fondazione arianna ANTICOAGULAZIONE PROMUOVE IL

2° CONVEGNO DI ANTICOAGULAZIONE.it
scienza e pratica clinica per il management dei pazienti anticoagulati
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I problemi pratici della terapia anticoagulante con AVK per il tromboembolismo venoso (TEV)

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Practical problems:

acute phase of venous thromboembolism (VTE)

1. Who are good candidates for vitamin K antagonists (VKA) versus the direct oral anticoagulants (DOACs)?

2. How should VKA be initiated?

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

Who are good candidates for VKA vs DOACs?

- *Patients with renal insufficiency*
- CrCl <30 mL/min (using Cockroft Gault formula)

(patients excluded from RCTs of DOACs vs.warfarin for VTE treatment)

- *Patients with bleeding risk factors*
- high bleeding risk pts specifically excluded from RCTs
- DOACs in such pts further complicated by lack of specific reversal agent in case bleeding (except for idarucizumab for dabigatran)

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

Who are good candidates for VKA vs DOACs?

- *Patients taking known interacting drugs*
- INR monitoring facilitates titration of anticoagulant response
- this option unavailable for DOACs
- Inhibitors or inducers of the P-gp efflux transporter or of CYP4503A4
- package labeling limited to drugs with known interaction potential and not to be considered a comprehensive list
- *Poor compliance (??)*
- Routine INR monitoring can identify poor adherence
- Not ideal in case of restricted mobility, poor venous access, or other barriers to successful INR monitoring

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

Who are good candidates for VKA vs DOACs?

- *Patient preference (and affordability)*
- *Patients who are breastfeeding*
- *Patients with antiphospholipid antibody syndrome (??)*

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How should VKA be initiated in VTE?

- as soon as possible following diagnosis of VTE, preferably on the same day, in combination with UFH, LMWH or fondaparinux for at least 5 days

Table 4—*[Recommendation 2.4] Summary of Findings: Early Warfarin (and Shorter Duration Heparin) vs Delayed Warfarin (and Longer Duration Heparin) for Acute VTE*[a-d,41,67,68]

Outcomes	No. of Participants (Studies), Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects: Risk With Delayed Warfarin Initiation (and Longer Duration Heparin)	Anticipated Absolute Effects: Risk Difference With Early Warfarin Initiation (and Shorter Duration Heparin) (95% CI)
Mortality	688 (3 studies), 3 mo[e]	Moderate[f,g] due to imprecision	RR 0.9 (0.41-1.95)	24 per 1,000[h]	2 fewer per 1,000 (from 14 fewer to 23 more)
Recurrent VTE	688 (3 studies), 3 mo[e]	Moderate[f,g] due to imprecision	RR 0.83 (0.4-1.74)	47 per 1,000[h]	8 fewer per 1,000 (from 28 fewer to 35 more)
Major bleeding	688 (3 studies), 3 mo[i]	High[f,j,k]	RR 1.48 (0.68-3.23)	16 per 1,000[h]	14 more per 1,000 (from 9 fewer to 66 more)

Chest ACCP 2012

How should VKA be initiated in VTE?

- warfarin initial dose should be 5 or 10 mg for most patients to avoid overdosage,
- acenocumarol: 4 mg (2:1 potency vs warfarin)

- Nomograms with initial doses <5 mg might be appropriate in patients >75 years, malnourished, with liver disease or congestive heart failure, receiving medications known to inhibit warfarin's metabolism, or with a high bleeding risk.

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How do the 10 mg and 5 mg warfarin initiation nomograms compare in people with venous thromboembolism?

Figure 3. Forest plot of comparison: 1 10-mg nomogram versus 5-mg nomogram, outcome: 1.1 therapeutic INR on fifth day.

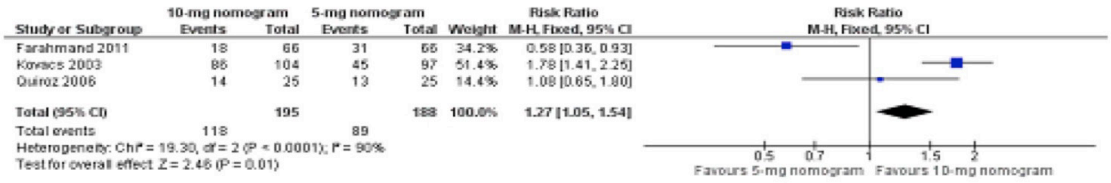


Figure 4. Forest plot of comparison: 1 10-mg nomogram versus 5-mg nomogram, outcome: 1.2 recurrent venous thromboembolism at 90 days.

