Perioperative Management of Patients on SGLT-2 inhibitors

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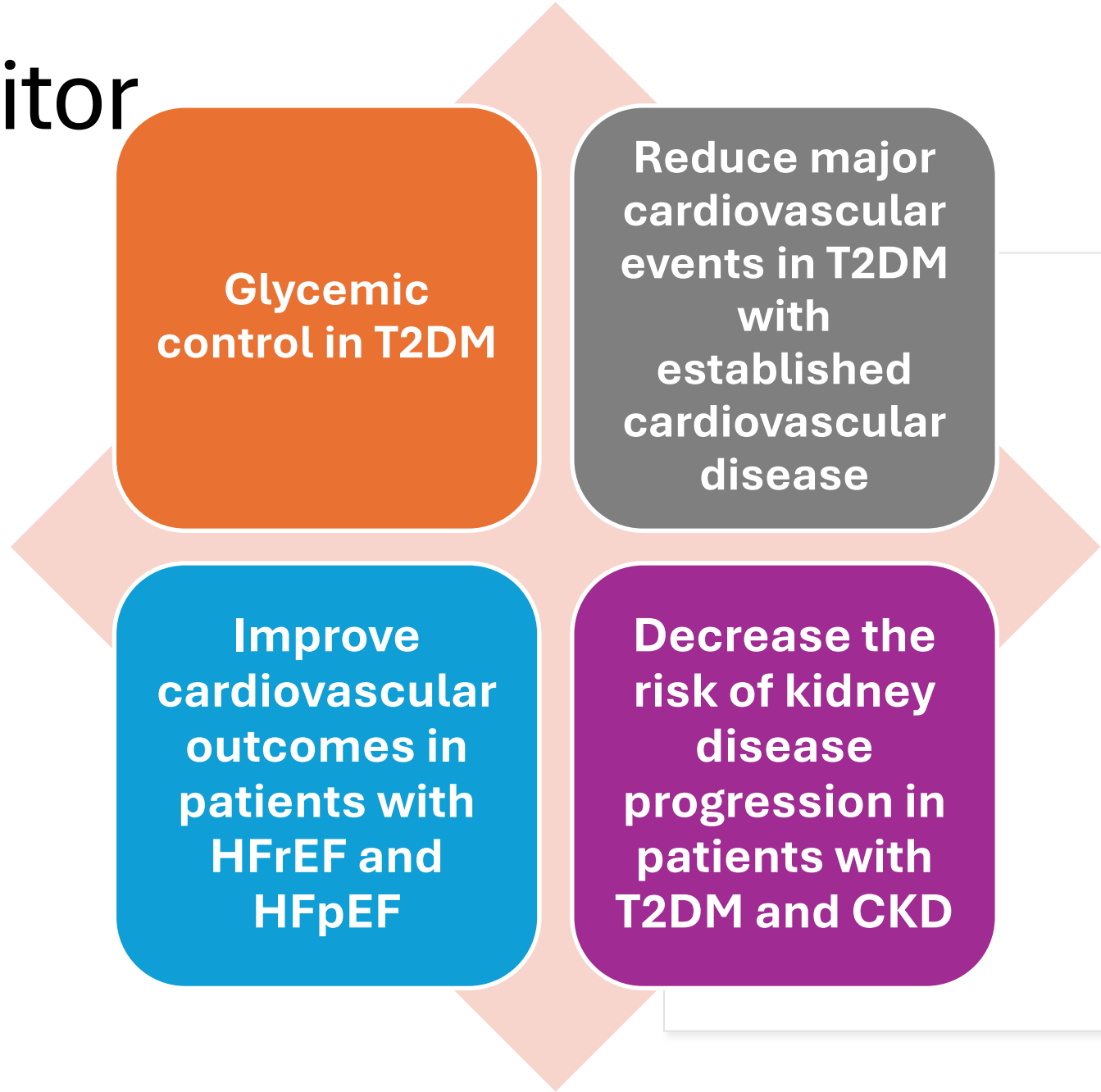
SGLT-2 inhibitors

SGLT2 is expressed in the proximal tubule of the kidney and mediates reabsorption of glucose from the tubular lumen.

In individuals without DM, the filtered glucose load is less than the maximal glucose transport capacity (~180 g/day).

SGLT2 inhibitors block the reabsorption of filtered glucose from the tubular lumen and thereby promote the renal excretion of glucose

