Leids Universitair Medisch Centrum

Dutch Thrombosis Network

LMWH en DOACs bij (extreme) obesitas en na bariatrie

Nederlands Trombose Congres

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Casus 1 – VTE en obesitas

50-jarige man met BMI 55 kg/m2

Presentatie met dyspneu en pijn bij ademen

Op CTPA: segmentale longembolie

Lab: Hb 6.0 mmol/L; eGFR 75 mL/min

Wat schrijft u voor?

a. Laag-moleculair-gewichts heparine (LMWH) gevolgd door VKA

b. Dabigatran of edoxaban na 5 dagen LMWH

c. Rivaroxaban 10 mg eenmaal daags

d. Apixaban 10 mg tweemaal daags

Indien u voor LMWH gevolgd door VKA kiest, meet u anti-Xa?

a. Ja

b. Nee

Dit staat in Richtlijn Antitrombotisch beleid 2016

Bij gebruik van LMWH:

Het is niet nodig om routinematig anti-Xa spiegels te controleren bij het gebruik van LMWH. Bij sommige patiënten met VTE is controle van spiegels wel noodzakelijk, bijvoorbeeld in geval van nierschade of insufficiëntie, zwangerschap of extreme obesitas (> 50 kg/m2)

Indien u voor DOAcs kiest, meet u anti-Xa?

a. Ja

b. Nee

Dit staat in Richtlijn Antitrombotisch beleid 2016

Bij gebruik van DOACs:

Niks

Ook in 2016 verschenen

Journal of Thrombosis and Haemostasis, **14**: 1308–1313 DOI: 10.1111/jth.13323

2016 RECOMMENDATIONS AND GUIDELINES

Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH

- Recommend appropriate standard dosing of direct oral anticoagulants (DOACs) in patients with BMI ≤ 40 kg/m^2 and weight ≤ 120 kg.
- Suggest not using DOACs in patients with BMI >40 kg/m^2 or weight >120 kg.
- If DOACs are used in BMI >40 kg/m^2 or weight >120 kg, suggest checking drug-specific peak and trough level.

➢ *DOACs= apixaban, dabigatran, edoxaban, rivaroxaban*

➢ *Based on limited clinical data and available PK data at the time*

PK/PD bij DOACs en obesitas

Rivaroxaban: weinig effect: sommige top spiegels laag

Apixaban: topspiegels en meeste dalspiegels binnen de range

Dabigatran: aanzienlijk aantal spiegels beneden verwachte range

Edoxaban: geen relevante impact op PK/PD

K Martin et al Guidance ISTH SSC J Thromb Haemost 2021

	Phase 3 Studies Comparing DOACs with VKA in VTE		Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)	
	BMI >35 or BW >120 kg	BMI >40	BMI >35 or BW >120 kg	BMI >40
Apixaban	X	X	Similar outcomes[6]	Similar outcomes[5,6]
Dabigatran	X	X	X	X
Edoxaban	X	X	X	X
Rivaroxaban	Similar outcomes[7]	X	Similar outcomes[5,8-10]	Similar outcomes[5,9]
Pooled DOAC	Similar outcomes[11]	X	Similar outcomes [12-16]	Similar outcomes[12]

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

Abbreviations: BMI, body mass index, expressed in kg/m^2; BW, body weight; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Einstein studies

- Similar outcomes of recurrent VTE and major bleeding in those treated with rivaroxaban compared with VKA, across BMI and body weight
  - Outcomes by BMI:

		BMI ≥35		P-value for interaction
		Incidence n/N (%)	HR (95 %CI)	
Recurrent VTE				
Whole study period	Rivaroxaban Enoxaparin/VKA	13/427 (3.0) 9/434 (2.1)	1.45 (0.62–3.39)	0.60
First 21 days	Rivaroxaban Enoxaparin/VKA	9/427 (2.1) 4/434 (0.9)	2.22 (0.68–7.26)	0.19
Major bleeding				
Whole study period	Rivaroxaban Enoxaparin/VKA	5/426 (1.2) 7/432 (1.6)	0.71 (0.22–2.24)	0.74
First 21 days	Rivaroxaban Enoxaparin/VKA	3/426 (0.7) 3/432 (0.7)	0.96 (0.19–4.78)	0.45

  - By Weight: ≥120–140 kg- no difference in VTE recurrence (2/119 vs 3/103)

