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RATIONALE FOR RECOMMENDATIONS ON PATIENT CATEGORIES

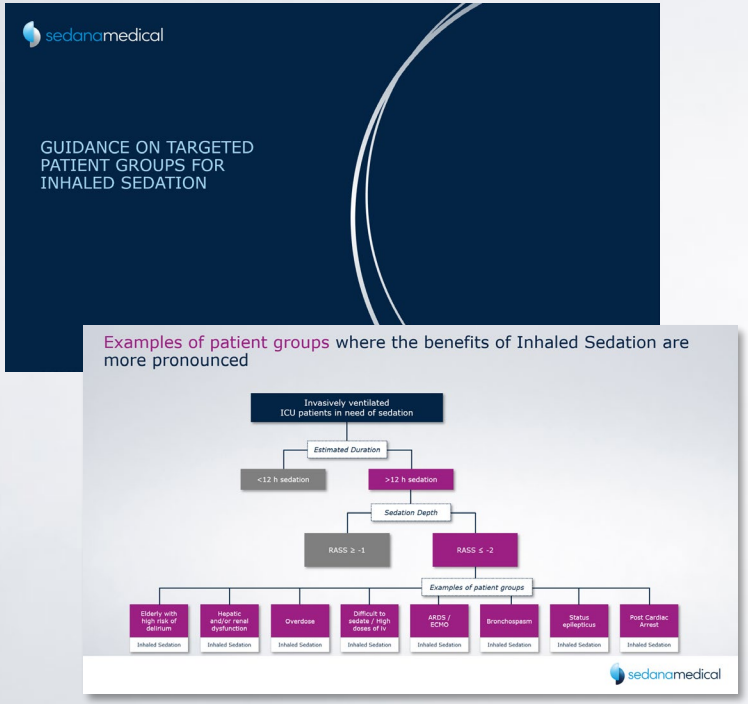
FOR INTERNAL USE ONLY

I/EN/NPR/220005

Material to support discussions on patient groups

"Guidance on targeted patient groups for Inhaled Sedation"

Slide deck for external use



"Rationale for recommendations on patient categories"

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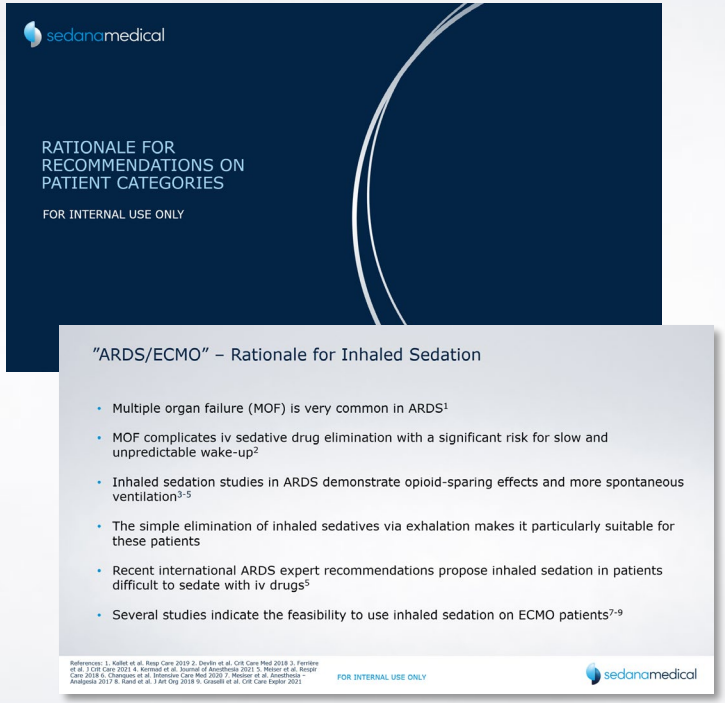

"FAQ Patient Categories"

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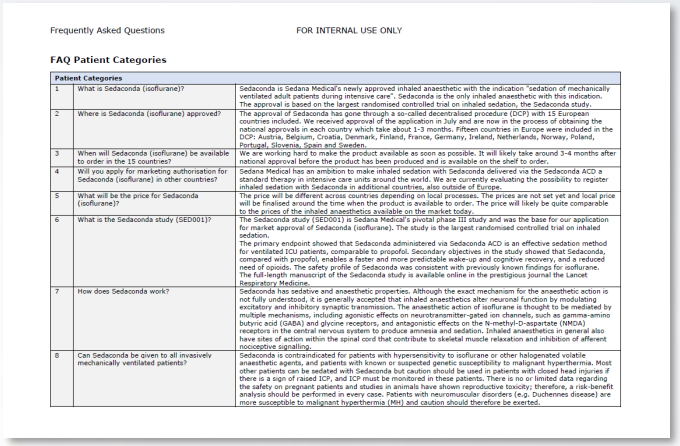
Frequently Asked Questions FOR INTERNAL USE ONLY

