

Perioperative Medication Management: GLP1s, SGLT2s, Anticoagulation

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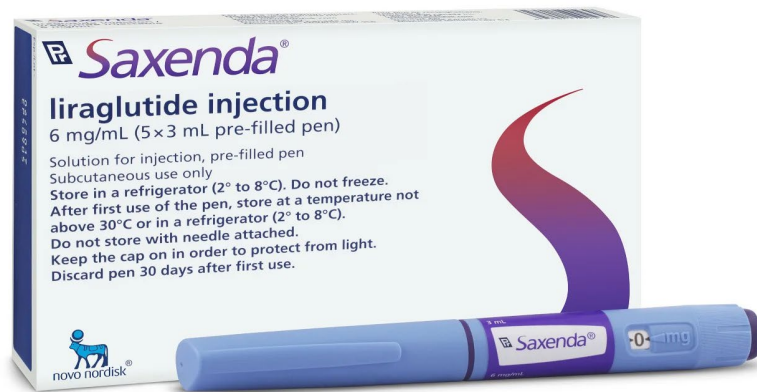


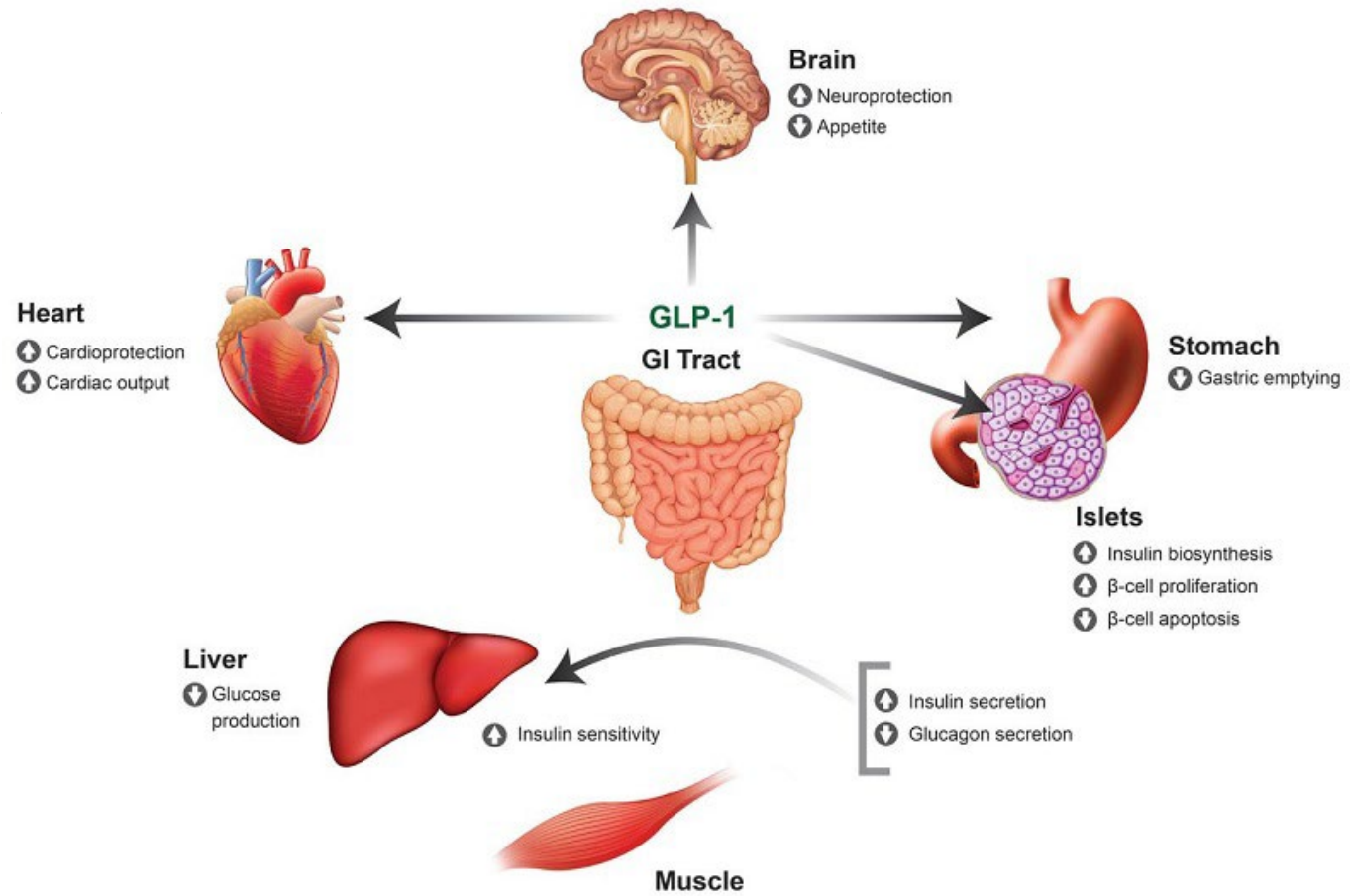
Objectives

- ❑ Review guidance on perioperative management of GLP1 receptor agonists
- ❑ Review guidance on perioperative management of SGLT2 inhibitors
- ❑ Review guidance on perioperative management of anticoagulation



GLP1 receptor agonists





American Society of Anesthesiologists (June 2023)

On GLP1 RAs: The evidence to provide guidance for preoperative management of these drugs to prevent regurgitation and pulmonary aspiration of gastric contents is sparse limited only to several case reports.

Nevertheless, given the concerns of GLP-1 agonist-induced delayed gastric emptying and associated high risk of regurgitation and aspiration of gastric contents, the task force suggests the following for elective procedures.

American Society of Anesthesiologists (June 2023)

Prior to the Procedure:

- Consider holding daily GLP1 agonists on the day of surgery
- Consider holding weekly GLP1s a week prior to surgery

Day of the Procedure:

- If GI symptoms such as severe nausea/vomiting/retching, abdominal bloating, or abdominal pain are present, consider delaying elective procedure
- There is no evidence to suggest the optimal duration of fasting for patients on GLP-1 agonists

ASA Recommendation - Evidence

Kobori et al conducted a single center matched-pair case-control study of Japanese patients with diabetes on GLP1 therapy undergoing elective endoscopy that demonstrated association of GLP1 use and increased gastric residual

- Single center observational study
- Total number of patients with high gastric residual was low
- How generalizable?

ASA Recommendation - Evidence