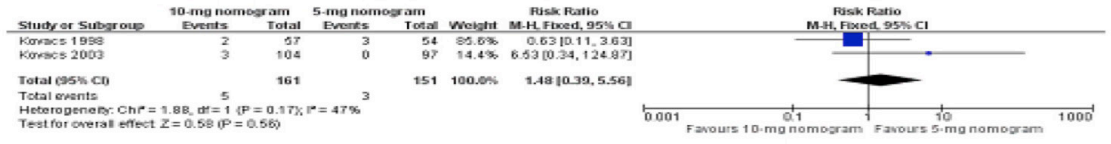
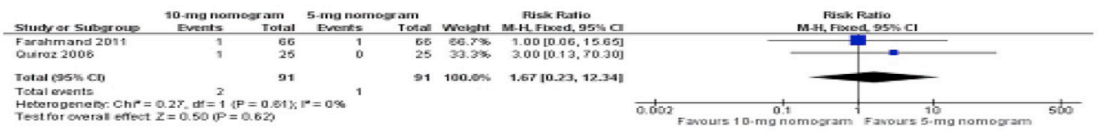


Figure 5. Forest plot of comparison: 1 10-mg nomogram versus 5-mg nomogram, outcome: 1.3 major bleeding at 14 days.



Garcia P et al. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD007699.

Table 2 Example of a warfarin dose-initiation nomogram [107]

Day	INR	Warfarin dose (mg)
5-mg warfarin initiation nomogram		
1		5
2		5
3	<1.5	10
	1.5–1.9	5
	2.0–3.0	2.5
	>3.0	0
4	<1.5	10
	1.5–1.9	7.5
	2.0–3.0	5
	>3.0	0
5	<2.0	10
	2.0–3.0	5
	<3.0	0
6	<1.5	12.5
	1.5–1.9	10
	2.0–3.0	7.5
	>3.0	0

Kovacs et al, Ann Int Med 2003

How should VKAs be initiated?

- For patients sufficiently healthy to be treated as outpatients, warfarin 10 mg daily for the first 2 days has been suggested.
- Initial warfarin doses > 10 mg should be avoided
- Beginning on day 3 of therapy, INRs should be measured daily and warfarin doses adjusted to achieve an INR>2.0 as soon after day 5 of therapy as possible.

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How should VKAs be initiated?

Table 9—*[Section 4.1.1] Optimal Therapeutic INR Range: Higher Target vs 2 to 3*[119]

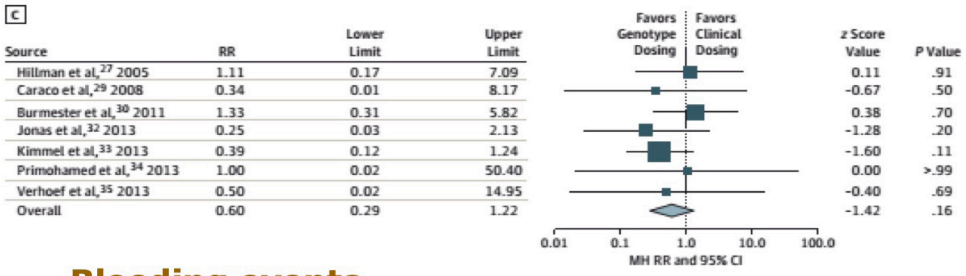
Outcomes	No. of Participants, (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects[a]	
				Risk With INR 2-3	Risk Difference With INR 3-5 (95% CI)
Major hemorrhage per 100 patient-y, various definitions	76,646 (17 studies[b]), 1.8 y	Low[c,d] due to risk of bias, dose-response gradient	RR 2.7 (1.8-3.9)	6 per 1,000	10 more per 1,000 (from 5 more to 17 more)
Thromboembolism per 100 patient-y, various definitions	835 (10 studies[e])	Very low[f,g] due to risk of bias, inconsistency	RR 0.9 (0.6-1.3)	Study population	
				46 per 1,000	5 fewer per 1,000 (from 18 fewer to 14 more)
				Moderate	
				50 per 1,000	5 fewer per 1,000 (from 20 fewer to 15 more)