FAQ Patient Categories

Patient Categories		
1	What is Sedaconda (isoflurane)?	Sedaconda is Sedana Medical's newly approved inhaled anaesthetic with the indication "sedation of mechanically ventilated adult patients during intensive care". Sedaconda is the only inhaled anaesthetic with this indication. The approval is based on the largest randomised controlled trial on inhaled sedation, the Sedaconda study.
2	Where is Sedaconda (isoflurane) approved?	The approval of Sedaconda has gone through a so-called decentralised procedure (DCP) with 15 European countries included. We received approval of the application in July and are now in the process of obtaining the national approvals in each country which take about 1-3 months. Fifteen countries in Europe were included in the DCP: Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Ireland, Netherlands, Norway, Poland, Portugal, Slovenia, Spain and Sweden.
3	When will Sedaconda (isoflurane) be available to order in the 15 countries?	We are working hard to make the product available as soon as possible. It will likely take around 3-4 months after national approval before the product has been produced and is available on the shelf to order.
4	Will you apply for marketing authorisation for Sedaconda (isoflurane) in other countries?	Sedana Medical has an ambition to make inhaled sedation with Sedaconda delivered via the Sedaconda ACD a standard therapy in intensive care units around the world. We are currently evaluating the possibility to register inhaled sedation with Sedaconda in additional countries, also outside of Europe.
5	What will be the price for Sedaconda (isoflurane)?	The price will be different across countries depending on local processes. The prices are not set yet and local price will be finalised around the time when the product is available to order. The price will likely be quite comparable to the prices of the inhaled anaesthetics available on the market today.
6	What is the Sedaconda study (SED001)?	The Sedaconda study (SED001) is Sedana Medical's pivotal phase III study and was the base for our application for market approval of Sedaconda (isoflurane). The study is the largest randomised controlled trial on inhaled sedation. The primary endpoint showed that Sedaconda administered via Sedaconda ACD is an effective sedation method for ventilated ICU patients, comparable to propofol. Secondary objectives in the study showed that Sedaconda, compared with propofol, enables a faster and more predictable wake-up and cognitive recovery, and a reduced need of opioids. The safety profile of Sedaconda was consistent with previously known findings for isoflurane. The full-length manuscript of the Sedaconda study is available online in the prestigious journal the Lancet Respiratory Medicine.
7	How does Sedaconda work?	Sedaconda has sedative and anaesthetic properties. Although the exact mechanism for the anaesthetic action is not fully understood, it is generally accepted that inhaled anaesthetics alter neuronal function by modulating excitatory and inhibitory synaptic transmission. The anaesthetic action of isoflurane is thought to be mediated by multiple mechanisms, including agonistic effects on neurotransmitter-gated ion channels, such as gamma-amino butyric acid (GABA) and glycine receptors, and antagonistic effects on the N-methyl-D-aspartate (NMDA) receptors in the central nervous system to produce amnesia and sedation. Inhaled anaesthetics in general also have sites of action within the spinal cord that contribute to skeletal muscle relaxation and inhibition of afferent nociceptive signalling.
8	Can Sedaconda be given to all invasively mechanically ventilated patients?	Sedaconda is contraindicated for patients with hypersensitivity to isoflurane or other halogenated volatile anaesthetic agents, and patients with known or suspected genetic susceptibility to malignant hyperthermia. Most other patients can be sedated with Sedaconda but caution should be used in patients with closed head injuries if there is a sign of raised ICP, and ICP must be monitored in these patients. There is no or limited data regarding the safety on pregnant patients and studies in animals have shown reproductive toxicity; therefore, a risk-benefit analysis should be performed in every case. Patients with neuromuscular disorders (e.g. Duchennes disease) are more susceptible to malignant hyperthermia (MH) and caution should therefore be exerted.

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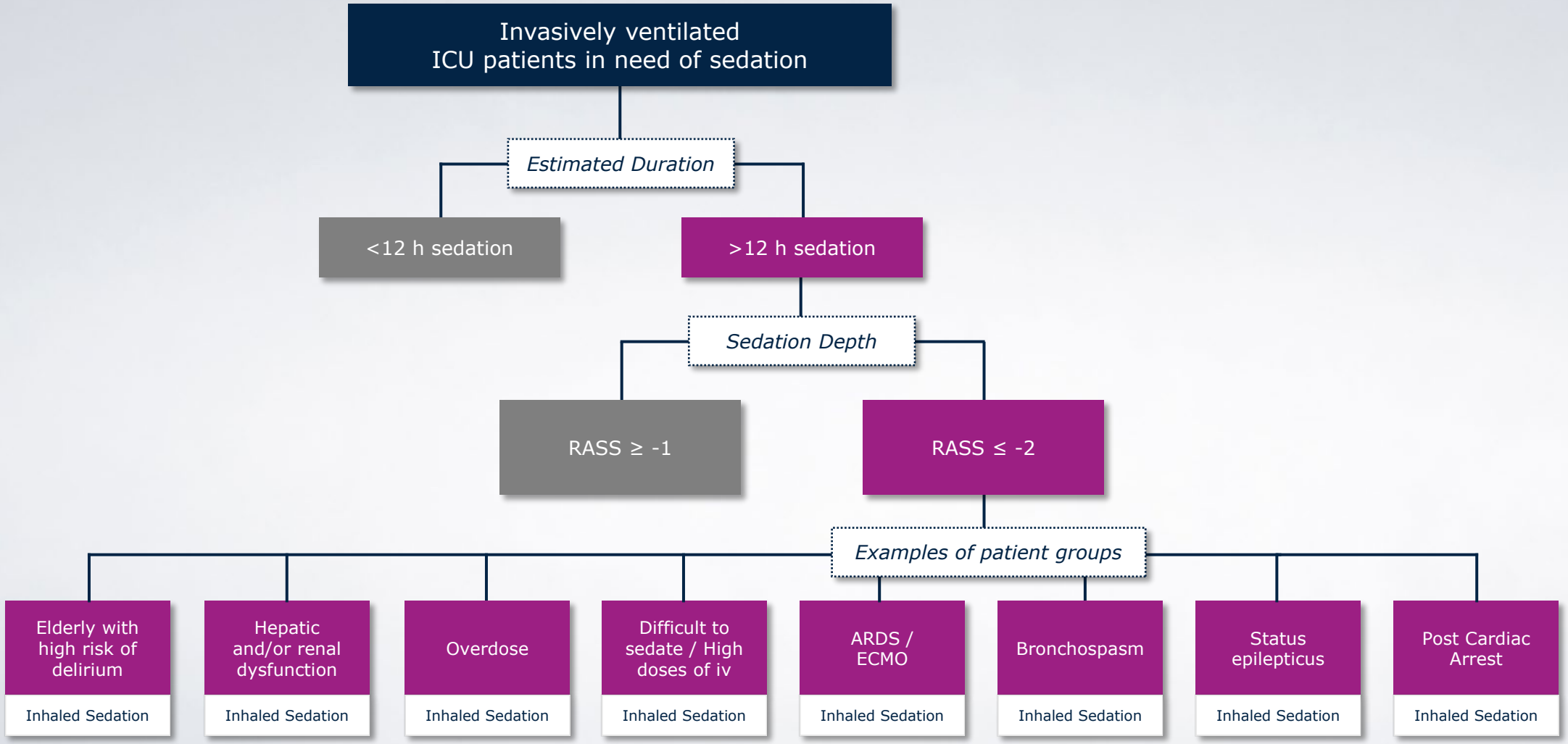
Which patients are recommended for a new ICU to start with? (Secure a first positive experience)

- Start with a patient group common in the ICU (site-specific)
  - Familiarity and "comfortable" to treat
  - Avoid the stress of a "difficult" patient AND a new therapy
  - Easy to evaluate the difference between inhaled sedation and standard of care
  - To get momentum and not have to wait for "the right" patient

- Find patients with a high likelihood of a "wow" moment
  - Patients with need of a quick wake-up
  - Difficult to sedate patient, high doses of iv sedatives and/or polypharmacy

! Do NOT start with a severely ill patient with bad prognosis.
The likelihood of a first positive experience is low.