SGLT-2 inhibitor Indications

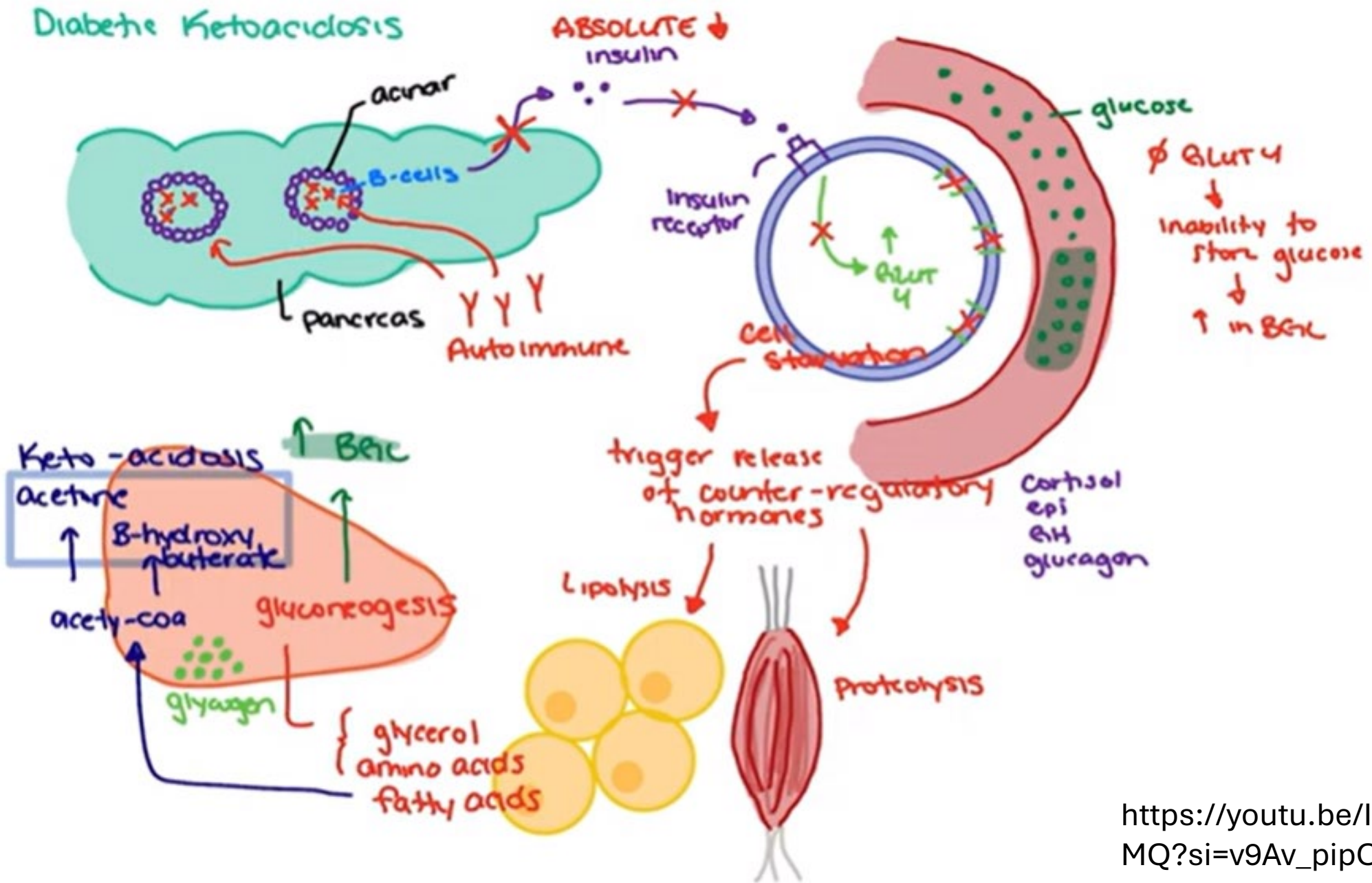


SGLT-2 inhibitors Currently Approved

- Canaglifozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)
- Bexagliflozin (Brenzavvy)

SGLT-2 inhibitors – Side Effects

- Urinary frequency
- UTI and pyelonephritis
- Fournier's gangrene (Necrotizing fasciitis of the perineum)
- Dehydration/hypotension/AKI
- Diabetic ketoacidosis



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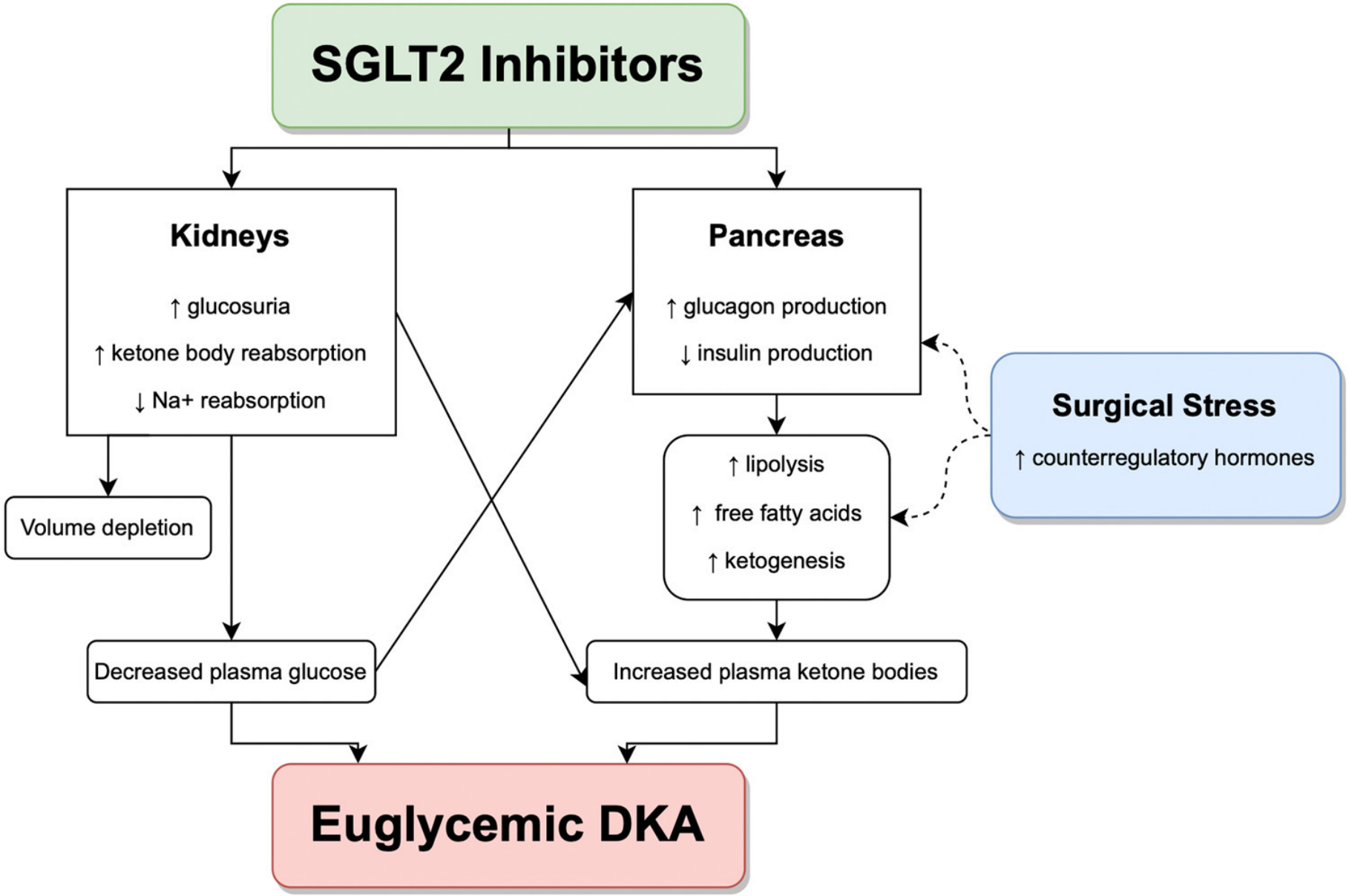
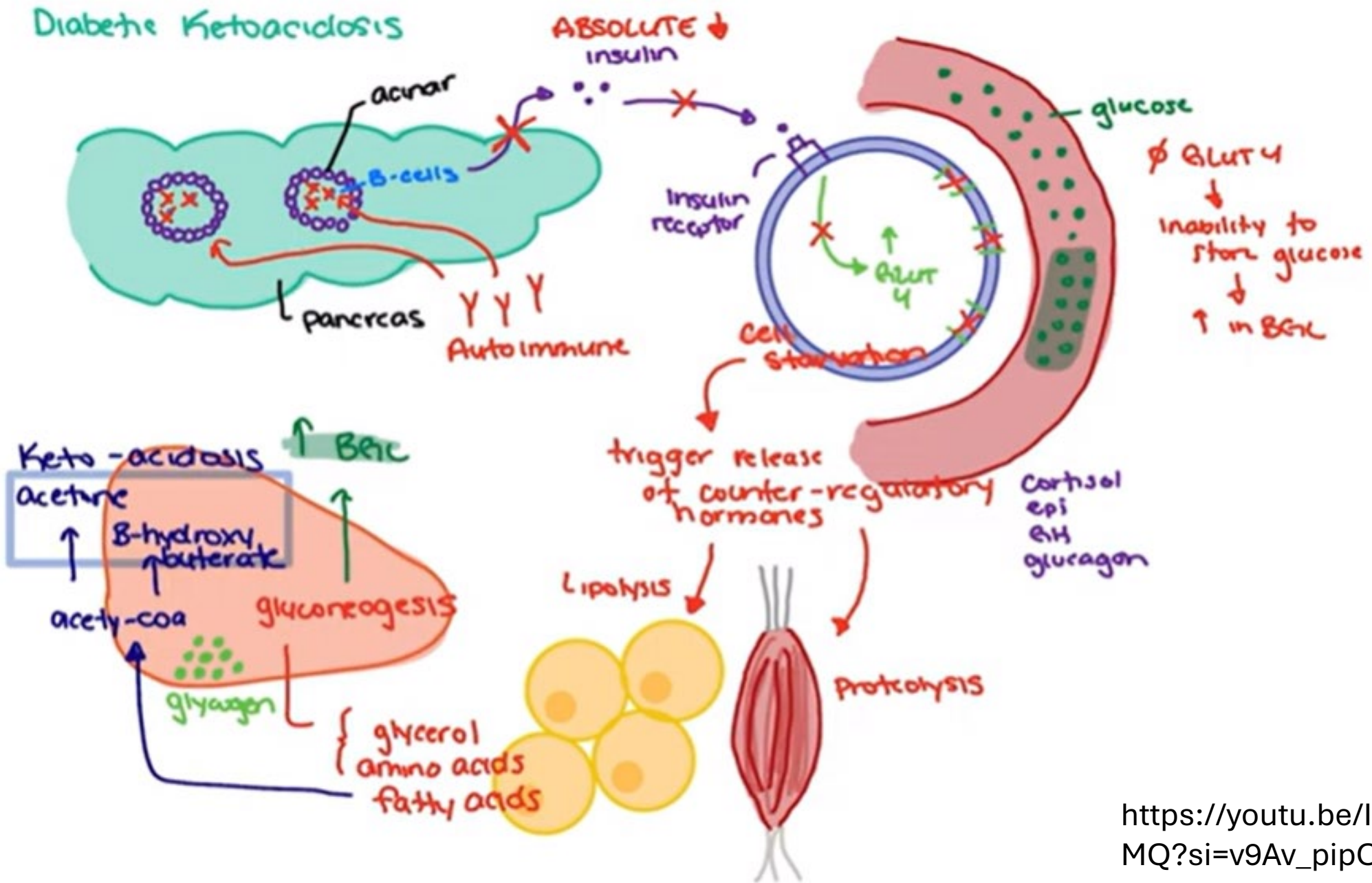


