



Staying Safe on Blood Thinners: Lessons from the Anticoagulants Clinics



Anticoagulants Clinics ?

- **Thrombosis service (Netherlands) 1949 ,Federation in 1971.**
- Anticoagulation management services (AMS) USA in 1950
- Anticoagulant Clinics (AC)
- Anticoagulant unit in UK 1959
- Federation of Thrombosis Centers , (federated clinics in Italy in 1989).
- Community Pharmacist Anticoagulation Management Service (CPAMS) (canada, NZ)

Centralized clinic dedicated entirely to patients on anticoagulant therapy (**University of Utrecht.**)

Medical team: Physicians specialized in anticoagulation management, Trained nurses for patient monitoring and follow-up

Laboratory within the clinic: Rapid reporting of results for timely dose adjustments in the same-visit, according to laboratory results.

Patient Education Instructions on treatment, diet, and drug interactions. Encouragement of adherence to therapy and regular follow-ups.

Clinical Follow-up Continuous monitoring for bleeding and thrombotic complications. Coordination with prescribing physicians to ensure safety/efficacy



Management of Vitamin K antagonist Treatment
Dose adjustment according to laboratory results (INR)

VKA and TTR

The Efficacy and Safety of warfarin treatment is dependent of the INR and correlated with the Time in to the Therapeutic range (TTR).

When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.

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Keeping the time in therapeutic range above 70% should be considered in patients taking a VKA to ensure safety and effectiveness, with INR checks at appropriate frequency and patient-directed education and counselling.^{304–308}

IIa

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What are mTTRs in trials?

	Anticoagulant	Mean time in the therapeutic range (%)
RE-LY	Dabigatran	64
ROCKET AF	Rivaroxaban	55
ARISTOTLE	Apixaban	62.2
ENGAGE AF	Edoxaban	64.9

Region	N	i-TTR, mean %	SD	Median (25th, 75th)	Parameter Estimate	P Value
East Asia	677	53.3	21.7	56 (40, 67)	-12.52	<0.0001
India	115	39.5	25.2	42 (21, 56)	-26.38	<0.0001
Eastern Europe	2462	53.0	21.5	55 (40, 68)	-12.82	<0.0001
Western Europe/similar	1019	66.6	17.7	69 (58, 79)	0.76	0.37
South Africa	115	57.6	21.1	59 (46, 74)	-8.19	<0.0001
Latin America	875	59.0	20.0	61 (48, 74)	-6.84	<0.0001
Canada/United States	1244	65.8	18.7	68 (56, 79)	Ref	

In usual care in France TTR about 50%

What are mTTRs in Anticoagulants clinics

	Software	Treatment	TTR
Dimberg 2012	Auricula	Warfarin	71,3 Target 2 - 3
Cafolla 2011	Zeus	Warfarin	64,53 % Target 2 - 3
Papaioannou 2010	MEDeINR	Warfarin	69% Target 2-3
Poller 2009	Dawn-AC	Warfarin	66,8 % Target 2-3
Kim 2009	Kaatz algorithm	Warfarin	73,2 % Target 2-3
Héritier 2007	Préviscan	Fluindion	71,79 % Target 2-3
Poller 1998	Dawn-AC	Warfarin	72,3 %
Cambus 2011	AVK Manager	Warfarin, fluindion	73% Target 2-3 → France

Group	Result		
	Time in therapeutic range (TTR)	% of patients with a TTR of 65% or greater	% of patients with a TTR of 75% or greater
All CPAMS patients (N = 930)	71.4%	67.3%	40.5%
All CPAMS patients, most recent 5 months (N = 785)	75.7%	72.5%	52.9%
Historical data for CPAMS patients with at least three historical tests (N = 867)	71.6%	63.3%	53.9%
Usual care ^{2,3}	50-60%	41%	Not available
Attrition (CPAMS patients who left the project; N = 184)	62.1%	40.8%	21.7%

Abbreviation: CPAMS, Community Pharmacist-led Anticoagulation Management Service.