DiNisio *Thromb Haemost.* 2016

Amplify studies

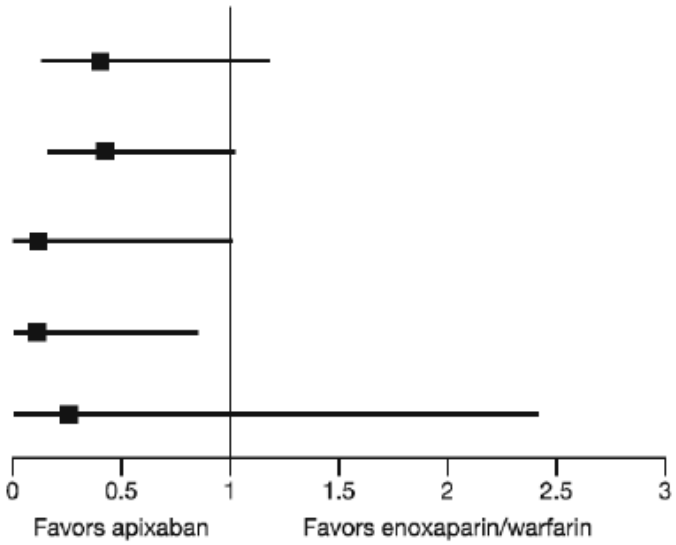
- Similar rates of recurrent VTE/ VTE-related death and lower rates of bleeding for apixaban compared with VKA across body weight and BMI categories

VTE or VTE-related death

BMI category	Apixaban, n/N	Enoxaparin/ warfarin, n/N
≤ 25 kg/m²	16/693	16/694
> 25 to 30 kg/m²	27/985	26/1014
> 30 to 35 kg/m²	9/568	16/575
> 35 to 40 kg/m²	4/227	6/201
> 40 kg/m²	3/122	6/134

Major bleeding

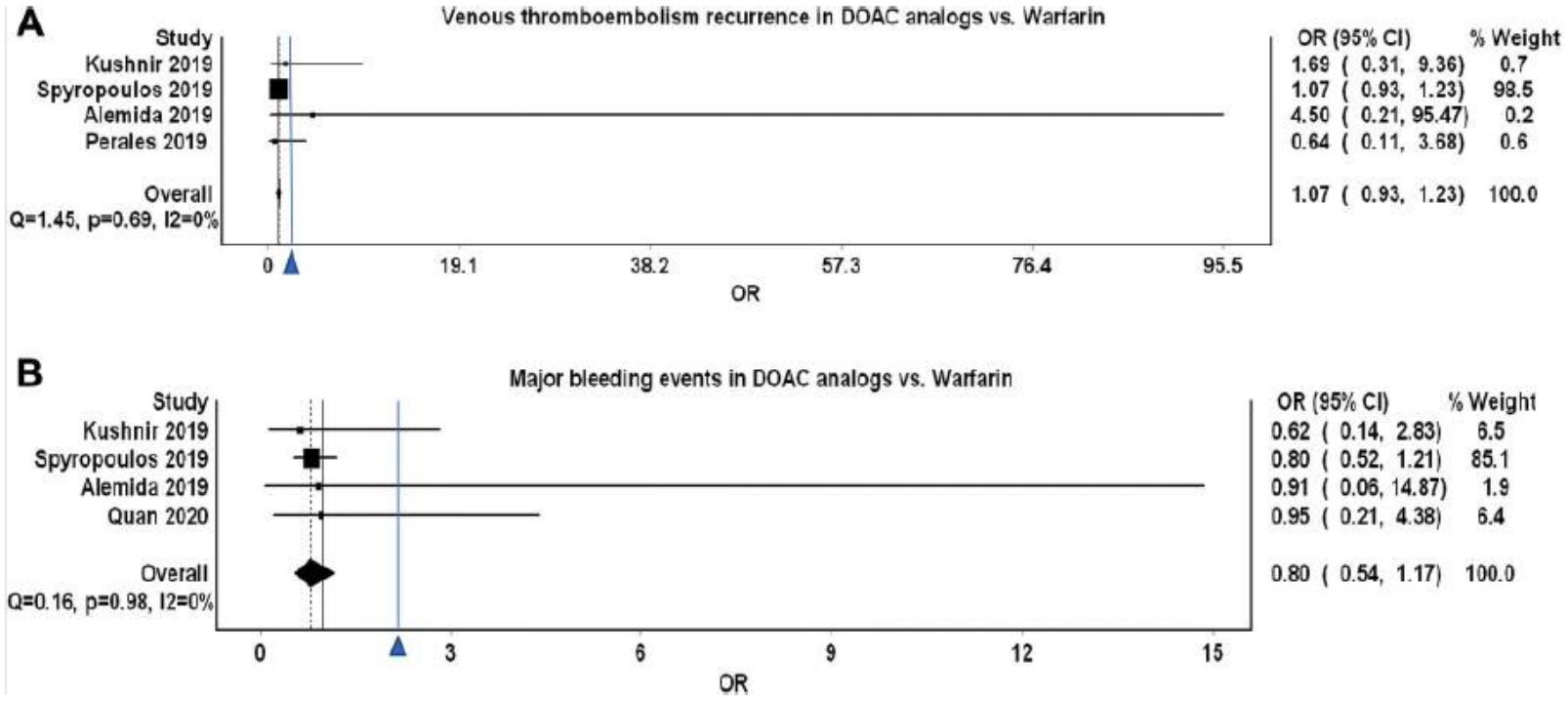
BMI category	Apixaban, n/N	Enoxaparin/ warfarin, n/N	RR (95% CI)	$P_{interaction}$
≤ 25 kg/m²	5/725	12/711	0.41 (0.15, 1.18)	0.66
> 25 to 30 kg/m²	7/999	17/1029	0.43 (0.18, 1.02)	
> 30 to 35 kg/m²	1/575	8/587	0.13 (0.02, 1.01)	
> 35 to 40 kg/m²	1/236	8/206	0.12 (0.02, 0.85)	
> 40 kg/m²	1/126	4/137	0.27 (0.03, 2.40)	



