MAYO CLINIC

REMIMAZOLAM

ANOTHER ROAD TO ROME

George Gilkey MD
Assistant Professor of Anesthesiology
Mayo Clinic Division of Cardiovascular Anesthesia

Shutterstock.com

Disclosures

- No financial disclosures
- OFF-Label use of medication WILL be discussed

Drug Development:

- Phase I trials: 2012
- Phase II 2015
- Phase III: 2018

- Remimazolam approved for use in Japan 2020
  - Approved for use in US: July 2020
  - Approved for use in EU: March 2021

  - First use at Mayo clinic: July 2021

PHARMACOLOGY

Image copyright GettyImages

Remimazolam

Formulation

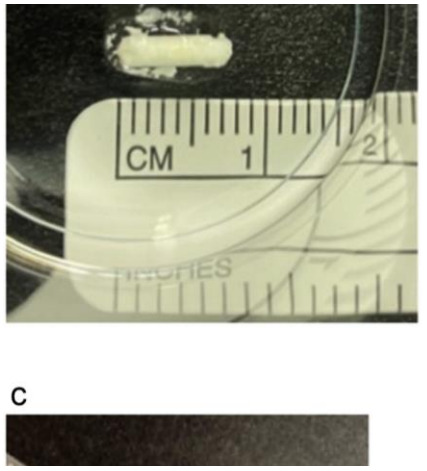
- 20mg lyophilized powder
- Reconstitute in saline 8.2mL - >2.5mg/mL
  - Real world: 20mg into 10mL = 2mg/mL
- For IV injection
- Reconstituted in vial: stable 8 hrs room temp
- Dosing:
  - ASA 1-2: 5mg IV with 2.5mg Q2min PRN
  - ASA 3+: 2.5mg with 1.25-2.5 Q2 PRN

Byfavo.com

Unusual Complications

IV compatibility

- Remimazolam forms precipitates in:
  - Lactated Ringer's
  - Acetated Ringer's
- Concentration 5mg/ml
  - -US concentration 2-2.5mg/mL

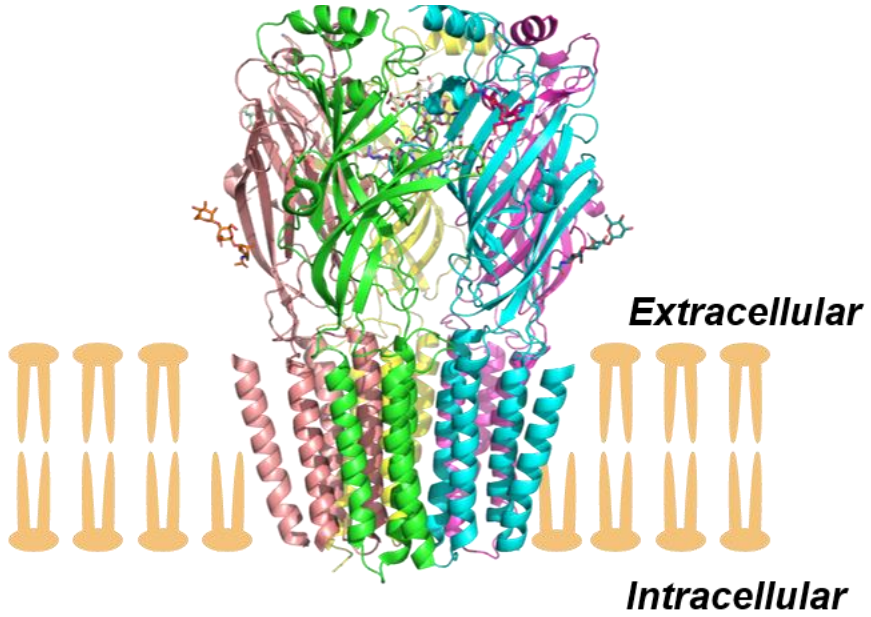


Sasaki et al. Br J Anaesth.2021 Mar;126(3):e87-e89

Remimazolam:

Mechanism

- $GABA_A$ Ligand
  - Binds gamma subunit
  - Increases chloride flux
- Produces sedation

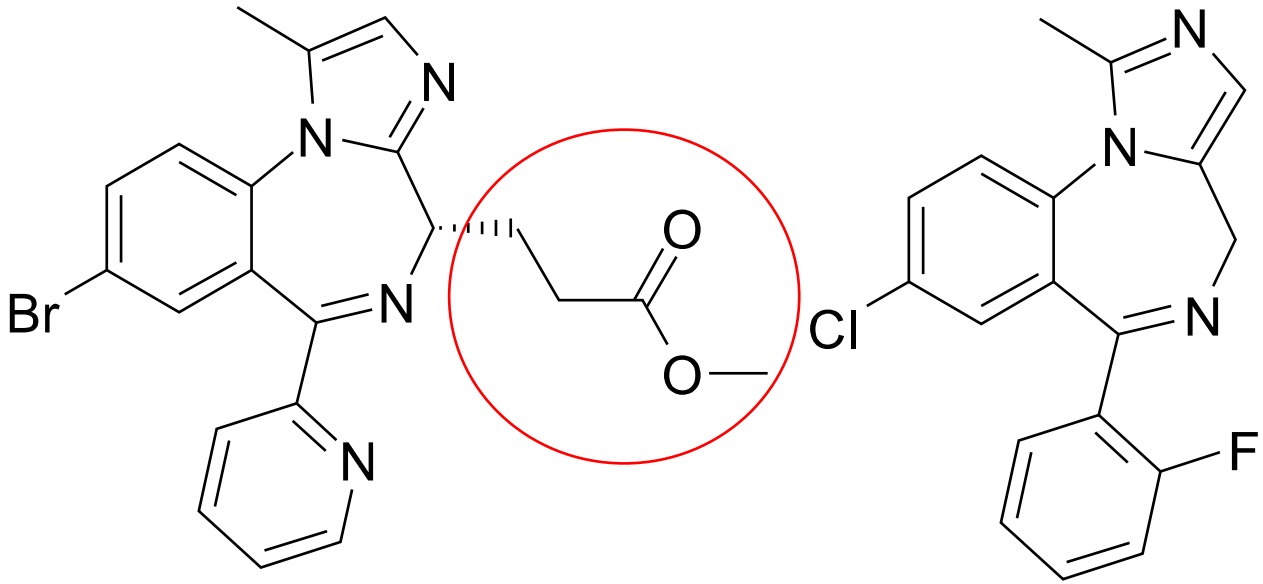


https://en.wikipedia.org/wiki/GABAA_receptor

Remimazolam:

Physiochemical Properties

- Additional Ester linkage
- pH 2.9-3.9 in saline



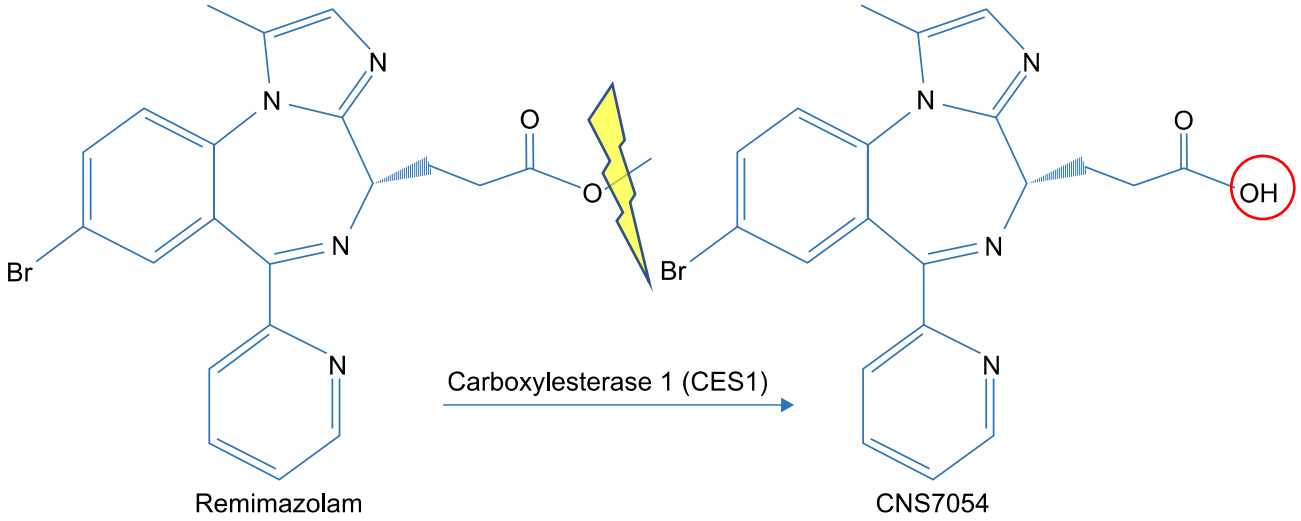
Remimazolam

Midazolam

British Journal of Anaesthesia, 127 (1): 41e55 (2021)

Remimazolam:

Metabolism



- Ester linkage hydrolyzed:
  - Tissue esterase
  - Carboxylesterase1 (CES1)
    - Hepatic
- Inactive metabolite:
  - CNS 7054

Drug Design, Development and Therapy 2019:13 1033–1047

©2021 Mayo Foundation for Medical Education and Research | slide-9

Remimazolam

Formal Pharmacokinetics

- Volume of distribution: 34 ± 9.4L
- Terminal Half-life: 45min ±9min
- Clearance time independent of body mass
- Extremes of hepatic dysfunction: apprx 30% increase in duration

Remimazolam

Practical pharmacokinetics

- Onset and offset:
  - 1-2 minutes for onset
  - Offset: dose dependent
    - roughly 10-12 minutes for an 8mg bolus

Remimazolam

Pharmacology: Bioavailability

- PO
  - 100% absorption as a liquid
  - 1.2% bioavailabilty PO
- Intranasal:
  - Bioavailability: 20-45%. (powder or solution)
  - Prohibitively painful to use intranasally

Pesic et al. Drugs in R&D (2020)20:267-77

Procedural Use

Remimazolam

Procedural Uses

- GI endoscopy
  - LVAD patients
  - ALS PEG tube patients
  - Feeding tube w/ odynophagia
- Cardiac Cath Lab:
  - Cardioversion
  - Congenital Percutaneous interventions
  - Induction agent
- Interventional Radiology
  - - vascular access w/ poor CV status vascular stenting, angiography, PICC/HD catheter placement)
- ultrasound guided procedures needing quick sedation
- - CT guided quicker procedures (bones biopsies, etc)
- Neurosurgical/ Neuro IR outpatient procedures:
  - - trigeminal ablations

Remimazolam

Procedural Advantages

- Very hemodynamically stable:
  - Minimal changes to SVR
  - Minimal Changes to HR
  - No rhythm disturbances
- Minimal respiratory depression
  - Spontaneous respiration preserved
- Rapid emergence
- Easily titrated due to short duration
- Reversible with flumazenil if needed

Remimazolam

Procedural Disadvantages

- Short duration = frequent dosing
  - Manage provider expectations
- IV compatibility issues
- $$

Conclusions:

- Pros and Cons: Context dependent
- Con: $
- Very titratable
- Reversible
- Quick wakeup with minimal grogginess
- Good hemodynamic profile
- Minimal respiratory depression when used as solo agent

Questions?

Gilkey.George@mayo.edu

Sedation Protocol

Remimazolam

- 5mg bolus
  - 2.5mg Q2min x4 PRN
- Fentanyl 75or 50 + 25mcg Q5-10 PRN max 200

Midazolam

- 1.75mg + 1mg x2 if <60yrs
- 1mg + 0.5mg x2 >60yrs or ill
- Dosing within 12 minutes

If any patient insufficiently sedated after protocol, then PRN Midaz given.

