Perioperative Antikoagulation: Ist das Heparin-Bridging noch aktuell? / Perioperative anticoagulation: Is Heparin Bridging still relevant?

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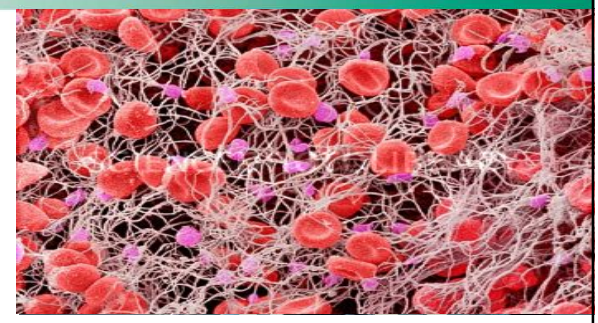

UNIVERSITÄT BERN

Universitätsklinik für Hämatologie und Hämatologisches Zentrallabor

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Introduction

- More than 6 million Europeans on long-term oral anticoagulation (OACs) therapy (infinite)
- About **10%** of them require annually anticoagulation discontinuation for procedures.
- The approval of direct oral anticoagulants (DOACs) and novel data on perioperative anticoagulation with heparins render the management of perioperative anticoagulation therapy complex.

BRIDGE study (patients with AF)

- 1884 patients (patient with moderate perioperative thromboembolic risk)
  - 950 received no bridging
  - 934 received bridging
- Incidence arterial TE
  - 0.4% in the non bridging group
  - 0.3% in the bridging group

Risk difference, 0.1 percentage points; 95% CI, 0.6-0.8; P=0.01 for inferiority

- Incidence major bleeding
  - 1.3% in the non bridging group
  - 3.2% in the bridging group

Relative risk 0.41; 95% CI, 0.20-0.78; P=0.005 for superiority

Douketis JD et al. NEJM 2015, 373:823-33

Case #1 - history

- 42 year-old man
- Unprovoked pulmonary embolism 2 years ago
- Antiphospholipid syndrome
  - positive lupus anticoagulant
  - high titer of both anticardiolipin and anti-β2-glycoprotein 1 antibodies IgG
- No report of bleeding complications
- Treatment: Marcoumar® (indefinite)

Please assess the periprocedural thromboembolic risk of this patient

Patient-related risk stratification for perioperative thromboembolism (ACCP, 2012 & *ESC/ESA, 2014*)

Risk category	Mechanical heart valve	Atrial fibrillation	VTE
HIGH >10%/y. risk of ATE or >10%/m risk of VTE	• Any mechanical mitral valve • Caged ball or tilting disk valve in mitral/aortic position • Recent (<6 months) stroke TIA	• *CHA2DS2-VASc score of 6-9* • Recent (<3 months) stroke or TIA • Rheumatic valvular heart disease	• Recent (<3 months) VTE • Deficiency of protein C, protein S or antithrombin • Antiphospholipid antibodies • Multiples thrombophilias
INTERMEDIATE 5-10%/y. risk of ATE or 4-10%/m. risk of VTE	• Bileaflet mechanical aortic valve with major risk factors for stroke	• *CHA2DS2-VASc score of 4-5*	• VTE within the past 3-12 months • Recurrent VTE • Non-severe thrombophilia • Active cancer
LOW <4%/y. risk of ATE or <2%/m. risk of VTE	• Bileaflet mechanical aortic valve without major risk factors for stroke	• *CHA2DS2-VASc score of 1-3 (and no prior stroke or TIA)*	• VTE >12 months

Case #1 – minimal bleeding risk procedure

- 42 year-old man
- Unprovoked pulmonary embolism 2 years ago
- Antiphospholipid syndrome with a positive lupus anticoagulant and high titer of both anticardiolipin and anti-β2-glycoprotein 1 antibodies
- No report of bleeding complications
- Treatment: Marcoumar® (indefinite)

→ High perioperative thromboembolic risk

→ Planed procedure: dental extraction

Periprocedural anticoagulant management ?