Examples of patient groups where the benefits of Inhaled Sedation are more pronounced



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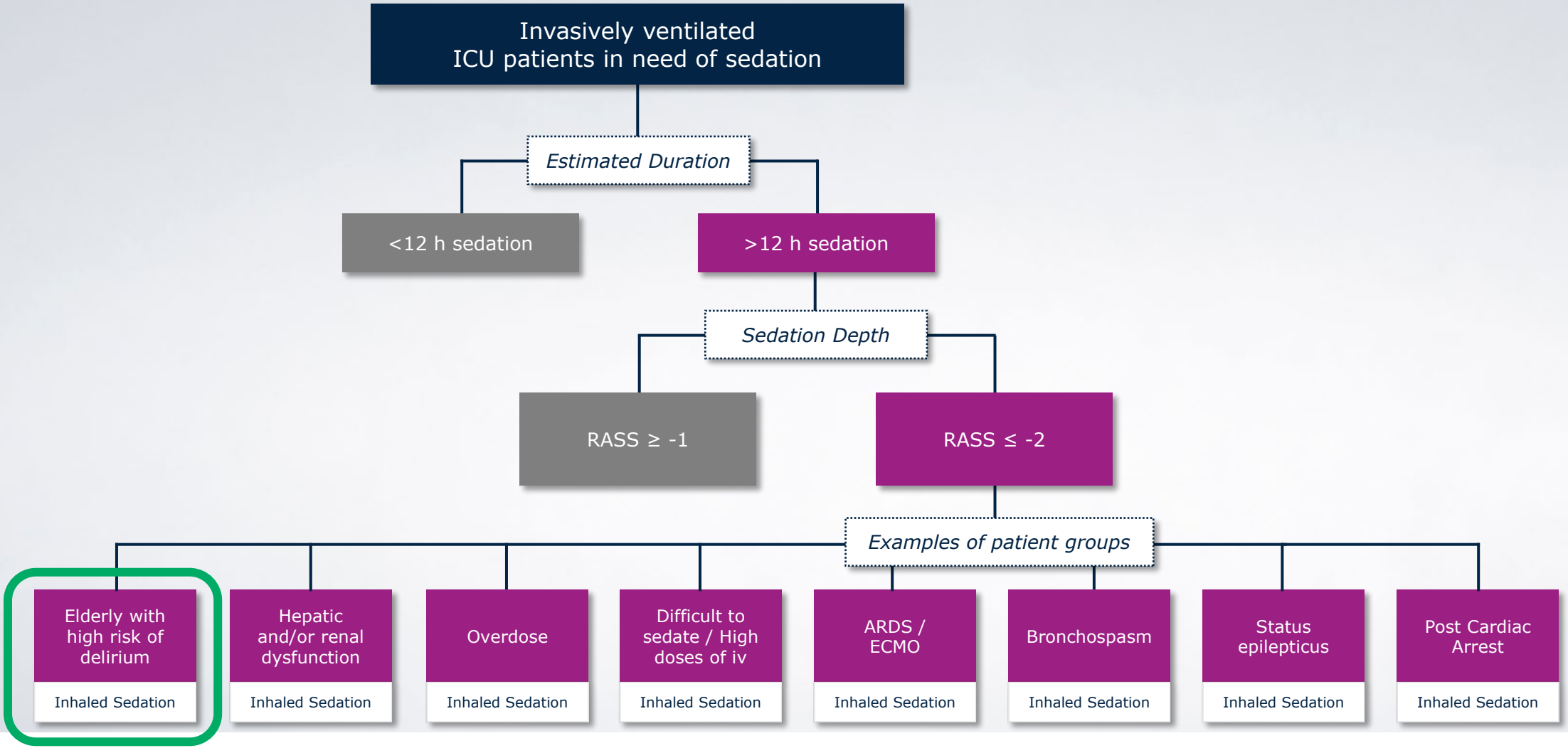

”Elderly with high risk of delirium” – Rationale for Inhaled Sedation

- High age is a risk factor for delirium[1]
- Elderly ICU patients have reduced metabolic capacity secondary to:
  - reduced hepatic blood flow[2]
  - reduced renal blood flow[3]
  - co-morbidities

  This affects the elimination of iv sedatives and analgesics[2]
- Wake-up from isoflurane sedation is short and predictable with no indications of age differences[4,5]
- Patients follow verbal commands and write their home address in the hours after isoflurane sedation[4-8]
- Rapid wake-up is consistent with the absence of delirium[9]

References: 1. Witlox et al. JAMA 2010 2. Kirkpatrick et al. Br J Anaesth 1988 3. Cheung et al. Drugs aging 2008 4. Sackey et al. Crit Care Med 2004 5. Meiser et al. Lancet Resp Med 2021 6. Hanafy et al. Eg J Anaesth. 2005 7. Kong et al. BMJ 1989 8. Spencer et al. Intensive Care Med 1992 9. Ely et al. Crit Care Med 2001