Raiten et al. Journal of Cardiothoracic and Vascular Anesthesia, Volume 38, Issue 1, 2024, Pages 57-66,



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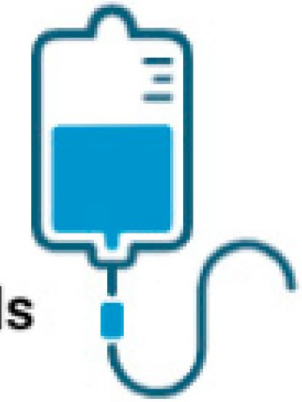
IV Fluids



Give 2-3 L of 0.9% NS over 1-3 H

Step down to 0.45% NS at 250-500ml/hr

when Bl. Glucose level = 250mg/dL

Add 5% Glucose to 0.45% NS at 150-250ml/ hr

Insulin drip

Give short acting/ regular insulin 0.1 units/kg IV bolus

0.1 units/Kg/hr IV infusion

0.05-0.1 units/kg/hr IV infusion

2-4 hr overalp in insulin infusion and long-acting insulin injection

K level

K<3.3 mEq/L

Hold insulin infusion
Give 20-30 mEq/hr untill K>3.3 mEq/L

K 3.3-5.2 mEq/L

Give 20-30 mEq/hr in each L of IV fluid to keep K between 4-5 mEq/L

K>5.2 mEq/L

Do not give K, but check serum K level every 2hours

El-Remessy AB. Diabetic Ketoacidosis Management: Updates and Challenges for Specific Patient Population. *Endocrines*. 2022; 3(4):801-812. https://doi.org/10.3390/endocrines3040066

Euglycemic DKA

BG <200 mg/dL, ketonemia (serum β-hydroxybutyrate≥3.0 mmol/L), and at least one of the following criteria to define EDKA:

1. Arterial pH≤7.3
2. Serum bicarbonate ≤18 meq/L
3. Anion gap >10.

- SGLT2 inhibitor use
- Fasting state, perioperative setting
- Surgery, e.g. bariatric operations
- Ketogenic diet
- Anorexia
- Intoxication, alcohol, cocaine
- Insulin pump
- Gastroparesis
- Glycogen storage disease
- Infections, sepsis
- Gastroenteritis, pancreatitis
- Renal disease
- Liver disease
- Pregnancy

Table 1. Conditions for increased risk of EDKA

Chow et al. *BMJ Open Diabetes Research and Care* 2023;**11:**e003666.