Minor bleeding risk procedures

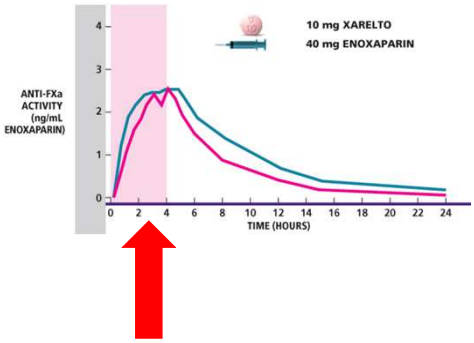
- Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi)
- Cataract procedures
- Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings
- Pacemaker or cardioverter-defibrillator device implantation
- Endoscopy without biopsy
- Endoscopic ultrasound without fine needle aspiration
- Endoscopic retrograde cholangiopancreaticography without intervention

Do not interrupt anticoagulant therapy (ACCP 2012, level 2C), whatever is the thromboembolism risk

Douketis JD et al. ACCP Evidenced-Based Clinical Practice Guidelines, Chest 2012, 141:e326S-50S; Spyrropulos AC JTH 2016, 14:875-885; Swiss Society of Gastroenterology and Working Party Hemostasis from the Swiss Society of Hematology, http://www.sggssg.ch/richtlinien-empfehlungen/oral-anticoagulants-practical-management-2016.html

Case #2 - excision of skin lesions

- 84 year-old man
- Chronic lymphocytic leukemia
  - 0 B-symptoms, 0 lymphadenopathy, 0 hepatosplenomegaly
  - Hb 146 g/L, Leucocytes 21 G/L (neutrophiles 1.8 G/L, lymphocytes 18.8 G/L), Thrombocytes 157 G/L
- Unprovoked pulmonary embolism 4 months ago
  - Xarelto 20 mg/day (infinite)
  - Intermediate perioperative thromboembolic risk
  - No previous bleeding history
- Excision of basal squamous cell skin cancer lesions 2.5 h after the uptake of Xarelto® 20 mg complicated by local bleeding



Minimal bleeding risk procedures on DOAC:
may consider interrupting DOAC therapy on the day of the procedure

Spyropoulos AC JTH 2016, 14:875-885

Case #1 – cardiac surgery

- 45 year-old man
- Unprovoked pulmonary embolism 5 years ago
- Antiphospholipid syndrome with a positive lupus anticoagulant and high titer of both anticardiolipin and anti-β2-glycoprotein 1 antibodies
- Coagulations tests (without Marcoumar®): Quick 36%, aPTT 105 sec., thrombin time 16.4 sec., fibrinogen 4.3 g/L, extrinsic and intrinsic factors normal
- No report of bleeding complications
- Treatment: Marcoumar® (indefinite)

→ High perioperative thromboembolic risk

→ Reconstruction or replacement of the mitral valve

Periprocedural anticoagulant management ?

High bleeding risk procedure (2-day of major bleed ≥2%)

- Major surgery with extensive tissue injury
- Cancer surgery
- Major orthopedic surgery
- Reconstructive plastic surgery
- Urologic or gastrointestinal surgery
- Transurethral prostate resection, bladder resection, or tumor ablation
- Nephrectomy, kidney biopsy
- Colonic polyp resection
- Bowel resection
- Percutaneous endoscopic gastrotomy placement, endoscopic retrograde cholangiopancreatography
- Surgery in highly vascular organs (kidneys, liver, spleen
- Cardiac, intracranial or spinal surgery
- Any major operation (procedure duration of >45 min)

Douketis JD et al. ACCP Evidenced-Based Clinical Practice Guidelines, Chest 2012, 141:e326S-50S; Spyropoulos AC JTH 2016, 14:875-885

Discontinuation of vitamin K antagonists with bridging (1)

Phenprocoumon (Marcoumar®)

Discontinuation with bridging (procedure = day 0)

• Day -7 to -5	Stop Phenprocoumon
• Day -4 to -2	INR testing; if INR <2.0 start LMWH (2 sc doses/day);
• Day -1	INR testing; if INR >1.5 administer vit. K 1-2.5 mg po; last LMWH dose >24 h before procedure, consider anti-factor Xa testing before procedure in renal insufficiency
• Day 0	If adequate hemostasis, LMWH at prophylactic or therapeutic (2 sc doses/day) level according to bleeding risk ≥ 6 h after procedure; resume phenprocoumon, stop LMWH when INR is within target range

