

Diagnosis and management of nocturia in current clinical practice

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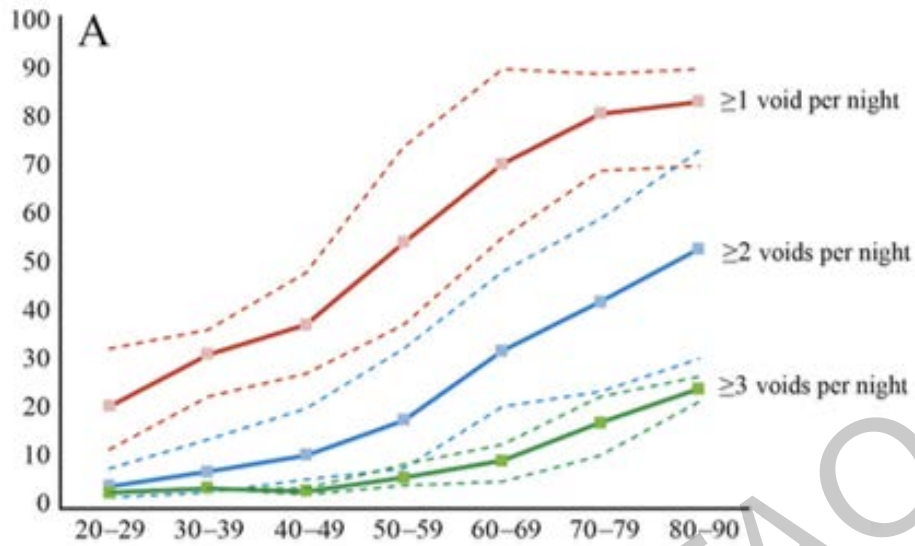
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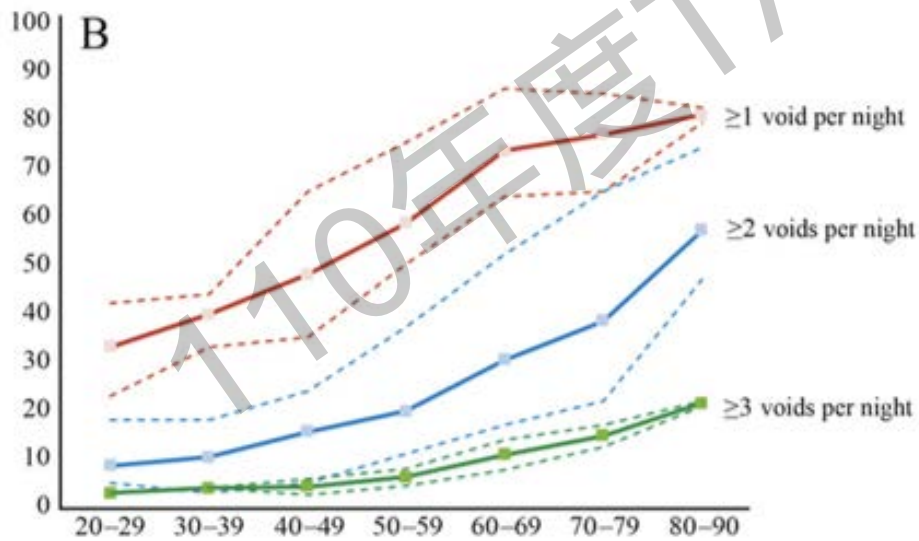
Prevalence of nocturia

	≥ 1 void / nt	≥ 2 voids / nt
Men		
20-40 years	11-35.2 %	2-16 %
>70 years	68.9-93 %	29-59.3 %
Women		
20-40 years	20.4-43.9 %	4.4-18 %
>70 years	74.1-77.1 %	28.3-61.5 %

Trends in prevalence of nocturia stratified by number of voids per night and age intervals



(A) Men



(B) Women



The Impact of Nocturia on Falls and Fractures: A Systematic Review and Meta-Analysis