¹Table used with permission, CPAMS Final Evaluation Results, 2019. <https://pans.ns.ca/cpams>.

mTTRs in a Dutch Thrombosis Centers

Retrospective, observational study
One center 3600-5500 patients annually

Time in therapeutic range for patients controlled by the Thrombosis Center "Neder-Veluwe".

Year	Patient category	Time in therapeutic range by linear interpolation method (%)			
		Non-self-management patients (NSM)		Self-management patients	
		TR: 2.0-3.5 INR	TR: 2.5-4.0 INR	TR: 2.0-3.5 INR	TR: 2.5-4.0 INR
2011	Long-term	77.5	75.3	83.5	80.6
2012	Long-term	81.2	77.3	86.2	82.9
2013	Long-term	82.6	76.6	85.9	82.6
2014	Long-term	86.0	79.7	82.5	81.7
2015	Long-term	88.9	84.1	85.4	80.6
		TR: 2.0-3.0 INR	TR: 2.5-3.5 INR	TR: 2.0-3.0 INR	TR: 2.5-3.5 INR
2016	Long-term	76.5	69.6	77.9	71.6
2017	Long-term	74.4	66.7	81.2	73.3
2018	All	72.7	64.2	79.2	71.4
2019	All	73.5	66.2	81.7	75.0

Incidence of adverse events reported by Thrombosis Center Neder-Veluwe (TCNV) and other Dutch centers.

Year	Mean age of TCNV patients (years)	Incidence (% per patient-year)					
		All major bleeding		Intracranial bleeding		Fatal bleeding	
		TCNV	FNT ^a	TCNV	FNT ^a	TCNV	FNT ^a
2011	72.35	1.30	1.1 (0.2-3.1)	0.30	0.3 (0-0.8)	0.13	0.2 (0-0.5)
2012	72.76	1.70	1.1 (0-3.0)	0.31	0.2 (0-1.0)	0.20	0.1 (0-0.6)
2013	73.08	1.30	1.2 (0.3-5.7)	0.30	0.2 (0-0.8)	0.28	0.1 (0-0.6)
2014	73.48	1.84	1.2 (0.1-2.6)	0.33	0.3 (0-0.7)	0.17	0.2 (0-0.4)
2015	73.87	2.67	1.3 (0.1-3.3)	0.73	0.3 (0-0.8)	0.49	0.1 (0-0.8)
2016	74.33	1.70	1.4 (0.1-5.6)	0.46	0.2 (0-0.9)	0.14	0.1 (0-0.5)
2017	74.88	2.34	1.3 (0.2-3.8)	0.62	0.3 (0-1.2)	0.29	0.2 (0-2.0)
2018	75.33	2.41	1.2 (0.4-3.3)	0.59	0.3 (0-0.6)	0.38	0.2 (0-0.5)
2019	75.23	3.02	1.4 (0.5-3.9)	0.75	0.3 (0-1.0)	0.41	0.2 (0-0.6)

^a Median (range) of incidences reported by members of the Federation of Netherlands Thrombosis Centers (FNT).

Trial	warfarine	Major Bleeding	HIC Bleeding
RE-LY (AF)	Dabi (150 mg)	3,36%	0,74%/
ROCKFET AF	Riva	3,4%	1,2%
ARISTOFLE (AF)	Apix	3,09%	0.8%
ENGAGE AF	Edox (60 mg)	3,43%	0.39%
AMPLIFY (VTE)	Apix	1,8%	-
EINSTEIN (VTE)	Riva	1,2-2,2 %/yr	-
RECOVER(VTE)	Dabi	1, 7-1,9%	-
HOSUKAI (VTE)	Edox	1,6%/y	-

BEAUJON's CAC

80% of the patients Hepatology/Acute Mesenteric Ischemia Unit

Created in 2007

Individuals remote and face to face sessions and group based education sessions.
Evaluation: knowledge, transition, adherence, dangerous activities sports activities, quality of life++



Patient Education



Multidisciplinary Team

Thrombocytopenia
Portal Hypertension
Liver Disease , LT

Gut Resection
Malabsorption
Comorbidities

Inclusion visit nurse/physician : Indication or no, bleeding risk, type of treatment, duration, doses, Target INR, drug interactions, patient's understanding, expectations, way of life, share decision
Individualized follow-up plan, patient **agreement**.

