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Consideration for BID Regimen: Potential Impact on Adherence and Persistence

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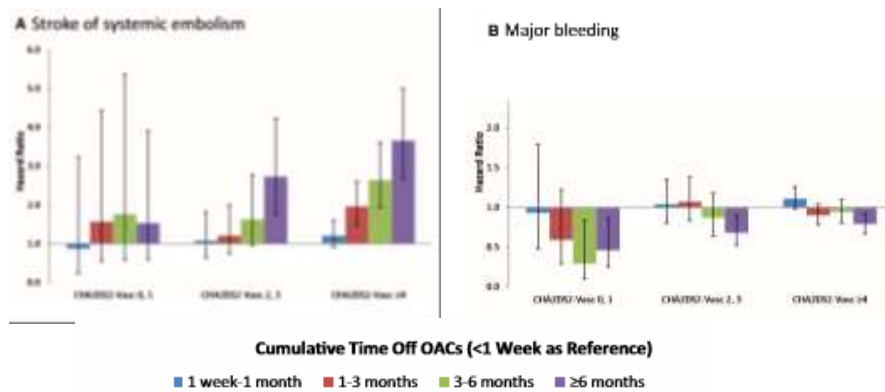


Disclosure

I am a full time employee of WestRock Healthcare,
a company specialized in adherence-enhancing packaging



Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among patients With Atrial Fibrillation



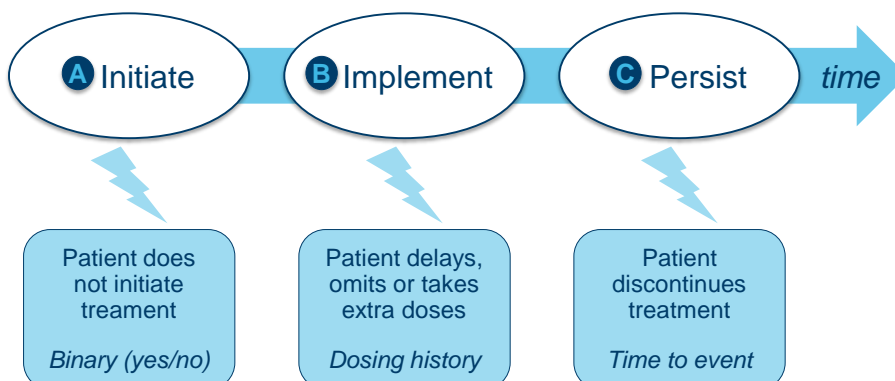
→ Adherence is Key to Therapeutic Success

Yao et al., J Am Heart Assoc. 2016, in press.

3

Medication adherence: ABC Taxonomy

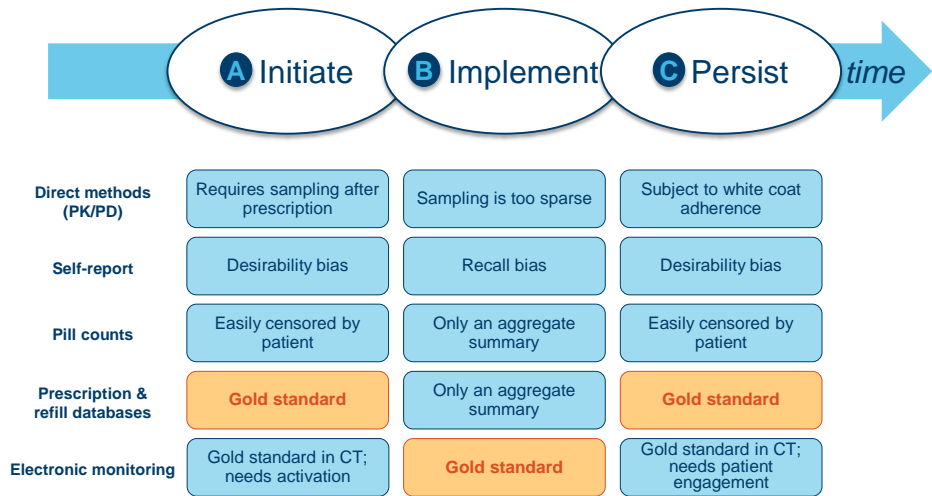
The process by which patients take their medications as prescribed



EU-sponsored research

Vrijens et al., Br J Clin Pharmacol 2012;73:691-705.

