



**Tartu University Hospital**  
Anaesthesiology and Intensive Care Clinic



UNIVERSITY OF TARTU  
Institute of Clinical Medicine

# Remimazolam – a „silver“ bullet

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BaltAnestIC 2023

11th International Baltic Congress of Anaesthesiology and Intensive care  
September 28–30, 2023, Tartu, Estonia

Estonian National Museum

# 01

Remimazolam short  
pharmacology  
update

- side effects

# 02

Pharmacoeconomics

# 03

Small personal  
experience

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Ready-to-use  
injectable  
presentation

Formulation does  
not support  
bacterial growth

Free from lipid  
accumulation

Free from pain on  
injection

Rapid onset

Rapid offset

Reversal drug

No active  
metabolite

Free from  
extraneous muscle  
movements

Airway obstruction  
unlikely

Minimal  
hypotension

No adrenocortical  
suppression

# Remimazolam is?

01

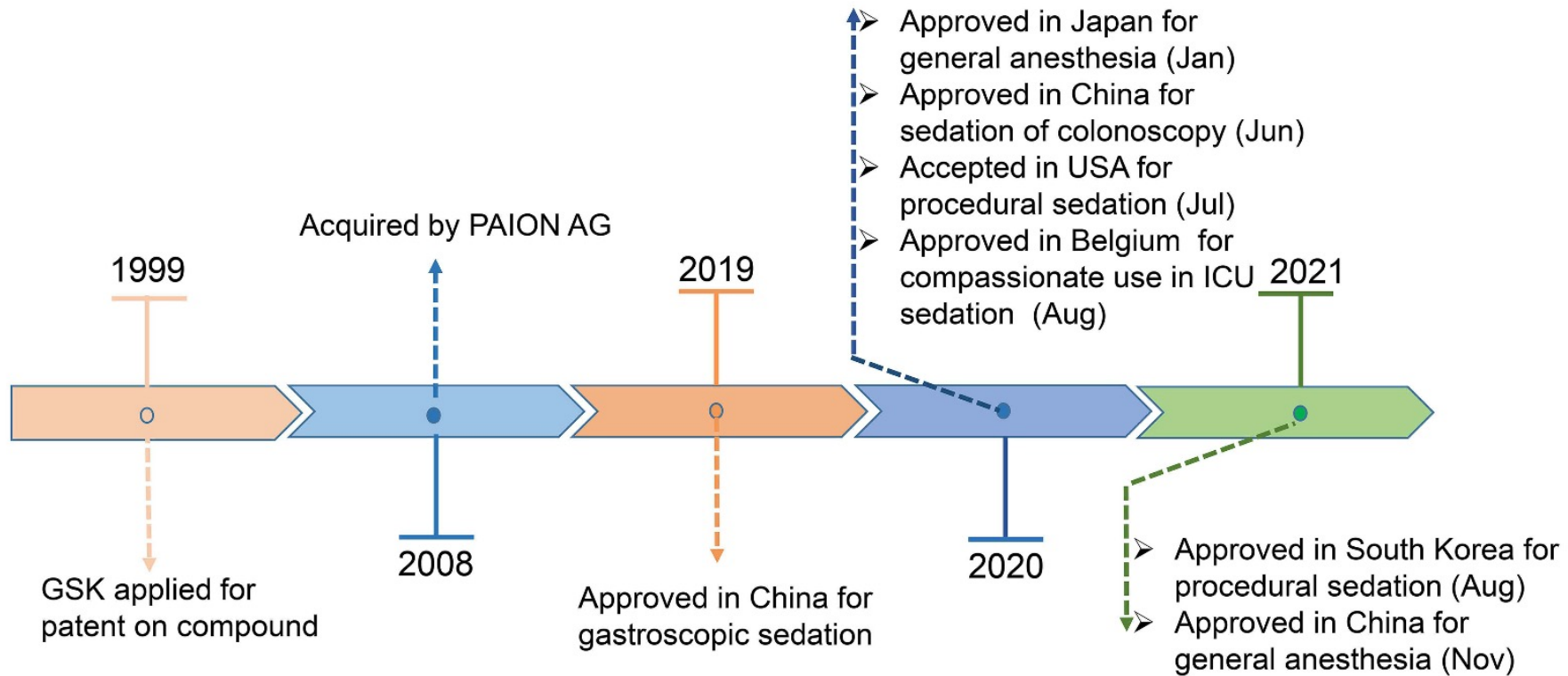
Combination of remifentanil and midazolam in one syringe