Silveira et al performed a multicenter retrospective observational study of 404 elective EGD/EGD+cscopes for patients on semaglutide primarily for weight loss. Divided into two groups – had/had not taken their semaglutide in the last - days.

- Semaglutide use was associated with increased residual gastric contents – 24.2% in SG vs 5.1% in the NSG
- Even more highly if GI symptoms were reported
- Interestingly, a **protective** effect was found in patients undergoing EGD AND colonoscopy
- Only 1 case of pulmonary aspiration was reported

ASA Recommendation - Evidence

A 42-yr-old patient with Barrett's esophagus underwent repeat EGD – he had started semaglutide 2 months prior – and significant gastric residual was noted during the procedure. Intraoperative pulmonary aspiration occurred requiring bronchoscopy for removal of food remains. He remained asymptomatic 4 hours post procedure.

ASA Recommendation - Evidence

Friedrichsen et al performed a double-blind parallel group trial with 72 adults with obesity randomized to semaglutide 2.4mg weekly or placebo for 20 weeks. When evaluated at 20 weeks, those on semaglutide did NOT demonstrate increased gastric emptying.

Nauck et al demonstrated that there may be rapid tachyphylaxis to the decreased gastric emptying action of GLP1 agonism in 2011 (“reaches full expression after several weeks or months”)

ASA Recommendation - ... Evidence?

One study of Japanese patients with diabetes

- GLP1s associated with increased gastric residual

One study of Brazilian and Canadian patients with primarily obesity

- SG associated with increased gastric residual, moreso with GI symptoms, and bowel prep was protective

There is probably some increased risk of increased gastric residuals – but in whom?

- Depending on indication?
- Complications of diabetes?
- Chronicity of treatment?
- Duration of action of the GLP1 RA?