Discontinuation of vitamin K antagonists with bridging (2)

Acenocoumarol Sintrom®

Discontinuation with bridging (procedure = day 0)

• Day -4 to-3	Stop Acenocoumarol
• Day -3 to-2	INR testing; if INR <2.0 start LMWH (2 sc doses/day);
• Day -1	INR testing; if INR >1.5 administer vit. K 1-2.5 mg po; last LMWH dose >24 h before procedure, consider anti-factor Xa testing before procedure in renal insufficiency
• Day 0	If adequate hemostasis, LMWH at prophylactic or therapeutic(2 sc doses/day) level according to bleeding risk ≥ 6 h after procedure; resume acenocoumarol, stop LMWH when INR is within target range

Case #1 – Low bleeding risk procedure

- 46 year-old man
- Unprovoked pulmonary embolism 6 years ago
- Antiphospholipid syndrome with a positive lupus anticoagulant and high titer of both anticardiolipin and anti-β2-glycoprotein 1 antibodies
- Reconstruction of the mitral valve 1 year ago
- Coagulation tests (without Marcoumar®): Quick 36%, aPTT 105 sec., thrombin time 16.4 sec., fibrinogen 4.3 g/L, extrinsic and intrinsic factors normal
- Iron-deficiency anemia
- Treatment: Marcoumar® (indefinite)

→ High perioperative thromboembolic risk

→ Colonoscopy

Periprocedural anticoagulant management ?

Low bleeding risk procedures
(2-day bleeding risk of major bleed of <2%)

- Arthroscopy
- Cutaneous/lymph node biopsies
- Shoulder/foot/hand surgery
- Coronary angiography
- Gastrointestinal endoscopy ± biopsy
- Colonoscopy ± biopsy
- Abdominal hysterectomy
- Laparoscopic cholecystectomy
- Abdominal hernia repair
- Hemorrhoidal surgery
- Bronchoscopy ± biopsy
- Epidural injections with INR <1.2

Douketis JD et al. ACCP Evidenced-Based Clinical Practice Guidelines, Chest 2012, 141:e326S-50S; Spyrropulos AC JTH 2016, 14:875-885

Bleeding risk of gastrointestinal procedures

Procedures without bleeding risk	Procedures with low-bleeding risk	Procedures with high-bleeding risk
Endoscopy without biopsy	Endoscopy with biopsy	Polypectomy*
EUS without FNA	ERCP with stent placement	Sphincterotomy
ERCP without intervention	Enteroscopy with/without biopsy	Sphincterotomy with large ballon dilatation
		Dilatation of digestive stenosis
		Digestive stenting
		PEG
		EUS with FNA
		Laserablation, APC
		Therapy of varices
		EMR, ESD, ampullary resection
		Ligation of hemorrhoids
		Transcutaneous liver biopsy and FNA

APC = argon plasma coagulation; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; ERCP = endoscopic retrograde cholangiopancreaticography; EUS = endoscopic ultrasound; FNA = fine needle aspiration; PEG = percutaneous endoscopic gastrostomy

* Details see page: polypectomy in patients taking antiplatelet agents and oral anticoagulants

Antiplatelet agents, oral anticoagulants, and assessment for bleeding diathesis in elective gastrointestinal procedures (endoscopy, liver biopsy and FNA) Practical Management 2016, Swiss Society of Gastroenterology and Working Party Hemostasis from the Swiss Society of Hematology, http://www.sggssg.ch/richtlinien-empfehlungen/oral-anticoagulants-practical-management-2016.html

Procedures without bleeding risk

Aspirin	
Clopidogrel	
Aspirin + P2Y12 receptor antagonist	
VKA	Continue
DOAC	
VKA + Aspirin or Clopidogrel	
DOAC + Aspirin or Clopidogrel	
VKA or DOAC + Aspirin + P2Y12 receptor antagonist	

Caution:
Do not do an endoscopy in patients with severe bleeding disorders (e. g., hemophilia, VWD type 3 etc.), contact hematology