02

Midazolam with adjustments

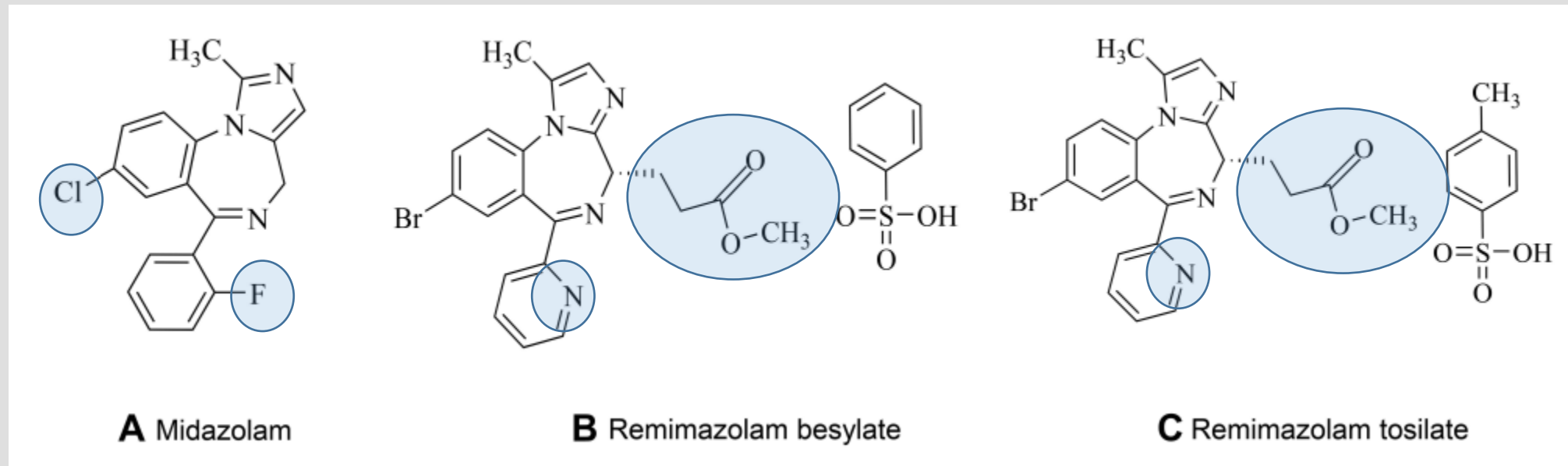
03

Completely new molecule



**Figure I** The main milestones in the development of remimazolam.

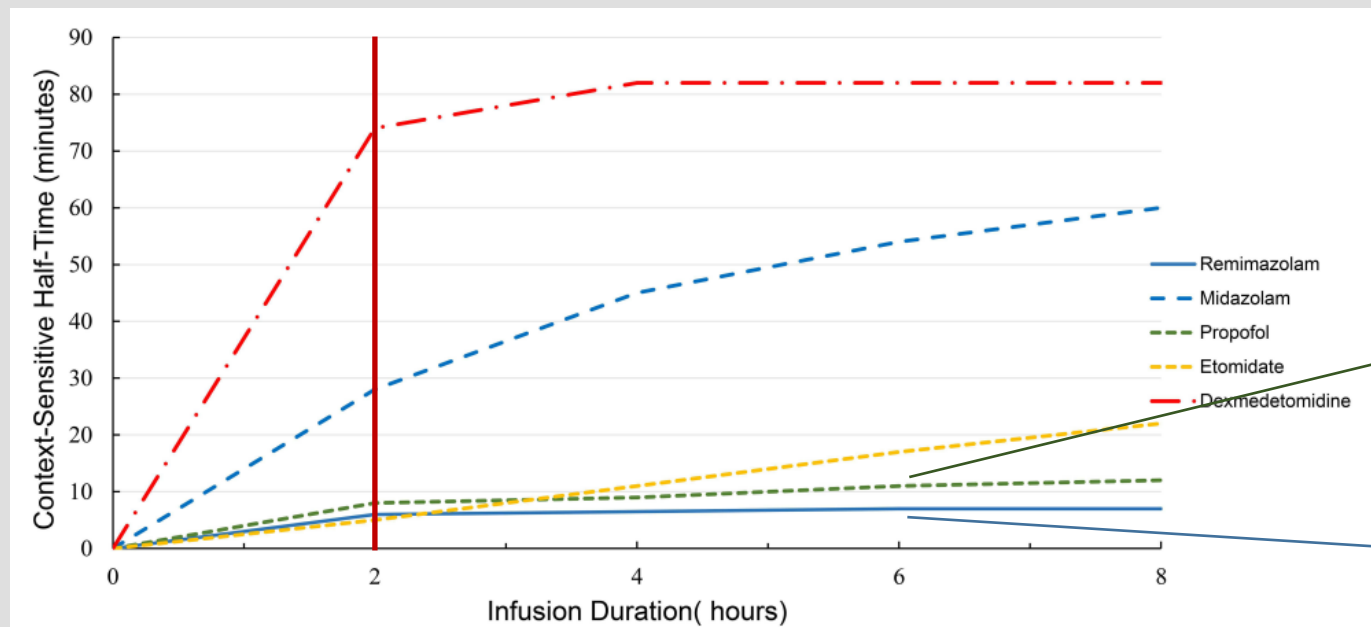
# Chemical structure



Self metabolising and Organ independent drug

# Organ independent fast metabolism

Drug	Onset (min)	Duration (min)	CL (l/h)	Vss (l)	T <sub>1/2</sub> (h)	MRT (hours)
Remimazolam	1-3	8	70.3±13.9	34.8±9.4	0.75±0.15	0.51
Midazolam	3-5	12	23±4.5	81.8±27.1	2.89±0.65	3.6



**Figure 4** The context-sensitive half-times (the time required for the plasma level of the drug to decrease 50% after the infusion is stopped) for the sedatives remimazolam, midazolam, propofol, etomidate, and dexmedetomidine.

**Notes:** Data from Whizar et al,<sup>10</sup> Wiltshire et al,<sup>22</sup> Schüttler et al,<sup>23</sup> and Iiro et al.<sup>33</sup>