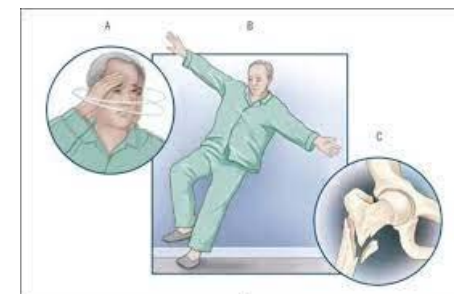
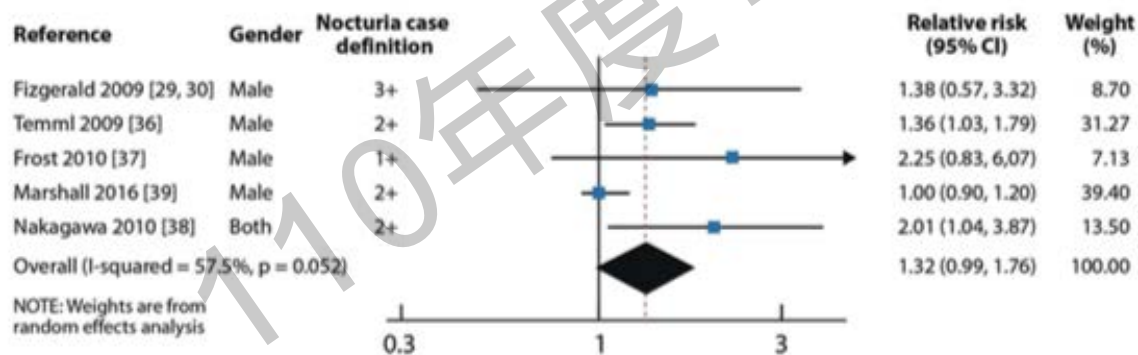


Figure 5. Forest plot of relative risks of fractures in people with nocturia



The Impact of Nocturia on Mortality: A Systematic Review and Meta-Analysis

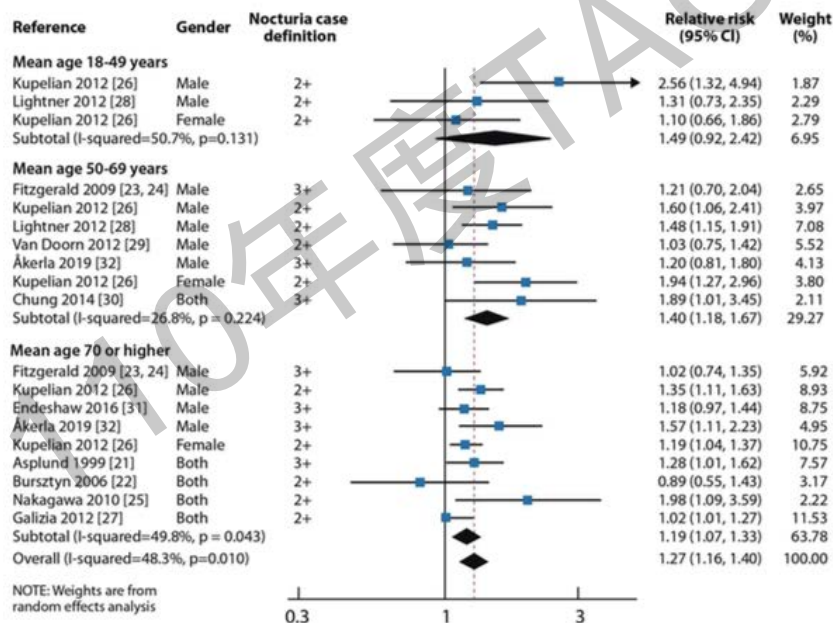


Figure 3. Forest plot of death RR in individuals with nocturia

- Nocturia
- Nocturnal polyuria (NP)

110年度TAOG年會專用

- **Nocturia**

- the need to wake up to pass urine during the main sleep period, with each urination followed by sleep or the intention to sleep

~ *International Continence Society (ICS) 2018*

- awakening **2 or more times** per night to void may be considered a clinically relevant definition

~ *International Consultation on Incontinence Research Society 2018*

- Nocturnal polyuria (NP)

- Nocturia

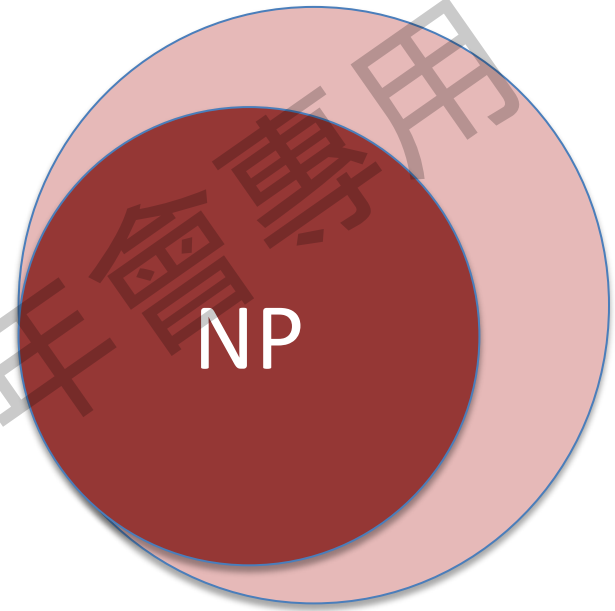
- **Nocturnal polyuria (NP)**

- Overproduction of urine at night, **>20%-33%** of total 24-hour urine volume depending on age