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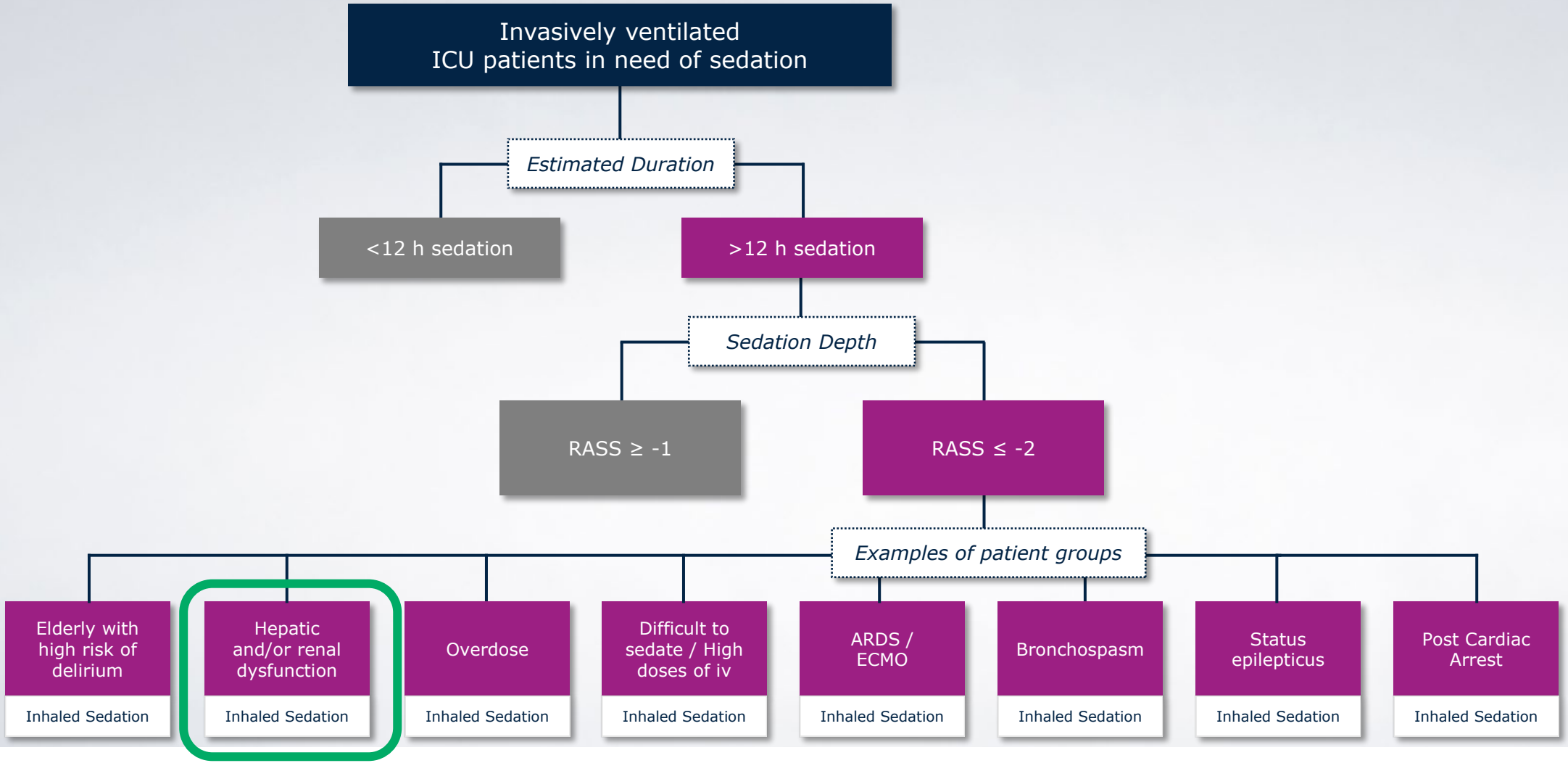

”Hepatic and/or renal dysfunction” – Rationale for Inhaled Sedation

- Elimination of propofol and midazolam depend on hepatic metabolism[1,2]
- Elimination of midazolam and some opioids depend on renal function[3,4]
- Isoflurane elimination and recovery from sedation do not depend on liver or kidneys functions[5]

References: 1. Sahinovic et al. Pharmacokinet 2018 2. Spina et al., Pharmacotherapy 2007 3. Shelly et al. Eur J Anaesthesiol 1991 4. Höhne et al. Anaesthetist 2004 5. Eger. Br J Anaest 1984 6. Meiser et al. Resp Care 2018 7. Ferriere et al J Crit Care 2020 8. Meiser et al. Lancet Resp Med 2021

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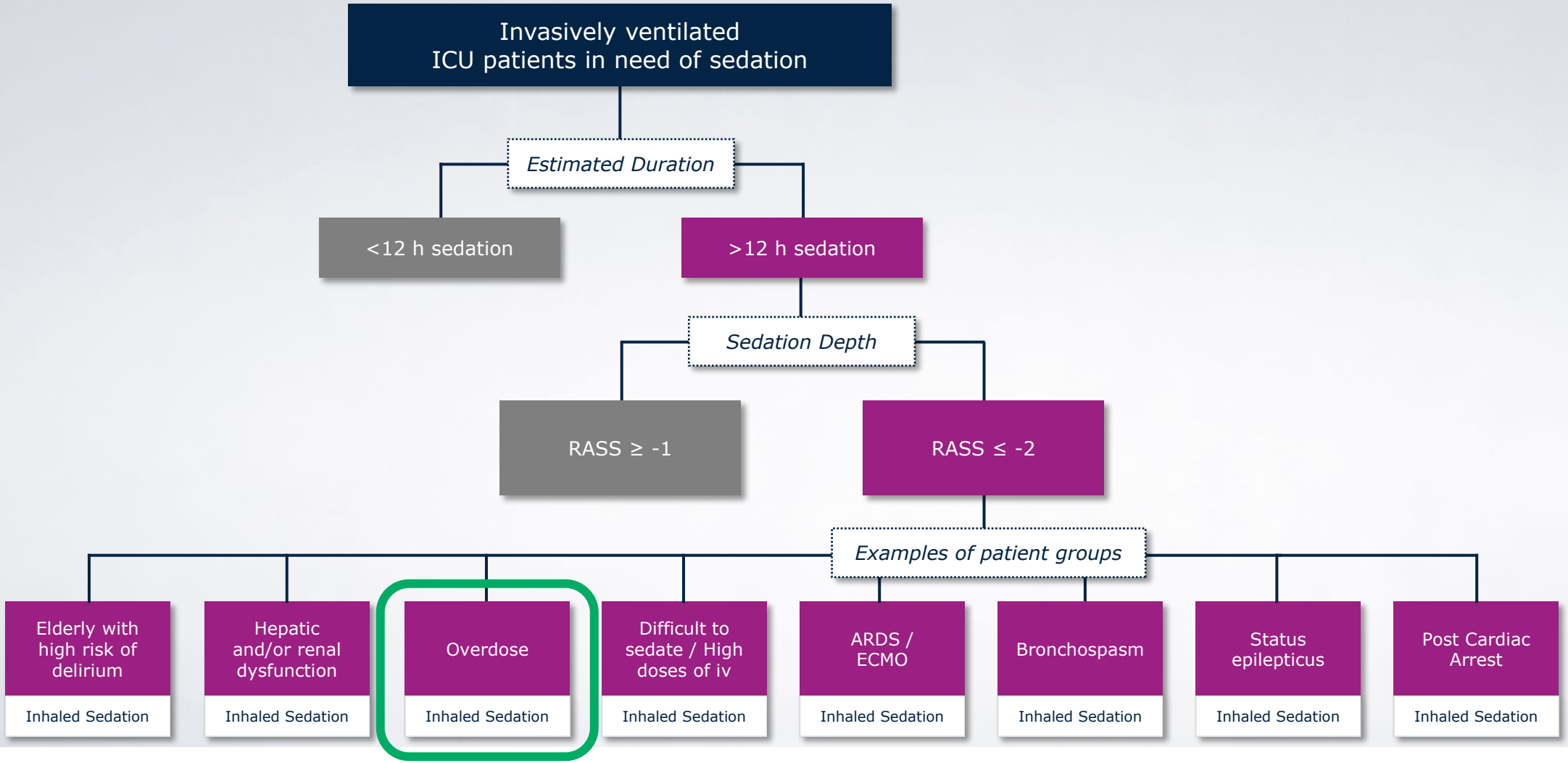