Cohen et al *Adv in Therapy* 2021

Meta-analyse van 5 observationele studies in VTE

Citation	Sample	Context	Conclusions
Elshafei J Thromb Thrombolysis 2020	6,500 patients; BMI ≥ 40 kg/m² or weight >120 kg	Meta-analysis of 5 observational studies; DOAC (rivaroxaban, apixaban, dabigatran) vs VKA	recurrent VTE: OR 1.07; 0.93–1.23 MB: trend toward reduced risk (OR 0.80; 0.54–1.17)



Guidance ISTH SCC Martin K et al JTH 2021

2). For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight-based LMWH (per manufacturers' recommendations), and fondaparinux are also options.

5). We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.

Martin K et al. JTH 2021. DOI: 10.1111/jth.15358

Anusim et al Eur J Haemat 2022 accepted online

Up to 900,000 Americans each year may be affected by obesity-related VTE

499 morbidly obese patients with provoked VTE (309, 62.1%) and unprovoked VTE (189, 37.9%)

Median (range) BMI at which a DOAC was initiated was 44.6 (39.5, 88.4)

Apixaban prescribed in 203 (40.7%) and rivaroxaban in 296 (59.3%) patients

New VTE or progression of VTE was seen in 0.6% of patients over 60 days of follow-up

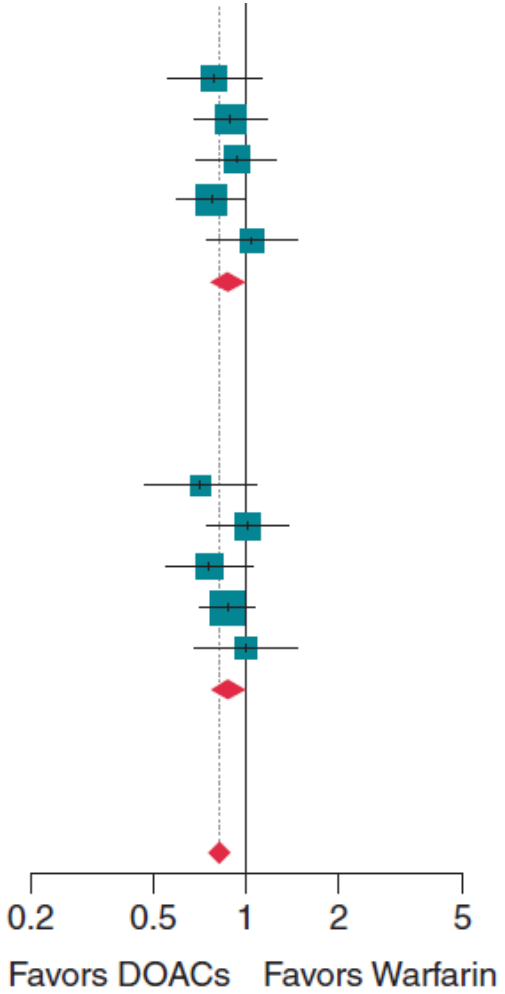
Bleeding complications were seen in 7.0% of patients

