SGLT2 Inhibitors

Ellen N Behrend, VMD, PhD, DACVIM (SAIM)

- **Disclosure: I am a paid consultant of Boehringer Ingelheim**

veterinary sciences

MDPI

Article

The Big Pet Diabetes Survey: Perceived Frequency and Triggers for Euthanasia

Stijn J.M. Niessen [1,2,*], Katarina Hazuchova [1], Sonya L. Powney [3], Javier Guitian [4], Antonius P.M. Niessen [5], Paul D. Pion [6], James A. Shaw [2] and David B. Church [1]

2017

30% euthanasia in first year

Owners' concerns – vets' opinion

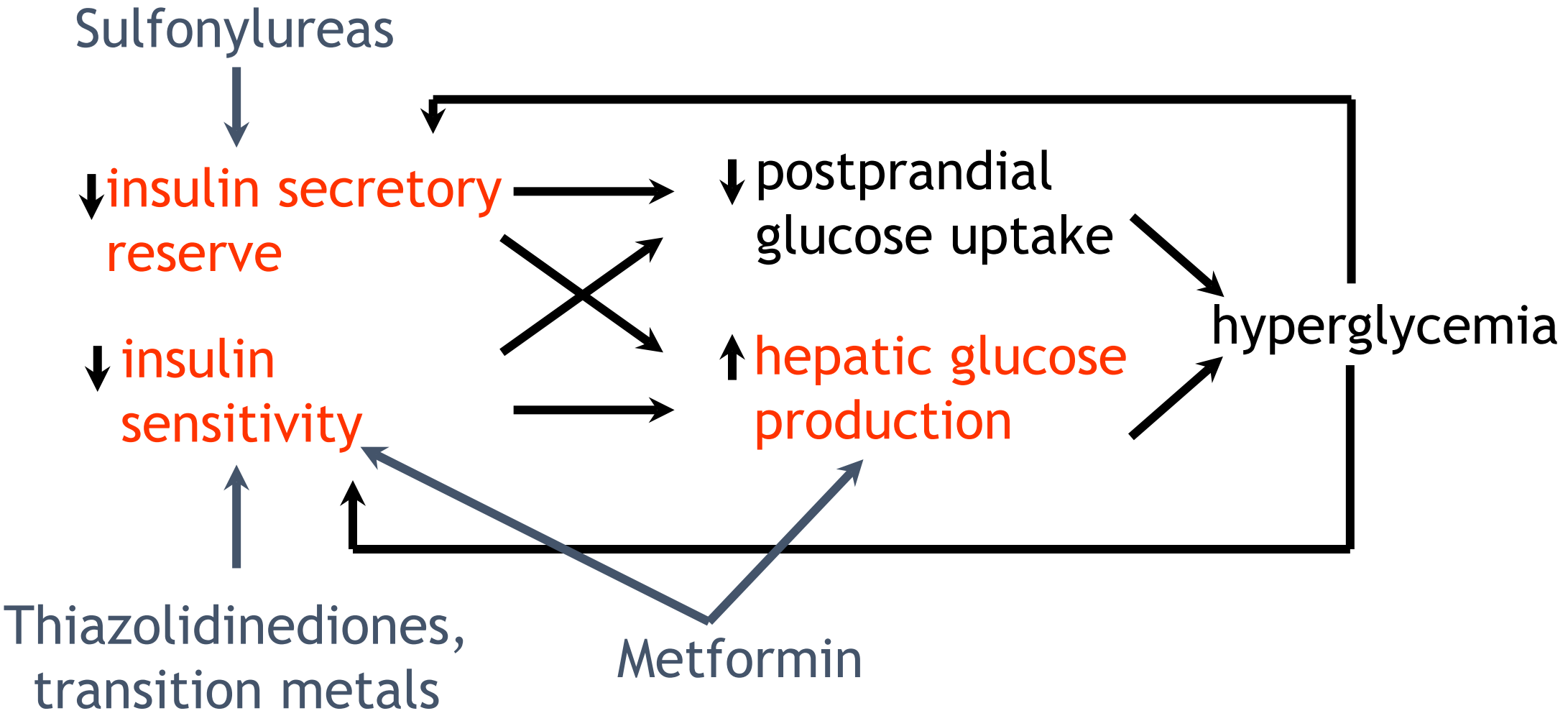
Of great concern:

1. Quality pet life – 60%
2. Cost– 52%
3. Injection – 48%
4. Lifestyle changes – 38%
5. Hypoglycemia - 23%
6. DKA – 7%

Etiologic classification

Type	Description
1	β-cell destruction (absolute insulin deficiency)
2	Relative insulin deficiency: ↓ insulin secretion and peripheral insulin resistance
Others	a. Diseases of the exocrine pancreas
	b. Endocrinopathies
Gestational	↑ Resistance + β-cell dysfunction or loss

Abnormalities of type 2 DM



Sodium-glucose cotransporters (SGLTs) (Sodium-glucose linked transporters)