CHEST ACCP

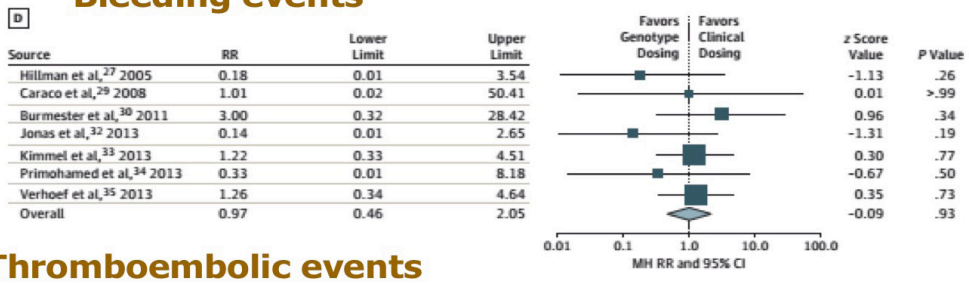
Original Investigation

Genotype-Guided vs Clinical Dosing of Warfarin and Its Analogues
Meta-analysis of Randomized Clinical Trials

2812 pts



Bleeding events



Thromboembolic events

CYP2C9,VKORC1,CYP4F2

Stergiopoulos K, Brown DL.
JAMA Intern Med. 2014;174:1330-1338

Practical problems: VTE long term and extended phase

1. How to optimize anticoagulation control?
2. How to manage VKA during invasive procedures?
3. How to manage sub-therapeutic anticoagulation and recurrent VTE?
4. How to switch between anticoagulants?
5. What is an appropriate follow-up?
6. How to manage challenging clinical situations?
7. *How to manage VKA-induced over-anticoagulation and bleeding?*
8. *How to manage VKA drug–drug and drug-dietary interactions?*

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How to optimize anticoagulation control?

- Computer- aided warfarin dosing
- Anticoagulation management services

Table 3 Outcomes of anticoagulation management service versus usual care [55]

Outcomes	Events in AMS/patients (%)	Events in UC/patients (%)	Risk ratio (95 % CI)	I^2 (%)
Major bleeding				
RCTs	5/367 (1)	10/368 (3)	0.64 (0.18–2.36)	12.2
Non-RCTs	49/4619 (1)	91/4595 (2)	0.49 (0.26–0.93)	46.7
Thromboembolic				
RCTs	8/367 (2)	11/368 (3)	0.79 (0.33–1.93)	0.0
Non-RCTs events	44/5335 (1)	133/5250 (3)	0.37 (0.26–0.53)	3.7
All cause mortality				
RCTs	10/299 (3)	11/299 (4)	0.93 (0.41–2.13)	0.0
Non-RCTs	5671/88,480 (6)	44,763/633,499 (7)	0.85 (0.37–1.98)	15.7

AMS anticoagulation management service, *UC* usual care, *CI*, confidence interval, I^2 measures the heterogeneity of pooled studies, *RCT* randomized controlled trial

Saokaew S et al J Thromb Haemost (2010) 8:2418–2427

How to optimize anticoagulation control?

- *Patient education*:
- all patients and their caregivers should receive patient-centered education regarding VKA for VTE treatment at the initiation of therapy and periodically thereafter

- *Patient self-testing and patient self-management*
- RCTs in VTE patients are lacking

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

Raccomandazioni FCSA -2016

- In pazienti con INR sub-terapeutico, in assenza di specifiche raccomandazioni è importante considerare: a) il valore assoluto dell'INR, b) il valore del precedente INR, c) il tempo intercorso tra i 2 valori, d) il rischio tromboembolico assoluto correlato alla indicazione, e) il rischio tromboembolico individuale.

- La dose di AVK deve essere temporaneamente aumentata anche attraverso la somministrazione di una dose di carico. Il controllo di INR deve essere eseguito entro 2-3 giorni per assicurarsi che il valore di INR sia rientrato nel *range*.

- Una eventuale *bridging therapy* con EBPM deve essere considerata nei pazienti ad alto rischio.

How to manage VKAs during invasive procedures?

- Stopping warfarin 4–5 days prior to the procedure to return the INR to near-normal values for procedures with high bleeding potential.

- No bridge therapy for most patients
- exceptions: VTE within the previous month
- prior history of recurrent VTE during anticoagulation therapy interruption

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How to manage sub-therapeutic anticoagulation and recurrent VTE?

- For most patients with VTE and subtherapeutic warfarin anticoagulation we suggest reestablishing therapeutic anticoagulation as quickly as possible without bridge therapy

- For recurrent VTE not associated with subtherapeutic warfarin anticoagulation we suggest either increasing the target INR range or switching to an alternative anticoagulant.

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How do I switch between anticoagulants?