No significant differences between apixaban and rivaroxaban

Data suggest apixaban and rivaroxaban administration is safe and efficacious in the morbidly obese patients with VTE

Meta-analysis RCT's in AF Europace 2020: efficacy similar

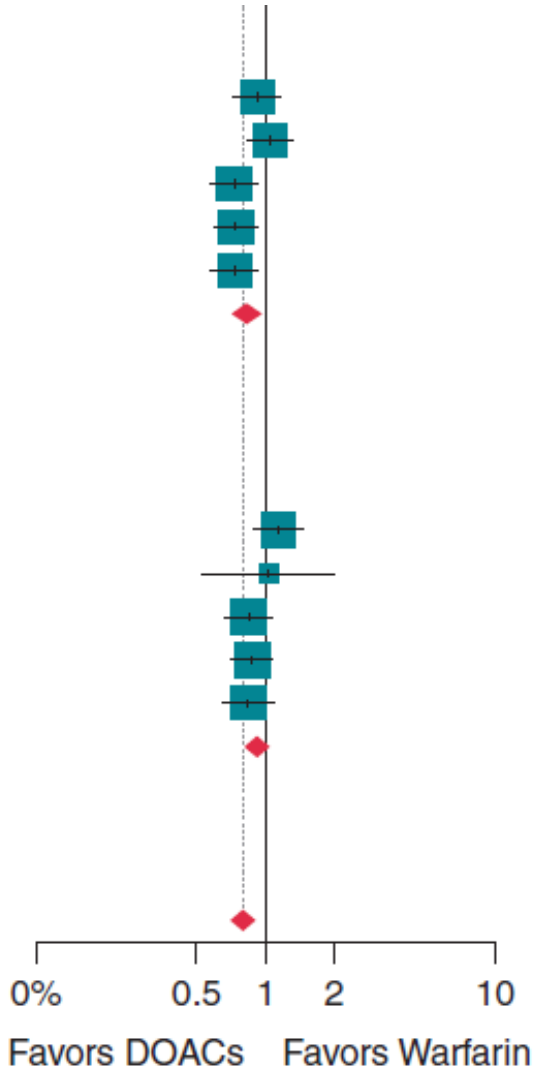
BMI = Overweight				
RE-LY_150mg	–0.24	0.1814	4.9%	0.79 [0.55; 1.13]
ROCKET AF	–0.12	0.1362	7.6%	0.89 [0.68; 1.16]
ARISTOTLE	–0.07	0.1536	6.4%	0.93 [0.69; 1.26]
ENGAGE AF TIMI 48	–0.26	0.1277	8.4%	0.77 [0.60; 0.99]
RE-LY_110mg	–0.04	0.1720	5.3%	1.04 [0.74; 1.46]
Total (95% CI)			32.6%	0.87 [0.76; 0.99]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.49$, df = 4 ($P = 0.65$); $I^2 = 0\%$				
Test for overall effect: Z = –2.10 ($P = 0.04$)				
BMI = Obese				
RE-LY_150mg	–0.34	0.2122	3.7%	0.71 [0.47; 1.08]
ROCKET AF	0.01	0.1537	6.4%	1.01 [0.75; 1.37]
ARISTOTLE	–0.27	0.1650	5.7%	0.76 [0.55; 1.05]
ENGAGE AF TIMI 48	–0.14	0.1046	10.9%	0.87 [0.71; 1.07]
RE-LY_110mg	0.00	0.1967	4.3%	1.00 [0.68; 1.47]
Total (95% CI)			30.9%	0.87 [0.76; 1.00]
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.03$, df = 4 ($P = 0.55$); $I^2 = 0\%$				
Test for overall effect: Z = –2.03 ($P = 0.04$)				
Total (95% CI)			100.0%	0.82 [0.75; 0.89]
Heterogeneity: $Tau^2 = 0.0069$; $Chi^2 = 23.32$, df = 19 ($P = 0.22$); $I^2 = 19\%$				
Test for overall effect: Z = –4.57 ($P < 0.01$)				