Overview of assessment methods of adherence in ambulatory patients

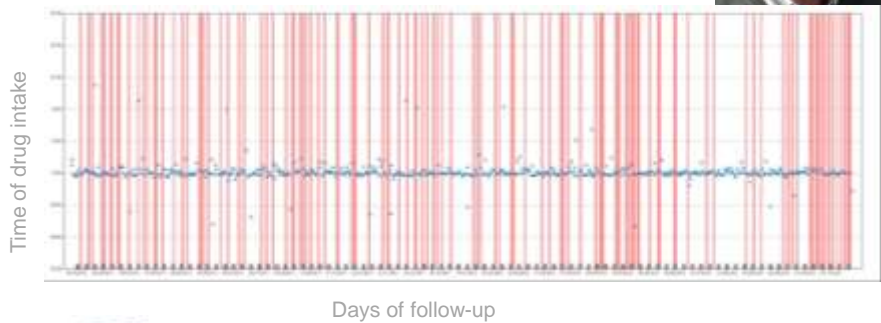


Vrijens B, Heidbuchel H, Europace, 17(8):1317-8, 2015

Case study



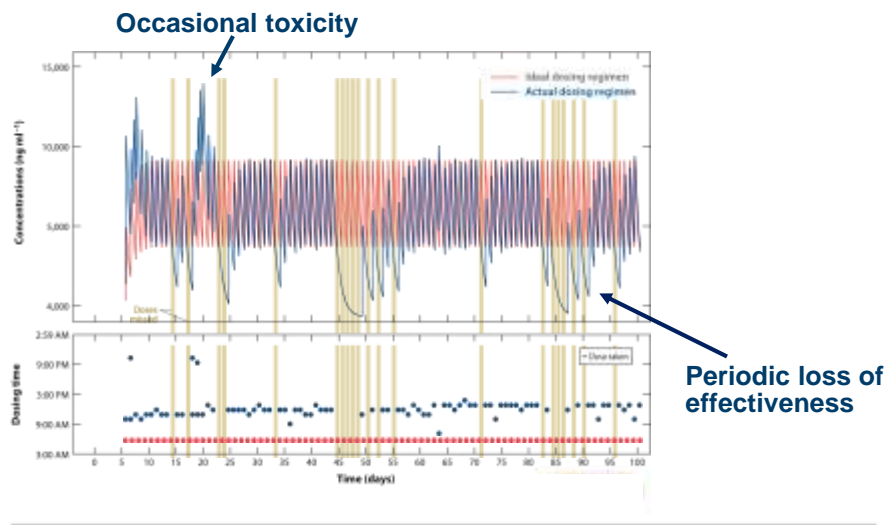
Dosing History Data over ~2 years (2011-2012)