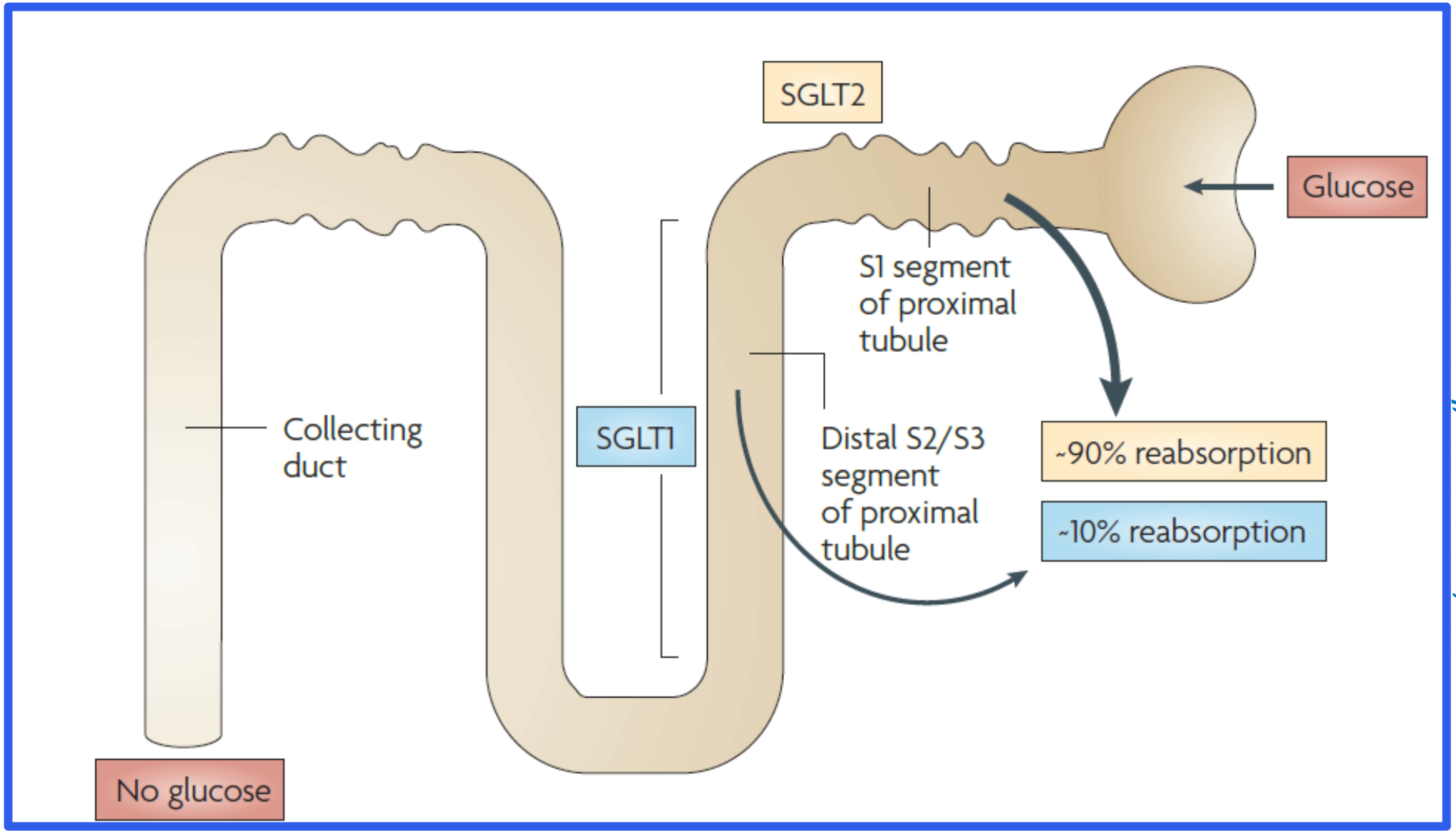
Family of proteins

Move glucose across membranes

Several types, various locations

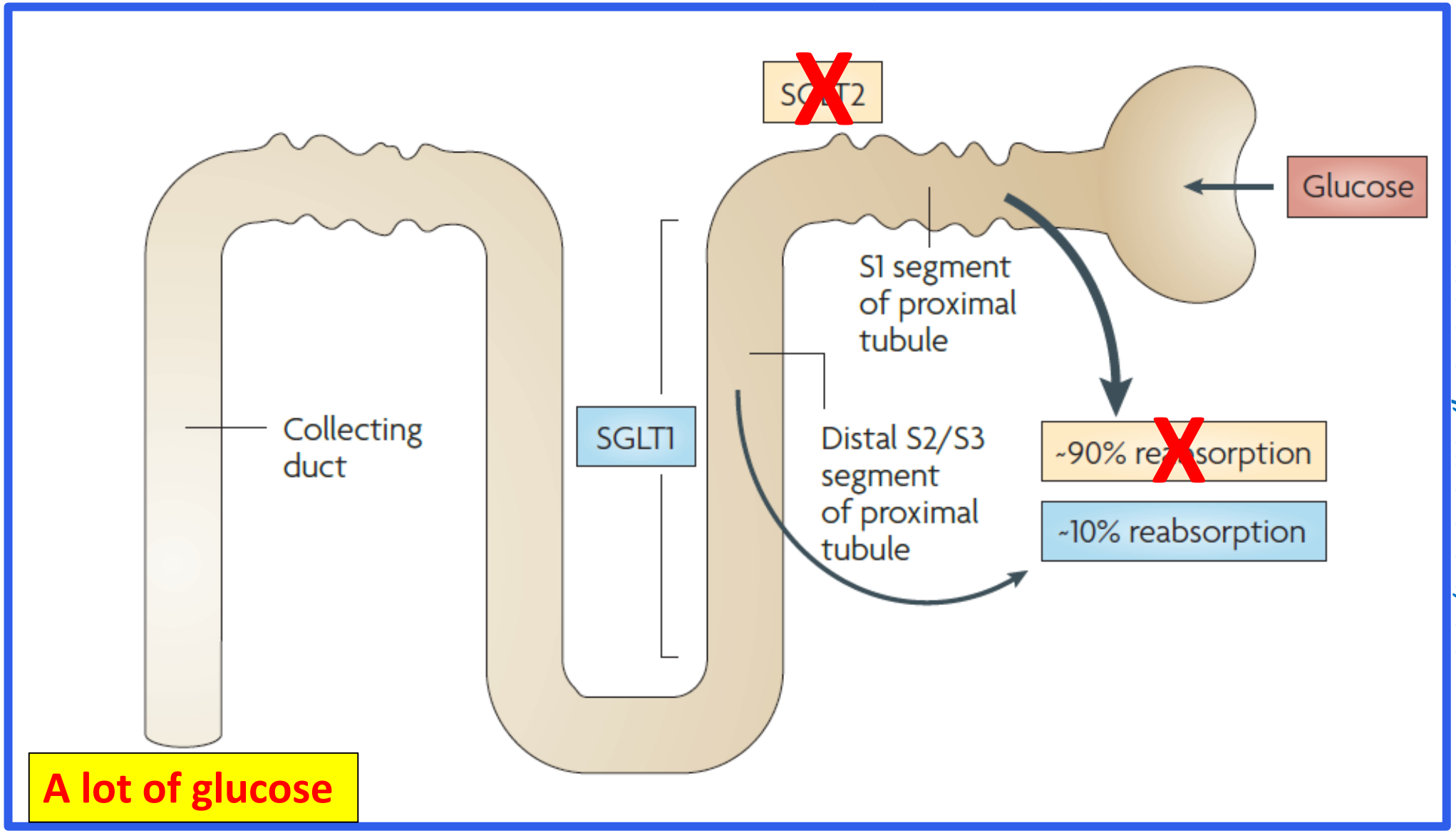
- kidney: SGLT1 and SGLT2
- GI tract: SGLT1

SGLT2



Chao and Henry, Nature Reviews, 2010

SGLT2 inbitors (SGLT2i)



Chao and Henry, Nature Reviews, 2010

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

- -gliflozins
- First approved to treat type 2 diabetes in people in 2013

Insulin requirement

- SGLT2i lower BG without insulin
- Insulin prevents ketosis
- Type I vs Type 2 (dog vs. cat)
- No way to tell

Risk of hypoglycemia VERY low

SGLT1

- mainly intestinal
- normally accounts for 10% renal reabsorption
- upregulated with SGLT2i

Change in glucagon secretion

Genetic SGLT2 alterations do not cause hypoglycemia

Received: 8 November 2022 | Accepted: 15 April 2023

DOI: 10.1111/jvim.16730

Journal of Veterinary Internal Medicine
Open Access

ACVIM
American College of Veterinary Internal Medicine

STANDARD ARTICLE

Safety and effectiveness of the sodium-glucose cotransporter inhibitor bexagliflozin in cats newly diagnosed with diabetes mellitus

Michael J. Hadd[1] | Stephen E. Bienhoff[2] | Susan E. Little[3] | Samuel Geller[4] | Jennifer Ogne-Stevenson[2] | Thomas J. Dupree[1] | J. Catharine Scott-Moncrieff[5]

JAVMA

AVMA

Velagliflozin, a once-daily, liquid, oral SGLT2 inhibitor, is effective as a stand-alone therapy for feline diabetes mellitus: the SENSATION study

Ellen N. Behrend, VMD, PhD, DACVIM[1*]; Cynthia R. Ward, VMD, PhD, DACVIM[2]; Victor Chukwu, DrPH[3]; Audrey K. Cook, BVM&S, DACVIM, DECVIM, DABVP[4]; Carla Kroh, Dr med vet[5]; Patty Lathan, VMD, MS, DACVIM[6]; Jacky May, DVM[7]; Thomas Schermerhorn, VMD, PhD, DACVIM[8]; J. Catharine Scott-Moncrieff, VetMB, MS, DACVIM, DECVIM[9]; Rebecca Voth, DVM[10]

10.2460/javma.24.03.0174

Senvelgo vs. Bexacat

I consider them highly similar

Differences

- dosing (by weight vs. per cat)
- form (liquid vs. pill)

