabigatran calibrators (normal and low range) (Hyphen BioMed)	Dabigatran calibrators (Instrumentation Laboratory)	Biophen dabigatran calibrators (Hyphen BioMed)	Technoview dabigatran calibrator set (Technoclone GmbH)
Controls	STA-dabigatran controls (Diagnostica Stago)	Biophen dabigatran controls (normal and low range) (Hyphen BioMed)	Dabigatran controls (Instrumentation Laboratory)	Biophen dabigatran controls (Hyphen BioMed)	Technoview dabigatran controls (Technoclone GmbH)
Clinic	Cremona	Bologna	Florence	Bologna	Bologna

Diagnostica Stago, Asnières sur Seine, France; Hyphen BioMed, Neuville-sur-Oise, France; Sysmex Europe GmbH, Norderstedt, Germany; Instrumentation Laboratory, Bedford, MA, USA; Siemens Healthcare Diagnostics, Marburg, Germany; Technoclone GmbH, Wien, Austria.

DOI: 10.1111/ijlh.12772

ORIGINAL ARTICLE

WILEY ISLH International Journal of Laboratory Hematology

Comparison of five specific assays for determination of dabigatran plasma concentrations in patients enrolled in the START-Laboratory Register

M. Cini[1] | C. Legnani[1] | B. Cosmi[1] | S. Testa[2] | C. Dellanoce[2] | O. Paoletti[2] | R. Marcucci[3] | D. Poli[3] | R. Paniccia[4] | V. Pengo[5] | A. Tripodi[6,7] | G. Palareti[8] | for the START-Laboratory Register

[1]Department of Angiology and Blood Coagulation, S. Orsola-Malpighi University Hospital, Bologna, Italy
[2]Haemostasis and Thrombosis Center, Department of Laboratory Medicine, AO Istituti Ospitalieri, Cremona, Italy
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[5]Department of Cardiothoracic and Vascular Sciences, University Hospital of Padua, Padua, Italy
[6]Department of Clinical Sciences and

Abstract

Introduction: Several specific assays are commercially available to determine dabigatran anticoagulant activity. Aims of this multicenter and multiplatform study were to compare five methods for dabigatran measurement and investigate their performances in the low concentration range.

Methods: Dabigatran levels were analyzed in 295 plasma samples from patients enrolled in the START-Laboratory Register by the following methods using dedicated calibrators and controls: STA-ECA II (Diagnostica Stago), standard and low range Hemoclot Thrombin Inhibitors (Hyphen BioMed), Direct Thrombin Inhibitor Assay (Instrumentation Laboratory), Direct Thrombin Inhibitor Assay (Siemens), Technoclot DTI (Technoclone).

Int J Lab Hem. 2018;40:229–236.

Measurement of anticoagulant level/activity - beyond INR – Why? – Especially in the ED!

- Unintentional/intentional overdose of the OAC, but there are no related symptoms;
- Spontaneous episode of external/internal bleeding, or the latter may be suspected.
- Injury causing external/internal bleeding.
- An urgent surgical or other invasive procedure is deemed necessary because of trauma or acute illness, and it is essential for the surgical team to know the level of anticoagulation in the patient.

NOAC measurements in the ED

Table 2 Coagulation assays responsive to dabigatran, rivaroxaban, apixaban and edoxaban

Assay	Responsive within therapeutic range?	Included in US drug prescribing information?*
Dabigatran[22–24 26 28 45–47]		
aPTT	Provides estimate of effect	Yes
ECT	Quantifiable dose–response	Yes
TT	Too sensitive to give quantifiable results	No
Diluted TT	Quantifiable dose–response	Not in the USA
Rivaroxaban[29–31 48–52]		
PT (rivaroxaban-calibrated)	Quantifiable dose–response if PT performed with neoplastin	Yes
aPTT	Dose-dependent, but variable and less sensitive than PT	No
FXa (clot-based, eg, HepTest)	Quantifiable dose–response	No
FXa (chromogenic)	Quantifiable dose–response	No
Apixaban[42 43 53 54]		
PT/INR	Small and variable response	No
aPTT	Small and variable response	No
FXa (chromogenic)	Quantifiable dose–response	No
Edoxaban[80]		
PT	Large variability between reagents	No
aPTT	Less variability between reagents	No
Thrombin generation	Three times more sensitive to edoxaban	No

Assays that can give quantifiable responses will typically require drug-specific and laboratory-specific calibration.
*Routine use of coagulation assays is not required with the novel oral anticoagulants.
aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; FXa, factor Xa; INR, international normalised ratio; PT, prothrombin time; TT, thrombin time.