Ongoing evaluation at least once / year;.stop treatment + **Transitions**. Modification, Invasive procedures.

Coordination ++ Hepato/Gastro/GP/cardiologists/others
Quality of life: women, young patients

Opening hours, phone numbers, email address...
Communication ++ , listening, understanding.



DOACs cac

Scheduled clinical and biological monitoring
Renal and liver functions, Blood cells count
DOACs dosings teleconsultations /emails

VKA cac



Baseline INR, target Remote monitoring INR++. Patient self management. Dose adjustment by the nurse/ regular TTR monitoring.
Switch or not to DOACs
teleconsultations/emails

mTTRs at BEAUJON Anticoagulant Clinic

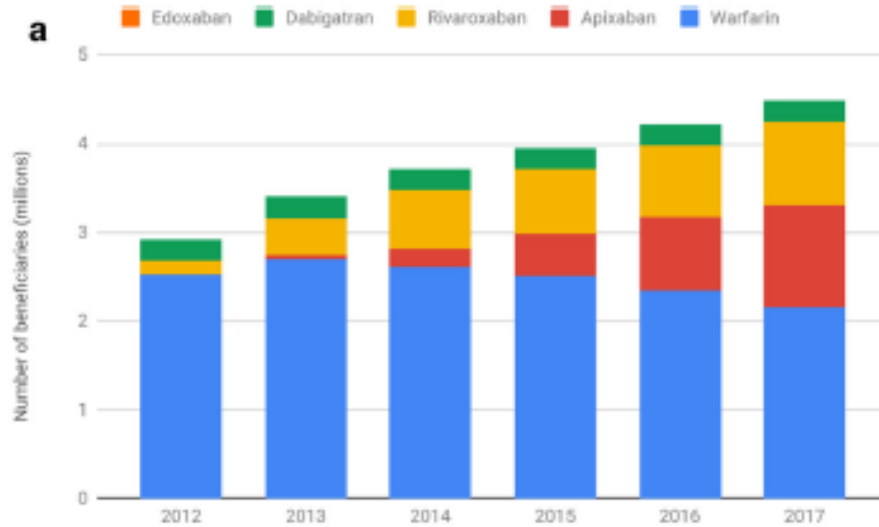
Year	Number of patients	INR	% TTR	% Time INR > 5	% Time INR > 6	% Time INR > 10
2017	360	5116	71.3	1.4	0.46	0.004
2018	421	6360	71.2	0.39	0.13	0.02
2019	502	7603	69.8	1	0.10	0
2020	507	7107	72.3	0.39	0.14	0.02
2021	537	7455	73.5	1	0.5	0.01
2022	456	6144	71.4	0.43	0.16	0.01
2023	384	5450	70.9	1.4	0.58	0.01

→ **Anticoagulants clinics and DOACs**

DOACs Pivotal Trials Major Bleeding Outcomes (AF and VTE)