Studies impossible to compare

SENSATION! US pivotal field efficacy & safety study

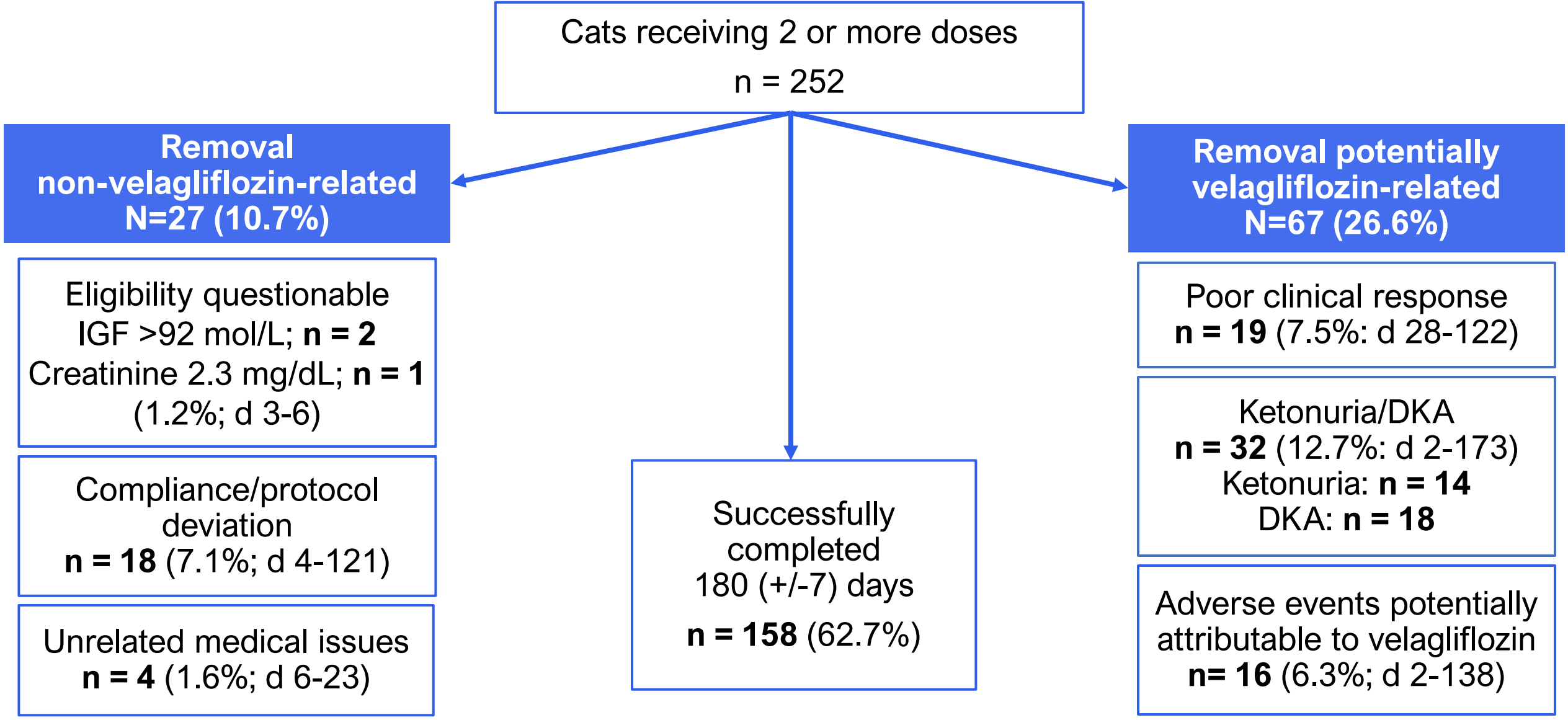
Objective: To investigate the safety and efficacy of velagliflozin oral solution for reduction of hyperglycemia and hyperglycemia-associated clinical signs of diabetes mellitus in cats

Administration

1 mg/kg q24 hours

Into mouth OR on small amount of canned food

Could re-dose within 30 minutes if 1st attempt not successful


Cats receiving 2 or more doses
n = 252
Removal non-velagliflozin-related N=27 (10.7%)
Eligibility questionable
IGF >92 mol/L; n = 2
Creatinine 2.3 mg/dL; n = 1
(1.2%; d 3-6)
Compliance/protocol deviation
n = 18 (7.1%; d 4-121)
Unrelated medical issues
n = 4 (1.6%; d 6-23)
Site closure
n = 2 (0.08%: d 44-149)
Successfully completed
180 (+/-7) days
n = 158 (62.7%)
Removal potentially velagliflozin-related N=67 (26.6%)
Poor clinical response
n = 19 (7.5%: d 28-122)
Ketonuria/DKA
n = 32 (12.7%: d 2-173)
Ketonuria: n = 14
DKA: n = 18
Adverse events potentially attributable to velagliflozin
n= 16 (6.3%; d 2-138)