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"Overdose" – rationale for Inhaled Sedation

- The pharmacokinetics of isoflurane enables
  - wake-up and extubation within minutes[1-3]
  - early return of cognitive function[1-3]

- A rapid transition from sedation to wide awake within minutes may facilitate early patient cooperation.

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References: 1. Kong et al. BMJ 1989 2. Sackey et al. Crit Care Med 2004 3. Spencer et al. Intensive Care Med 1992

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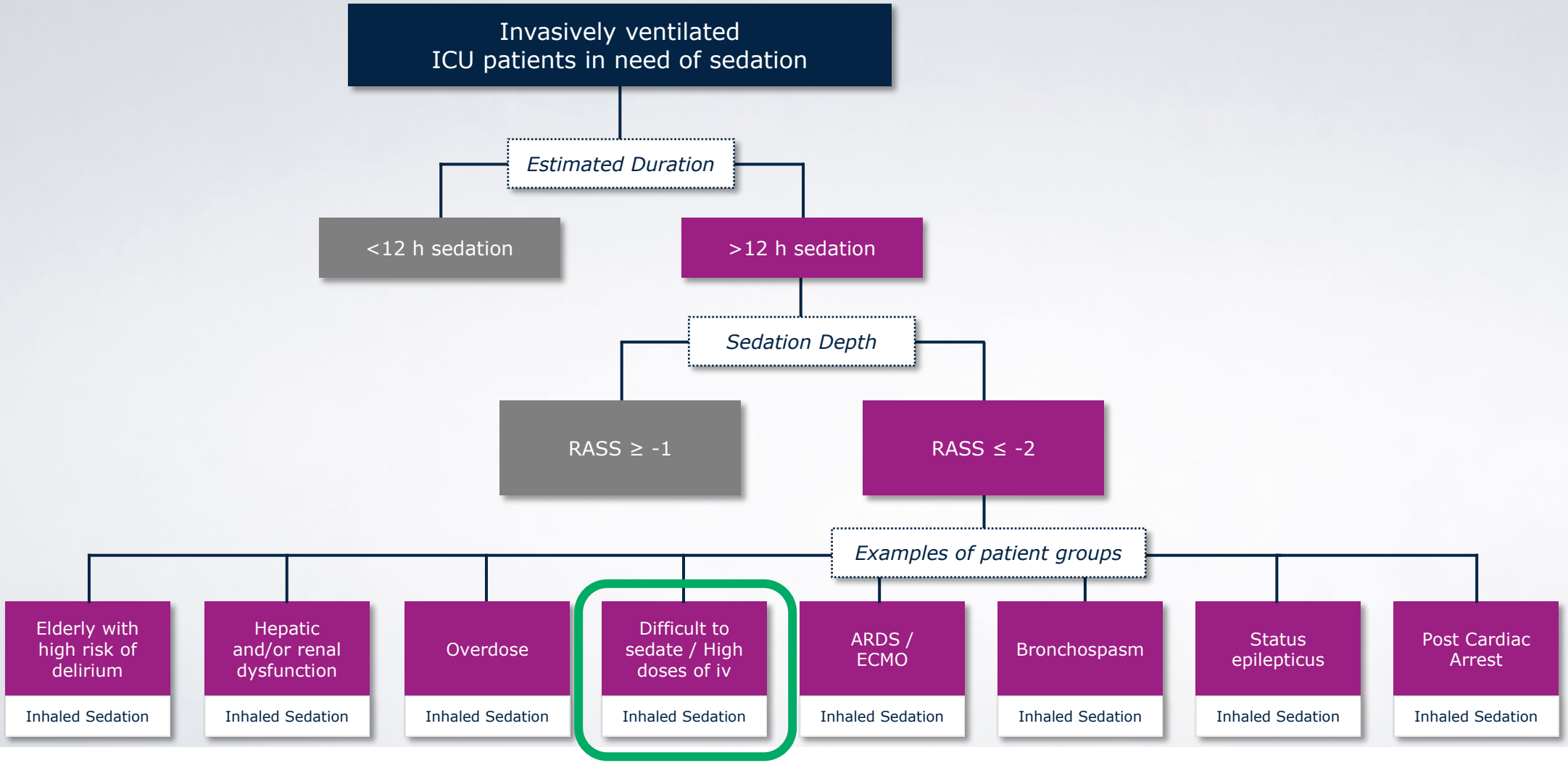

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"Difficult to sedate / High doses of iv" – Rationale for Inhaled Sedation

- The difficult to sedate patient needs high doses or multiple sedatives and analgesics
- High doses of intravenous sedatives and opioids increase the risk of significant side effects[1-3]
- Isoflurane can replace polypharmacy and reduce opioid needs[4-6]
- There are no published reports of isoflurane non-responders to date

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References: 1. Pandharipande et al. Anesthesiology 2005 2. Krajcova et al. Crit Care 2015 3. Schug et al Drug Safety 1992 4. Meiser et al. Respiratory Care 2018 5. Eifinger et al. Klin Padiatr 2013 6. Ferriere et al. J Crit Care 2020