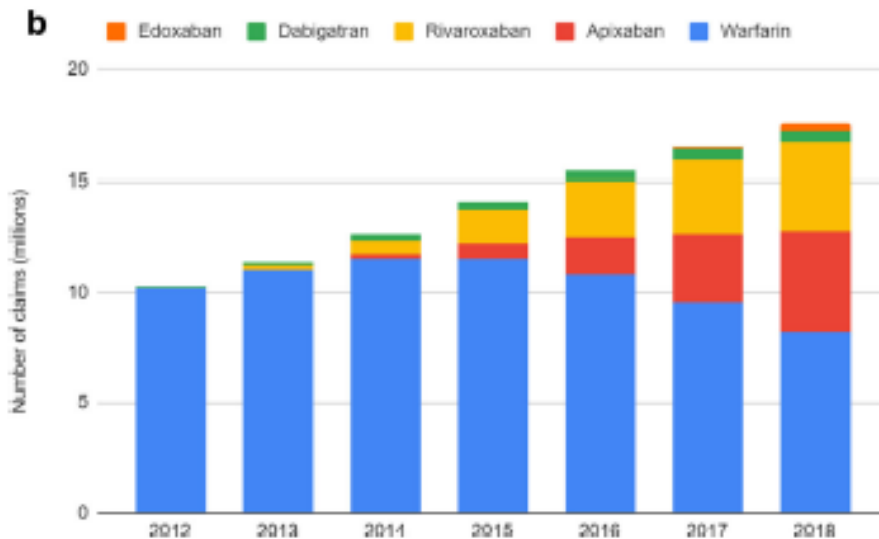
Author (Year of Publication)	Study Inclusion	Fatal Bleeding	Major Bleeding	ICH	Major GI Bleeding	CRNMB
Van Der Hulle et al. (2014)	Five randomized controlled trials (2 evaluating rivaroxaban; 1, dabigatran; 1, apixaban; and 1, edoxaban)	0.06% vs. 0.17% N _d = 12,197 N _k = 12,193	1.1% vs. 1.7% N _d = 12,197 N _k = 12,193	0.09% vs. 0.25% N _d = 12,197 N _k = 12,193	0.35% vs. 0.53% N _d = 12,197 N _k = 12,193	6.6% vs. 8.4% N _d = 12,197 N _k = 12,193
Chai-Adisaksopha et al. (2014)	Twelve randomized controlled trials (4 evaluating dabigatran; 4, rivaroxaban; 2, apixaban; and 2, edoxaban)	0.30% vs. 0.52% N _d = 57,850 N _k = 44,757	4% vs. 4.64% N _d = 57,850 N _k = 44,757	0.51% vs. 1.08% N _d = 57,850 N _k = 44,757	2.09% vs. 1.70% N _d = 53,753 N _k = 40,650	10.24% vs. 11.05% N _d = 45,774 N _k = 38,750