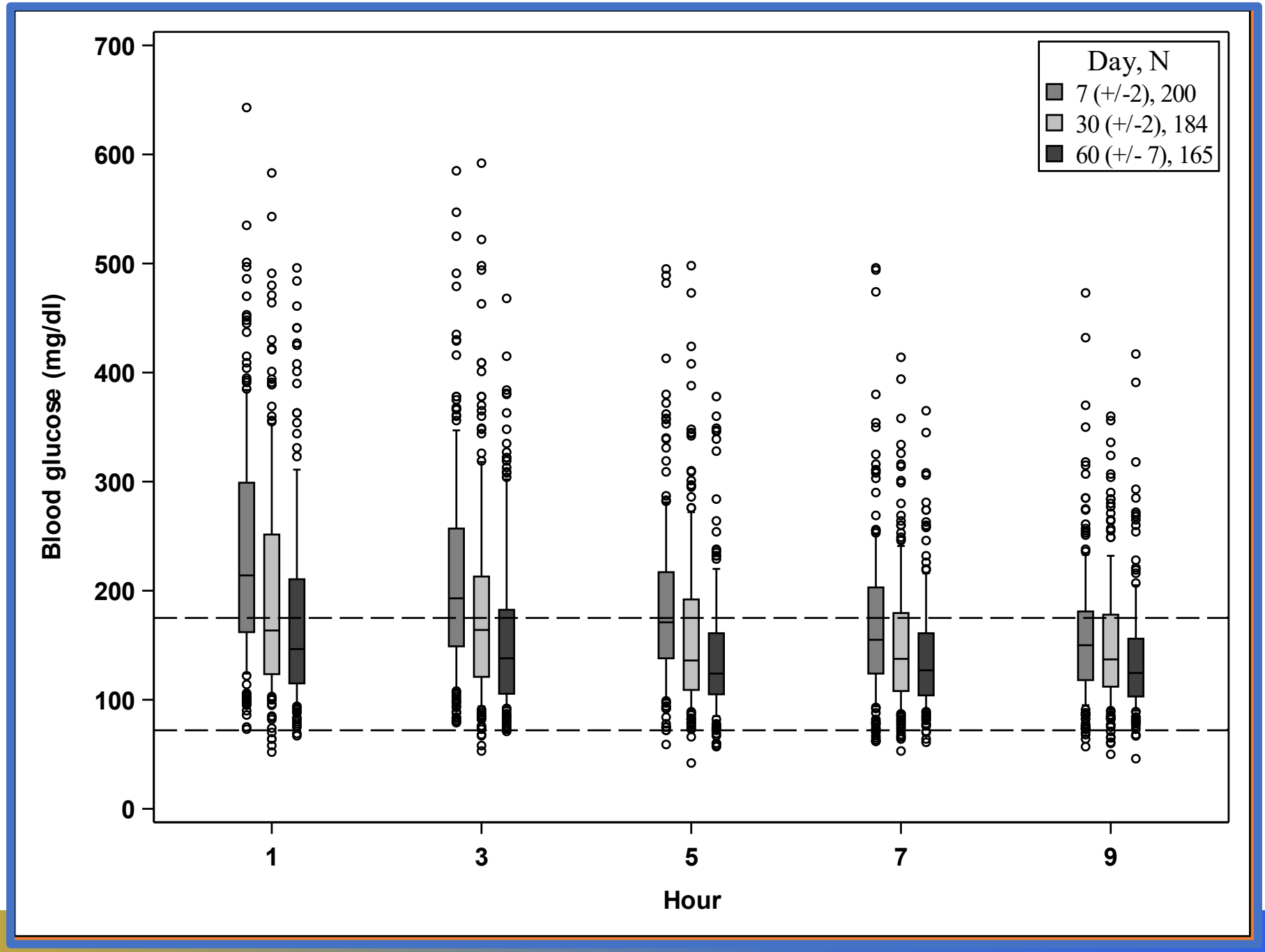
Treatment groups – 252 cats

	Naïve diabetic (ND)	Pre-treated (IT)
N	214 (84.9%)	38 (15.1%)
Body weight (kg)	5.2 (2.6-9.5)	6.4 (3.2-8.8)
Age (yr)	11 (4-18)	12 (6-18)

- Age and body weight similar
- Median insulin duration (IT) 83 d (5-2,549)
- IT more likely to not complete: RR 2.8 (p=0.0016; 95% CI 1.5-5.2)