What are others saying? (CPOC)

“GLP-1 receptor agonists should be taken as normal the day prior to surgery”

“Following the press release from the American Society of Anesthesiologists on 29th June 2023 regarding the potential effects of GLP-1 Receptor Agonists on gastric emptying, this monograph is currently under review.”

What are others saying? (AGA et al)

“No data to support stopping GLP-1 agonists prior to elective endoscopy”

“AGA, AASLD, ACG, ASGE and NASPGHAN recognize that ... GLP-1 receptor agonists ... may be associated with delayed gastric emptying .. we also acknowledge that there is little, or no data related to the relative risk of complications from aspiration.”

What are others saying? (CAS)

For patients taking GLP-1s, consider holding drug for at least three half lives – for semaglutide this would be three weeks

Prolongation of the fasting time is unlikely to be required (or reasonable)

If GLP-1 cannot be held for at least three half-lives, consider performing rapid sequence induction if general anesthesia is required

Consider the use of point-of-care gastric ultrasound to assess the volume and character of any residual volume in the stomach

What is Tower saying?

In light of mounting data demonstrating a significant increase in the percentage of patients on GLP1's with high residual gastric volumes presenting for elective EGD, we agree with the ASA recommendations pending further literature (August 2023)

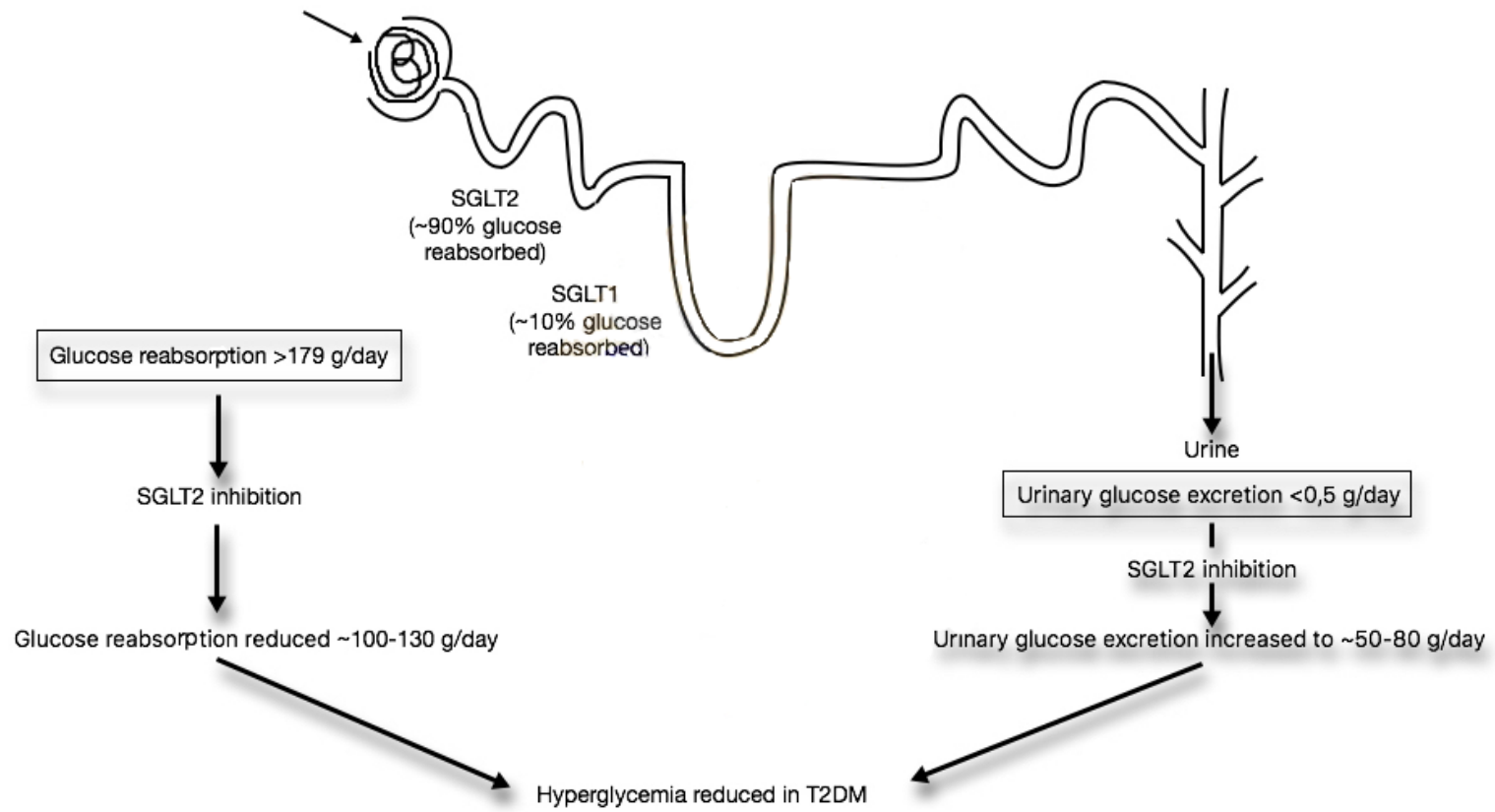
If GLP1 is not held, the surgical/procedural/anesthesia team will determine timing and management of the patient's care