Antiplatelet agents, oral anticoagulants, and assessment for bleeding diathesis in elective gastrointestinal procedures (endoscopy, liver biopsy and FNA) Practical Management 2016, Swiss Society of Gastroenterology and Working Party Hemostasis from the Swiss Society of Hematology, http://www.sggssg.ch/richtlinien-empfehlungen/oral-anticoagulants-practical-management-2016.html

TABLE 4

Recommended procedure in the case of elective endoscopy in patients being treated with vitamin K antagonists (VKA)

	Risk of thromboembolism	
Bleeding risk	**Low** (Group C in *Table 3*)	**High** (Group A in *Table 3*)
Low (<1.5%)	Continue VKA treatment unchanged	Continue VKA treatment unchanged
High (≥ 1.5%)	Interrupt VKA treatment, no bridging with heparin	Interrupt VKA treatment, bridging with heparin indicated

Individual decisions are necessary in patients with moderate risk of TE undergoing a procedure with high bleeding risk

Lange CM et al. Dtsch Arztrbl Int 2016, 113:129-35; Müller-Lissner S & Riess H Z Gastroenterol 2010, 48:1219-24

Discontinuation of vitamin K antagonists
Phenprocoumon (Marcoumar®)

Discontinuation without bridging (procedure = day 0)

- Day -7 to -5 — Stop Phenprocoumon; consider INR testing before
- Day -2 — INR testing; if INR >1.5 administer vitamin K 1-2.5 mg po
- Day 0 to +1 — Resume phenprocoumon (evening after procedure)

Discontinuation of vitamin K antagonists (2)
Acenocoumarol (Sintrom®)

Discontinuation without bridging (procedure = day 0)

- Day -3 — Stop Acenocoumarol; consider INR testing before
- Day -1 — INR testing; if INR >1.5 administer vitamin K 1-2.5 mg po
- Day 0 to +1 — Resume phenprocoumon (evening after procedure)

Discontinuation of DOACs (1)

- Before procedure:
  - Discontinue DOAC; no bridging
- After procedure:
  - Low bleeding risk
    - → restart DOAC the next morning
  - High bleeding risk
    - → low thromboembolic risk: restart after 24-48 hrs(or longer if very high risk of bleeding as e. g. EMR, ESD)
    - → high thromboembolic risk: UFH at prophylactic or therapeutic level, switch to DOAC when lower bleeding risk
  - Patients with high thromboembolic risk + high bleeding risk + renal insufficiency
    - → consult hematology

Discontinuation of DOAC (1)

Procedure with low bleeding risk (for example, cardiac catheterization, diagnostic endoscopy, breast biopsy, minor orthopedical procedures)

Substance	CCL (*)	Last dose before procedure (d 0)
Rivaroxaban	> 50	d -1 (morning)
(15-20 mg/d)	< 50	d -1 (morning)
Apixaban	> 50	d -1 (morning)
(2.5-5 mg bid)	< 50	d -1 (morning)
Edoxaban	> 50	d -1 (morning)
(30-60 mg/d)	< 50	d -1 (morning)
Dabigatran	> 50	d -1 (morning)
(110-150 mg bid)	< 50	d -1 (morning)

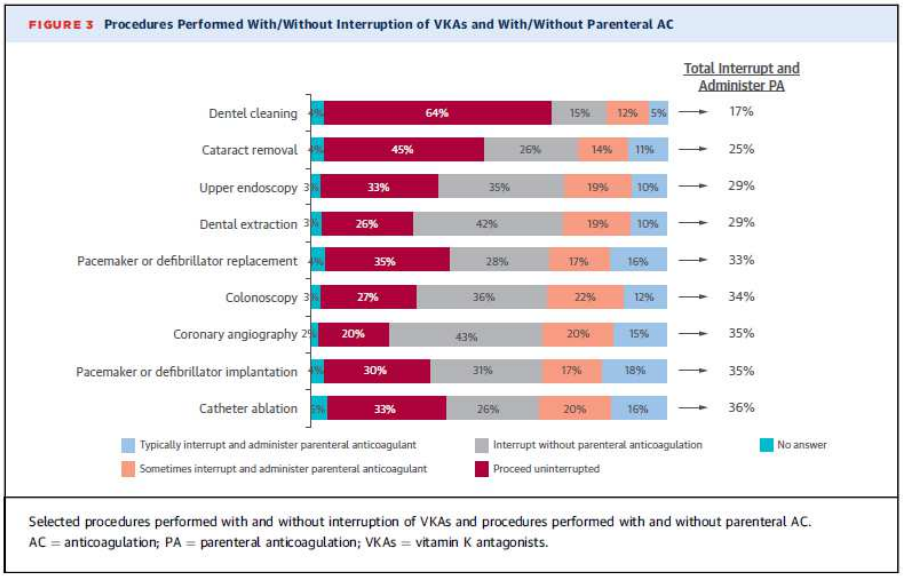
(*) CCL = creatinine clearance (ml/min) estimated according to Cockroft-Gault. It is assumed that CCL is not severely reduced (contraindication to DOAC use)