Follow-up: 632 days – 14 days (2%) with double dose
115 days (18%) with no doses

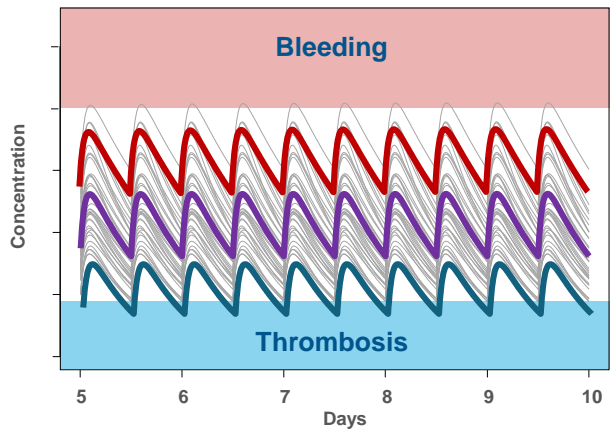
➔ 84% of prescribed doses taken

Variable adherence creates drug-specific issues of efficacy & safety

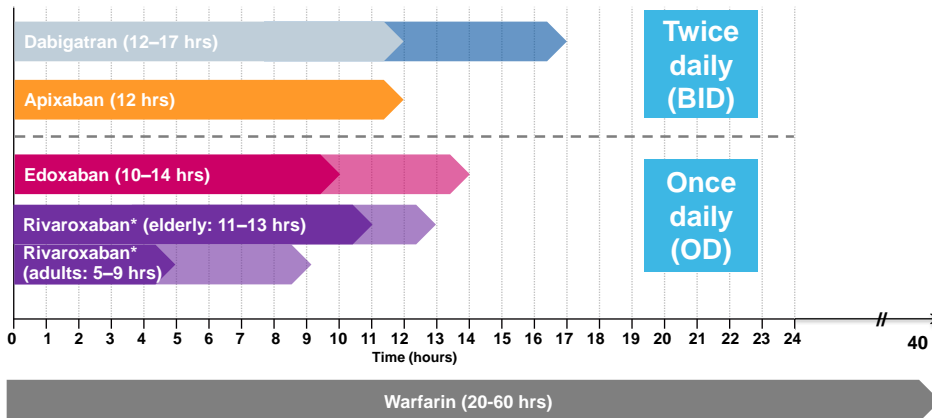


Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301

Therapeutic Range and Biologic Variability for AntiCoagulants



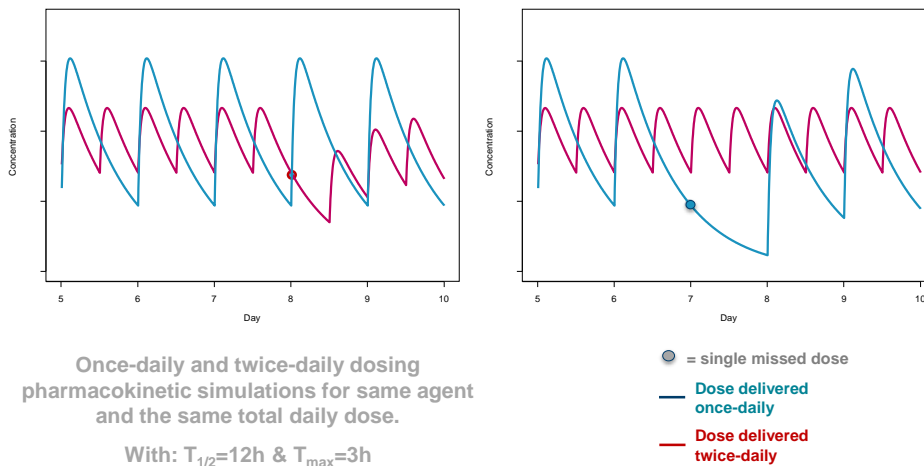
Half-lives of all NOACs are similar,
but **dosing regimens in AF differ**



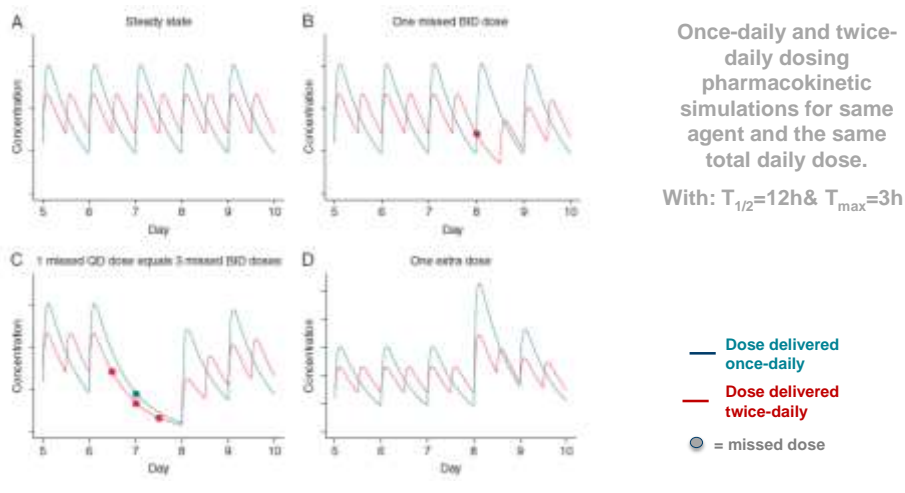
*The approved dosing regimen of rivaroxaban is OD for stroke prevention in patients with nonvalvular AF, prevention of VTE after orthopaedic surgery, and long-term secondary prevention of VTE. Rivaroxaban is administered as a BID regimen for the initial treatment of VTE and secondary prevention after acute coronary syndromes (Xarelto: EU SPC 2015)