Euglycemic DKA

BG <200 mg/dL, ketonemia (serum β-hydroxybutyrate≥3.0 mmol/L), and at least one of the following criteria to define EDKA:

1. Arterial pH≤7.3
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Category	Blood ketones	Urine ketones
Parameter (measured)	β-hydroxybutyrate as ketone body predominantly produced in DKA measures current concentration, progress controls useful for therapy monitoring	Acetoacetate as by-product measures average urine concentration
Reliability of results	Higher sensitivity and specificity for DKA	Lower sensitivity and specificity for DKA
Time	Rapid, immediate measurement	Possibly delayed at sample collection due to dehydration
Measurement method	POCT meter	Urine test (strip)

Table 2. Comparison of the advantages and disadvantages of ketone measurement methods
DKA = diabetic ketoacidosis. Adapted according to Dhatariya et al. 2016

Chow et al. *BMJ Open Diabetes Research and Care* 2023;**11:**e003666.

Risk factors identified in SGLT2i-associated DKA

- **Population-based cohort study of adults started on SGLT2i use from 2013 to 2017**
- **Primary objective was to identify potential predictors of diabetic ketoacidosis**
- **N=111,442 adults**
  - **<u>DKA</u>**
    - **N=475 (0.4%) Inpatient or Outpatient**
    - **N=192 (0.2%) Inpatient**

Table 2 Risk Factors for Diabetic Ketoacidosis Using Variables Identified Up to 180 Days Prior to SGLT2 Inhibitors

	Inpatient diagnosis of DKA			Inpatient or outpatient diagnosis of DKA		
	OR	95% CI		OR	95% CI	
Prior DKA	2.43	0.33	17.82	24.07	14.28	40.59
Hypoglycemia	5.43	1.92	15.32	2.46	0.98	6.17
Hemoglobin A1C > 10%	3.16	1.97	5.08	1.89	1.38	2.59
Bicarbonate < 18 mmol/L	5.10	1.58	16.42	2.93	1.17	7.32
Creatinine ≤ 0.5 mg/dL	2.55	0.79	8.17	1.03	0.33	3.26
Creatinine >1.5 mg/dL	0.50	0.06	3.86	1.54	0.66	3.60
Delirium	3.22	0.68	15.14	2.26	0.75	6.89
Dementia medication	7.65	2.57	22.76	3.47	1.34	8.96
Digoxin	3.97	1.20	13.09	5.45	2.71	10.93
Intracranial hemorrhage	11.46	1.45	91.38	5.30	0.71	39.52

FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections

FDA Drug Safety Communication

3-19-2020 Update; Revised 3-15-2022

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.

Problem Statement

Patients who present for surgery without discontinuing their SGLT2i, whether due to emergency circumstances or simply forgetting to pause the medication, need further risk assessment and monitoring perioperatively given eDKA concerns.

Guideline Scope

Adult patients >18 years

Both with and without diabetes

Undergoing surgery or procedures at Michigan Medicine across all surgical sites including both elective and urgent/emergent cases.

Guideline Team

Anesthesia Representatives

Ross Blank

David Garcia

Ellen Janke

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Pharmacy Representatives

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Guideline Development - Our Goal

The overall goal is to mitigate risk of eDKA in high-risk patients while avoiding unnecessary cancellations of low-risk patients.

Help surgical and anesthesia teams stratify which patients/scenarios are high risk for development of euglycemic diabetic ketoacidosis (eDKA) and advise appropriate diagnosis, monitoring, and treatment strategies

Status Active PolicyStat ID 14343439

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Origination	11/30/2023
Last Approved	11/30/2023
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Last Revised	11/30/2023
Next Review	11/29/2026

Owner	Simona Butler: Clinical Pharmacist and Adjunct Clinical Associate
Area	Pharmacy Services
Applicability	UMHS Clinical
References	Guideline

Pharmacy Services Perioperative/Procedure Management of Adult Patients on Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors Guideline

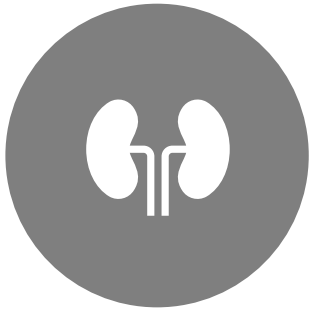
Elective Procedures

SGLT-2 INHIBITORS HELD APPROPRIATELY -> PROCEED

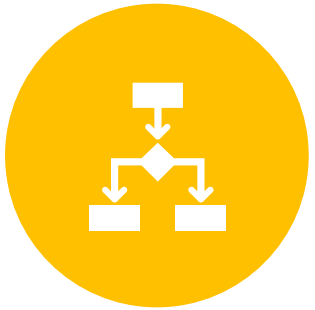
ADVISE THE PATIENT TO RESUME SGLT-2 INHIBITORS ONCE THE DIET IS BACK TO NORMAL.

Elective Procedures

IF IMAGING ONLY (CT, MRI, PET) -> **PROCEED**



ALL ENDOSCOPIC PROCEDURES -> **PROCEED**



LOW-RISK PROCEDURES BASED ON CLINICAL JUDGMENT -> **PROCEED**

ADVISE THE PATIENT TO RESUME SGLT-2 INHIBITORS ONCE THE DIET IS BACK TO NORMAL.

Elective Procedures

Patient does not have diabetes -> **proceed**

- **outpatient procedure** -> Provide instructions on signs and symptoms of diabetic ketoacidosis upon discharge. Hold medication until the diet is back to normal.
- **inpatient procedure** -> Check VBG in PACU/ICU. Follow the post-op algorithm.

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Preventing eDKA After Taking SGLT2 Inhibitors Before Surgery

SGLT2 inhibitors are non-insulin medications used to treat diabetes. Some examples of these medications include: canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®), bexagliflozin (Brenza ertrugliflozin (Steglatro®).

Usually, your surgery team will tell you to **stop taking SGLT days before your surgery**.

What is euglycemic diabetic ketoacidosis (eDKA)?

- If you have surgery and you forget to stop taking you you are at risk for something called **eDKA**, or **euglyc ketoacidosis**. eDKA is a rare but serious condition th

What are some signs and symptoms of eDKA to watch for?

- Nausea, vomiting, or abdominal (stomach) pain
- Being really thirsty or having a dry mouth
- Peeing often
- Fast breathing or shortness of breath
- Fatigue (tiredness), weakness, or confusion
- Your breath smells “fruity”
- Changes in appetite (like not feeling hungry or not wanting to eat)

What should I do if I have possible symptoms of eDKA?