Pollack CV. *Emerg Med J* 2016;**33**:423–430. doi:10.1136/emermed-2015-204891

Thromboelastography – TEG/ROTEM

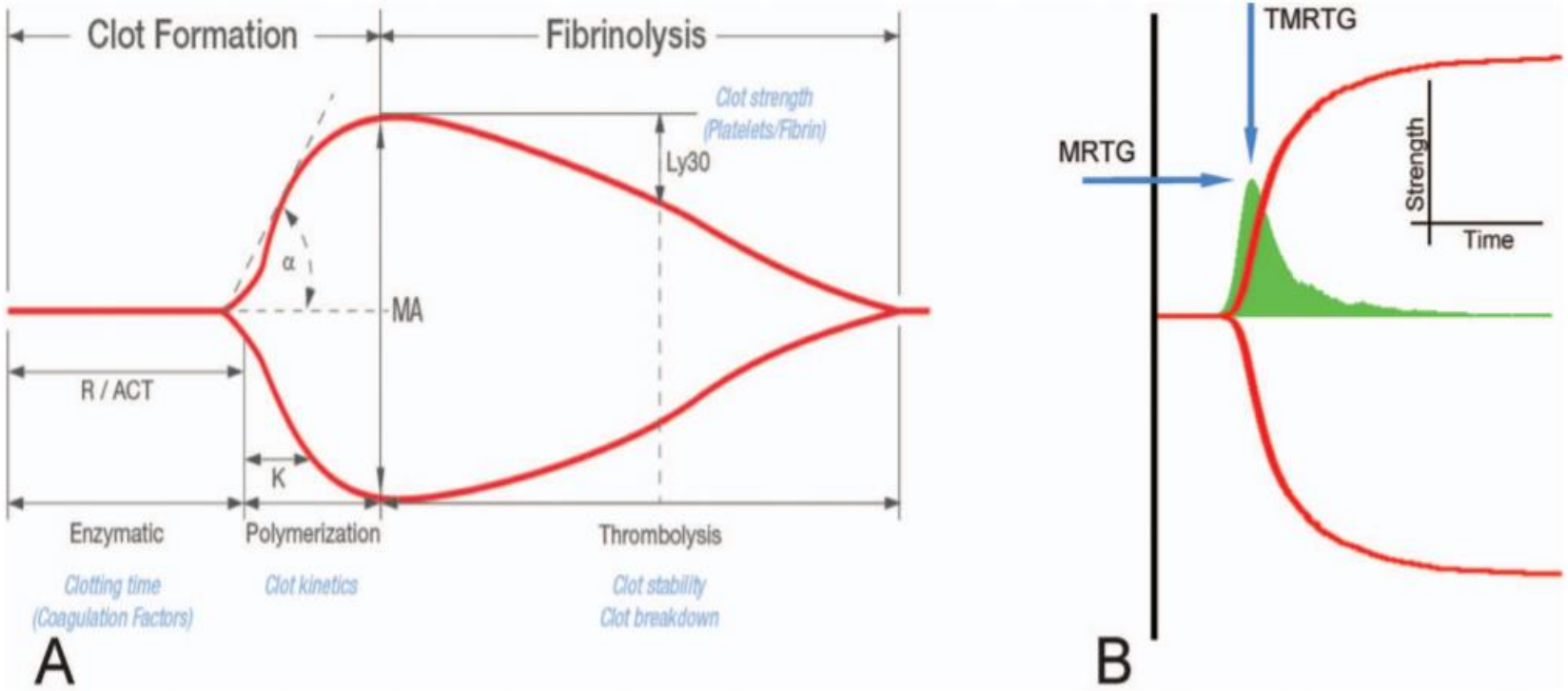

Figure 1. *Illustration of a thromboelastography tracing and accompanying parameters. A, Depiction of a thromboelastography tracing and parameters measured throughout the life span of a clot. B, Thrombus generation curve (V-curve in green) overlaying a thromboelastography tracing. A V-curve is plotted from the first derivative of changes in clot resistance, expressed as a change in clot strength per unit of time (dynes/cm²/s), representing the maximum velocity of clot formation. Abbreviations: ACT, activated clotting time; α, α angle; K, coagulation time; Ly30, percentage lysis 30 minutes after maximum amplitude; MA, maximum amplitude; MRTG, maximum rate of thrombus generation; R, reaction time; TMRTG, time to maximum rate of thrombus generation.*