Heidbuchel et al. Europace 2015

Pharmacokinetic considerations suggest
that **twice-daily regimen increases forgiveness** for single missed doses

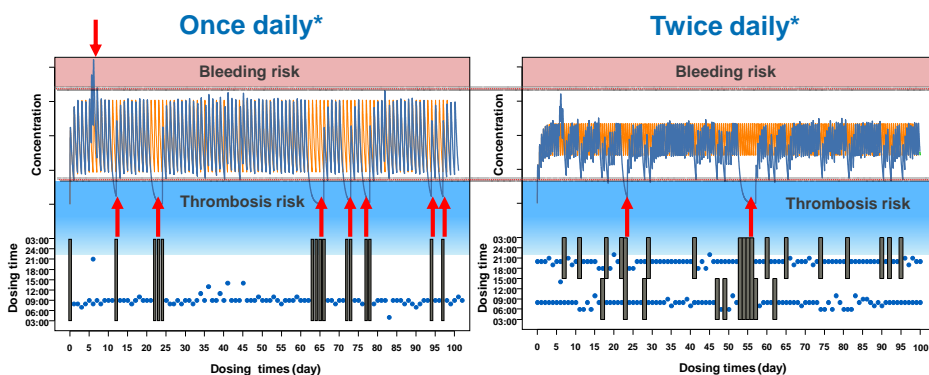


Trade-off between better daily adherence and remaining in the therapeutic range



Vrijens & Heidbuchel, *Europace*, 2015; 17:514-523

Twice-daily regimen increases forgiveness for similar deviations in adherence



* Once-daily and twice-daily dosing for same agent and the same total daily dose

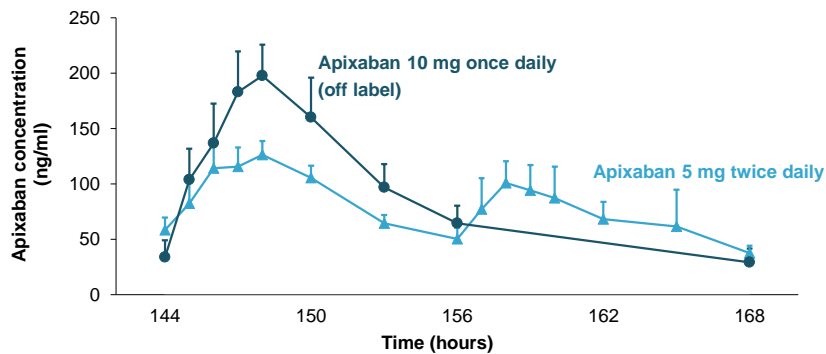
Assuming $T_{1/2}=12\text{h}$; $T_{\max}=3\text{h}$

- 15% missed doses
- 15 once-daily missed doses vs. 30 twice-daily missed doses over 100 days