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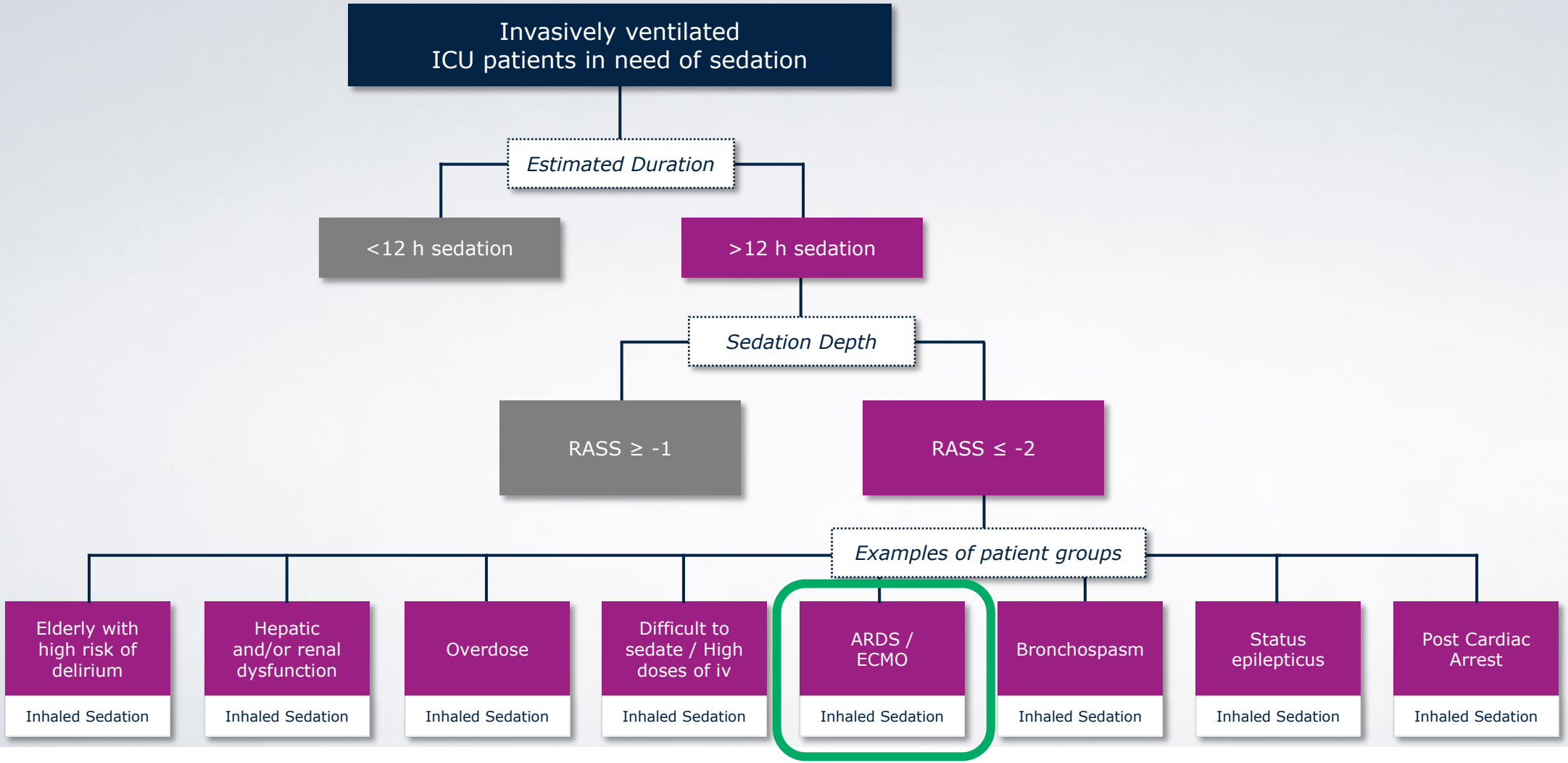

”ARDS/ECMO” – Rationale for Inhaled Sedation

- Multiple organ failure (MOF) is very common in ARDS[1]
- MOF complicates iv sedative drug elimination with a significant risk for slow and unpredictable wake-up[2]
- Inhaled sedation studies in ARDS demonstrate opioid-sparing effects and more spontaneous ventilation[3-5]
- The simple elimination of inhaled sedatives via exhalation makes it particularly suitable for these patients
- Recent international ARDS expert recommendations propose inhaled sedation in patients difficult to sedate with iv drugs[5]
- Several studies indicate the feasibility to use inhaled sedation on ECMO patients[7-9]

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References: 1. Kallet et al. Resp Care 2019 2. Devlin et al. Crit Care Med 2018 3. Ferrière et al. J Crit Care 2021 4. Kermad et al. Journal of Anesthesia 2021 5. Meiser et al. Respir Care 2018 6. Chanques et al. Intensive Care Med 2020 7. Mesiser et al. Anesthesia – Analgesia 2017 8. Rand et al. J Art Org 2018 9. Graselli et al. Crit Care Explor 2021