~ ICS 2002

- A major contributing factor in nocturia cases

~ J Urol.2011;186:1358



Voiding diary parameters and definitions

Parameter	Definition	
NUV (Nocturnal urine volume)	Total volume of urine passed during the night, including the first morning void	
MVV (Maximum voided volume)	The largest single voided volume in 24 hours	
Ni (Nocturia index)	NUV/MVV Ni >1.3	
NPi (Nocturnal polyuria index)	NUV/24-h urine volume	*NP: NPi > 0.20-0.33 (age dependent)
NUP (Nocturnal urine production)		*NP: NUP >90mL/h

Definitions of NP

- $\text{NPi} > 20\%$ in the young and $\text{Npi} > 33\%$ ($\text{NPi} 33$) in the old
- Urine production per kg or time unit ($\text{NUP} > 90$ mL/h [NUP90])

110年度TACOG年會專用

Causes of nocturia

1. Global polyuria
2. Nocturnal polyuria
3. Reduced bladder capacity
4. Mixed

110年度TAOG年會專用

Global polyuria

- Urine production: $> 40 \text{ ml/kg /24-hour}$
 - Increased fluid intake
 - Underline disease
 - ✧ Renal or endocrine system
 - ✓ Poorly controlled diabetes mellitus
 - ✓ Central or nephrogenic diabetes insipidus (DI)
 - ✓ Primary polydipsia
(psychogenic/behavioral dipsogenic, latter due to brain trauma, radiation, or surgery with attendant dysfunctional thirst mechanism)

Nocturnal polyuria

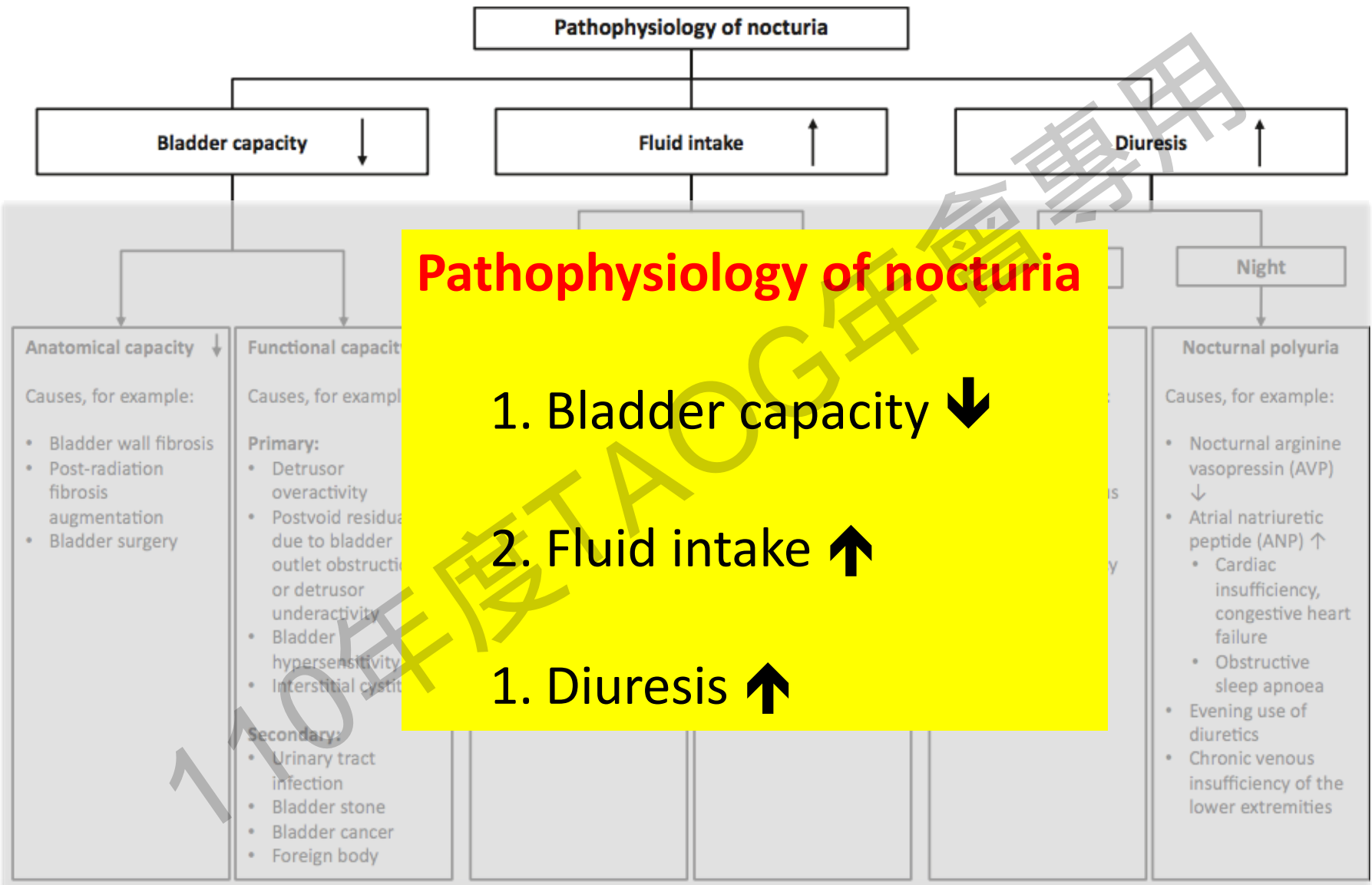
- Overproduction of urine at night
- ICS definition:
 - > 33% of the 24-hr urine volume, > 65years, excluding 24-hour polyuria (>40mL/Kg/d)
 - >20% in younger (21-35 years)
- The FDA's regulatory decision-making regarding **desmopressin** based on these definitions