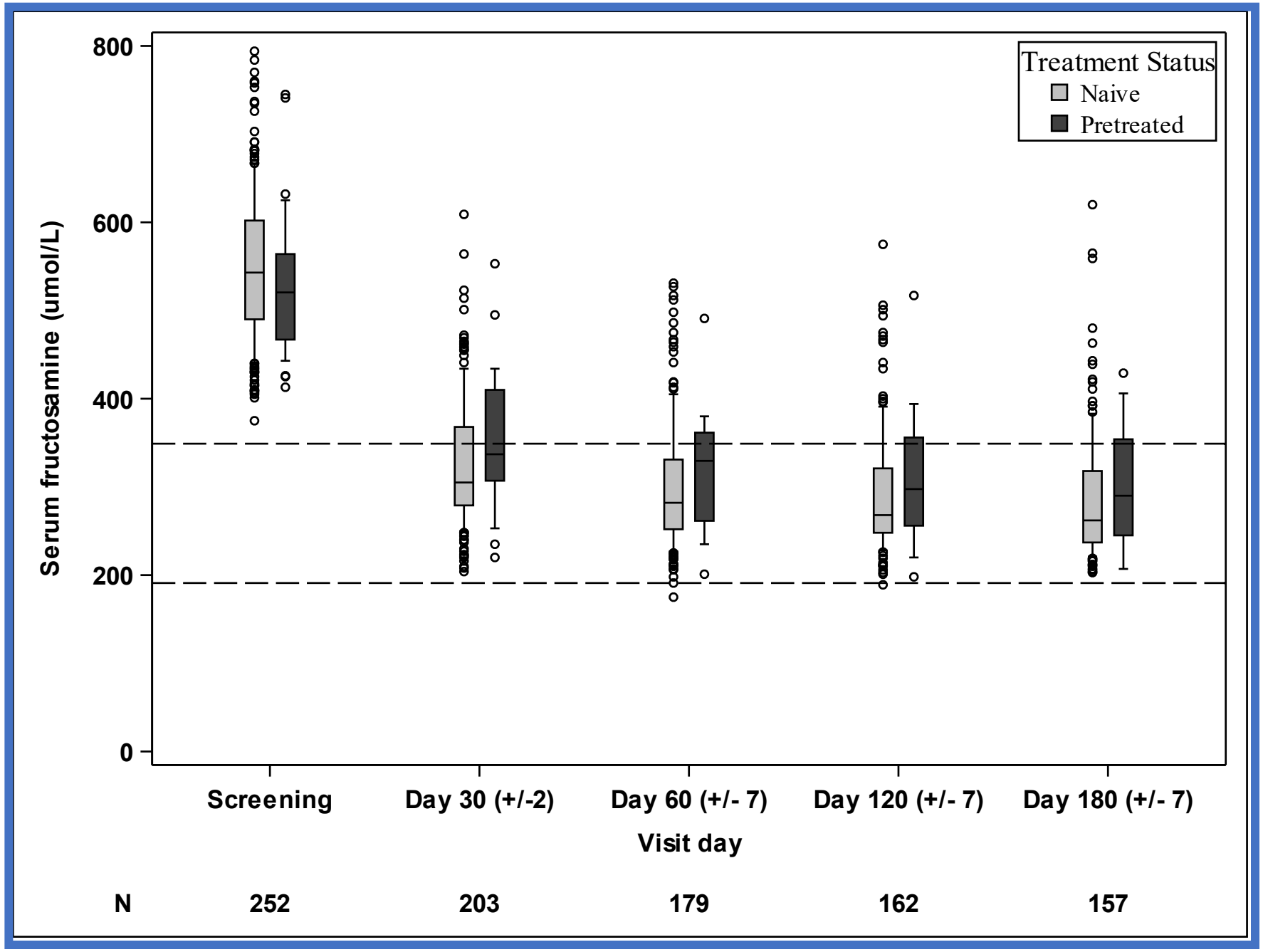
BG curves

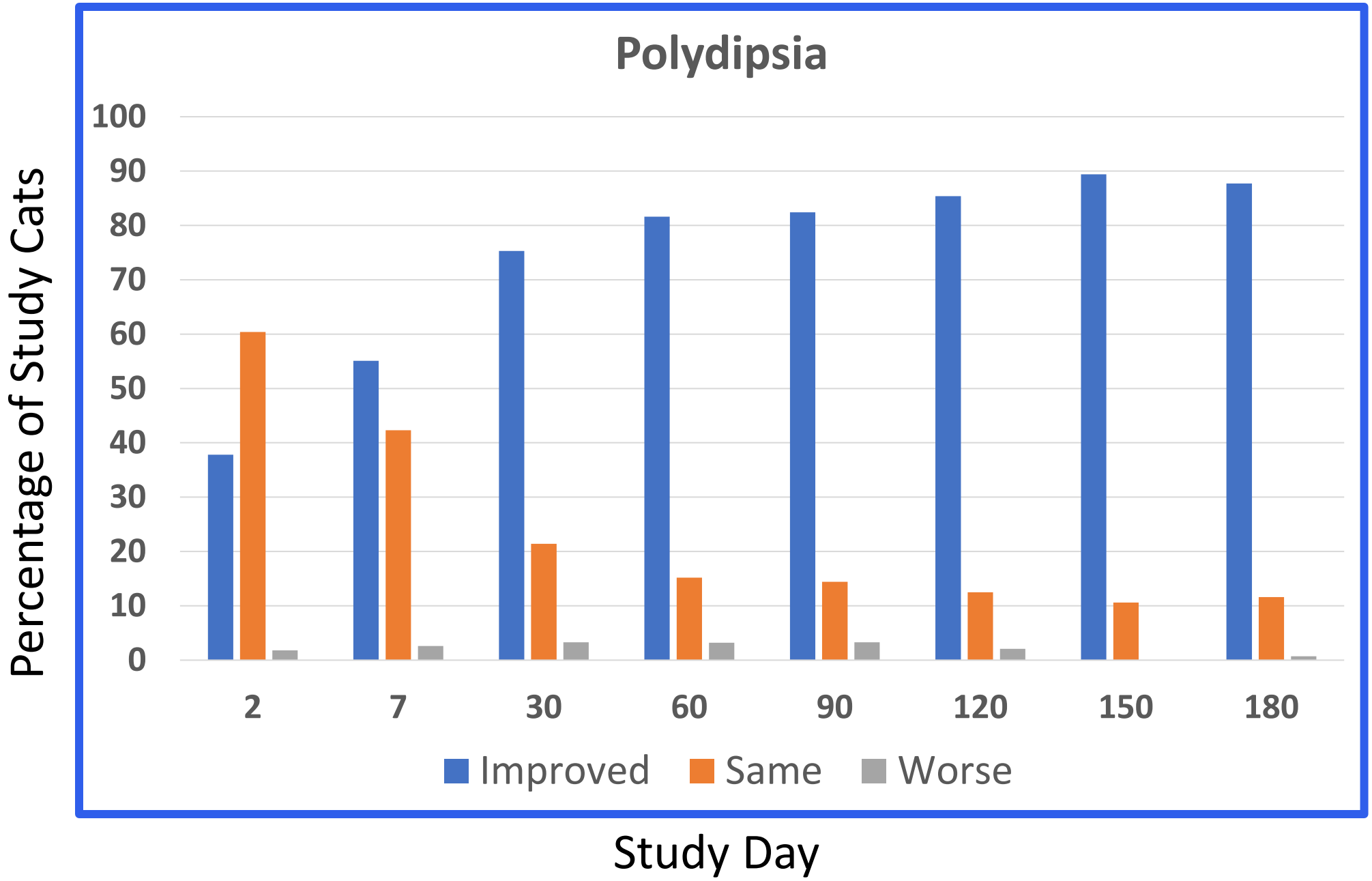
ND cats



Fructosamine

81% in RR d180




Polydipsia
Percentage of Study Cats
100
90
80
70
60
50
40
30
20
10
0
2
7
30
60
90
120
150
180
Improved
Same
Worse
Study Day

Ketonuria and DKA

Incidence: 35 cats (13.9%)

- 17 ketonuric (6.8%)
- 18 DKA (7.1%) - 14 eDKA (5.6%) and 4 DKA (1.3%)

Timing: 30/35 (85.7%) within 14d (3 d [range 1-9])

- 16 ketonuria
- 14 DKA

31.6% IT / 10.7% ND: RR 2.9 (p=0.0017, 95% CI 1.6-5.2)

Ketonuria and DKA

Incidence by population:

	IT (n=38)	ND (n=214)
Ketonuria: N (%)	5 (13.2%)	12 (5.6%)
DKA: N (%)	7 (18.4%)	11 (5.1%)
Combined: N (%)	12 (31.6%)	23 (10.7%)

- 31.6% IT vs. 10.7% ND: RR 2.94 (p=0.0017, 95% CI 1.58-5.23)

GI adverse events

Diarrhea/soft stool

- 126 cats (50%)
- started by d7 in 73/126 (57.9%)
- reason for removal n=2

Vomiting – 85 cats (33.7%)

Bexacat: vomiting #1, diarrhea #2

Pancreatitis

8 cats (3.2%)

d55 (2-146)

Concurrent DKA 3 cats

3 cats remained in study

Hypoglycemia

No episode clinical hypoglycemia

9 cats; 15 BG <60 mg/dL (3.3 mmol/L) on 11 days

- 42-59 mg/dL (2.3-3.2 mmol/L)
- 14/15 read on AlphaTrak® 2

Fructosamine (RR 191-349 umol/L)

- 2 cats
- 175 umol/L d60; 189 umol/L d120

Elevated IGF-1?

Elevated 37/235 (7 QNS)

- 186 nmol/L (93-521); RI 12-92
- 65% completed (4 removed non-vela reasons)

> 131 nmol/L (1000 ng/mL)

- 95% predictive
- 23 cats; 16 completed (69.6%)

Renal function

Outcome/diagnosis	Number	Comment
AKI	2	1 had mitigating factors
Removed due to increase (non-AKI)	1	Removed from study
Creatinine normalized	6	Finished study
Creatinine remained high	10	Above RI (>2.5 mg/dL) in 3
Removed from study for other reasons	8	

Using an SGLT2i

Dietary Therapy – the old and the new

Get to and maintain IDEAL body weight

Do not need to pair SGLT2i and food (as long as cat eating)

Low carb, high protein, fat

Low carb AND SGLT2i?

- cats are not small people
- may help remission

Initiating therapy

History

Physical examination

Diagnostics

- CBC/chemistry/urinalysis
- T4
- fPLI (>5.3 ug/L?)
- IGF-1??

“No go” for starting SGLT2i

Ketosis (blood ketones >2.4 mmol/L (25 mg/dL); ketonuria)

Lethargy, inappetence

Vomiting

Diarrhea

Pancreatitis (active)

Dehydration

Cachexia

Consider not using SGLT2i

Blood ketones 1-2.4 mmol/L???

Renal disease – IRIS stage 3 or 4

Elevated liver enzymes/bilirubin

Hypercalcemia

Diabetes secondary to pancreatitis

Diseases not a “no go”