Anticoagulation use with DOACs



USA +54%

Increasing use across Europe +++

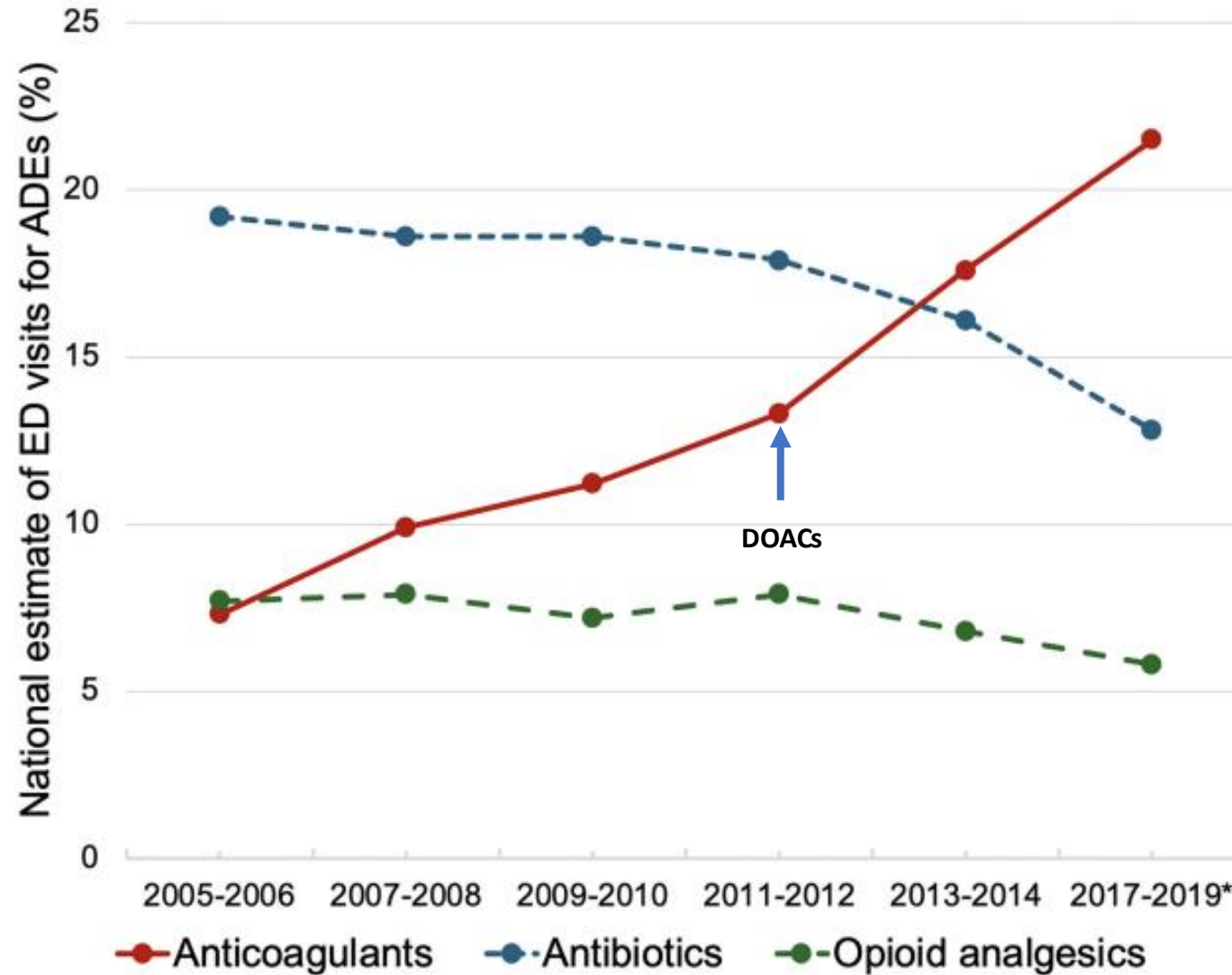


UK +71%

-convenient treatment
-Population ageing

> 10 millions of patients treated