Discontinuation of DOAC (2)

Procedure with high bleeding risk (for example, cardiac surgery, vascular surgery, abdominal surgery, spinal or neurosurgery)

Substance	CCL (*)	Last dose before procedure (d 0)
Rivaroxaban	> 50	d -3
(15-20 mg/d)	< 50	d -3
Apixaban	> 50	d -3
(2.5-5 mg bid)	< 50	d -3
Edoxaban	> 50	d -3
(30-60 mg/d)	< 50	d -3
Dabigatran	> 50	d -3
(110-150 mg bid)	< 50	d -5

(*) CCL = creatinine clearance (ml/min) estimated according to Cockroft-Gault
It is assumed that CCL is not severely reduced (contraindication to DOAC use)



Flaker GC et al. J Am Coll Cardiol 2016, 68:217-26

Case #3

- 67-jähriger Patient
- April 2016
  - Ausgeprägter multilokaler Wangenabszess, Fossa Canina Abszess rechts
- Chronische Niereninsuffizienz
  - GFR 58 ml/min.
- Vorhofflimmern
  - Unter Pradaxa® (Dabigatran)

Laborbefunde

- Quick 64%
- aPTT 52.1 sec. (25-36)
- Thrombinzeit >120 sec. (15.5-19.4)
- Anti-IIa Aktivität 119 ng/ml

Behandlung

- Praxbind® (Idarucizumab) 2x 2.5 g i.v.
  - 25 min. nach Praxbind:
    - Thrombinzeit 16.2 sec. (15.5-19.4)
    - Anti-IIa Aktivität <40 ng/ml
- Abczessinzision
- Intravenöse Antibiotikatherapie

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

Pollack et al. NEJM 2015

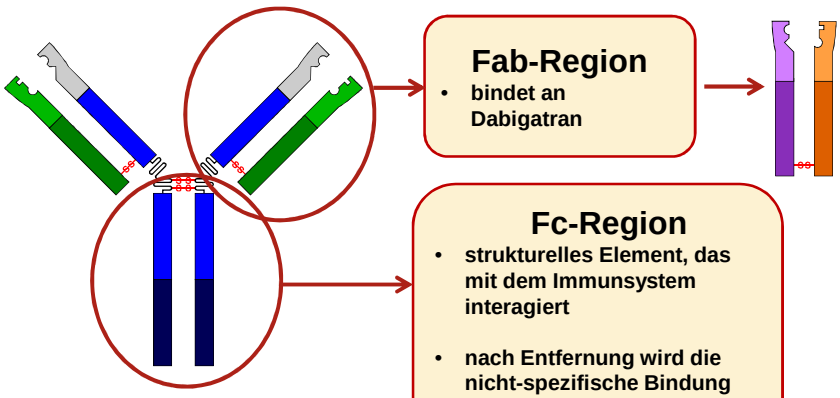
Ein Antidot → eine zusätzliche Option für die Behandlung von Patienten in seltenen Notfallsituationen

Die meisten Patienten sprechen auf unterstützende Massnahmen oder Absetzen des Antikoagulans an

Nur eine Minderheit der Patienten wird ein Antidot benötigen

- **Lebensbedrohliche Blutung**
- **Notfalloperation**

Idarucizumab→ein humanisiertes Antikörper Fragment (Praxbind® , Boehringer Ingelheim)