Endpoints
Adequate Sedation or Recovery

- Procedure started when MOAA/S score ≤ 4
- Fully Alert (recovered) = MOAA/S 5 x 3

TABLE 2. Description of Modified Observer's Assessment of Alertness/ Sedation scores

Score	Description
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Gastrointest Endosc 2018;88:427-37

Endpoints:
Timing

- Time to MOAA/S ≤3 (responds to loud calling of name)
  - Remimaz: 5.1 (±3.82) min
  - Midaz: 16.9(±6.31) min
  - Placebo: 20.3 (±4.34) min

TABLE 7. Mean times for recovery (minutes)

	Remimazolam	Placebo	Midazolam	*P* value (remimazolam vs placebo)
From end of procedure to fully alert	7.35 (5.78)	21.95 (17.74)	15.84 (11.57)	< .0001
From procedure and until walking test passed	43.81 (13.26)	54.50 (20.26)	48.75 (14.44)	< .0001
From last study medication until walking test passed	50.94 (13.84)	65.10 (18.77)	58.07 (14.4)	< .0001
From start of medication to ready for discharge	60.34 (13.7)	87.95 (21.07)	77.27 (15.85)	< .0001
End of study medication to back to normal	330.71 (484.09)	572.67 (626.75)	553.11 (502.92)	.001
Time to fully alert from last dose of IMP/rescue, min	14.36 (5.39)	31.93 (16.81)	25.19 (11.26)	< .0001
Time to ready for discharge from end of procedure, min	42.65 (13.74)	53.18 (20.55)	47.92 (14.68)	< .0001
Time to ready for discharge from last dose of IMP/rescue, min	49.78 (14.33)	63.78 (19.09)	57.44 (14.56)	< .0001

Endpoints:

COgnition

Remimazolam

- Better verbal learning recall scores with remimazolam v. midaz.
- Intraop Recall: similar rates for Remimazolam, midaz, placebo

Cognition

- Long term cognitive effects of benzo on elderly NOT examined

Endpoints
Hemodynamics and Respiration

- Remimazolam:
  - Less hypotension
- Remimazolam:
  - Less respiratory depression/ hypoxia

TABLE 9. Incidence of treatment-emergent adverse events

System organ class and preferred term	Remimazolam N = 296 no. (%)	Placebo N = 60 no. (%)	Midazolam N = 102 no. (%)	Total N = 458
Any treatment-emergent adverse events	218 (73.6%)	47 (78.3%)	93 (91.2%)	358 (78.2%)
Vascular disorders	184 (62.2%)	41 (68.3%)	83 (81.4%)	308 (67.2%)
Hypotension	115 (38.9%)	25 (41.7%)	63 (61.8%)	203 (44.3%)
Hypertension	59 (19.9%)	17 (28.3%)	18 (17.6%)	94 (20.5%)
Diastolic hypertension	29 (9.8%)	6 (10.0%)	9 (8.8%)	44 (9.6%)
Diastolic hypotension	23 (7.8%)	4 (6.7%)	9 (8.8%)	36 (7.9%)
Systolic hypertension	16 (5.4%)	5 (8.3%)	6 (5.9%)	27 (5.9%)
Cardiac disorders	53 (17.9%)	14 (23.3%)	26 (25.5%)	93 (20.3%)
Bradycardia	33 (11.1%)	7 (11.7%)	16 (15.7%)	56 (12.2%)
Tachycardia	23 (7.8%)	7 (11.7%)	13 (12.7%)	43 (9.4%)
Respiratory, thoracic and mediastinal disorders	11 (3.7%)	4 (6.7%)	6 (5.9%)	21 (4.6%)
Bradypnea	4 (1.4%)	2 (3.3%)	3 (2.9%)	9 (2.0%)
Hypoxia	3 (1.0%)	2 (3.3%)	1 (1.0%)	6 (1.3%)
Respiratory depression	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)

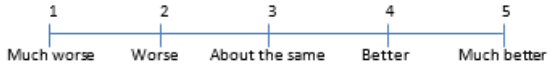
Gastrointest Endosc 2018;88:427-37

CARDIOVERSION
ROCHESTER PILOT

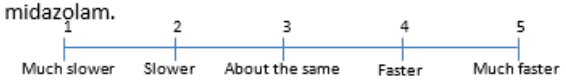
- Pts presenting for straight cardioversion (no TEE)
- Standard: propofol + Lidocaine
- Remimaz per package (initially)
- pilot from 6/21-11/21
- 67 Rochester pts

Survey

1) How many times have you administered remimazolam previously?
   □ Never □ Once □ Twice □ 3 or more
2) If you were not using remimazolam, which sedative would be your primary sedating agent used for this patient/procedure?
   □ Midazolam □ Propofol □ Other_____
3) Did you dose remimazolam using the ASA physical status classification?
   □ Yes □ No
   a. If yes, did this dosing guide result in adequate sedation/anxiolysis?
   □ Yes □ No
   b. If no, please explain: _____
4) Did you at any point feel your patient was over-sedated?
   □ Yes □ No
5) Did the patient have respiratory depression requiring intervention?
   □ Yes □ No
   a. If yes, describe intervention(s): _____
6) Did the patient experience an adverse event?
   □ Yes □ No
   a. If yes, please explain: _____
7) Rate your experience with remimazolam **sedation** compared to sedation with midazolam for procedural sedation.



8) Rate the **recovery time** from remimazolam compared to recovery time from midazolam.



9) Would you recommend expanded use of remimazolam to nurse-sedation practices?
   □ Yes □ No
10) Would you recommend expanded use of remimazolam to other anesthesia practices?
   □ Yes □ No
11) Please share any other feedback about the use of remimazolam below:

Remimazolam Procedural Sedation Pilot

Cath Lab (MB4)

Affix Patient Label Here

Mixing instructions:

1. Prepare a syringe of 0.9% sodium chloride with a volume of 8.2 mL
2. Mix with one 20 mg vial of remimazolam
3. Final concentration 2.5 mg/mL

Dosing guide:

ASA PS Score	Initial Dose	Subsequent Doses
1-2	5 mg	2.5 mg
3-4	2.5 mg	1.25 mg

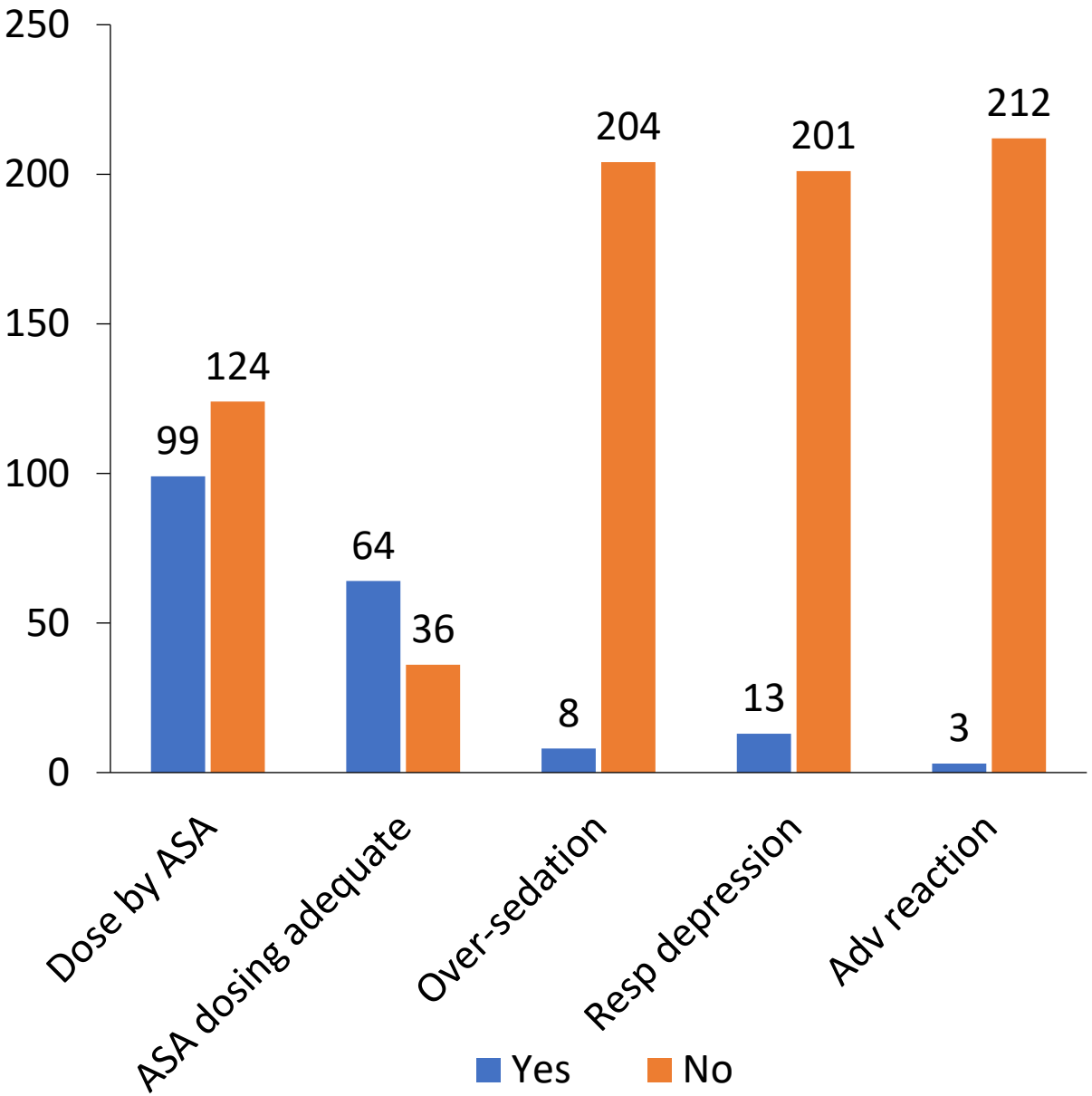
Remimazolam is NOT compatible with Lactated Ringer's

***Flush the line with saline before and after administration.** *

Questions:

If you have any questions about this pilot, please contact any of the following: George Gilkey, MD, Nathan Brinkman, PharmD, RPh, or Karen Nase, APRN, CRNA, DNP