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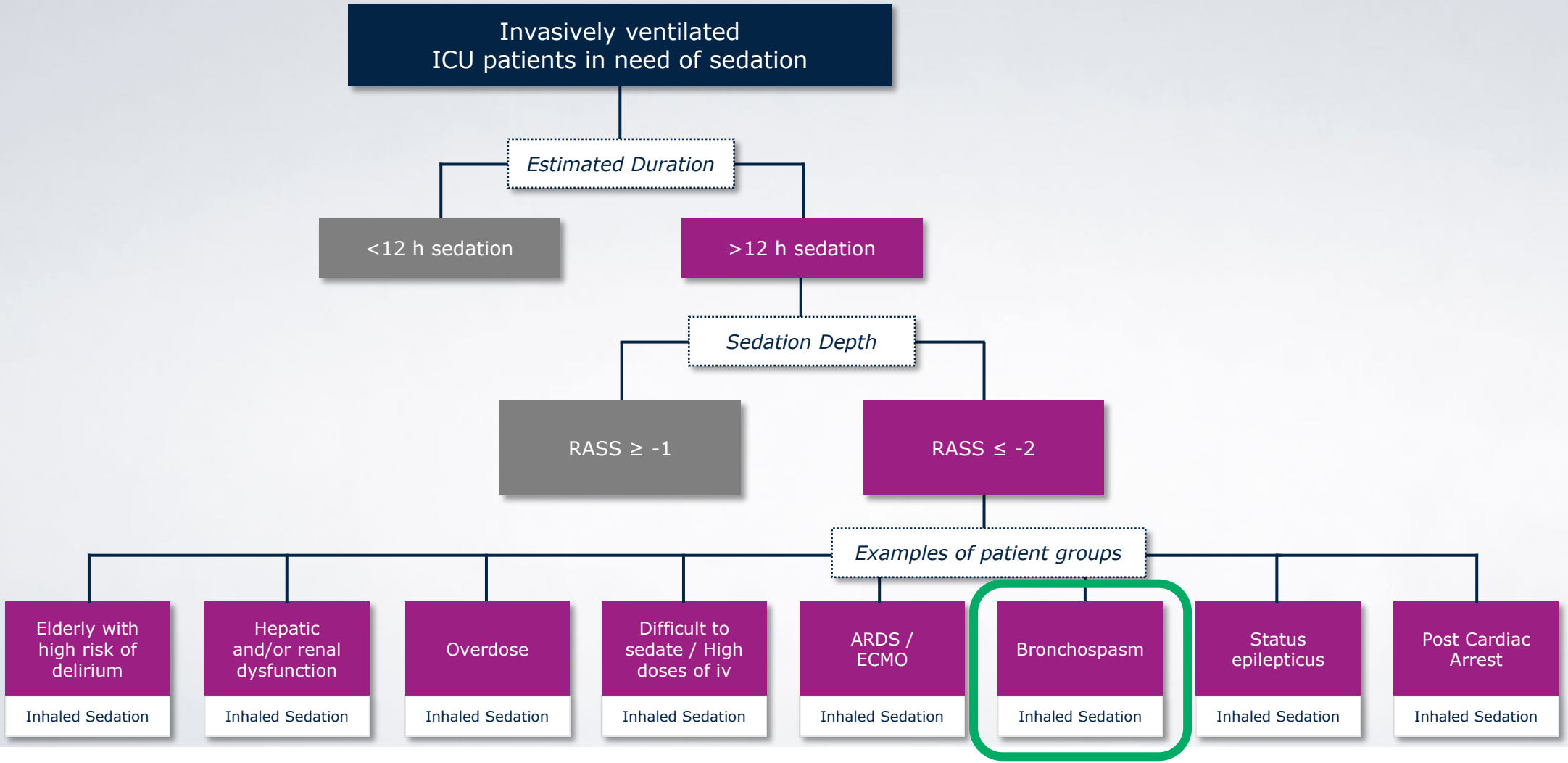

”Bronchospasm” – Rationale for Inhaled Sedation

- The bronchodilator effects of isoflurane have been utilized in the management of severe asthma for decades.
- Case series and reports in children and adults with therapy-refractory asthma demonstrate how respiratory acidosis is reversed and pulmonary mechanics improve over hours[1-5]
- Doses may be somewhat higher than merely for sedation[4,5]

References: 1. Gradisek & Dolenc. Brain Injury 2016 2. Hornuss et al. Case Reports in Medicine 2010 3. Johnston et al. Chest 1990 4. Shankar et al. Intensive Care Med 2006 5. Turner et al. Respir Care 2012

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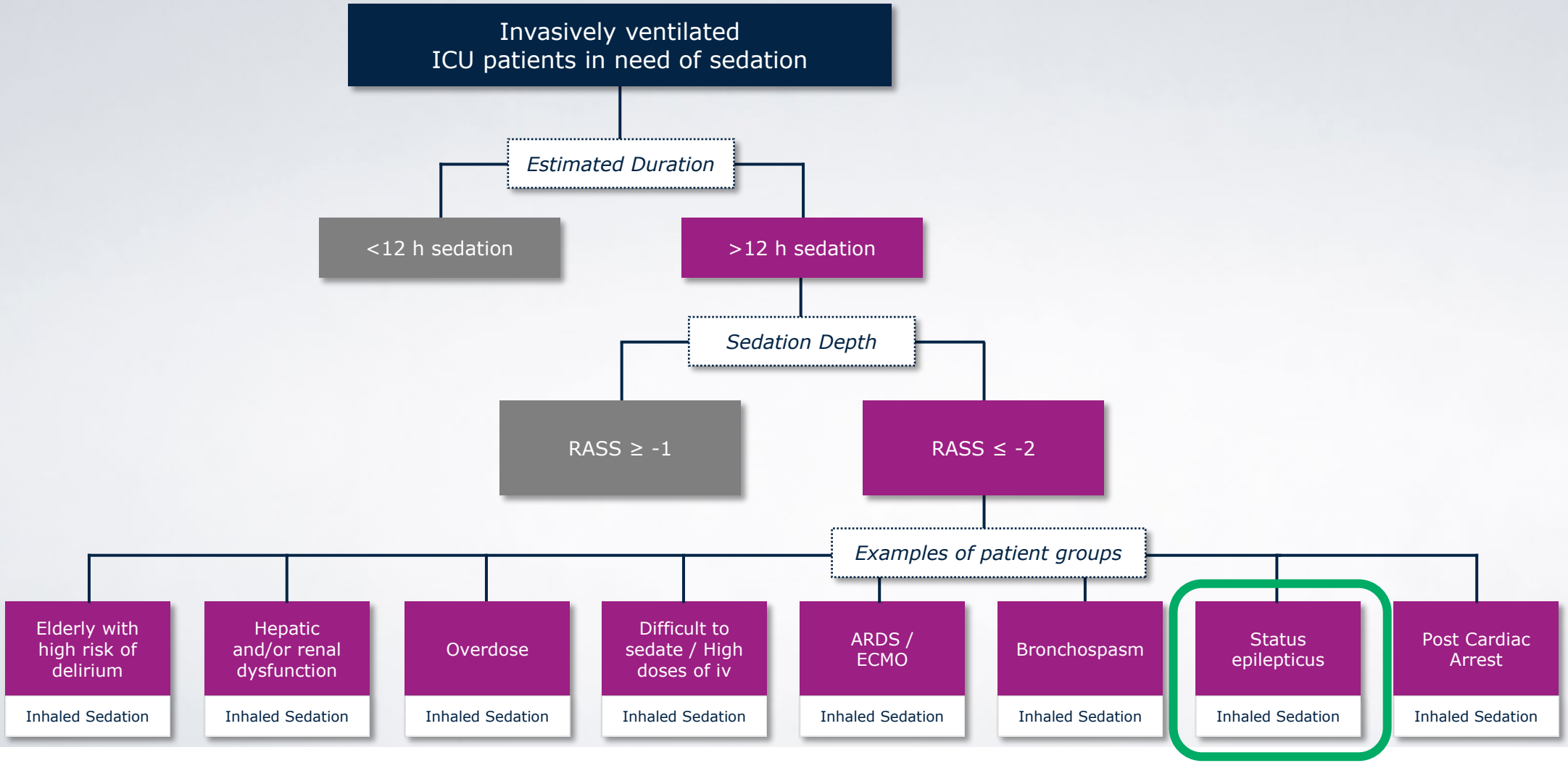