If you notice any of these signs and symptoms, contact your healthcare provider or go to the nearest emergency room. **Be sure to tell them that you are taking an SGLT2 inhibitor and you have recently had surgery.** This information is important for your doctors to treat you and manage eDKA.

Elective Procedures

Person with DM & high-risk criteria -> postpone

High-risk Criteria

- **Surgery/procedure duration > 3-4 hours**
- **If patient not anticipated to resume oral intake post-op**
- **Diagnosis of T1D/LADA/diabetes due to pancreatitis or pancreatic surgery**
- **H/o DKA if known**
- **Pre-op HbA1c > 10%**
- **ASA status > 3**
- **Excessive alcohol intake**

Check VBG

If AG > 12 and bicarb ≤ 18, refer to ER for eDKA management.
If AG > 12 and bicarb is > 18, consider other causes of the anion gap. If otherwise clinically stable resume diet. Provide instructions on signs and symptoms of diabetic ketoacidosis upon discharge

Elective Procedures

DM, no high-risk criteria -> Check preop VBG

-- If **AG ≤ 12** -> **proceed**

re-check VBG Q1-2 hr during the procedure, if AG becomes >12, follow the **blue box.** If AG stays ≤ 12 during the procedure, check VBG in PACU/ICU and follow the post-op algorithm.

-- If **AG > 12** -> **postpone**

If AG > 12 and bicarb ≤ 18, refer to ER for eDKA management.

If AG > 12 and bicarb is > 18, consider other causes of the anion gap. If otherwise clinically stable resume diet. Provide instructions on signs and symptoms of diabetic ketoacidosis upon discharge.

If you have a gap…

<u>If AG > 12, look at bicarb.</u>
If bicarb ≤ 18,

- **Check stat serum ketones (beta-hydroxybutyrate)**
- **Start standard anesthesia insulin infusion protocol.**
  - **5% dextrose fluid at 50 ml/hr if BG 150-250 mg/dl***
  - **10% dextrose fluid at 50 ml/hr if BG < 150 mg/dl***
- **Monitor glucose checks Q1hr and VBG Q1-2hr while intra-op.**
- **Once in PACU/ICU, can transition to standard DKA protocol insulin drip with glucose and VBG/ BMP monitoring per protocol until the anion gap closes. If serum ketones come back negative, consider alternative causes of anion gap acidosis, and discontinue insulin drip if clinically appropriate.**
- **Consult endocrine post-op: when the patient is admitted to the unit or the floor.**

If bicarb > 18, Consider alternative causes of anion gap, and continue checking VBG Q1-2 hr. Consider sending ketones or starting an insulin drip if the etiology remains unclear.

*** If appropriate for volume status/clinical scenario.**

Urgent & Emergent Procedures

All urgent/emergent cases-> **proceed**

Check stat VBG:
If **AG > 12** → follow the **blue box** below
If **AG ≤ 12** → proceed with case and monitor VBG Q1-2hr, if AG becomes > 12 then follow the **blue box**. If AG remains < 12 during the procedure, follow the post-op algorithm.

If you have a gap…

<u>If AG > 12, look at bicarb.</u>
If bicarb ≤ 18,

- **Check stat serum ketones (beta-hydroxybutyrate)**
- **Start standard anesthesia insulin infusion protocol.**
  - **5% dextrose fluid at 50 ml/hr if BG 150-250 mg/dl***
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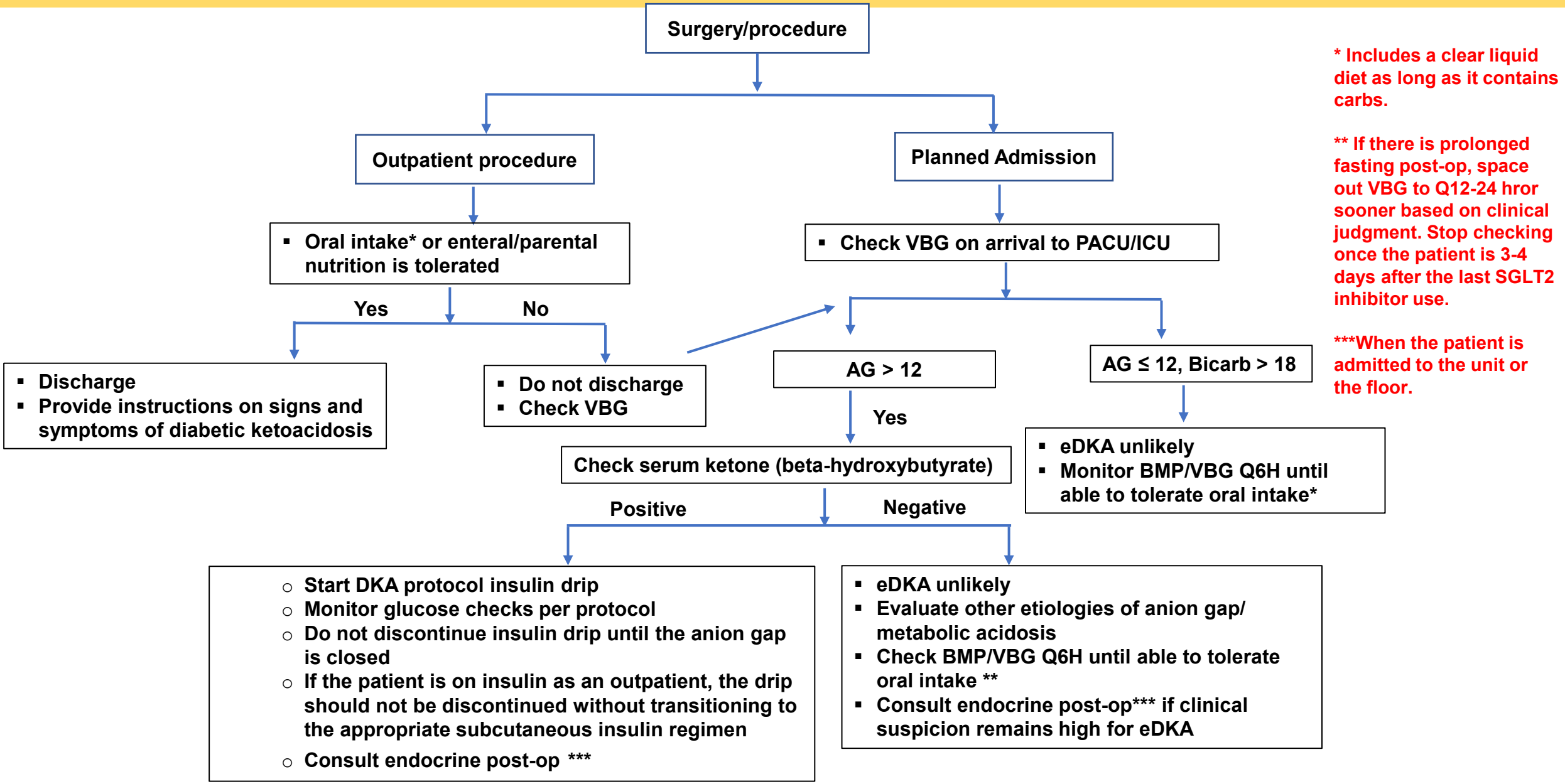
If bicarb > 18, Consider alternative causes of anion gap, and continue checking VBG Q1-2 hr. Consider sending ketones or starting an insulin drip if the etiology remains unclear.