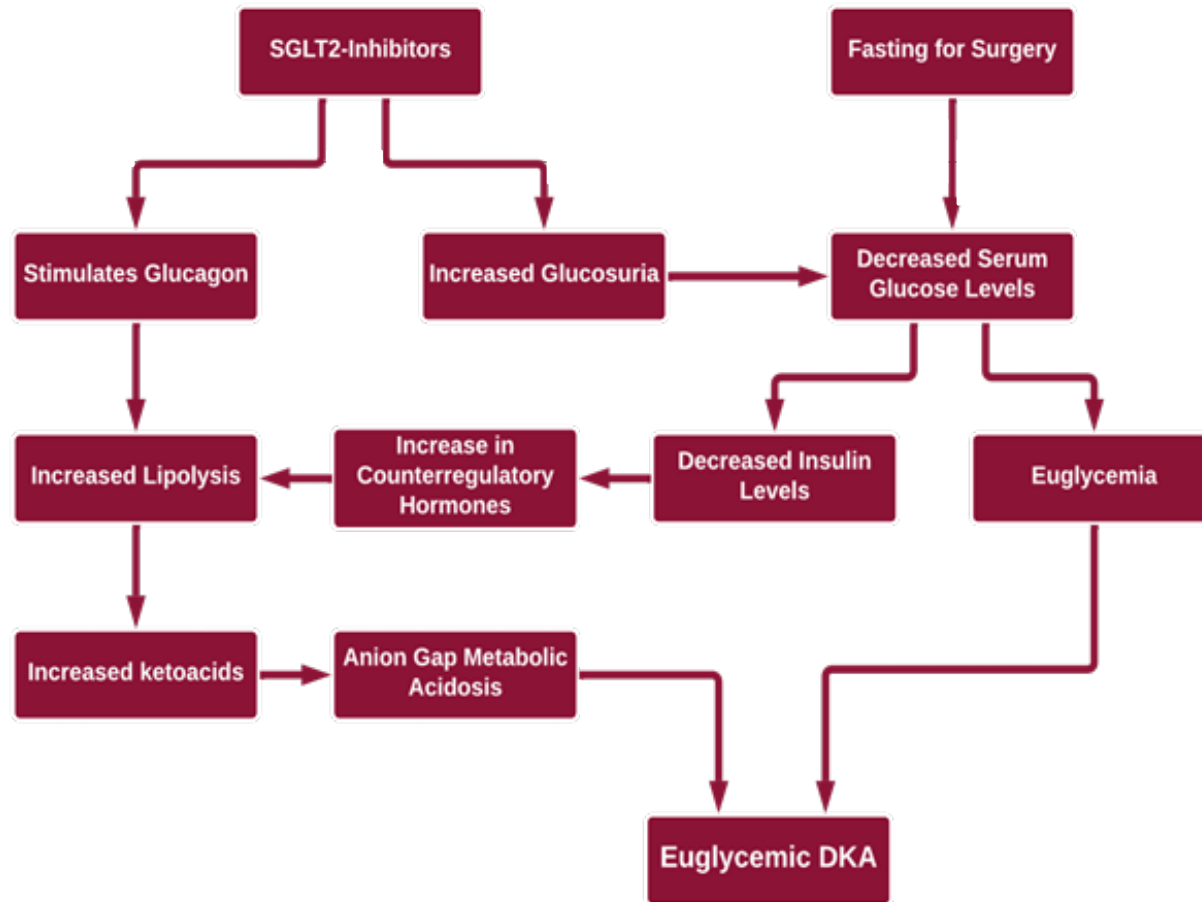
Precautionary Principle





SGLT2 inhibitors





Evidence for SGLT2s and EDKA

- Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care*. **2015 Sep – 13 episodes of SGLT2i associated EDKA**
- Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, Gudbjörnsdóttir S, Hveem K, Jonasson C, Pasternak B. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register-based cohort study. *BMJ*. **2018 Nov 14 – Large cohorts from Sweden and Denmark confirm relationship with EKDA.**
- Chacko B, Whitley M, Beckmann U, Murray K, Rowley M: Postoperative euglycaemic diabetic keto-acidosis associated with sodium-glucose cotransporter-2 inhibitors (gliflozins): A report of two cases and review of the literature. *Anaesth Intensive Care* **2018; 46:215–9 – Hold SGLT2 3 days prior to surgery.**
- Jean-Charles Preiser, Bruna Provenzano, Wasineeart Mongkolpun, Katarina Halenarova, Miriam Cnop; Perioperative Management of Oral Glucose-lowering Drugs in the Patient with Type 2 Diabetes. *Anesthesiology* **2020 – Hold SGLT2 on day of surgery.**