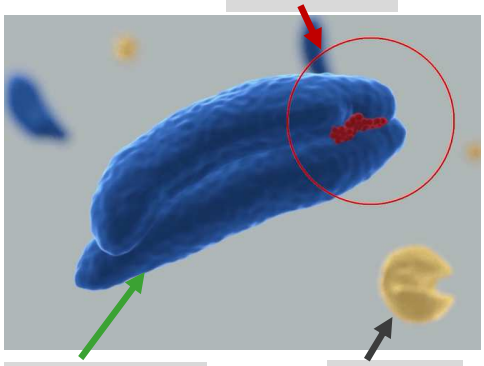


Fab-Region
- **bindet an Dabigatran**

Fc-Region
- **strukturelles Element, das mit dem Immunsystem interagiert**
- **nach Entfernung wird die nicht-spezifische Bindung reduziert**

van Ryn J. AHA 2013 presentation 9928

Worauf beruht die Wirkweise von Idarucizumab?



- humanisiertes mAb-Fragment
- >350-fach höhere Affinität für Dabigatran als Dabigatran für Thrombin
- keine prothrombotische Wirkung
- kurze Halbwertszeit
- überwiegend renale Ausscheidung
- intravenös verabreicht als eine einfache, 5g-Kurzzeitinfusion; schneller Wirkungseintritt

The NEW ENGLAND JOURNAL of MEDICINE

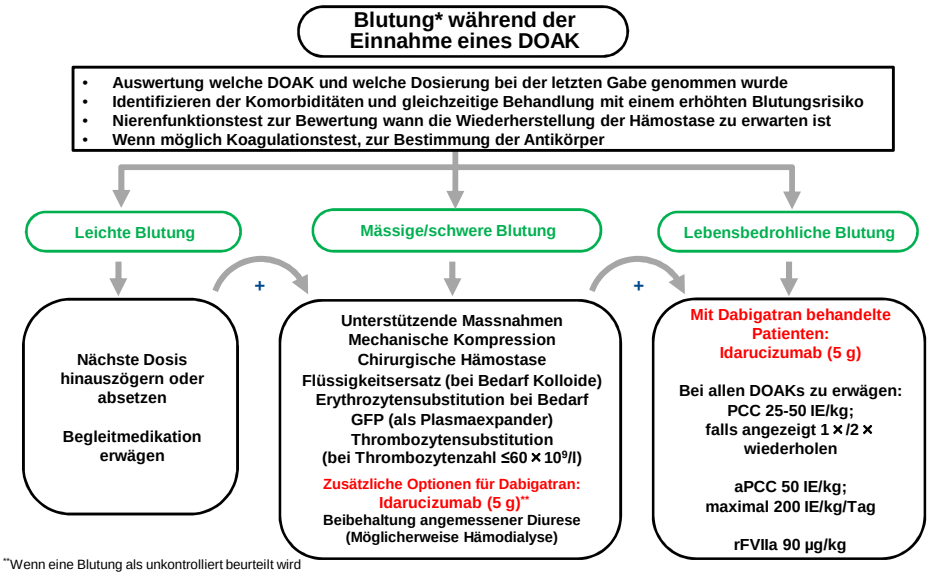
ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

Siegal DM et al. NEJM 2015, 373: 2413-2424

Idarucizumab wird die verfügbaren Behandlungen von Blutungen bei mit Dabigatran behandelten Patienten verbessern



**Wenn eine Blutung als unkontrolliert beurteilt wird

Adapted from EHRA Practical Guide on the use of NOACs (Heidbuchel H et al. Europace 2013;15:625–51)

Key messages

- Updated clinical guidelines suggest that heparin bridging is unnecessary for patients anticoagulated with DOACs.
- Heparin/LMWH bridging should be considered for patients on long-term therapy with VKA temporarily interrupted in the periprocedural context if these patients are at highest risk of TE (≥ 10% per year).
- The decision of heparin bridging in these patients should be carefully weighted in presence of a concomitant high bleeding risk. Conversely, patients at low risk for TE should not be bridged.
- Treatment with VKA, DOACs can be continued unchanged in minimal bleeding risk procedure (minor dermatologic, dental and gastroenterologic procedures, cataract procedure and pacemakeror cardioverter-defibrillator device implantation
- Specific antidotes for DOACs represent a major advance in the safe use of these anticoagulants