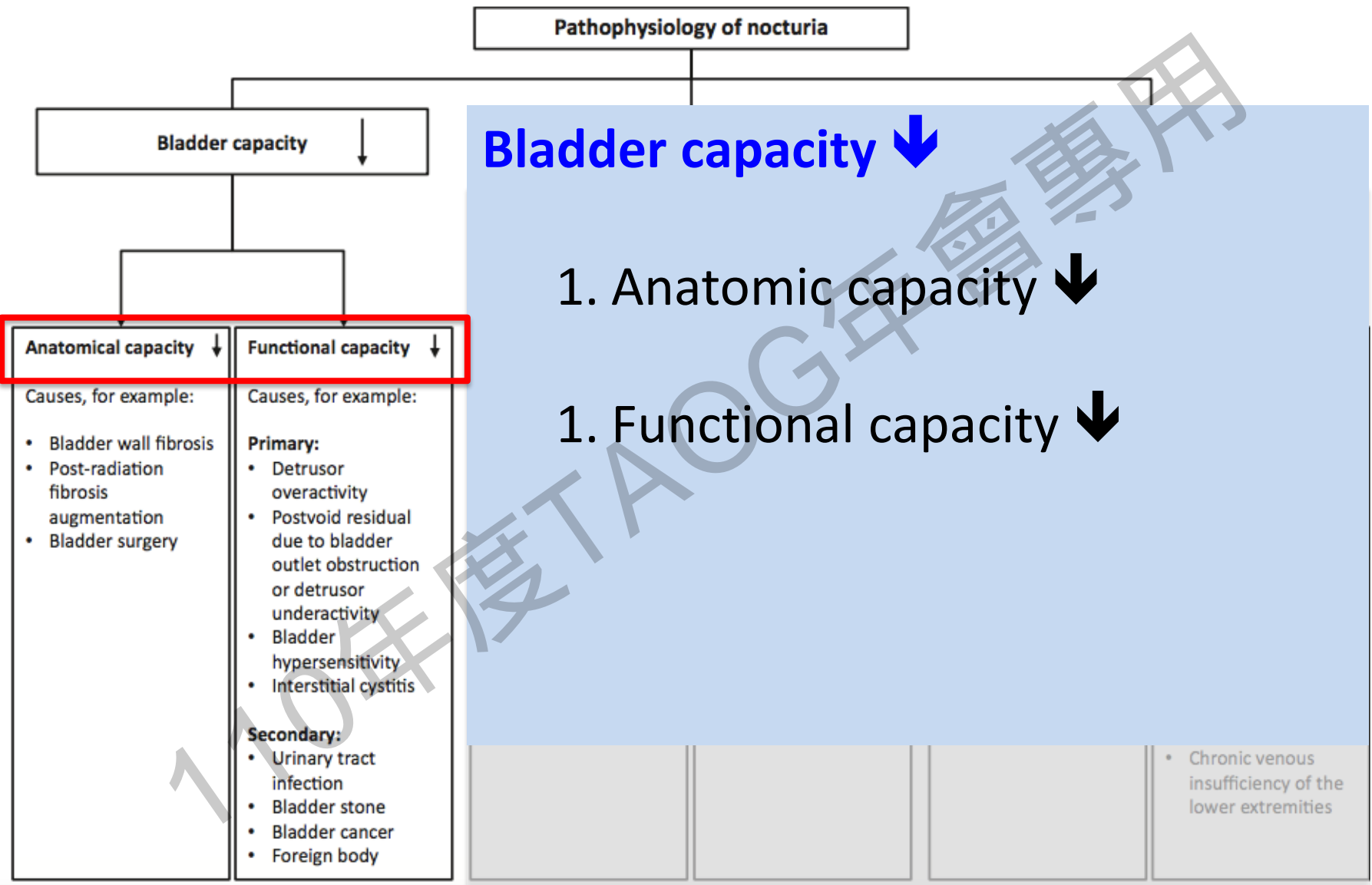
Reduced bladder capacity

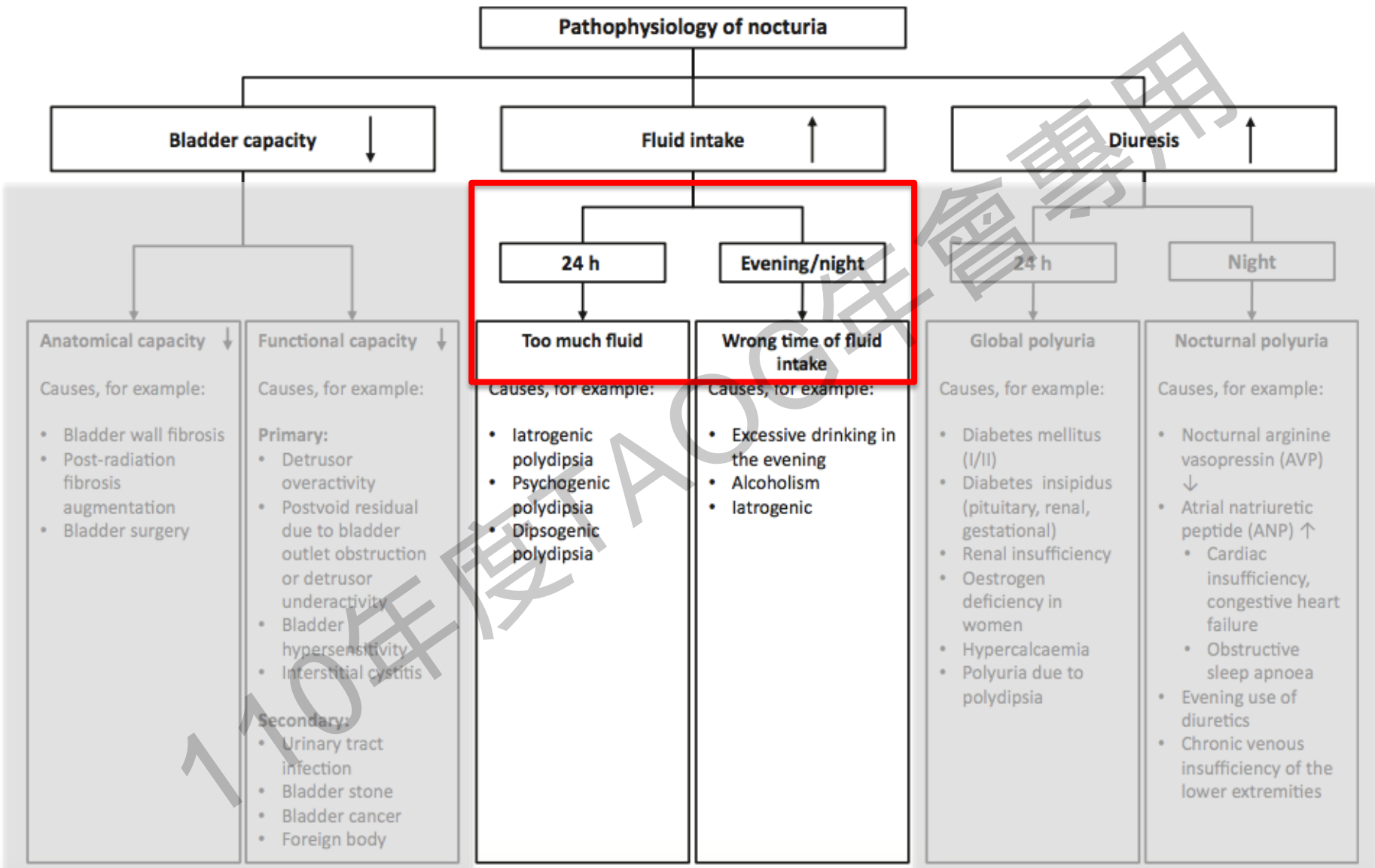
- Overactive bladder (OAB)/detrusor overactivity (DO)
- Benign prostatic hyperplasia (BPH)/bladder outlet obstruction (BOO)
- Bladder/ureteral calculi
- Neoplasms of bladder, prostate, or urethra
- Anxiety disorders
- Learned voiding dysfunction
- Pharmacologic agents
- Neurogenic bladder
- Cystitis
- Extrinsic compression