Propofol  
11 min

Remimazolam  
8 min

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# Metabolites

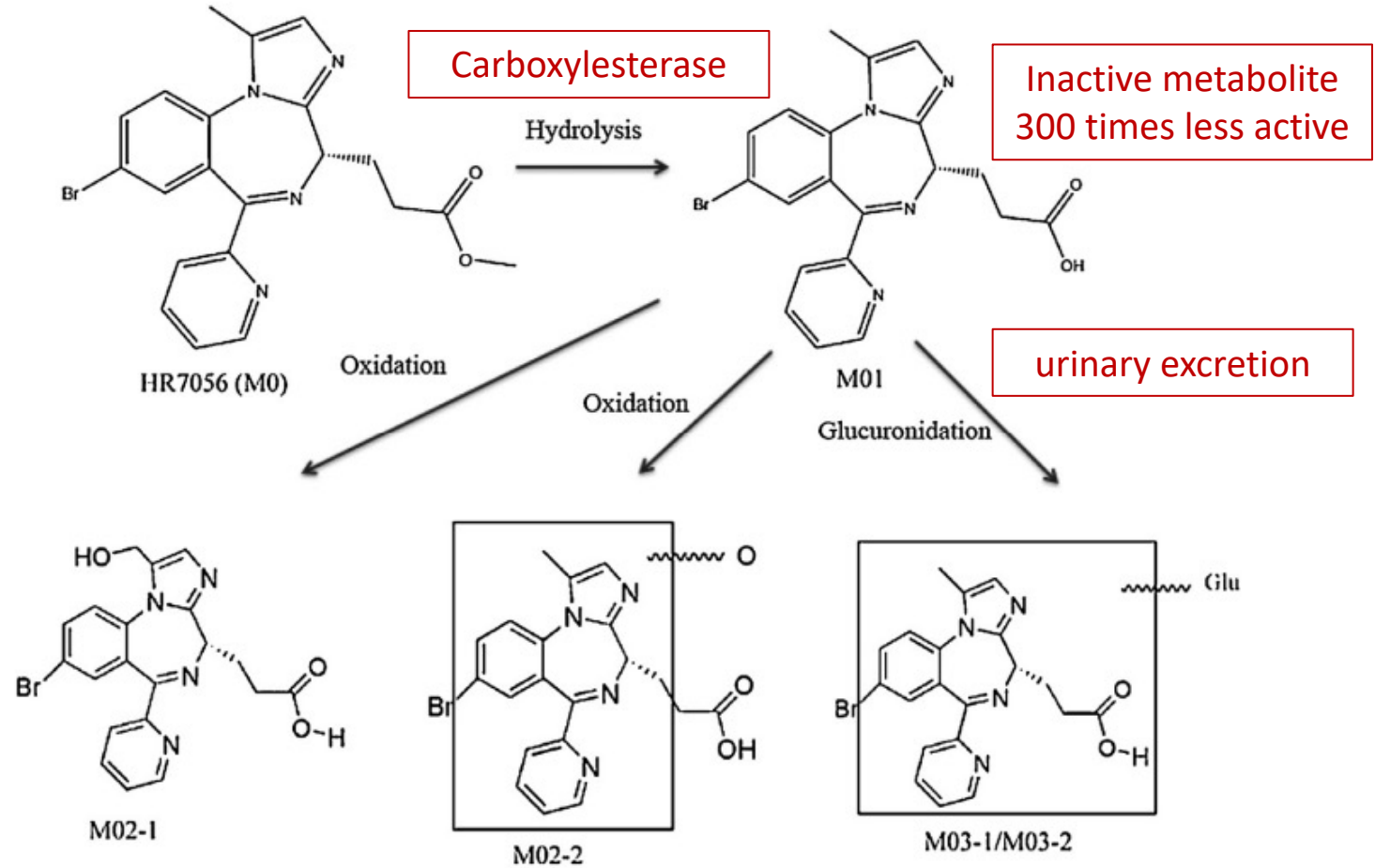
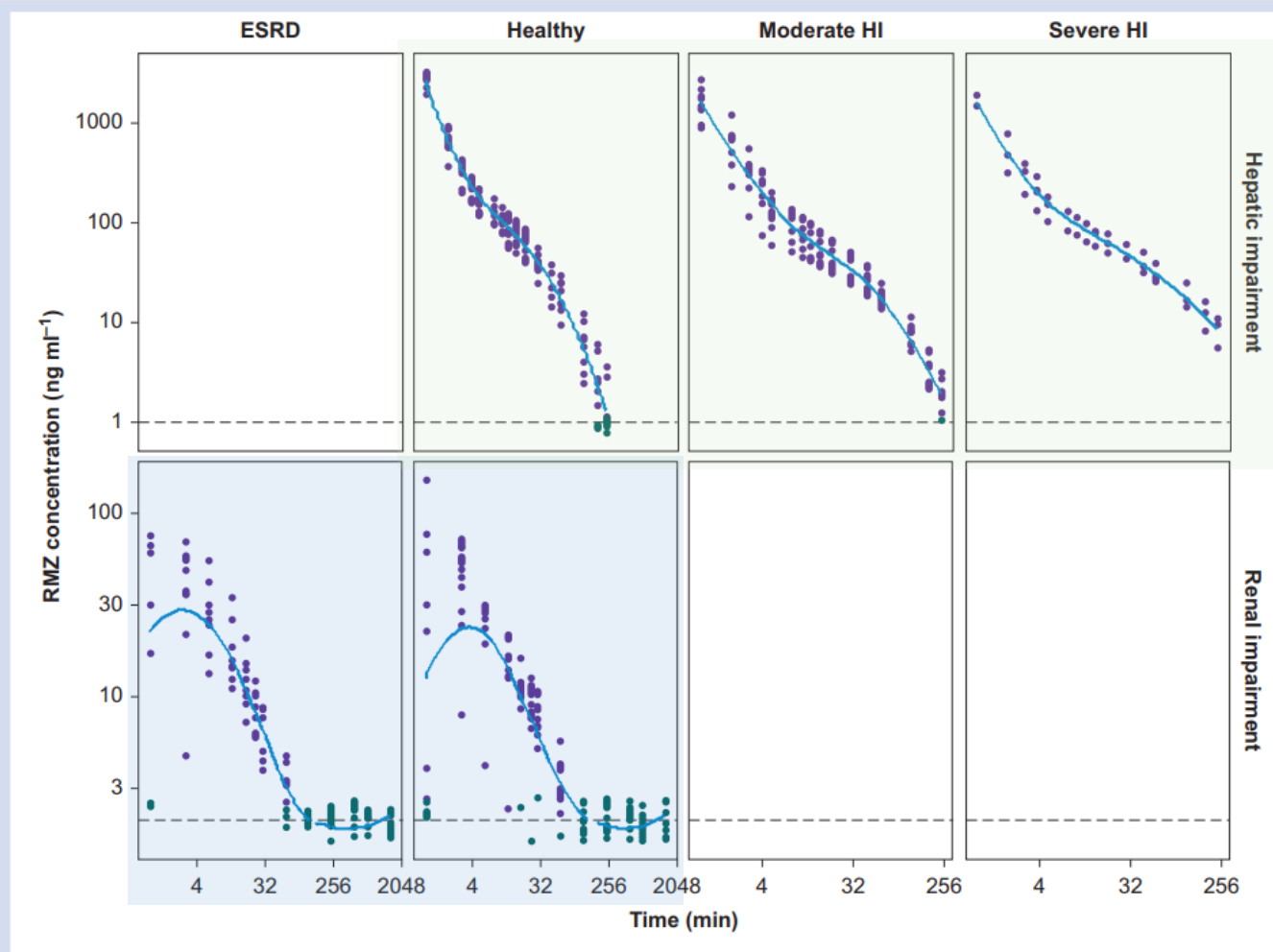