Malik et al. Europace 2020. doi:10.1093/europace/euz361

Malik et al: major bleeding similar

BMI = Overweight				
RE-LY_150mg	–0.08	0.1181	6.4%	0.92 [0.73; 1.16]
ROCKET AF	–0.05	0.1130	6.6%	1.05 [0.84; 1.31]
ARISTOTLE	–0.31	0.1221	6.3%	0.73 [0.57; 0.93]
ENGAGE AF TIMI 48	–0.30	0.1090	6.7%	0.74 [0.60; 0.92]
RE-LY_110mg	–0.32	0.1250	6.2%	0.73 [0.57; 0.93]
Total (95% CI)			32.2%	0.83 [0.71; 0.96]
Heterogeneity: $Tau^2 = 0.0150$; $Chi^2 = 8.37$, df = 4 ($P = 0.08$); $I^2 = 52\%$				
Test for overall effect: Z = –2.51 ($P = 0.01$)				
BMI = Obese				
RE-LY_150mg	0.13	0.1250	6.2%	1.14 [0.89; 1.46]
ROCKET AF	0.03	0.3430	2.0%	1.03 [0.53; 2.02]
ARISTOTLE	–0.17	0.1190	6.4%	0.84 [0.67; 1.06]
ENGAGE AF TIMI 48	–0.14	0.1046	6.9%	0.87 [0.71; 1.07]
RE-LY_110mg	–0.17	0.1320	6.0%	0.84 [0.65; 1.09]
Total (95% CI)			27.5%	0.91 [0.81; 1.03]
Heterogeneity: $Tau^2 = 0.0017$; $Chi^2 = 4.37$, df = 4 ($P = 0.36$); $I^2 = 9\%$				
Test for overall effect: Z = –1.44 ($P = 0.15$)				
Total (95% CI)			100.0%	0.79 [0.71; 0.88]
Heterogeneity: $Tau^2 = 0.0340$; $Chi^2 = 48.94$, df = 18 ($P < 0.01$); $I^2 = 63\%$				
Test for overall effect: Z = –4.17 ($P < 0.01$)				



Malik et al. Europace 2020. doi:10.1093/europace/euz361

AF richtlijn ESC 2021 Steffel J et al Europace doi:10.1093/europace/euab065

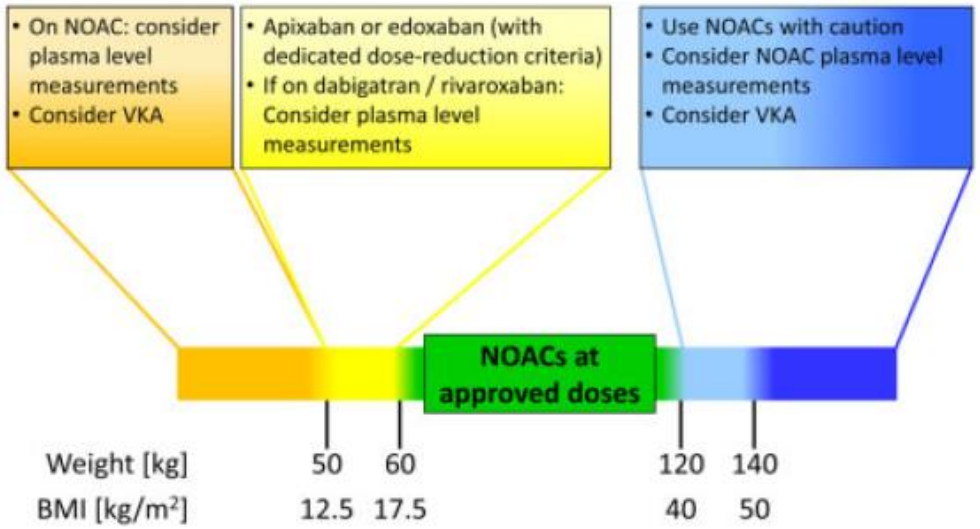


Figure 23 NOACs in under- and overweight patients. See text for details. BMI, body mass index; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; RCT, randomized clinical trial.