Vrijens & Heidbuchel, *Europace*, 2015

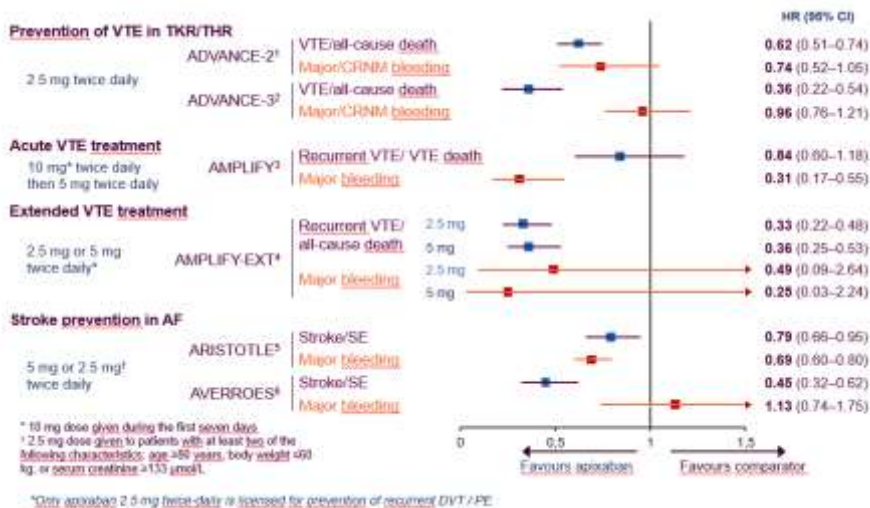
Apixaban has more consistent drug levels, day and night, for twice-daily compared to once-daily

Mean plasma concentration following multiple oral apixaban doses



Frost et al. Br J Clin Pharmacol 2013;76:776-86

Clinical validation of apixaban twice-daily dosing regimen across indications



1. Lassen et al. N Engl J Med 2010; 2. Lassen et al. Lancet 2010;375:807-15; 3. Agnelli et al. N Engl J Med 2013;369:799-808; 4. Agnelli et al. N Engl J Med 2013; 368:699-708; 5. Granger et al. N Engl J Med 2011;365:981-92; 6. Connolly et al. N Engl J Med 2011;364:806-17.

Ultimately adherence (persistence) is a measure of patient satisfaction

Table 3. Adherence to OACs (PDC ≥80%), Stratified by Index Medication (N=64 661)

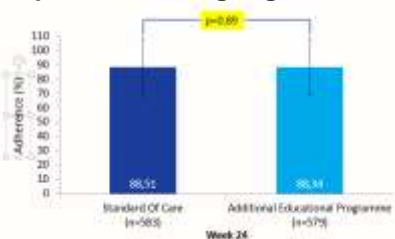
	Apidras® (n=3900)	Dabigatran (n=19 236)	Rivaroxaban (n=12 306)	All NOACs (n=28 471)	Warfarin (n=38 190)	P Value (All NOACs Pooled vs Warfarin)
Unadjusted adherence*						
All	61.9%	58.5%	50.5%	47.5%	40.2%	<0.001
CHA ₂ DS ₂ -VASC score 0 or 1	50.1%	24.6%	36.5%	32.6%	27.1%	<0.001
CHA ₂ DS ₂ -VASC score 2 or 3	62.0%	40.3%	52.6%	49.1%	58.1%	<0.001
CHA ₂ DS ₂ -VASC score ≥4	64.0%	42.4%	53.2%	51.1%	42.3%	<0.001
Adjusted adherence, 95% CI†						
All	52.1% (50.3–53.9)	45.9% (44.8–47.1)	47.6% (46.6–48.7)	47.5% (46.7–48.2)	38.7% (38.1–39.3)	<0.001
CHA ₂ DS ₂ -VASC score 0 or 1	40.6% (35.8–45.4)	28.6% (26.3–30.9)	30.6% (28.7–32.3)	30.8% (29.3–32.3)	25.2% (23.4–27.0)	<0.001
CHA ₂ DS ₂ -VASC score 2 or 3	51.9% (48.9–55.0)	46.9% (45.1–48.6)	48.8% (47.2–50.5)	48.3% (47.2–49.5)	57.3% (56.3–58.4)	<0.001
CHA ₂ DS ₂ -VASC score ≥4	54.1% (51.8–56.5)	48.7% (47.1–50.3)	50.1% (48.7–51.5)	50.1% (49.0–51.1)	42.0% (41.3–42.7)	<0.001

OAC, oral anticoagulant; PDC, proportion of days covered; NOAC, non-vitamin K antagonist oral anticoagulant; CHA₂DS₂-VASC, risk based on the presence of congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, sex category.
 *Unadjusted adherence was the percentage of patients with PDC ≥80%.
 †Adjusted adherence was the predicted probability of PDC ≥80% based on multivariable logistic regression.