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”Status epilepticus” - Rationale for Inhaled Sedation

- Isoflurane has been used as a rescue medication to manage status epilepticus on patients of all ages[1-3]
- Isoflurane effectively abolishes epileptic activity at end-tidal concentrations[2,3] slightly higher than that used for sedation in general ICU patients[4,5]

References: 1. Zhumadilov et al. Frontiers in Neurology 2014 2. Kofke et al. Anesthesiology 1989 3. Mirsattari et al. Archives of Neurology 2004 4. Meiser et al. Lancet Respir Med 2021 5. Sackey et al. Crit Care Med 2004

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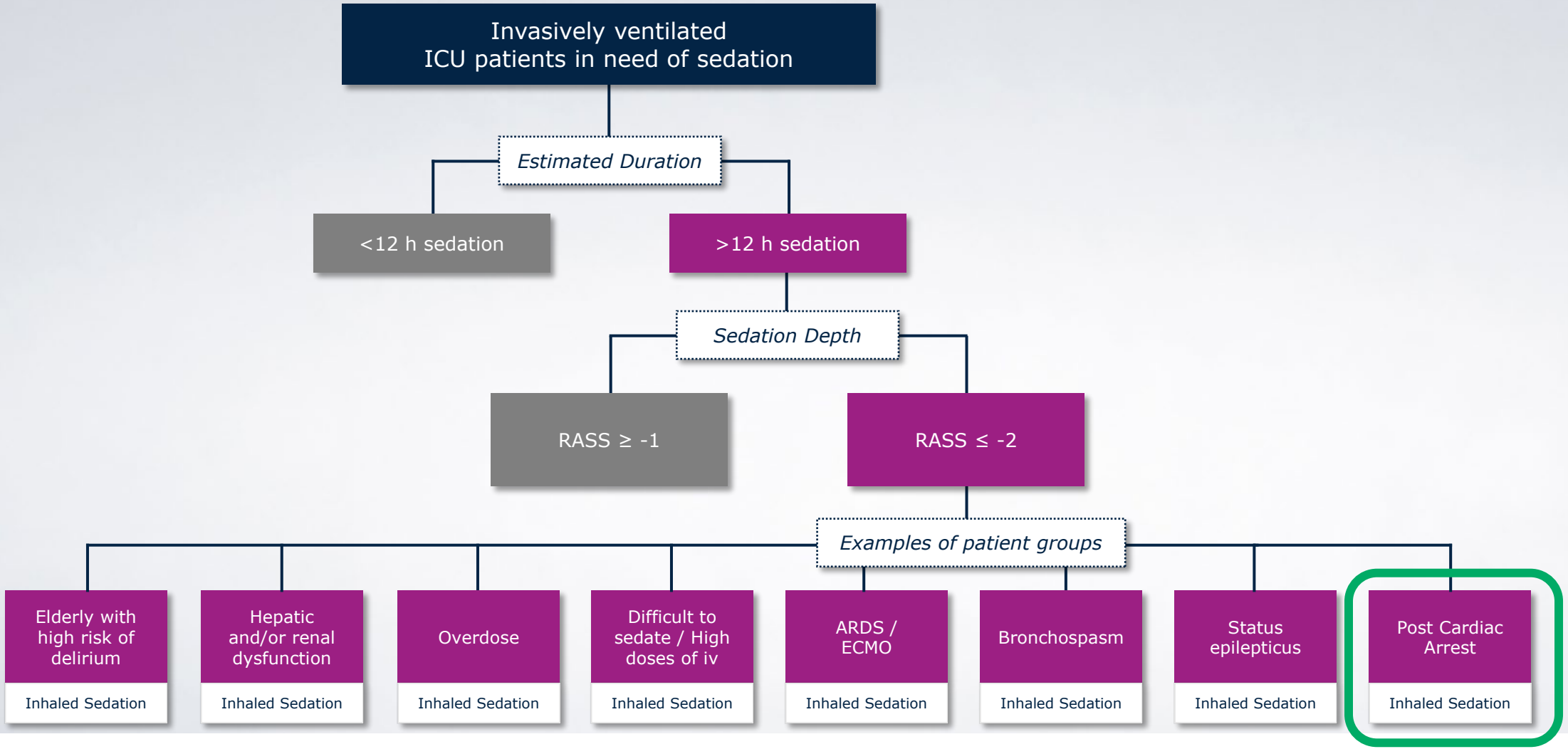

”Post Cardiac Arrest” – Rationale for Inhaled Sedation

- Patients undergoing targeted temperature management (TTM) need to be deeply sedated in order to tolerate cooling and avoid shivering[1]
- Neurological assessment is the centerpiece of prognostication after TTM[1]
- Metabolic rate is reduced during hypothermia, leading to
  - accumulation of intravenous sedatives and opioids[2], which are potentially confounding neurological assessment after TTM
- Fast elimination of isoflurane contributes to reliable wake-up after isoflurane sedation[3,4]
- Isoflurane sedation after TTM has been associated with shorter ventilator time and ICU time compared to iv sedation[4]

References: 1. Riker el al. Best Pract Res Clin Anaesthesiol 2013 2. Leslie et al. Anesth Analg 1995 3. Hellstrom et al. Crit Care Med 2014 4. Krannich et al. Crit Care Med 2016

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