- Branco A, Fatima R, Liblik K, Jackson R, Payne D, El-Diasty M. Euglycemic Diabetic Ketoacidosis Associated With Sodium-Glucose Cotransporter-2 Inhibitors After Cardiac Surgery: A Review of Current Literature. *J Cardiothorac Vasc Anesth*. **2022 Oct – Narrative review of 17 papers describing SGLT2 associated EKDA in perioperative cardiac surgical patients.**
- Mehta PB, Robinson A, Burkhardt D, Rushakoff RJ. Inpatient Perioperative Euglycemic Diabetic Ketoacidosis Due to Sodium-Glucose Cotransporter-2 Inhibitors - Lessons From a Case Series and Strategies to Decrease Incidence. *Endocr Pract*. **2022 Sep – retrospective study of SGLT2 associated EKDA perioperatively; more common in emergency surgeries as SGLT2s were not held as they were routinely 3 days prior to elective surgeries.**

FDA revises labeling for SGLT2 Inhibitors

Updated 3/19/20 and revised 3/15/22

To lessen the risk of developing ketoacidosis after surgery, FDA has approved changes to the prescribing information for SGLT2 inhibitor medicines. Health care professionals should consider stopping canagliflozin, dapagliflozin, and empagliflozin at least three days before, and ertugliflozin at least four days before scheduled surgery.

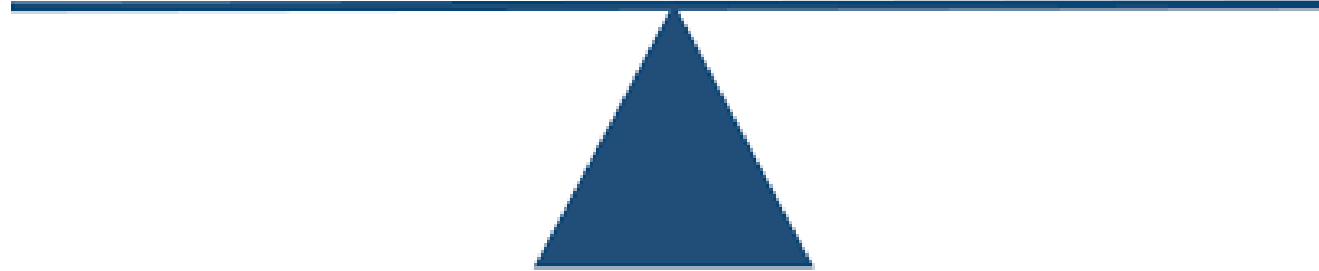
What does Tower say?