Fig. 4. The proposed metabolic pathways of remimazolam (HR7056) in human plasma and urine after a 1-min IV injection of 0.35 mg/kg.



# Kidney and Liver



11 patients ESRD, GFR < 30 ml/h

1.5 mg iv bolus

11 patients with liver impairment, Child-Pugh

7-9 and Child-Pugh 10-15

0.1 mg/kg iv bolus

- Remimazolam has predictable pharmacokinetic properties, and does not require dose adjustments in subjects with hepatic or renal impairment.

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# Remimazolam *versus* propofol for procedural sedation: a meta-analysis of randomized controlled trials

Yu Chang<sup>1,\*</sup>, Yun-Ting Huang<sup>2,\*</sup>, Kuan-Yu Chi<sup>3,4</sup> and Yen-Ta Huang<sup>1</sup>

- 12 trials 2170 patients
  - 1119 remimazolam and 1051 propofol

**Table 2** Summary of meta-analyses.

Outcome	OR	WMD	Number of included studies	I <sup>2</sup>
Bradycardia	0.28 (0.14–0.57)		6	0%
Hypotension	0.26 (0.22–0.32)		11	0%
Respiratory depression	0.22 (0.14–0.36)		11	27%
PONV	0.65 (0.15–2.79)		8	70%
Dizziness	0.93 (0.53–1.61)		7	41%
Injection pain	0.06 (0.03–0.13)		9	37%
Successful sedation	1.40 (0.41–4.76)		8	41%
Time to LOC		12.68 (–5.55–30.9)	7	99%
Time to recovery		–84.55 (–258.34–89.23)	9	100%
Time to discharge		–2.52 (–6.82–1.78)	7	99%

**Notes.**

LOC, loss of consciousness; OR, odds ratio; WMD, weighted mean difference.