*** If appropriate for volume status/clinical scenario.**

Post-operative management of patients who did not hold SGLT-2 inhibitors at least 3 days (4 days for ertugliflozin) undergoing emergent/urgent or elective surgery/procedure



* Includes a clear liquid diet as long as it contains carbs.

** If there is prolonged fasting post-op, space out VBG to Q12-24 hror sooner based on clinical judgment. Stop checking once the patient is 3-4 days after the last SGLT2 inhibitor use.

***When the patient is admitted to the unit or the floor.

Guideline Development - Our Goal

The overall goal is to mitigate risk of eDKA in high-risk patients while avoiding unnecessary cancellations of low-risk patients.

Help surgical and anesthesia teams stratify which patients/scenarios are high risk for development of euglycemic diabetic ketoacidosis (eDKA) and advise appropriate diagnosis, monitoring, and treatment strategies

Plan – Do – Check - Act

Baseline survey

October 2024

Guideline approved

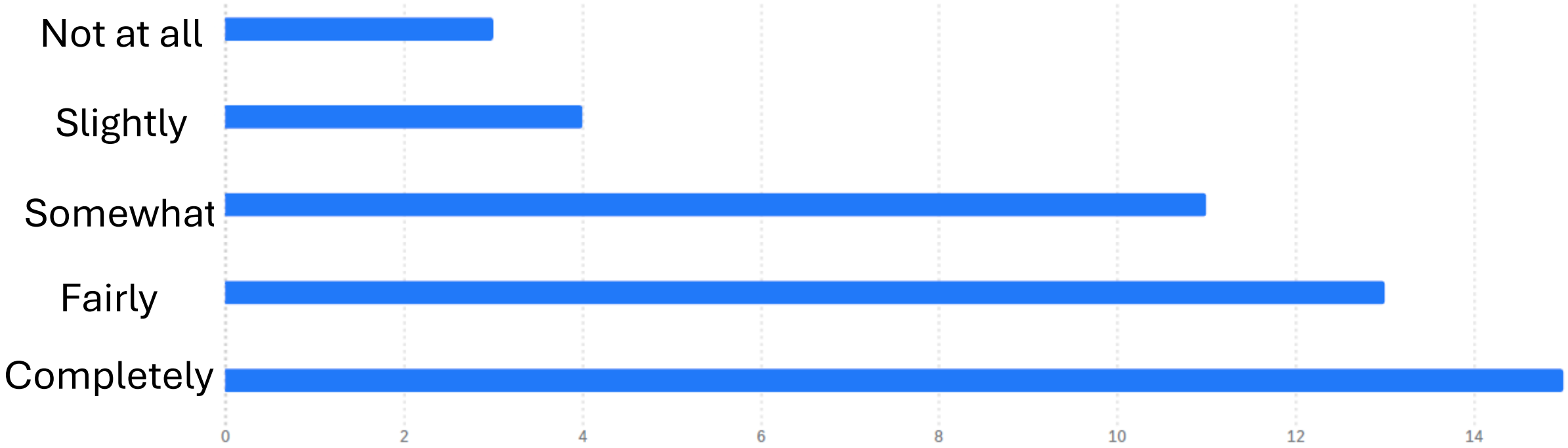
November 2023

Follow-up survey

April 2024

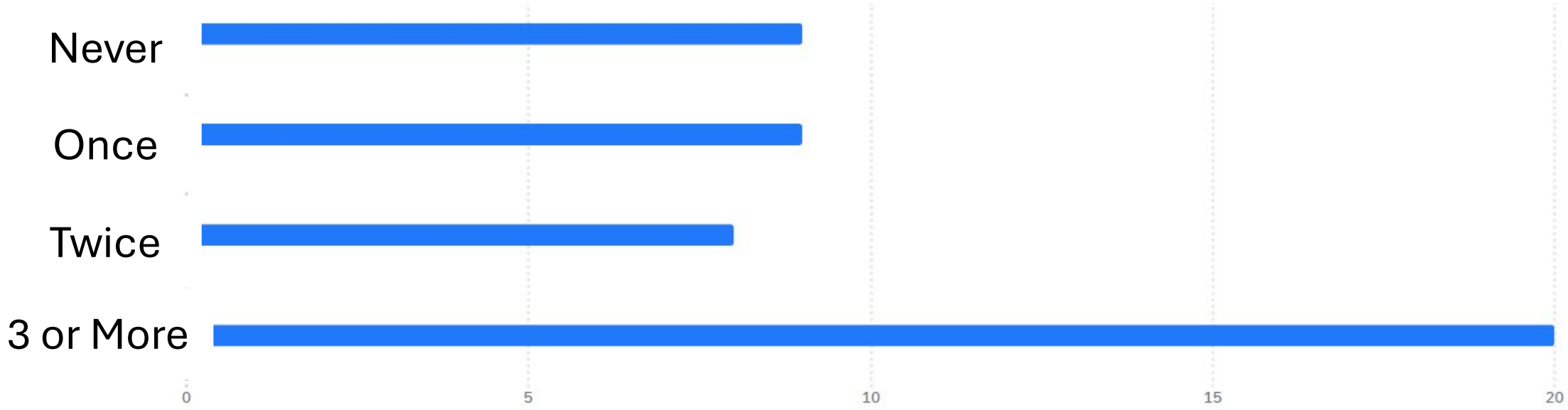
Follow-up Survey (n=46)

How familiar are you with the Michigan Medicine Perioperative SGLT-2i Guideline?