US Emergency Department Visits Attributed to Medication Harms, 2017-2019

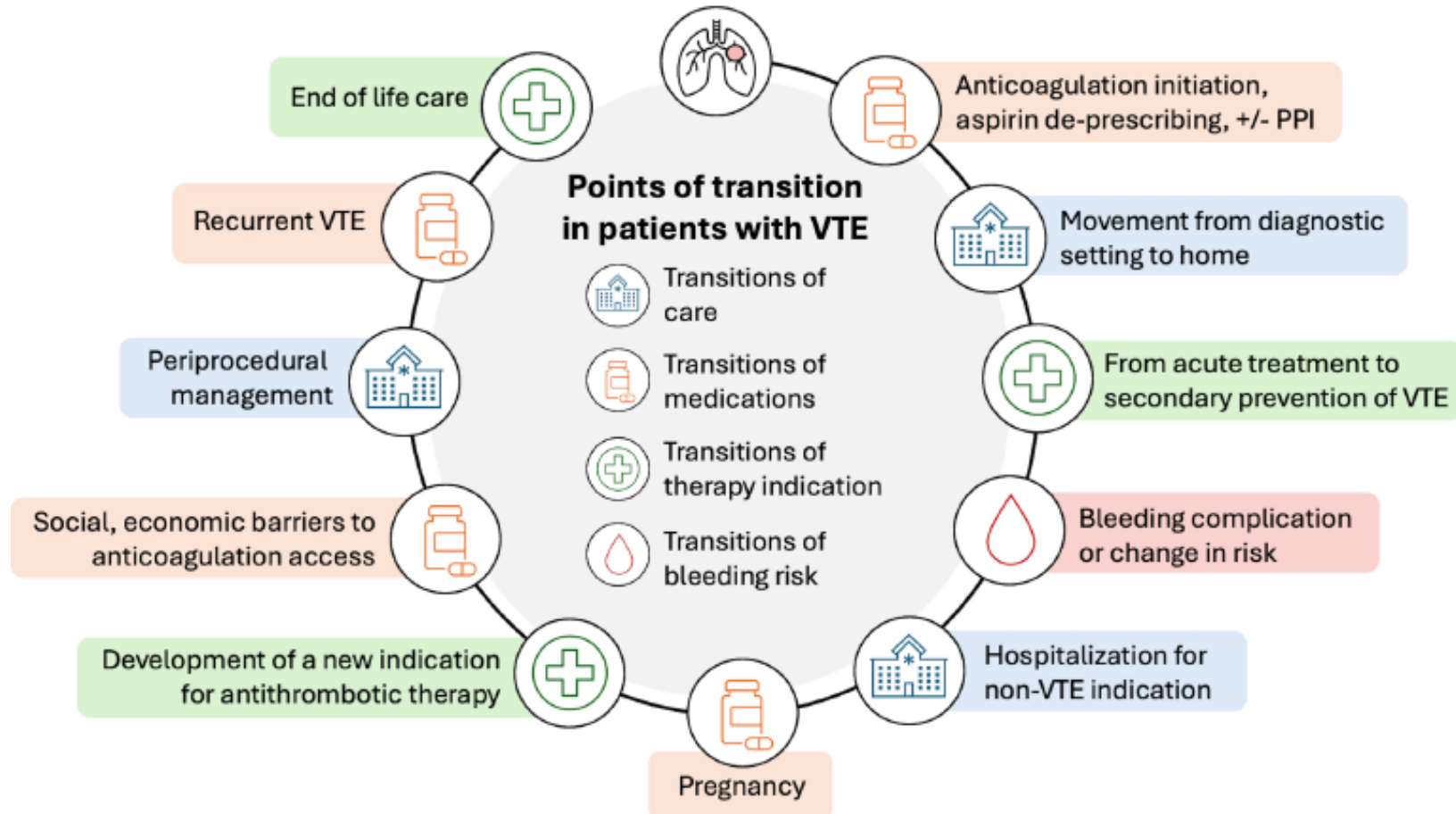


- Inappropriate doses (off label dosing)
- Drug interactions
- Points of Transition
- observance/adherence