- Four days prior to surgery: discontinue SGLT2 inhibitors (Jan 2023)

Perioperative Management of Anticoagulation

Clotting risk

Bleeding risk



Clotting Risk

Table 1—[Introduction] Suggested Risk Stratification for Perioperative Thromboembolism

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High ^a	<ul style="list-style-type: none"> Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack 	<ul style="list-style-type: none"> CHADS₂ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Rheumatic valvular heart disease 	<ul style="list-style-type: none"> Recent (within 3 mo) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	<ul style="list-style-type: none"> Bileaflet aortic valve prosthesis and one or more of the of following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 y 	<ul style="list-style-type: none"> CHADS₂ score of 3 or 4 	<ul style="list-style-type: none"> VTE within the past 3-12 mo Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
Low	<ul style="list-style-type: none"> Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke 	<ul style="list-style-type: none"> CHADS₂ score of 0 to 2 (assuming no prior stroke or transient ischemic attack) 	<ul style="list-style-type: none"> VTE > 12 mo previous and no other risk factors

CHADS₂ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.

^aHigh-risk patients may also include those with a prior stroke or transient ischemic attack occurring > 3 mo before the planned surgery and a CHADS₂ score < 5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

Bleeding Risk

What is “major” bleeding?

- Fatal bleeding

- Critical anatomic site (intracranial, etc.)

- Requires surgery to correct

- Lowers Hgb by 2g/dL

- Requires transfusion ≥ 2 units pRBCs

Bleeding Risk

HAS-BLED score

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

Pisters R et al. Chest 2010;138(5):1093-1100.

High (2-day risk of major bleed 2%-4%)

- Heart valve replacement
- Coronary artery bypass
- Abdominal aortic aneurysm repair
- Neurosurgical/urologic/head and neck/abdominal/breast cancer surgery
- Bilateral knee replacement
- Laminectomy
- Transurethral prostate resection
- Kidney biopsy
- Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
- PEG placement
- Endoscopically guided fine-needle aspiration
- Multiple tooth extractions
- Vascular and general surgery
- Any major operation (procedure duration > 45 minutes)

Low (2-day risk of major bleed 0%-2%)

- Cholecystectomy
- Abdominal hysterectomy
- Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endonasonography without fine-needle aspiration
- Pacemaker and cardiac defibrillator insertion and electrophysiologic testing
- Simple dental extractions
- Carpal tunnel repair
- Knee/hip replacement and shoulder/foot/hand surgery and arthroscopy
- Dilatation and curettage
- Skin cancer excision
- Abdominal hernia repair
- Hemorrhoidal surgery
- Axillary node dissection
- Hydrocele repair
- Cataract and noncataract eye surgery
- Noncoronary angiography
- Bronchoscopy ± biopsy
- Central venous catheter removal
- Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies

This table is based on definitions derived from surgical/subspecialty societies in anticoagulant bridging or anticoagulant bridging management studies.



Development and Validation of the DOAC Score: A Novel Bleeding Risk Prediction Tool for Patients With Atrial Fibrillation on Direct-Acting Oral Anticoagulants

Rahul Aggarwal^{ID}, MD; Christian T. Ruff^{ID}, MD, MPH; Saverio Virdone^{ID}, MSc; Sylvie Perreault^{ID}, BPharm, PhD; Ajay K. Kakkar, MBBS, PhD; Michael G. Palazzolo^{ID}, MPH; Marc Dorais, MSc; Gloria Kayani^{ID}, BSc; Daniel E. Singer^{ID}, MD; Eric Secemsky^{ID}, MD; Jonathan Piccini^{ID}, MD, MHS; Usman A. Tahir, MD, MBI; Changyu Shen^{ID}, PhD; Robert W. Yeh^{ID}, MD, MSc

DOAC Score

The risk score was developed among 5684 patients in the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Further developed in 12 296 individuals in the GARFIELD-AF registry (Global Anticoagulant Registry in the Field-Atrial Fibrillation)

Then validated among 25 586 individuals in the COMBINE-AF trials (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) as well as 11 945 individuals in the Quebec Régie de l'Assurance Maladie du Québec and Med-Echo Administrative Databases (RAMQ) administrative database.