Table 11 Plasma levels and coagulation assays in patients treated with NOACs for stroke prevention in AF

	Dabigatran[97,548,549]	Apixaban[550]	Edoxaban[98,100]	Rivaroxaban[519,520,551]
Expected plasma levels of NOACs in patients treated for AF*				
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137

Casus 2 – status na gastric bypass - sleeve

65-jarige man met BMI 55 kg/m2 is eergisteren geopereerd

Voorgeschiedenis AF met CHADsVASC score 5

Medicatie: antidiabetica antihypertensiva apixaban

Wat schrijft u voor?

a. Laag-moleculair-gewichts heparine (LMWH) gevolgd door VKA

b. DOAC

c. LMWH – na 1 maand DOAC starten

TABLE 2 Expected impact of bariatric surgery procedures on absorption of DOACs

DOAC	Site of Absorption in Gastrointestinal Tract	Surgical Intervention and Anticipated Effect on Absorption		
		Gastric Banding	Partial/Sleeve Gastrectomy	RYGB
Apixaban	Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration[39]	Unlikely affected	Unlikely affected	Possibly reduced
Dabigatran	Lower stomach and proximal small intestine[41,42,49]	Possibly reduced	Possibly reduced	Possibly reduced
Edoxaban	Proximal small intestine, dependent on acidic environment [43,44]	Possibly reduced	Possibly reduced	Possibly reduced
Rivaroxaban	Largely stomach, some small intestine, but absorption reduced when released distal to stomach[43-45]	Possibly reduced	Possibly reduced	Possibly reduced

Abbreviations: DOAC, direct oral anticoagulant; RYGB, Roux-en-Y gastric bypass.

Types of Bariatric Surgery

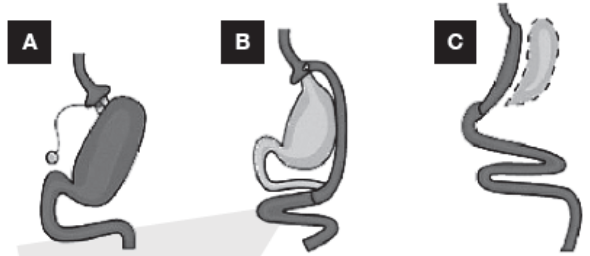


Image Credit: Walter Pories, M.D. FACS
https://www.news-medical.net/health/Bariatric-Surgery-Types.aspx

A **Adjustable gastric banding (AGB):**
Adjustable silicone band placed around stomach to create a smaller pouch.

B **Roux-en-Y gastric bypass (RYGB):**
Stomach stapled to form gastric pouch that connects to distal jejunum, excluding the duodenum and proximal jejunum.

C **Gastrectomy (partial/sleeve):**
Sleeve gastrectomy results in longitudinal resection of 80% of stomach.

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5). We suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.

6). We suggest not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. We suggest that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

Martin K et al JTH. DOI: 10.1111/jth.15358

Samenvatting anti-Xa meten bij obesitas en na bariatrie

Anti-Xa meting voor LMWH bij BMI boven de 50 kg/m2

Anti-Xa meting voor DOACs bij BMI boven de 50 kg/m2 – dal spiegels

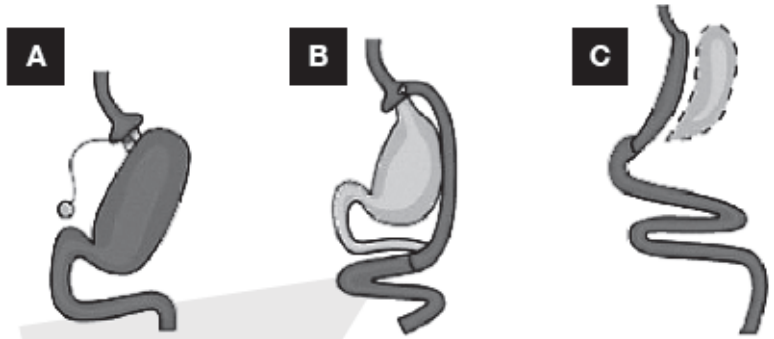
Na bariatrie maand wachten tot start DOACs – LMWH VKA

Na start DOACs dalspiegel meten ter controle van de absorptie

Na bariatrie en impact op absorptie van DOACs

Bariatric Surgery

Types of Bariatric Surgery



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Stomach stapled to form gastric pouch that connects to distal jejunum, excluding the duodenum and proximal jejunum.

C **Gastrectomy (partial/sleeve):**
Sleeve gastrectomy results in longitudinal resection of 80% of stomach.

D **Colectomey:**
Surgical removal of all or part of the colon. (visual not provided)

Potential impact of surgical intervention on absorption

	Apixaban	Dabi	Edoxaban	Riva
A	UA	PR	PR	PR
B	PR	PR	PR	PR
C	UA	PR	PR	PR
D	PR	UA	UA	UA

PR Possibly Reduced UA Unlikely Affected