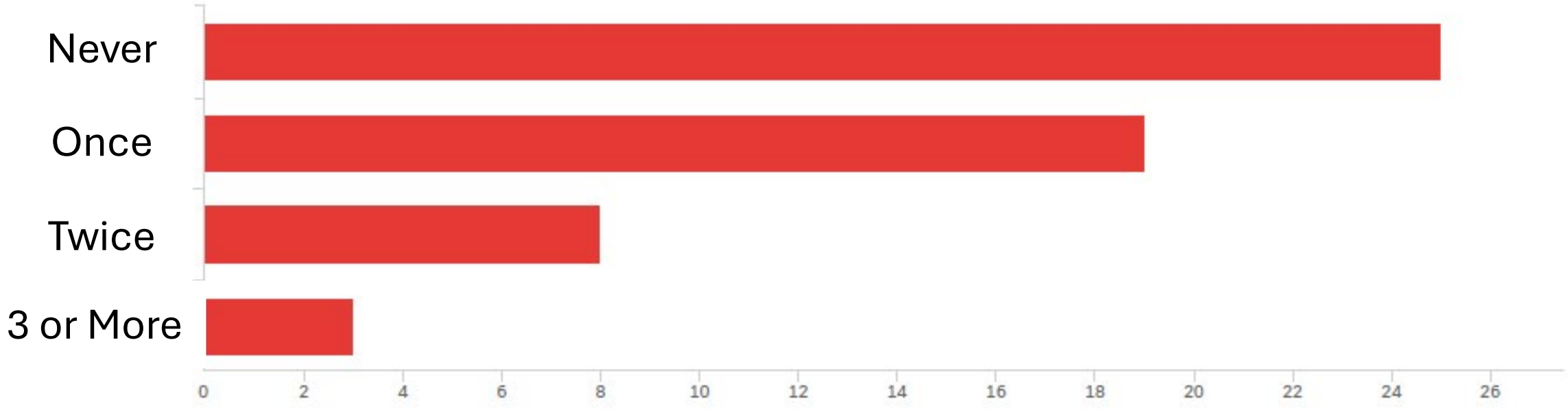
Follow-up Survey (n=46)

How many times have you used the Michigan Medicine Guideline to help with decision-making for a patient on an SGLT-2 inhibitor?



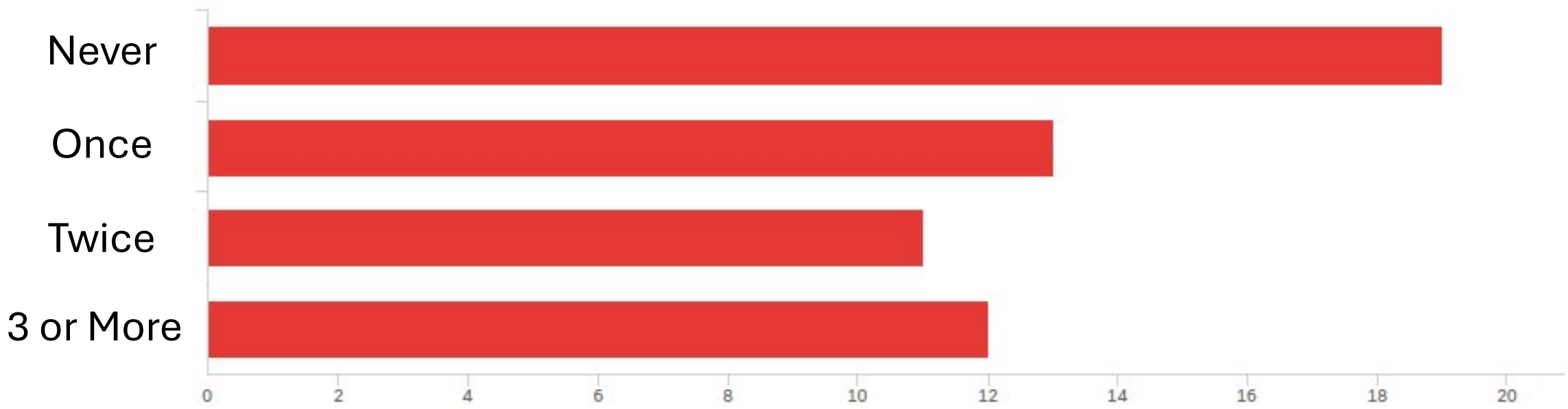
Baseline Survey (n=55)

How many times in the last 3 months have you had a case canceled due to a patient not properly holding their SGLT-2i



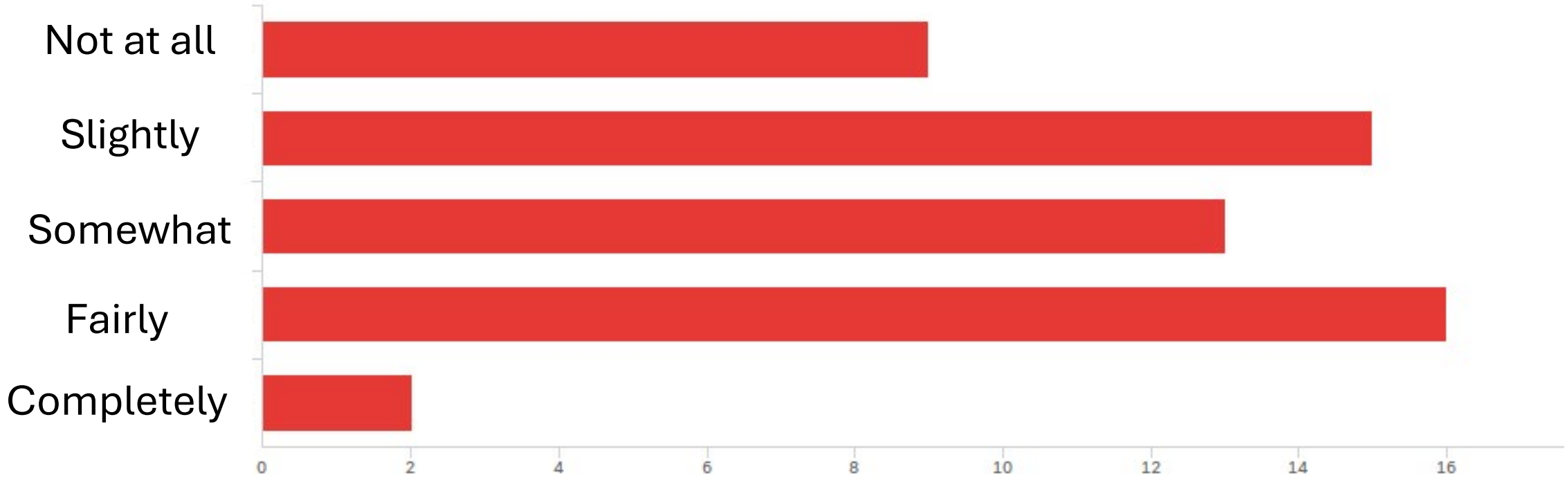
Baseline Survey (n=55)