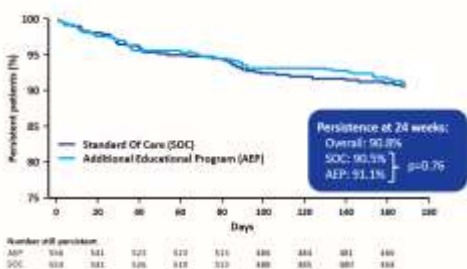
Yao et al., J Am Heart Assoc. 2016, in press.

Assessment of an education and guidance program for apixaban adherence in non-valvular atrial fibrillation: the AEGEAN study

Implementation of the apixaban dosing regimen



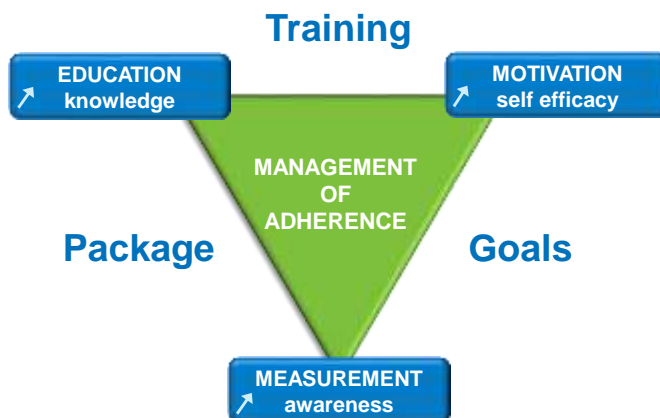
Persistence with apixaban



There was no additional value of a proactive educational program on adherence in the first 6 months of treatment

1. Montalescot et al. Presented at ESC Congress 2015.

Elements to change patients' behaviour

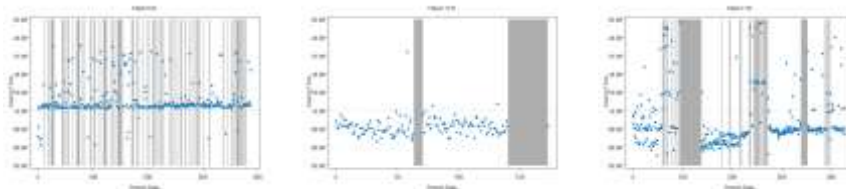


Vrijens, Urquhart, White, 2014, *Expert Rev Clin Pharmacol*; 7(5):633-44

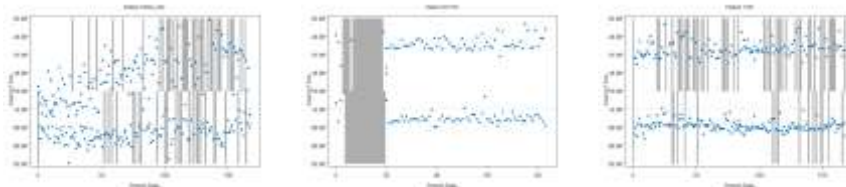
What Can Be Measured Can Be Managed—Deming, WE

Each of these 6 patients took the same percentage (81%) of prescribed doses

Once daily dosing



Twice daily dosing



Vrijens B, *Drug Utilization Research: Methods and Applications*, First Edition, John Wiley & Sons, Ltd., 2016

Conclusion

- In atrial fibrillation, warfarin is associated with sub-optimal implementation and high discontinuation rates, which affect the level of anticoagulation control^{1,2}
- Clinical trials with NOACs have demonstrated non-inferiority or superiority in efficacy vs. VKA, but adherence to the prescribed regimen is of great importance for translating trial results into clinical practice
- Recent simulated PK modelling data for a theoretical drug ($t_{1/2}$ ~12 h and T_{max} = 3 h) has provided reassurance that selection of a twice-daily dose for apixaban rather than a once-daily dose was the correct decision³
- Patient-tailored and measurement-guided intervention are required to achieve sufficient adherence to therapeutic drug regimens³

1. Kimmel et al. *Arch Intern Med* 2007;167:229-35
2. Gallagher et al. *J Thromb Haemost* 2008;6:1500-06
3. Vrijens & Heidbuchel, *Europace*, 2014, inpress