Urinary tract infection

Hyperthyroidism

Acromegaly

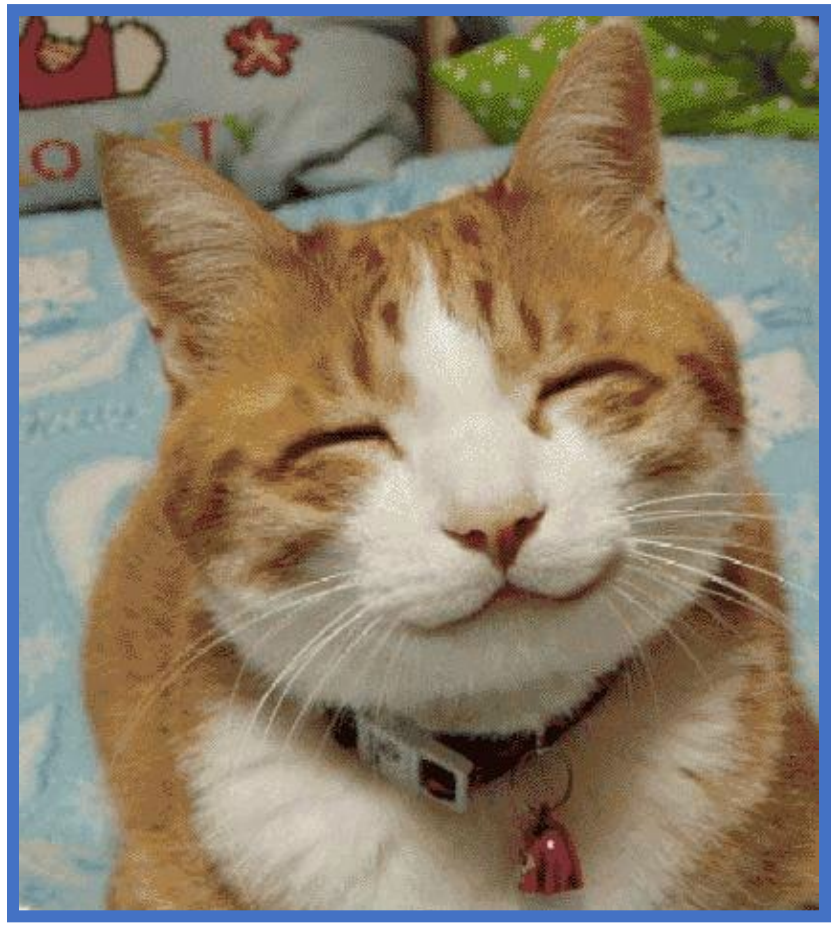
Initial monitoring

Day 2 or 3 – ketones

Day 7 – ketones, “control”, PE, weight

Day 14 - ketones, “control”, PE, weight

Day 28 - ketones, “control”, PE, weight



Monitoring after first 30 days

As long as doing well, monitor “control”, PE, weight

- day 90
- every 90 days

CBC/chemistry/UA q 6 mths

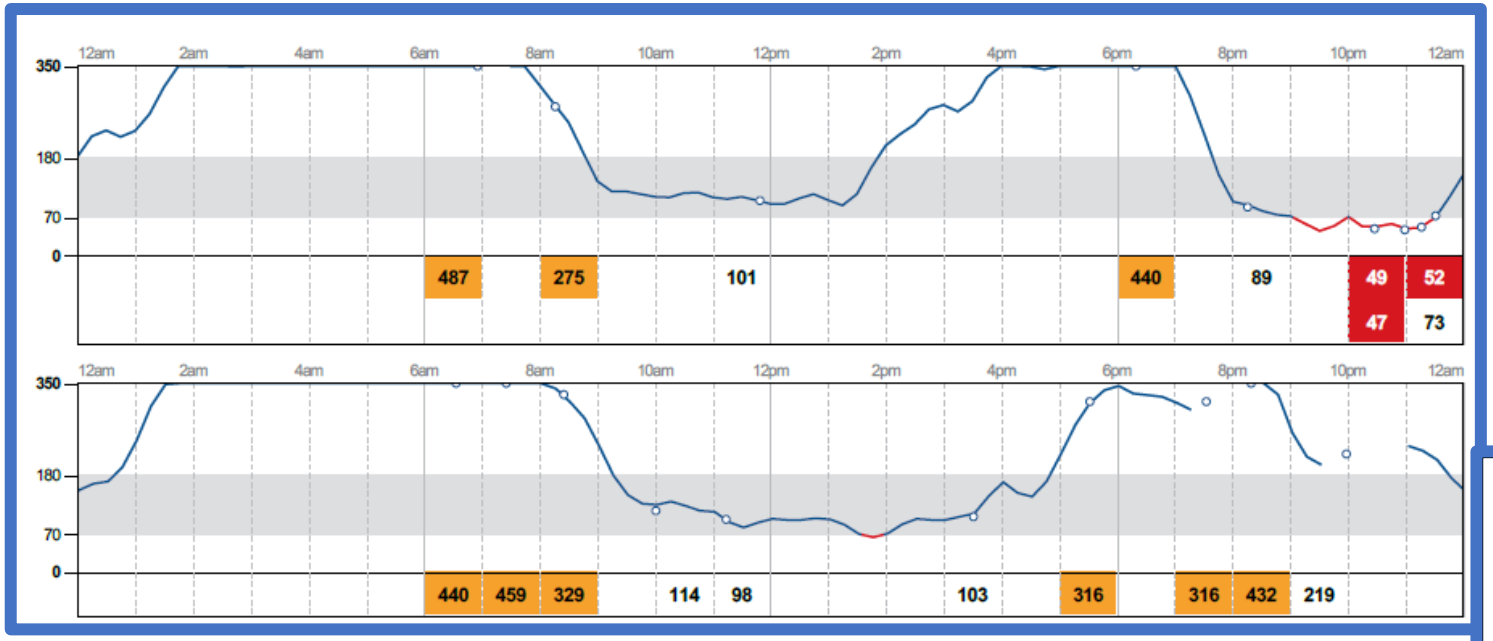
What does monitoring “control” mean?

Remains TBD!

Two parts

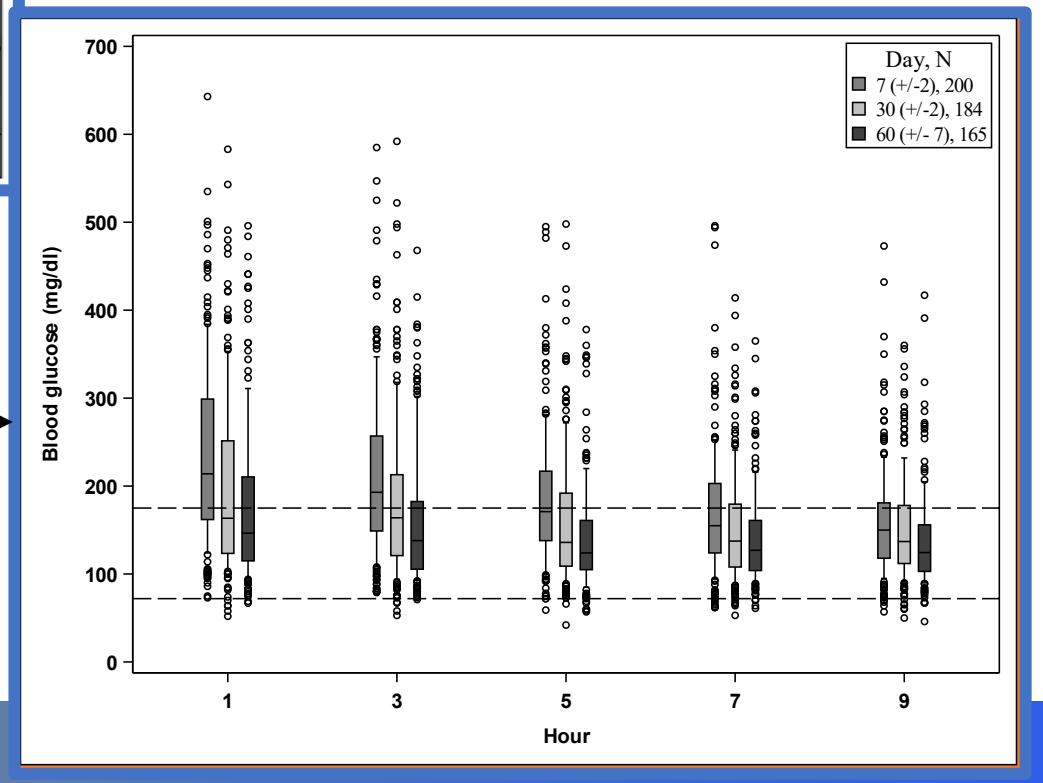
- clinical signs
- biochemical parameters

Role of fructosamine?