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36 case reports identified

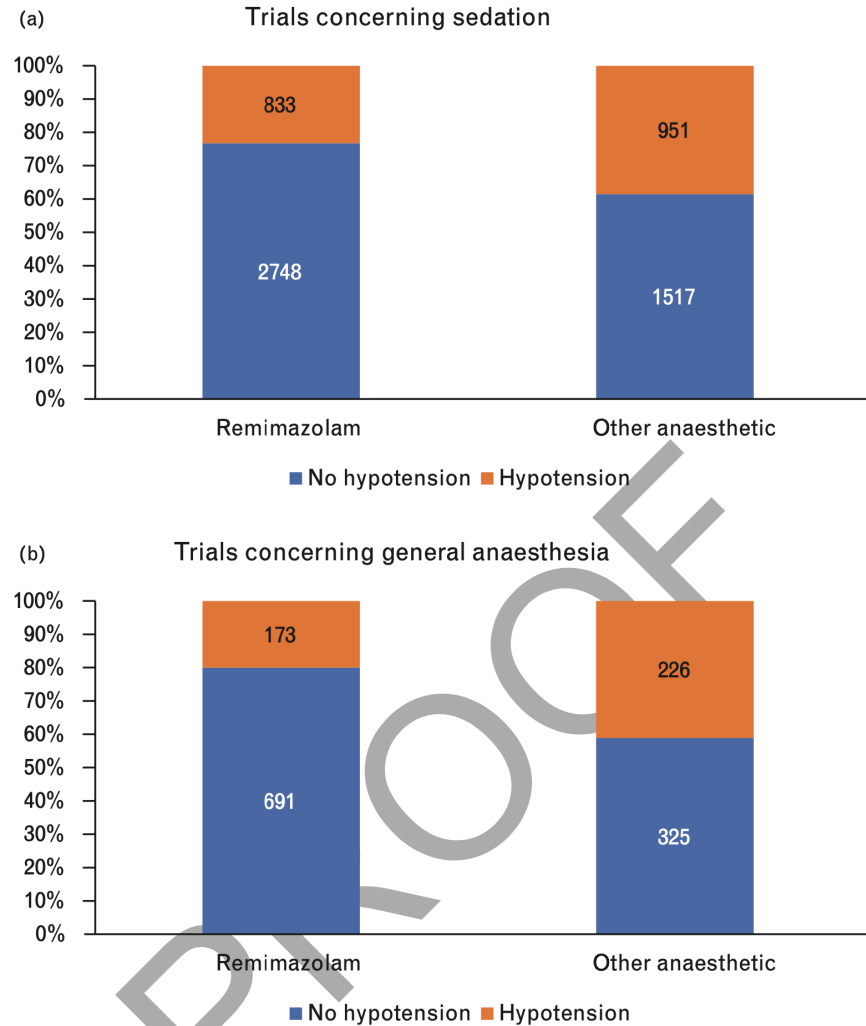
72 trials identified

46 editorials, reviews, ... identified

6806 patients with remimazolam  
1006 – hypotension  
68 – delayed emergence  
10 – anaphylaxis  
8 – re-sedation

Sander Kempnaers, Tom G. Hansen and Marc Van de Velde

Fig. 2 (a and b) Cumulative incidence of hypotension in comparative trials.



# Hypotension

Four meta-analysis confirm that, remimazolam had less hypotension

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# Delayed emergence 68 and re-sedation 8

## Delayed emergence

- General anaesthesia, not sedation
- Unreported, different criteria
- Liver impairment
- Genetic variations
- Inhibition of carboxylesterase
  - flavonoids
  - fat
  - alcohol
- Using BIS monitor

## Re-sedation

- Only with flumazenil
- Fast bolus

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# Anaphylaxis 10 cases – only case reports

No anaphylaxis described in clinical trials with 7000 patients

**Table 5** Case reports of anaphylaxis

First author	RMZ induction dose and infusion rate	Organ systems involved (except for cardiovascular)	Previous exposure to MDZ/RMZ	Tryptase peak (baseline) ( $\mu\text{g l}^{-1}$ )	Skin test MDZ	Skin test RMZ-solution
Hasushita <sup>103</sup>	12 mg, bolus	Skin	MDZ, last 2 years	8.7 (4.8)	NA	ID RMZ at 0.1 and 0.01 mg ml <sup>-1</sup>
Tsurumi <sup>104</sup>	12 mg, 6 mg kg <sup>-1</sup> h <sup>-1</sup>	Skin	MDZ, 1 month before	5.8 (4.7)	ID MDZ at 0.5 mg ml <sup>-1a</sup>	ID RMZ at 0.5 mg ml <sup>-1a</sup>
Yamaoka <sup>105</sup>	12 mg, 12 mg kg <sup>-1</sup> h <sup>-1</sup>	Respiratory	NA	23.8 (4.3)	NA	ID RMZ at 0.01 mg ml <sup>-1</sup>
Uchida <sup>106</sup>	4 mg, bolus		RMZ, 1 month before	8.3 (2.9)	NA	NA
Uchida <sup>106</sup>	9 mg, three boluses		No previous exposure	7.8 (4.1)	NA	Negative (not specified)
Kim <sup>107</sup>	NA, 12 mg kg <sup>-1</sup> h <sup>-1</sup>		NA	10.1 (4.4)	Negative	Negative
Kim <sup>107</sup>	NA, 12 mg kg <sup>-1</sup> h <sup>-1</sup>		NA	14 (6.3)	NA	NA
Kim <sup>107</sup>	NA, 12 mg kg <sup>-1</sup> h <sup>-1</sup>		NA	12.8 (4.2)	Negative	Negative
Kim <sup>107</sup>	NA, 12 mg kg <sup>-1</sup> h <sup>-1</sup>	Skin	NA	2.6 (1.5)	Negative	Negative
Kim <sup>107</sup>	NA, 2 mg kg <sup>-1</sup> h <sup>-1</sup>	Skin	NA	9.2 (4.2)	Negative	Negative