Slide courtesy of Nate Brinkman PharmD



SURVEY DATA AS OF 11/30/21
AGGREGATED AZ, FL, & RST

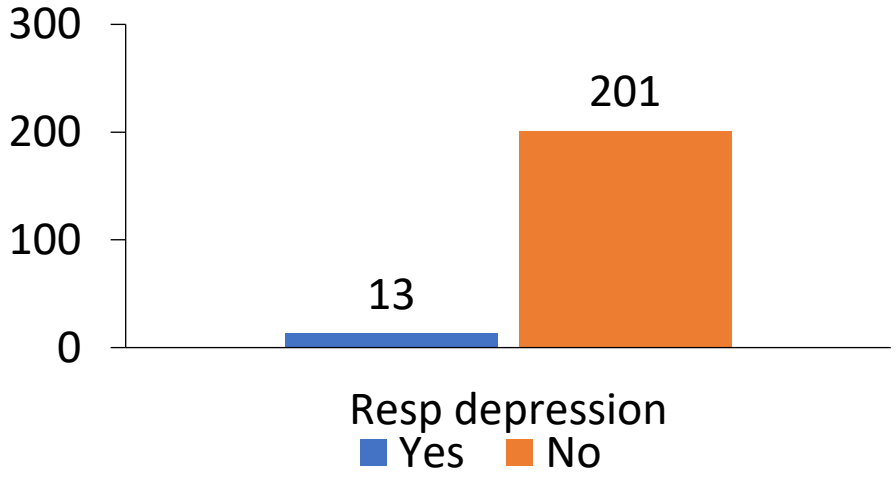
- Survey responses

Slide courtesy of Nate Brinkman PharmD

Respiratory Depression

survey data

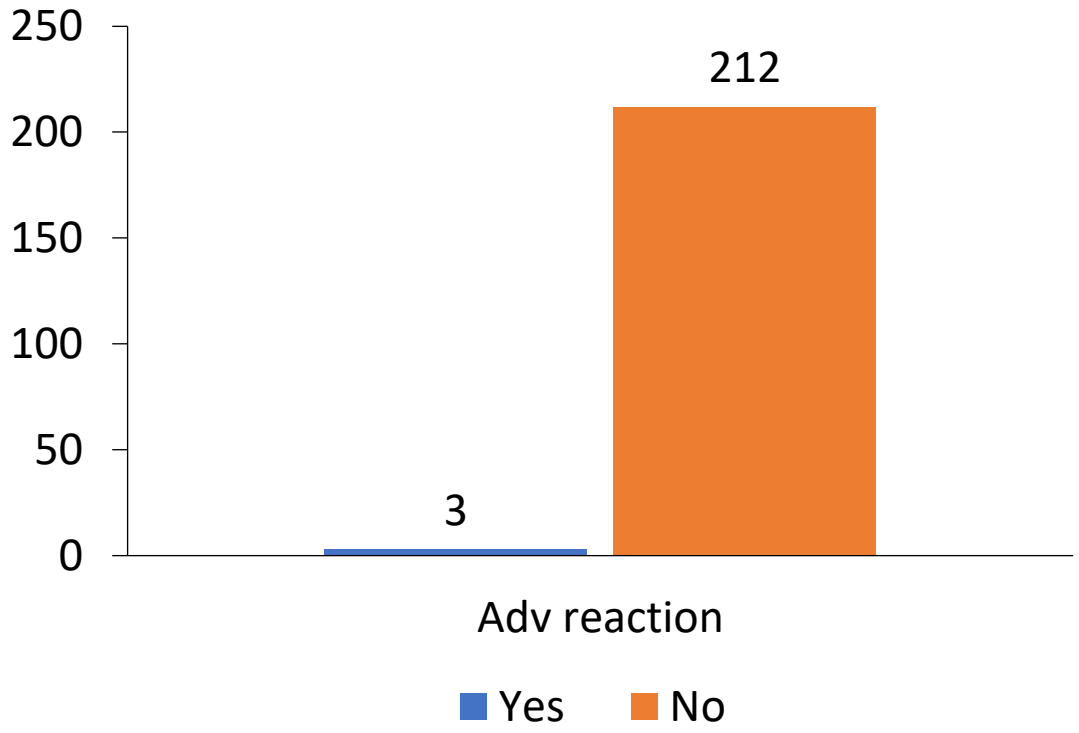
- Chin lift/jaw thrust (10 patients)
- Mild apnea, resolved spontaneously
- Used ‘awake’ intubation
- Held mask over face; snoring
- Obstructed
- Reminded to breath



Adverse reactions

survey data

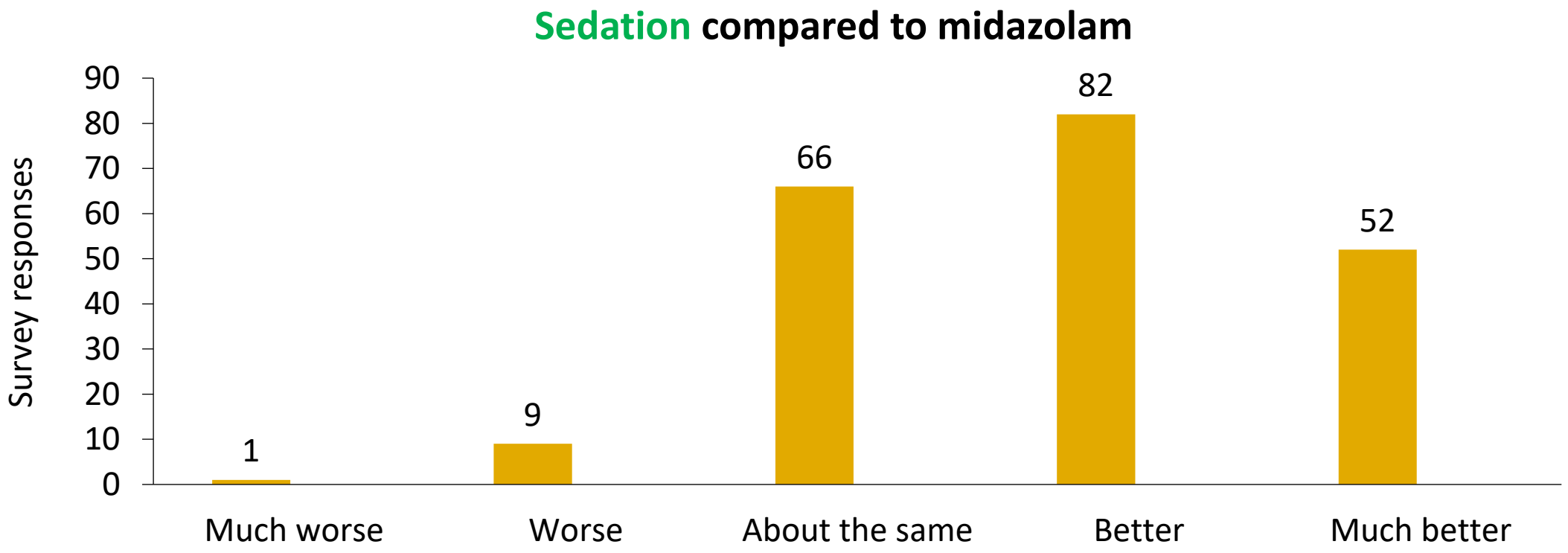
- Itching arm and eyes, redness
- Patient moving a lot
- Patient yelled “ouch that hurts” with cardioversion
    - NB: no recall!