Table 5 Switching to DOACs

Warfarin to DOAC	
Dabigatran[a]	Start when INR < 2.0
Rivaroxaban[a]	Start when INR < 3.0
Apixaban[a]	Start when INR < 2.0
Edoxaban[a]	Start when INR ≤ 2.5
LMWH to DOAC	
Dabigatran	Start DOAC within 0–2 h of the time of next scheduled dose of LMWH
Rivaroxaban	
Apixaban	
Edoxaban	
(iv) UFH to DOAC	
Dabigatran[a]	Start DOAC immediately after stopping iv UFH
Rivaroxaban[a]	
Apixaban[a]	
Edoxaban[a]	Start Edoxaban 4 h after stopping iv UFH

As a general rule, we suggest that as INR drops below 2.5, a DOAC can be started

As a general rule, we suggest that each DOAC can be started within 30 min after stopping (iv) UFH

[a] Recommendations adapted from company's package insert

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

How do I switch between anticoagulants?

Table 6 Switching to Warfarin

DOAC to warfarin	
Dabigatran[a]	Start warfarin & overlap with dabigatran; CrCl ≥ 50 mL/min, overlap 3 days CrCl 30-50 mL/min, overlap 2 days CrCl 15-30 mL/min, overlap 1 day
Rivaroxaban[a] Apixaban[a]	Stop DOAC; start warfarin & LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Edoxaban[a]	For 60 mg dose reduce dose to 30 mg & start warfarin concomitantly. For 30 mg dose reduce dose to 15 mg and start warfarin concomitantly. Stop edoxaban when INR ≥ 2.0

As a general rule, we believe either approach (i.e. stop DOAC then start LMWH & warfarin; or overlap warfarin with DOAC, measure INR just before next DOAC dose and stop DOAC when INR ≥ 2.0) can be used for all DOAC to warfarin transitions

CrCl creatinine clearance

[a] Recommendations adapted from company's package insert. Overlap intended to avoid under-anticoagulation while warfarin effect developing. When DOAC overlapped with warfarin, measure INR just before next DOAC dose since DOAC can influence INR

- For patients at high risk of VTE recurrence, we suggest overlapping apixaban, rivaroxaban, edoxaban, or dabigatran with warfarin therapy for at least 3 days combined with measuring the INR just before the next DOAC dose to limit any DOAC effect on the INR and discontinue DOAC therapy when an INR > 2.0 is achieved.

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

What is an appropriate follow-up?

- Length of VKA treatment after VTE
- Low intensity VKA not recommended

- Periodic re-evaluation in case of extended therapy to assess the risk –benefit ratio

How to manage challenging clinical situations?

- *liver disease*

- When warfarin therapy is deemed necessary in patients with liver disease with VTE we suggest a starting dose of 1 mg daily with careful dose titration to achieve an INR between 2 and 3.

- For patients with esophageal varices who require warfarin therapy we suggest banding of varices prior to beginning therapy when possible.

Witt DM et al, J Thromb Thrombolysis (2016) 41:187–205

Epatopatie croniche

- Prima di iniziare il trattamento anticoagulante in pazienti con epatopatia cronica, devono essere messe in atto tutte le misure atte a ridurre al minimo il rischio di sanguinamento gastro-esofageo.
- L'indicazione al trattamento ed il rapporto rischi-benefici devono essere periodicamente rivalutate.
- Nella trombosi sintomatica del distretto mesenterico trova indicazione trattamento con eparina (ENF o EBPM) associata e seguita da AVK.
- La durata della terapia è correlata con il perdurare o meno della causa scatenante.

FCSA-2016

Soggetti anziani

- Il trattamento anticoagulante con AVK si dimostrato vantaggioso rispetto al rischio di emorragia.
- Particolare attenzione deve essere posta alla sorveglianza clinica di questi pazienti allo scopo mantenere il paziente nel *range* terapeutico.
- Sia per la FA che per il TEV l'intensità dell'anticoagulazione deve essere compresa tra 2.0 e 3.0.
- Gli anticoagulanti diretti rappresentano una valida alternativa in soggetti attentamente selezionati

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Insufficienza renale severa

- I farmaci AVK sono utilizzabili nel paziente con IR terminale.
- Per i pazienti con VTE il trattamento in acuto di prima scelta è rappresentato dall'ENF, seguita da AVK (INR tra 2.0-3.0)
- Gli AVK sono indicati anche nella terapia del TEV in periodo post acuto (INR 2.0-3.0).

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Neonati e bambini

- Nomogrammi specifici
- Uso di preparazione galenica in bambini < 5 mesi
- Educazione dei genitori
- Uso di coagulometri portatili

Presenza di lupus anticoagulant

- La maggior parte delle tromboplastine commerciali non sensibili a LA
- Se PT normale prima di iniziare AVK, la tromboplastina locale può essere utilizzata (Tripodi, SSC, JTH 2016)

FCSA-2016