Reversal agent to DOACs

PRAXBIND:

Immediate and Complete Reversal of PRADAXA with No Procoagulant Effects[1,2]

Median maximum reversal in evaluable patients was 100% in first 4 hours†

Most patients achieved complete reversal as measured by ECT (82%), or dTT (99%)‡

ANDEXXA is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

DOAC in the urine…

Detecting Anti-IIa and Anti-Xa Direct Oral Anticoagulant (DOAC) Agents in Urine using a *DOAC Dipstick*

Job Harenberg, MD[1,2] Rupert Schreiner, PhD[3] Svetlana Hetjens, PhD[4] Christel Weiss, PhD[4]

[1] DOASENSE GmbH, Heidelberg, Germany
[2] Medical Faculty Mannheim, Ruprecht-Karls University Heidelberg, Mannheim, Germany
[3] Medical Care Center Dr. Limbach and Colleagues, Heidelberg, Germany
[4] Division of Biometry and Statistics, Medical Faculty Mannheim, Ruprecht-Karls University Heidelberg, Mannheim, Germany

Address for correspondence Job Harenberg, MD, DOASENSE GmbH, Waldhofer Strasse 102, 69123 Heidelberg, Germany (e-mail: j.harenberg@doasense.de).

Semin Thromb Hemost

Functionality of the *DOAC Dipstick*

The reagents are immobilized on the surface of the *DOAC Dipstick* pads. When the reagents react with urine, specific colors develop according to the action of factor Xa or thrombin on the release of a chromophore bound to a substrate. Chromophore release is negatively related to the amount of DOAC in urine, and different chromophore colors indicate the absence or presence of factor Xa and thrombin inhibitors on the same test strip. Yellow indicates the absence of factor Xa inhibitors, and white indicates the presence of factor Xa inhibitors. Ochre indicates the absence of thrombin inhibitors, and rose indicates the presence of thrombin inhibitors. The pad colors can

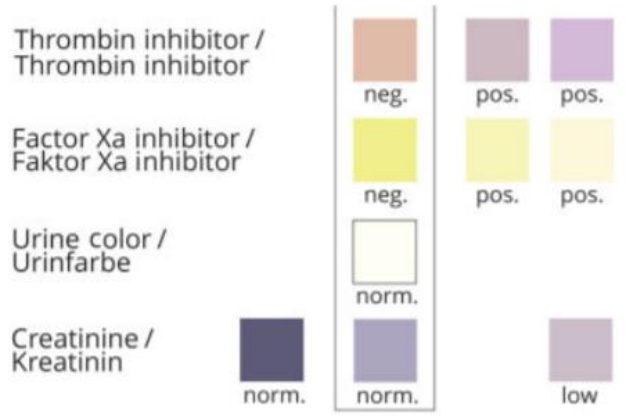

Fig. 2 Color label showing the direct oral anticoagulant (DOAC) *Dipstick* test results in the absence (negative (neg.) (left field) and presence (positive (pos.) (middle and right field) of thrombin inhibitor and factor Xa inhibitor, normal (norm.) urine color/Urinfarbe (English/German), and normal (norm.) (left and middle field) and low creatinine/Kreatinin in a urine sample.

For 2019…….

ClotPro®

Note:
The ClotPro® analyzer is for Research Use Only.
Not for use in clinical diagnostic procedures.

Summary

- Anticoagulation – a real balance of risk vs benefit
- Warfarin
  - INR diagnostics from hospital to home
- NOACs
  - It works (!)
  - …. But does it work FOR YOU (?!)
- "Companion diagnostics"
  - Empowering patients,
  - Improving outcomes

Sarawak Heart Centre

Disclaimer

Research/Educational Grants/Lecture Honoraria from Ministry of Health Malaysia, Astra Zeneca, Boehringer Ingelheim, B.Braun, Medtronic, Merck AG, MSD, Novartis AG, Orbus Neich, Pfizer Ltd, Roche Diagnositics, Siemens Diagnositics, Sanofi-Aventis. St Jude Medical.