ID, intradermal test; MDZ, midazolam; NA, not available; RMZ, remimazolam; SP, skin prick test. <sup>a</sup>Original case report reports a concentration of 500 mg ml<sup>-1</sup>; however, this a probable mistake and should have shown 500  $\mu\text{g ml}^{-1}$ .

**Adrenaline used in all cases**

# Mechanism of anaphylaxis

- IgE mediated – 8 cases had increased tryptase levels
- Cross-reactivity with midazolam???
- Drug excipients
  - Dextran – 40 (remimazolam besylate)
    - most express IgG antibodies (food, bacteria)
    - slow infusion rates reduces activation of complement
  - Remimazolam tosylate contains glycine, no reactions described yet

# Precipitation of solution

**Table 6** Case reports of precipitation in intravenous catheter

First author	RMZ-concentration	RMZ-solution	RMZ-flow rate	Infusion fluid	Infusion flow rate
Liu <sup>110</sup>	2 mg ml <sup>-1</sup>	Sodium-chloride 0.9%	1 mg kg <sup>-1</sup> h <sup>-1</sup>	Ringer's acetate	NA
Matsuo <sup>111</sup>	5 mg ml <sup>-1</sup>	Sodium-chloride 0.9%	1 mg kg <sup>-1</sup> h <sup>-1</sup>	Ringer's acetate	NA
Sasaki <sup>112</sup>	5 mg ml <sup>-1</sup>	Sodium-chloride 0.9%	1 mg kg <sup>-1</sup> h <sup>-1</sup>	Ringer's acetate + D1	150 ml h <sup>-1</sup>
Yoshida <sup>113</sup>	2 mg ml <sup>-1</sup>	NA	30 ml h <sup>-1</sup>	Ringer's acetate	180 ml h <sup>-1</sup>

D1, glucose 1%; NA, not available; RMZ, remimazolam.

**Table 7** Concentration and flow rate at which no precipitate is formed

Infusion fluid	RMZ concentration	Infusion flow rate
Ringer's acetate	0.75 mg ml <sup>-1</sup>	0 ml h <sup>-1</sup>
	1 mg ml <sup>-1</sup>	100 ml h <sup>-1</sup>
	2.5 mg ml <sup>-1</sup>	300 ml h <sup>-1</sup>
Ringer's lactate	1 mg ml <sup>-1</sup>	100 ml h <sup>-1</sup>
	2.5 mg ml <sup>-1</sup>	100 ml h <sup>-1</sup>
	5 mg ml <sup>-1</sup>	300 ml h <sup>-1</sup>

RMZ, remimazolam.