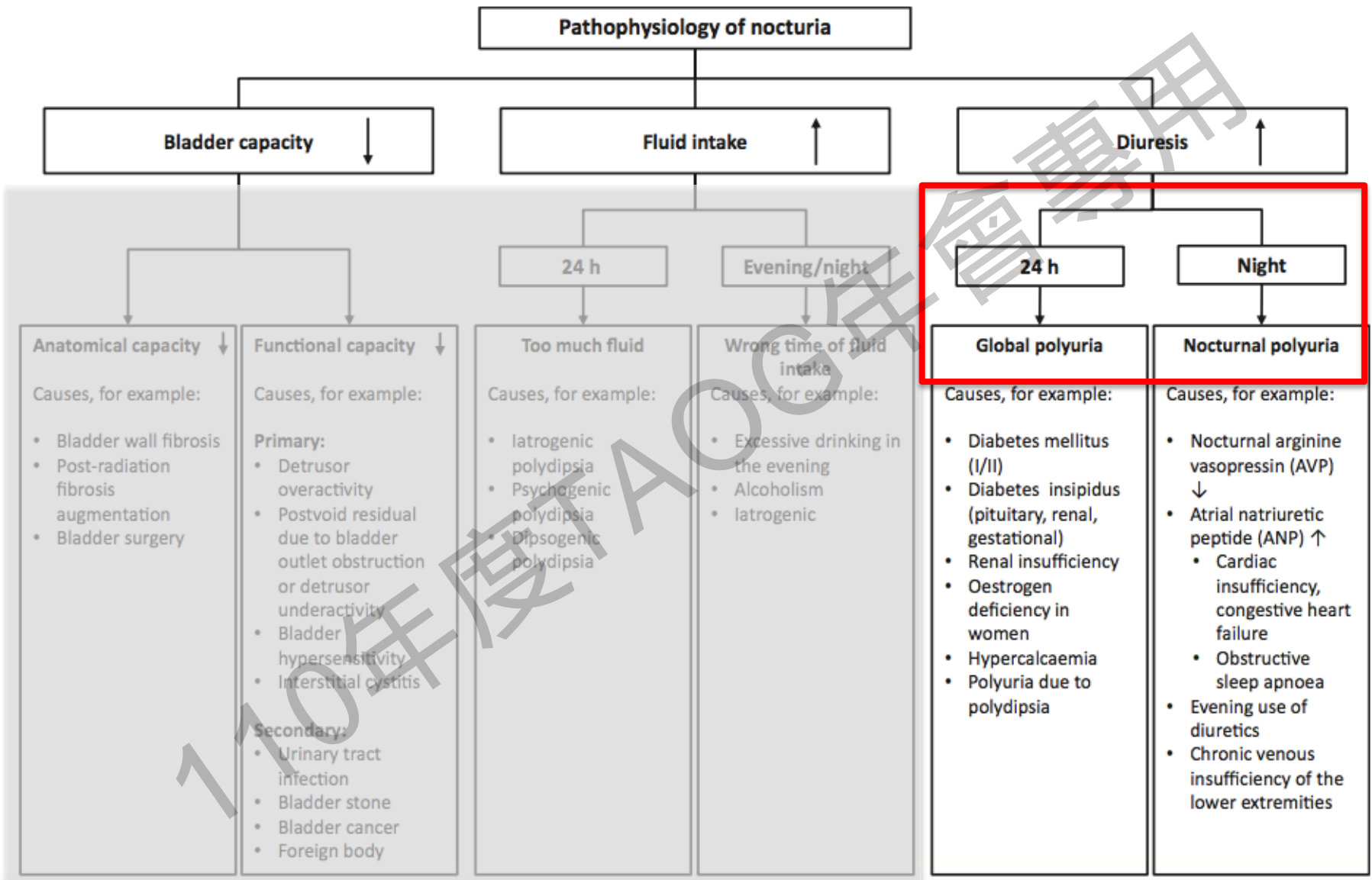
Mixed

- A retrospective study of 200 patients with nocturia found that **36%** were classified as mixed on the basis of having both **nocturnal polyruia** and a **reduced nocturnal bladder capacity**.









Assessment of nocturia

- **History taking**
 - Other LUTS, fluid intake, sleeping habits, medical Hx, obstructive sleep apnea
- **Review current medications**
 - eg, calcium channel blockers- amlodipine or nifedipine; diuretics- furosemide
- **Physical examination**
 - BP, PV, edema of the lower extremities, urine retention, obese
- **Frequency-volume chart (in call cases, 3 days)**
- **Investigations**
 - U/A, U/C, serum electrolytes, Cr, glucose, lipid profile
- **Additional tests, if required**
 - Cystoscopy, cardiology tests, PVR