Slide courtesy of Nate Brinkman PharmD

Survey Data

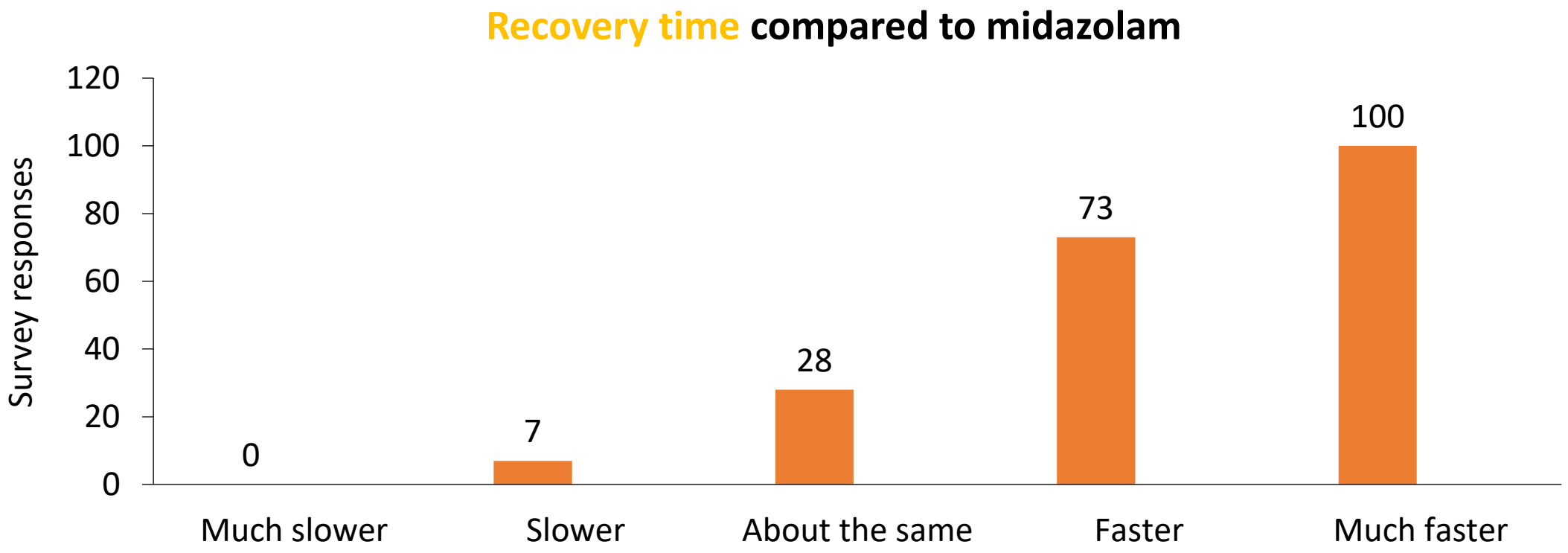
Aggregated AZ, FL, & RST



Slide courtesy of Nate Brinkman PharmD

Survey Data

Aggregated AZ, FL, & RST



Slide courtesy of Nate Brinkman PharmD

Cardioversion

What did we learn?

- Package dosing- too low. 8-12mg more realistic
- Slower onset than propofol- be patient
- Don’t expect it to be propofol
- Pts wake up quickly: 10min or less
- Reconstitute in 10ml = 2mg/mL
- Minimal respiratory depression
- Hemodynamic stability

Use at Mayo Clinic

Enterprise data (as of 1/25/22)

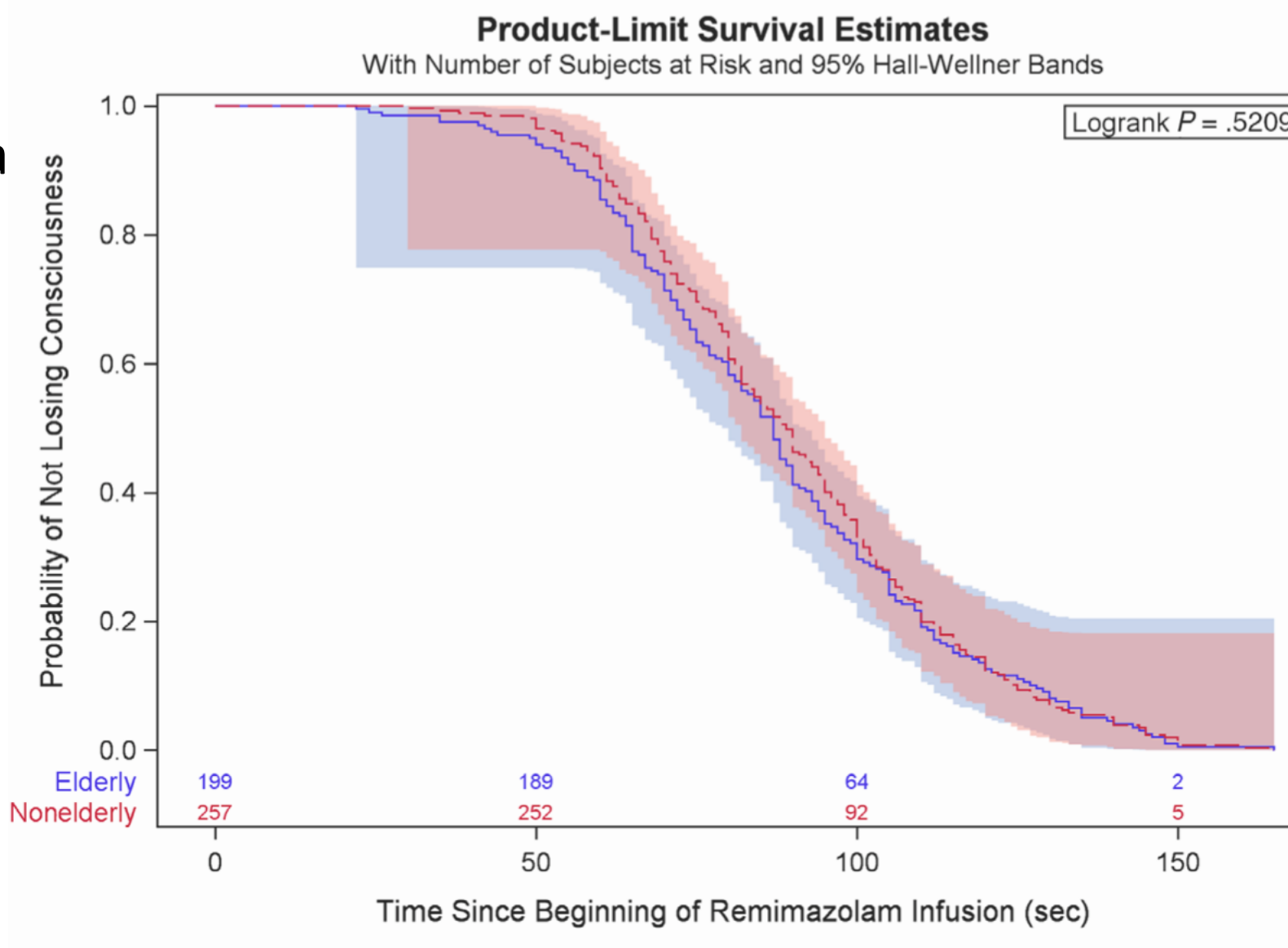
- 434 patients have been treated with Remimazolam
  - Rochester: 166
  - Florida:191
  - Arizona 64
- Mean dose 3.6mg Median dose 2.5mg
- 1634 total doses administered