Avoidable ADEs

Points of transition in patients with VTE



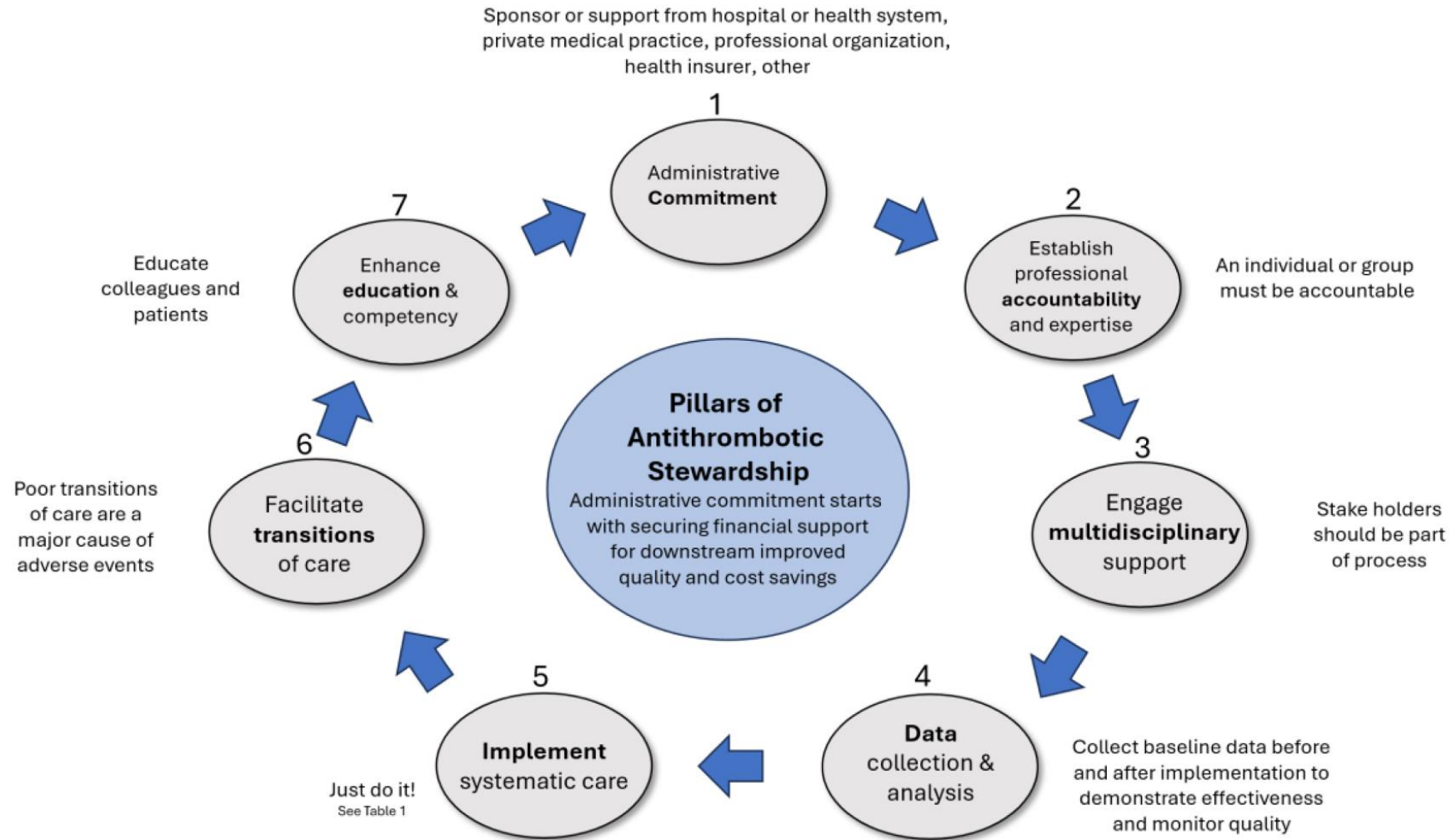
Increased risk of ADEs

FIGURE Points of transition in patients with venous thromboembolism. PPI, proton pump inhibitor; VTE, venous thromboembolism.

Patient education to inform the anticoagulant clinic at each transition point

Advancing anticoagulation stewardship: A call to action for stewardship from the US-based anticoagulation forum

It's time to improve antithrombotic therapy! *A global perspective for antithrombotic stewardship*



Multidisciplinary Anticoagulation Stewardship Programs (MASPs)

Examples of stewardship responsibilities within a program of systematic care. These are with regard to anticoagulant therapy but there are many other responsibilities within a comprehensive stewardship program especially within a hospital setting.

Selection of appropriate therapies and interventions at the time of diagnosis.

Review and address dosing, drug interactions and potential complicating conditions.

Identify duration of therapy and follow up.

Manage episodes of transition of care.

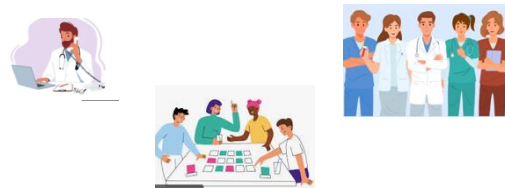
Manage periprocedural interventions as they occur over time.

Manage the use of anticoagulant reversal therapy in patients with bleeding.