This is a BG curve on insulin

This is a BG curve on vela



Biochemical parameters - new

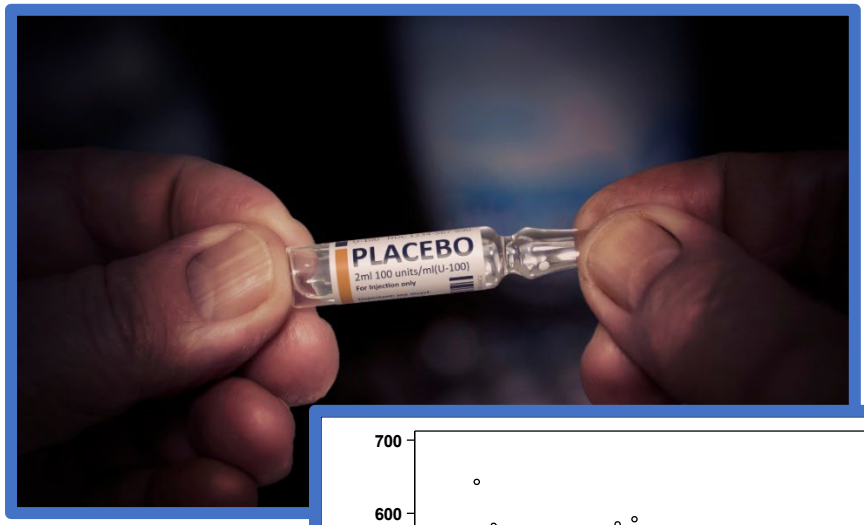
Fructosamine:

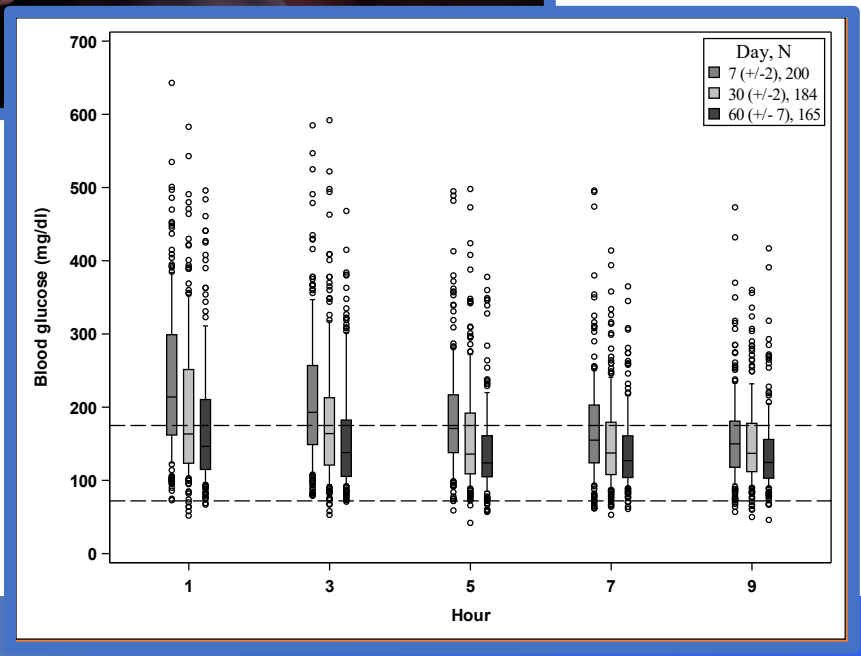
- my current recommendation
- looking for value in RI

Curves:

- conflicting data
- cat still pu/pd
- use once to see if BG responding?

Spot check BG: likely to be helpful





Diabetic ketoacidosis

"Severe diabetic metabolic complication and ***clinical decompensation*** characterized by acidosis (venous pH <7.35) and ketonuria or ketosis."

Presence of ketones ≠ DKA

Lack of ketones does not rule out DKA

Euglycemic DKA: blood glucose <250 mg/dL

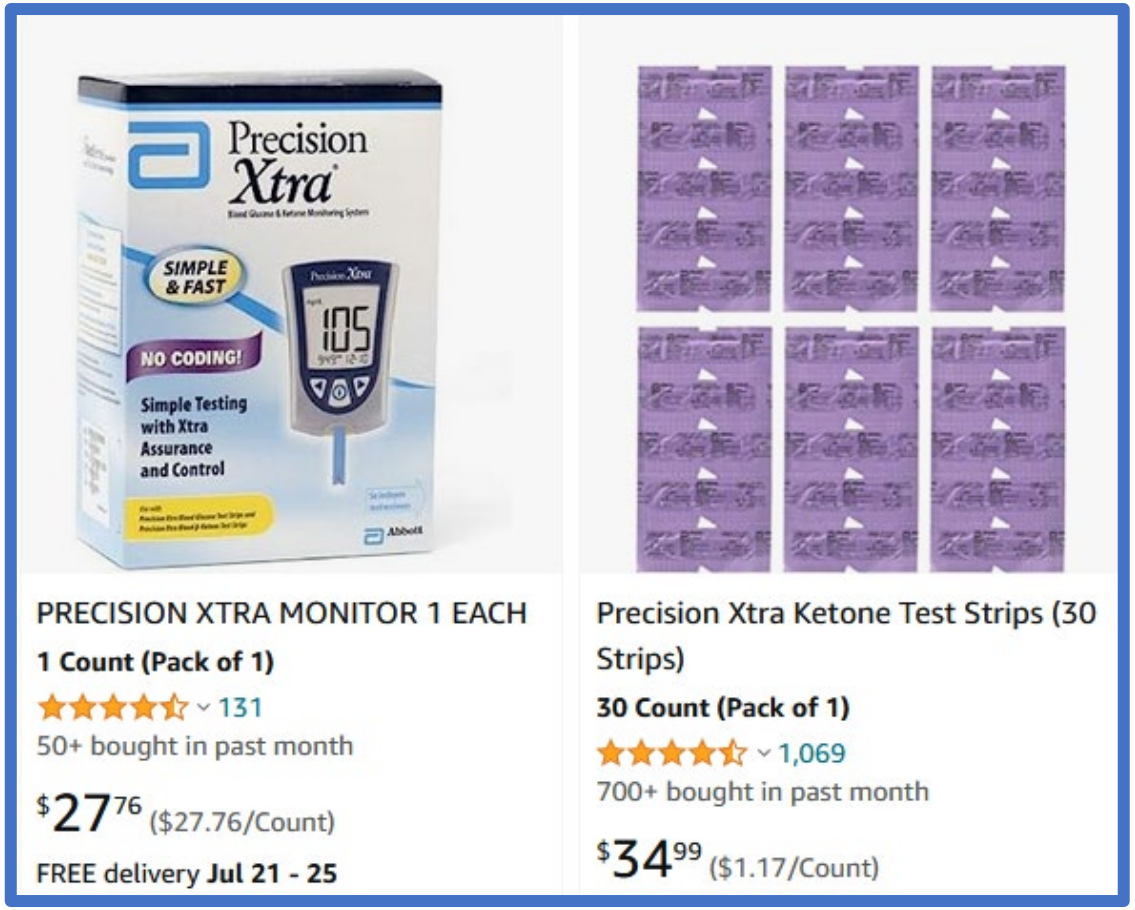
Precision Xtra - Abbott

ONLY validated meter

BOHB > 2.55 mmol/L*

- 94% sensitivity for DKA
- 68% specificity for DKA

Don’t use built-in glucometer



*Zeugswetter et al. J Small Anim Pract 2012

Ketone measurements using dipstick methodology in cats with diabetes mellitus

Zeugswetter et al, J Small Anim Pract 2009

Bayer Ketostix

		Positive test result	
	N	**Plasma***	**Urine**
Healthy	6	0.0%	0.0%
Ketosis	40	35.0%	5.0%
DKA	11	100.0%	81.8%

* heparinized

Treatment DKA

STOP the SGLT2i

Giving insulin an ABSOLUTE requirement regardless of BG

Components

- short-acting insulin, e.g., Regular
- IV fluids
- IV glucose if BG < 250 mg/dL
- address acid/base, electrolytes as needed

What to do with ketosis?