Other uses at Mayo Clinic

- Awake Fiberoptic intubation
- TEE
- Trans-carotid TAVR
- Awake Craniotomy (Jacksonville)
- G-tube placement (Jacksonville)
- GI cases (Jacksonville)

Off Label Use:

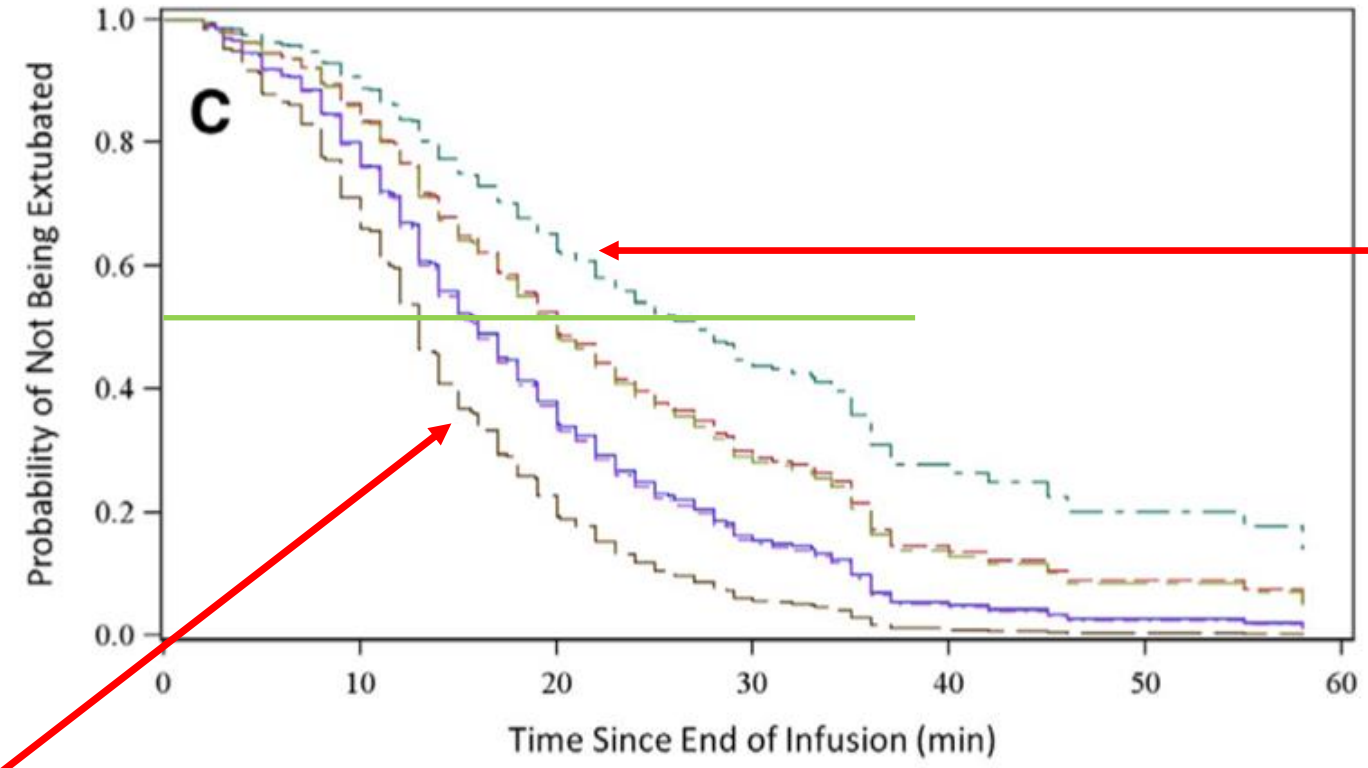
- Infusion for general anesthesia
  - Induction:
    - 12mg/kg/hr
    - 6mg/kg/hr (15-20s slower)
  - Maintenance:
    - 1-3mg/kg/hr



Lohmer et al. The Journal of Clinical Pharmacology 2020, 60(4) 505–514

Off Label:

Infusion Offset



Men: 1.5mg/kg/hr + BIS 60

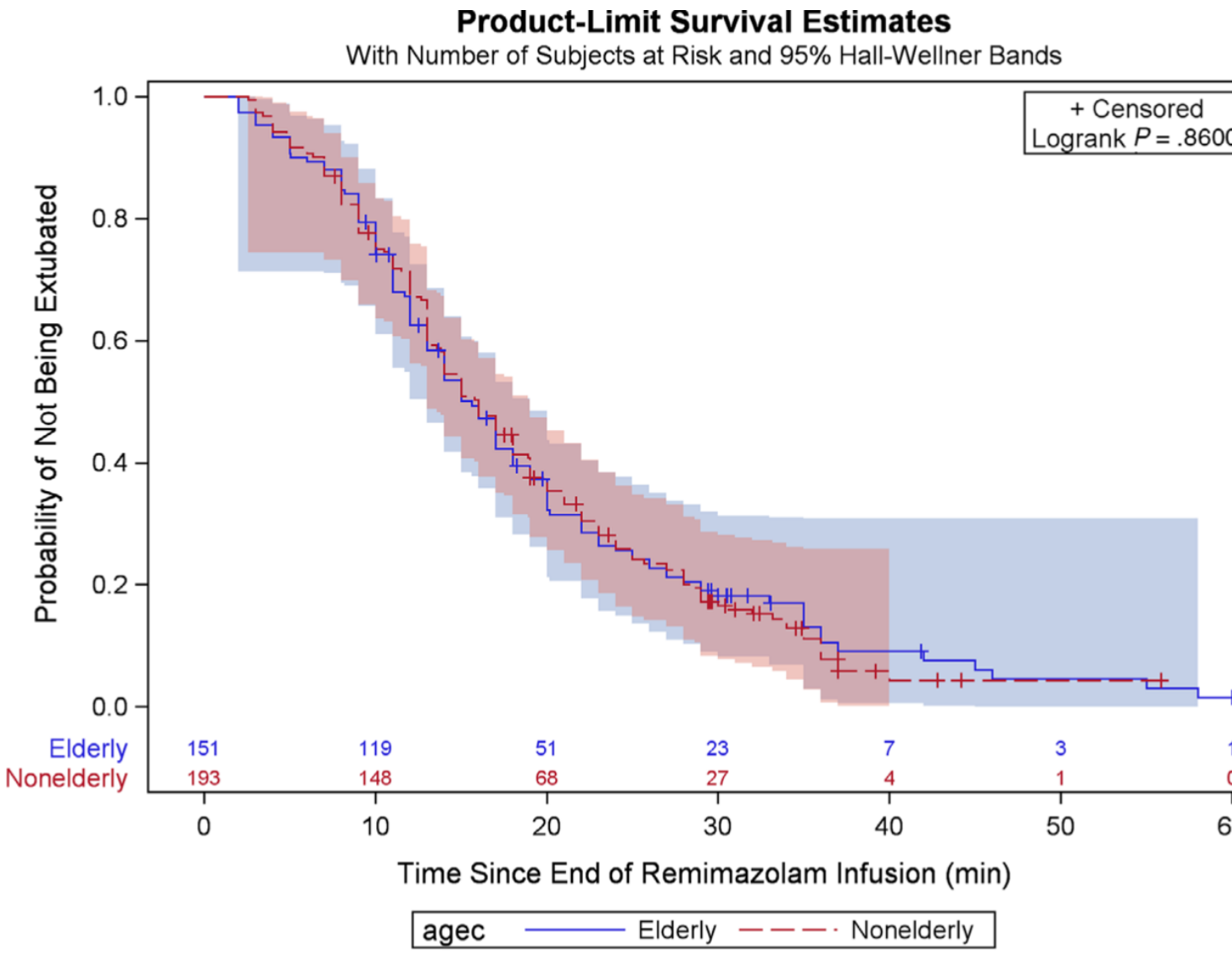
Women: 0.5mg/kg/hr + BIS 60

Lohmer et al. The Journal of Clinical Pharmacology 2020, 60(4) 505–514

Off Label use:

Time to emergence

- By 30 minutes: 20% probability of not being extubatable



Neurosurgery

Awake Craniotomy – Sato et al **Remimazolam v. Propofol**

Remimazolam Arm

- Induction 12mg/kg/hr Remimazolam
- Maintenance:
  - Rmz: 1mg/kg/hr
  - Remifent: 0.1mcg/kg/hr

Propofol Arm

- Propofol infusion
  - Remifent 0.1mcg/kg/hr

Journal of Anesthesia [0913-8668] Sato yr:2021

NeuroSurgery

Awake Craniotomy – Sato et al.

- LMA- iGel
- Leviteracetam + Dexamethasone
- 8/15 RMZ pt’s got flumazenil
- Remimazolam wakeup time: 14.8±2.6 minutes
- Propofol wakeup: 19 ±33 minutes
- More nausea with Remimazolam

NeuroSurgery

NeuroMonitoring- Tanaka et al

- Neurosurgery with SSEP and VEP. N=9
- Remimazolam 0.8mg/kg/hr + Remifentanil 0.2-0.4mcg/kg/hr v. propofol
- VEP:
  - Amplitude: greater with RMZ v. propofol
  - Latency: no difference
- SSEP: no significant difference RMZ v. Propofol for latency or amplitude

Minerva Anestesiologica 2021 Jul 14

Neuro Surgery

Motor Evoked Potentials –Arashiro et al

- N=1
- Pt with Alström syndrome
  - Dilated Cardiomyopathy, DM, HLD, obesity, scoliosis
- Spinal Fusion
  - Remifentanil 0.3mcg/kg/min
  - Remimazolam 0.5-1.0 mg/kg/hr
  - No changes in MEPs

Arashiro A, Shinzato H, Kamizato K, Kakinohana M. Spinal fusion with motor evoked potential monitoring using remimazolam in Alström syndrome: a case report. Medicine 2021;100:47(e27990

Rare disease populations:

- Myotonic dystrophy- Remimaz + Remifent
- Duchenne Muscular Dystrophy- Remimaz + remifent
- Extreme benzo tolerance-Remimaz infusion

Patient Subsets:

The unknowns:

- Pediatrics –no published studies on pediatric patients
- Obstetrics: unknown placental transfer
- Lactating Women- no published data on presence of remimazolam in breast milk or nursing infant

Conclusions:

Where do we go?

Availability

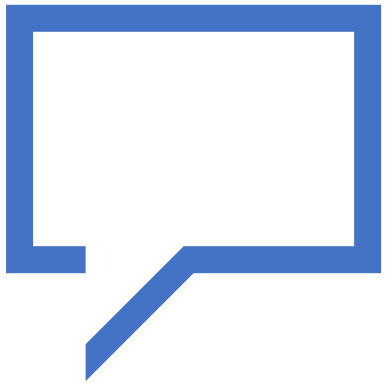
- Soon to be available in Anesthesia workroom pyxis
- Not yet available as infusion

Conclusions:

Where do we go?

- Pros and Cons: Context dependent
- Con: $40/vial
- Very titratable
- Reversible
- Quick wakeup with minimal grogginess
- Good hemodynamic profile
- Minimal respiratory depression when used as solo agent

QUESTIONS
& ANSWERS



Gilkey.George@mayo.edu

THIS SLIDE INTENTIONALLY BLANK