Provide ongoing monitoring and clinical support as needed.

Communicate and educate with collaborating clinicians in patient's care.

Review treatment intensity as treatment progresses.



Anticoagulant Clinics

Birth	Indication	Inclusion CAC	recurrent thrombosis	Bleedings	VKA	INR	FV	FII il	pPatelets	Target INR	Target FII	Commentaires
1987	BCS	2018	aucun	aucun	fluidion	1,51	59%	55%	125 G/L	2,5 - 3	25-35%	On going
1983	BCS + Jak2+	2007	2009 : 1 TIPS thrombosis 01/2015 : TIPS + PVT+ SMV related to thrombocytosis => Hydrea +	2015 and 2018 GIBs VO	warfarine	1,6	45%	86%	Sous Hydrea	3,5 - 4,5	25-30	on going
1964	BCS	2013	2016 : stent thrombosis 2021 : TIPS + partial stent thrombosis + VH droite	Aucun	warfarine	1,5	66%	78%	141G/L	2,5 - 3,5	20-30	on going
1972	BCS + Portal venous thrombosis + Jak2+	2018		2019 and 2023 :VO GI bleeding	warfarine	1,5	53	75%		2,5 - 3,5	25-35%	on going
1981	BCS	2011	2023 : thrombose TIPS => angioplastie	none	warfarine	1,6	35	55%	118 G/L	2,5-3,5	25-30	on going
2000	BCS + JAK2+ + PC à 29%	2020	Aucun	none	warfarine	1,4	38	66	330 G/L	2,5-3,5	25-35	Stop t in 2023
1961	Portal vein Thrombosis	2020	Aucun	none	warfarine	1,49	47%	50%	56 G/L	2,5-3,5	20-30%	Died 2025
1980	BCS +FV Leiden HTZ	2017	aucun	2016 VO	warfarine	1,55	55%	60%	152 G/L	2,5-3,5	25-35%	on going
1956	Cirrhosis + venous Hepatic thrombosis	2024	Aucun	none	warfarine	1,67	67%	49%	127 G/L	2,5-3,5	20-25%	Transplantation 2024
1995	BCS + Jak2+	2012	Aucun	2017 : GI / 2020 : GI	warfarine	1,45	60%	67	-	2,5-3,5	25-30%	on going
1974	Thrombose porte + VMS	2023	Aucun	none	warfarine	1,44	67%	51%	68 G/L	2,5-3,5	20-25%	Tranplantation i2024
1988	BCS and nocturn paroxystic hemolysis	2023	Aucun	none	warfarine	1,47	98%	76%	107 G/L	2,5-3,5	25-35%	witch AOD in 2023
1965	SBC	2008	07/2008 TIPS	none	warfarine	1,7	30%	45%	350 G/L	2,5-3,5	25-35%	on going
1977	PVT and APS	2010	2023/2025 : obstruction TIPS	GIB++	flunindione	1,4	55%	72%	53 G/L	3-3,5	20-30%	on going
1980	Portal veinous thrombosis since chidhood	2015	2020/2021 : stent trhombosis	GIB VO + menorrhagia	warfarine	1,7	30%	52%	25 G/L	2,5-3,5	25-30%	on going
1988	BCS + Jak2++ FV leiden HTZ	2024	2021 PVT 2024 2026 TIPS thrombosis + Mesentreic thrombosis extension.	2025 GIB VO	warfarine	1,49	28%	25%	Variable	2,-5-3,5	20-30%	TH switch innohep 02/2026
1963	Portal veinous thrombosis +NASH	2024	none	none	warfarine	1,5	47%	58%	127 G/L (2024)	2,5-3,5	20-30	Transplantation in 2025 : STOP AVK
1957	Portal Vein thrombosis 2018 / TIPS in 2024		Extension pf PVT in 2023 and 2024	GIB on ulcer	warfarine	1,2	58%	76%	70 G/L	2,5-3,5	20-30%	on going