≤1 mmol/L no concern

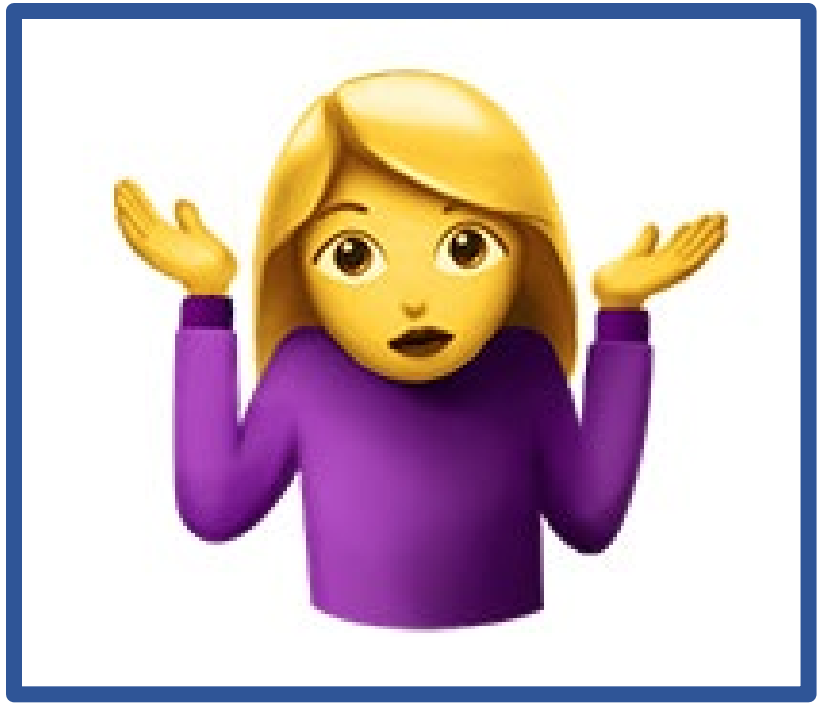
Cat sick or not?

BOHB 1-2.4 mmol/L: be careful!

- continuing
- starting

BOHB >2.4 mmol/L: ideal not to use/continue

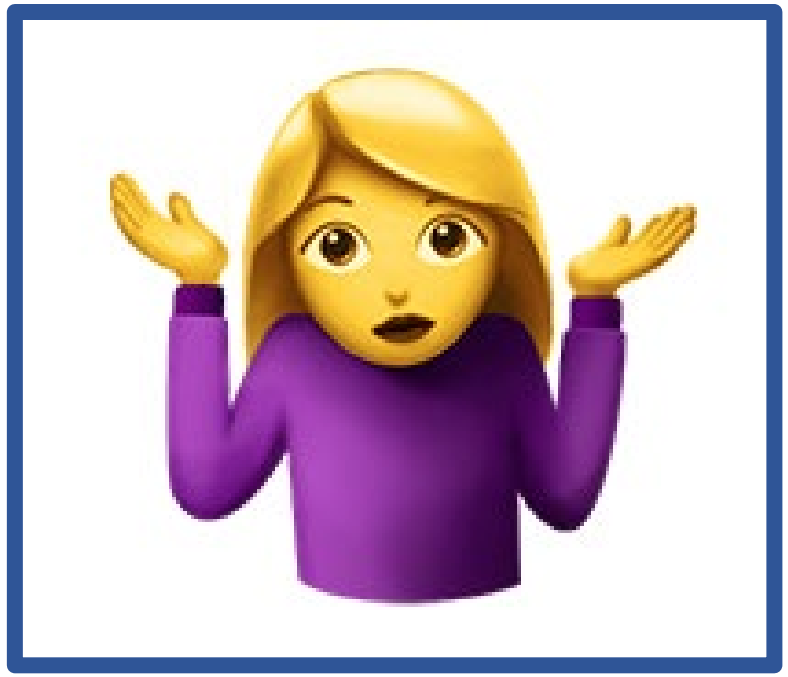
Insulin for a few days to resolve? (off-label)



What to do with sick non-ketotic cat on an SGLT2i?

Ideally switch to insulin while sick if not eating

Once healthy, could switch back (off-label)



Cat has already been on insulin

If doing well, why switch?

Could try SGLT2i off-label

Cats in trial

- insulin duration 83 d (5-2,549)
- more likely to not complete: RR 2.8 (p=0.0016; 95% CI 1.5-5.2)
- ~1/3 DKA

Issue is TIME, not insulin

Advantages of an SGLT2i

Oral

Once-daily

Does not need to be paired with food

After first 30 days,

- less monitoring
- no curves

Risk of hypoglycemia VERY low

What don’t we know?

Why does pu/pd get better?

Does it truly resolve?

Factors:

- RAAS system
- less glucose overall
- owner habitualization

What to do with a pu/pd cat on SGLT2i?

Differentials

- inadequate diabetic control
- normal
- other cause pu/pd

Action

- CBC/chem/UA
- fructosamine
- curve?

What to do with weight loss?

Humans lose weight on SGLT2i

- variable
- usually mild (ave. 2 kg)

Cats gained weight overall

Increased risk UTI?

At screening, 19 cats had positive culture

After screening, 25 cats (9.9%); 34 positive cultures

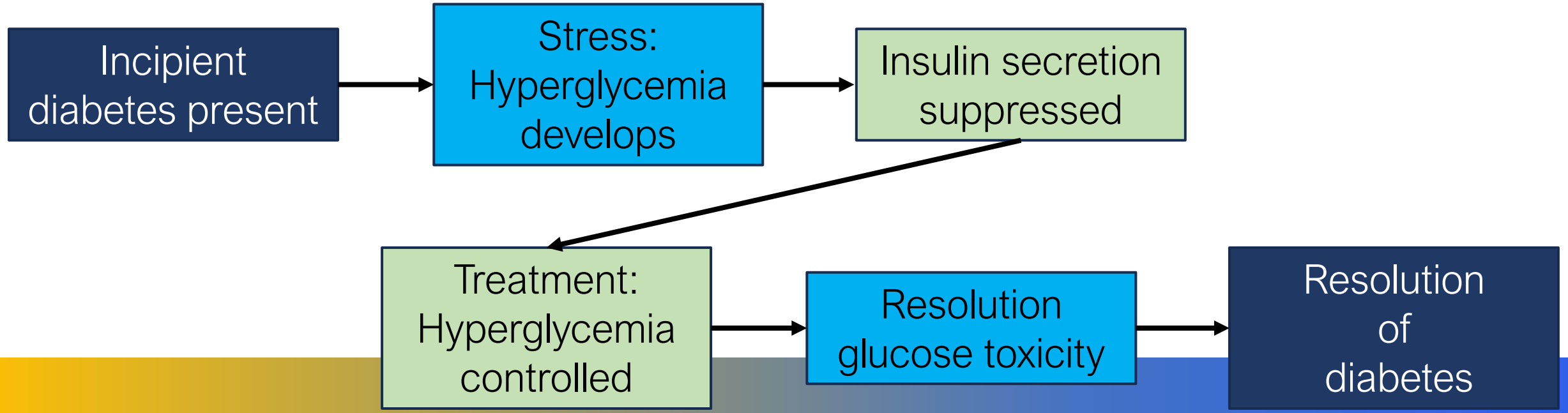
Positive culture vs asymptomatic bacteriuria

Remission

Cats on SGLT2i likely to go into remission (my guess)

How can we tell?

- insulin: very low dose needed and/or hypoglycemia
- SGLT2i: discontinue drug



Questions?