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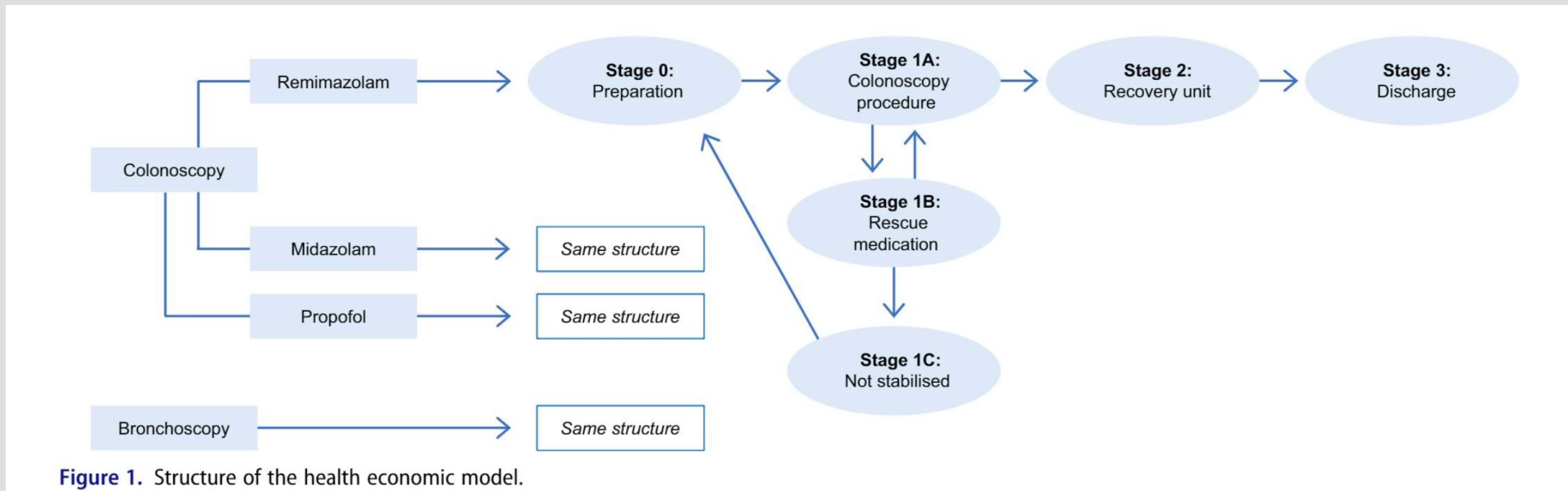
RESEARCH ARTICLE

 OPEN ACCESS 

## Economic benefits of remimazolam compared to midazolam and propofol for procedural sedation in colonoscopies and bronchoscopies

Mikkel H. Pedersen<sup>a</sup> , Anne Danø<sup>a</sup> , Ebbe Englev<sup>b</sup>, Lisbeth Kattenhøj<sup>b</sup> and Emma Munk<sup>a</sup> 

<sup>a</sup>EY Godkendt Revisionspartnerselskab, Frederiksberg, Denmark; <sup>b</sup>Paion Scandic, Odense, Denmark



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Preparation time  
Recovery time

**Figure 2.** Tornado diagrams from DSA, change in incremental cost of remimazolam compared to midazolam and propofol in colonoscopies and midazolam in bronchoscopies.

**Table 4.** Results: procedural sedation in colonoscopies.

	Remimazolam	Midazolam	Propofol	Difference	
				Remimazolam vs. Midazolam	Remimazolam vs. Propofol
Drug costs (DKK)	93	9	8	84	85
Hospital costs (DKK)	832	1024	978	-192	-147
Patient time and transport costs (DKK)	276	288	269	-12	7
Total costs (DKK)	1200	1320	1255	-120	-55
<b>Total cost in EUR</b>	<b>161</b>	<b>177</b>	<b>168</b>	<b>-16</b>	<b>-7</b>

Nurse anaesthetist  
Anaesthesiologist

CURRENT MEDICAL RESEARCH AND OPINION  
<https://doi.org/10.1080/03007995.2023.2196198>  
 Article RT-0034.R1/2196198

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RESEARCH ARTICLE OPEN ACCESS Check for updates

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# Personal small experience

- 15 patients for gastroscopy and coloscopy
- ASA I-III
- Age 30...75 years
- Sedation plan
  - Remimazolam 5 mg during 1 minute and then 2.5 mg addition as required
  - Remifentanil 20 µg boluses before start of procedure and as required (coloscopies only)
- Entropy® anaesthesia depth monitor
  - average 80-85 and in one case 60 (short period)
- One transition to propofol sedation, very technically demanding coloscopy
- Good drug, be careful in combination with remifentanil (additional oxygen)
- Endoscopist alone, probably yes

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# Summary for procedural sedation...

- SOFT drug
  - self-metabolising and organ independent
- Fast onset and fast offset in sedation dose range
- Less hypotension – be ready
- Rare anaphylaxis possible – be ready
- Economically meaningful, especially without anaesthesia personal
- Worth trying
- More data...

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