The DOAC Score had moderate discrimination in all cohorts and outperformed the HAS-BLED score.

DOAC Score

Clinical risk prediction tool	Points
Age, y	
65–69	2
70–74	3
75–79	4
≥80	5
Creatinine clearance/estimated glomerular filtration rate (mL/min)	
30–60	1
<30	2
Underweight (body mass index <18.5 kg/m ²)	1
Stroke/transient ischemic attack/embolism history	1
Diabetes	1
Hypertension	1
Antiplatelet use	
Aspirin	2
Dual-antiplatelet	3
Nonsteroidal anti-inflammatory (NSAID) use	1
Bleeding history	3
Liver disease*	2
Total score range: 0–10 (Maximum 10 points – individuals with scores ≥ 10 are assigned a score of 10)	

DOAC Score

Table 4. One-Year Bleeding Rates by Risk Category for Individuals in the Development and Validation Cohorts

Risk category (risk score)	RE-LY (N=5684)		GARFIELD-AF (N=12 296)		COMBINE-AF (N=25 586)		RAMQ (N=11 945)	
	N (Major bleeding events)	One-year rate	N (major bleeding events)	One-year rate	N (major bleeding events)	One-year rate	N (major bleeding events)	One-year rate
Very low (0–3)	767 (2)	0.8%	4360 (14)	0.3%	6038 (82)	1.5%	1832 (10)	0.6%
Low (4–5)	1249 (21)	1.6%	3735 (33)	0.9%	6630 (123)	2.0%	2834 (40)	1.4%
Moderate (6–7)	1727 (53)	3.4%	3263 (60)	1.9%	7348 (197)	3.1%	3418 (72)	2.1%
High (8–9)	1296 (87)	6.9%	748 (17)	2.4%	4015 (188)	5.4%	2274 (76)	3.3%
Very High (10)	645 (73)	13.9%	190 (7)	3.7%	1555 (102)	7.7%	1587 (60)	3.7%

Interrupting Warfarin

Stop: 5 days prior to elective surgery

Restart: 12-24 hours after surgery

Bridge?

- Rarely
 - Mechanical mitral valve, mechanical aortic valve with additional risks
 - CHAD₂s 5-6, prior embolic stroke within 3 months
 - VTE within previous 3 months
- Why not?
 - BRIDGE 2015 – AF, LMWH vs placebo, no reduction in thrombotic risk, but increased bleeding with LMWH
 - PERIOP-2 2021 – AF, MV, LMWH preop then LMWH vs placebo, no reduction in thrombotic risk or increase in bleeding
 - RE-LY (2009), ROCKET-AF (2011), ARISTOLE (2011) and real-world data from ORBIT-AF showed no effect on major outcomes with bridging vs non-bridging
 - Baumgartner et al SR in 2019: no reduction in thrombosis, increased bleeding with bridging for VTE patients
 - Siegal et al SR/MA in 2012: no reduction in thrombosis, increased bleeding with bridging for any indication

Interrupting DOACs

“PAUSE” approach:

HIGH BLEEDING RISK procedure			Day of surgery	No major bleeding		
Regular DOAC dose	X	X	X	X	Regular DOAC dose	Regular DOAC dose

LOW BLEEDING RISK procedure			Day of surgery	No major bleeding		
Regular DOAC dose	Regular DOAC dose	X	X	Regular DOAC dose	Regular DOAC dose	Regular DOAC dose

Bridge? Nope.

Return to Objectives

- ❑ Review guidance on perioperative management of GLP1 receptor agonists
 - ❑ Hold daily on day of surgery, hold weekly 1 week prior
 - ❑ Data quite limited, but reasonable to employ the “precautionary principle”
- ❑ Review guidance on perioperative management of SGLT2 inhibitors
 - ❑ Hold 3 days prior to surgery (4 for ertugliflozin) due to risk of EDKA
- ❑ Review guidance on perioperative management of anticoagulation
 - ❑ Evaluate thrombotic vs bleeding risk (new DOAC score)
 - ❑ Stop warfarin 5 days prior, restart 12-24 hours after, probably don't need to bridge outside of specific circumstances
 - ❑ Interrupt DOACs using the PAUSE strategy

Thanks!