How many times have you proceeded with a case despite a patient not properly holding their SGLT-2 inhibitor prior to surgery/procedure?



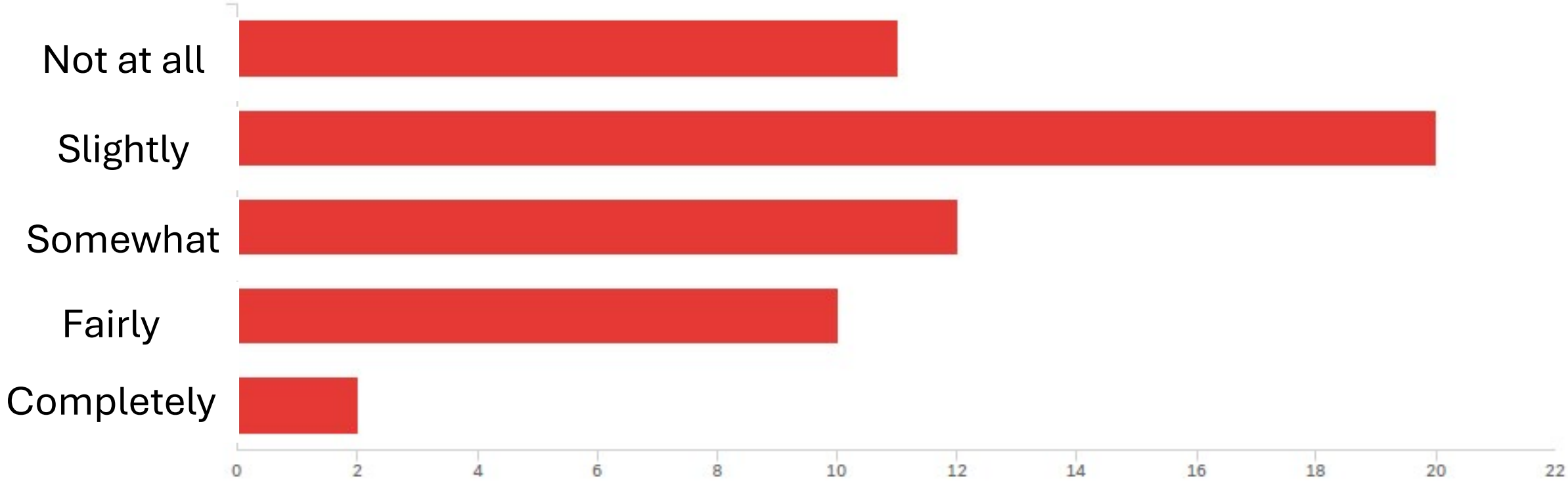
Baseline Survey (n=55)

How confident are you in your ability to recognize/diagnose euglycemic diabetic ketoacidosis (eDKA)?



Baseline Survey (n=55)

How confident are you in your ability to treat euglycemic diabetic ketoacidosis (eDKA)?



Follow-up Survey

	Before	After	Significant?
At least one case cancellation	55%	22%	p = <0.01
At least one case proceeded	65%	76%	p = 0.17
Felt “completely” or “fairly” confident in dx eDKA	33%	33%	p = 0.91
Felt “completely” or “fairly” confident in eDKA management	22%	28%	p = 0.28

Feedback

"I disagree with the guideline. The FDA very clearly states sedation cases or elective generals should not proceed. We are putting patients at risk and favoring RVU generation over patient safety."

"I am comfortable monitoring/managing these patients in the OR. I am more concerned about surgical teams managing or continuing to monitor on the floor. Surgical awareness seems low from my discussions and interactions."

"Challenging with ambulatory surgery center environment resources" and "We are unable to follow the guidelines at EAA as we do not have a pharmacy to prepare insulin infusion,, etc."

"The new changes are very helpful, thank you!"

University of Pennsylvania

In the first 6 months since the guidelines were implemented, among patients presenting for elective surgery who had a BMP checked preoperatively due to having not held their SGLT2i, only 1 patient had an anion gap of >12, and this patient had a normal BOHB. This suggested that the risk of eDKA may be quite low in patients before surgery, and checking a BMP may not be necessary in all patients who have not held these medications. From a workflow perspective, the decision to require screening for acidosis through the use of anion gap analysis has led to the greatest challenges. At the University of Pennsylvania, checking a BMP takes approximately 1 hour. Although all but 1 patient had a normal anion gap and were eligible to proceed with surgery, the surgeon occasionally canceled their procedure due to scheduling conflicts associated with waiting for the laboratory test results. This occurred more frequently in the endoscopy suite, where 1 procedure room may have 10-to-12 patients scheduled daily. Most surgical cancellations when patients failed to hold their SGLT2i were due to patient or surgical characteristics deemed high risk for postoperative eDKA, and a BMP was never drawn, as its results would not have changed care.

Raiten et al, Journal of Cardiothoracic and Vascular Anesthesia, Volume 38, Issue 1, 2024,

Possible Guideline Validation Strategies

Evaluate SGLT-2i case cancellation rates pre- and post- guideline.

Evaluate the number of elective cases where the guideline recommended proceeding where eDKA occurred.

Evaluate rates of eDKA among urgent/emergent cases where SGLT-2i could not be held and assess risk factors/contributors.

Evaluate all cases of DKA/eDKA to understand how many involved SGLT2i.

Evaluate effect of guidelines on costs

Thank You

QUESTIONS, COMMENTS, CONCERNS?

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