Frequency-volume chart

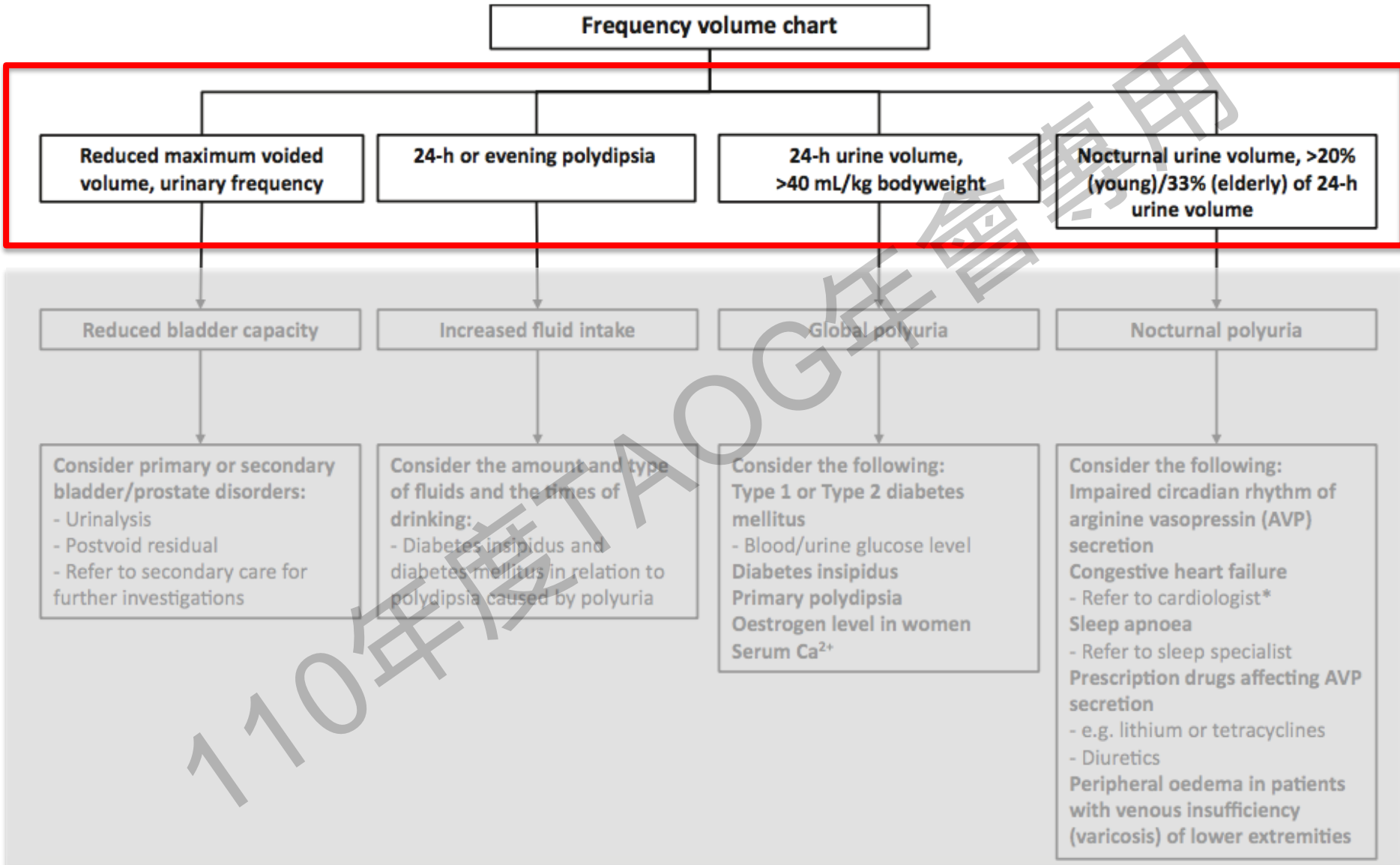
110年8月22日

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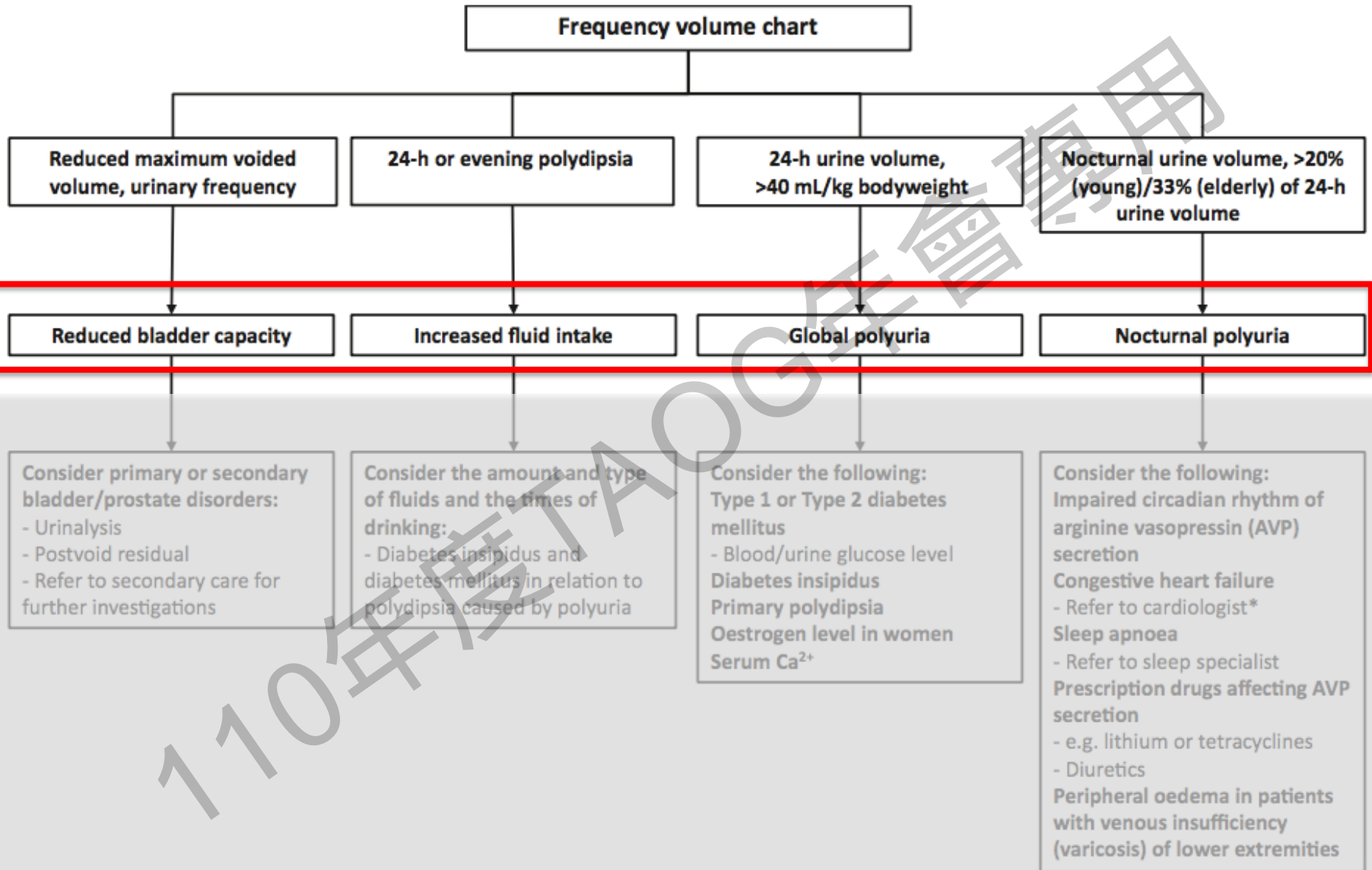
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時間	解尿量 (c.c.)	飲料量 (c.c.)	飲料種類	滲/漏尿量	滲/漏尿時之活動或感覺	時間	解尿量 (c.c.)	飲料量 (c.c.)	飲料種類	滲/漏尿量	滲/漏尿時之活動或感覺	時間	解尿量 (c.c.)	飲料量 (c.c.)	飲料種類	滲/漏尿量	滲/漏尿時之活動或感覺
1:40	250cc	100cc	水			01:50	400cc	150cc	水			00:58	250cc	150cc	水		
3:56	400cc	200cc	水			2:37	370cc	100cc	水			2:35	550cc	230cc	水	2	睡醒
6:05	680cc	100cc	水	2	睡醒	4:45	250cc	150cc	牛奶			4:55	550cc	100cc	水	2	睡醒
10:50	600cc	100cc	水			6:45	280cc	400cc	水			9:30	330cc	150cc	牛奶		
13:05	220cc	150cc	牛奶			9:27	450cc	250cc	湯			12:20	280cc	280cc	水		
16:20	350cc	250cc	水			11:25	180cc	280cc	水			15:40	160cc	250cc	湯		
18:05	210cc	200cc	湯			13:45	150cc	150cc	水			18:40	460cc	300cc	水		
20:22	350cc	250cc	水			16:55	220cc	480cc	水			20:40	200cc	250cc	水		
22:26	450cc	200cc	水			19:00	260cc	400cc	水				300cc	水			
		250cc	水			22:20	450cc	200cc	水				100cc	水			
		250cc	舒跑					300cc	水				200cc	水			
		280cc	水										100cc	水			
		100cc	湯										200cc	水			
		200cc	水														
		100cc	水		1 坐著起身												
		100cc	水														
總量	3510	2830	白天解尿次數	5		總量	3040	2860	白天解尿次數	5		總量	2780	2710	白天解尿次數	4	
平均量	390	176	晚上解尿次數	4		平均量	304	480	晚上解尿次數	5		平均量	347	208	晚上解尿次數	4	
最大量	680	280	滲/漏尿次數	1:		最大量	480	100	滲/漏尿次數	1:		最大量	550	380	滲/漏尿次數	1:	
最小量	210	100		2: 1		最小量	150			2: 2		最小量	160	100		2: 2	
				3:						3:						3:	

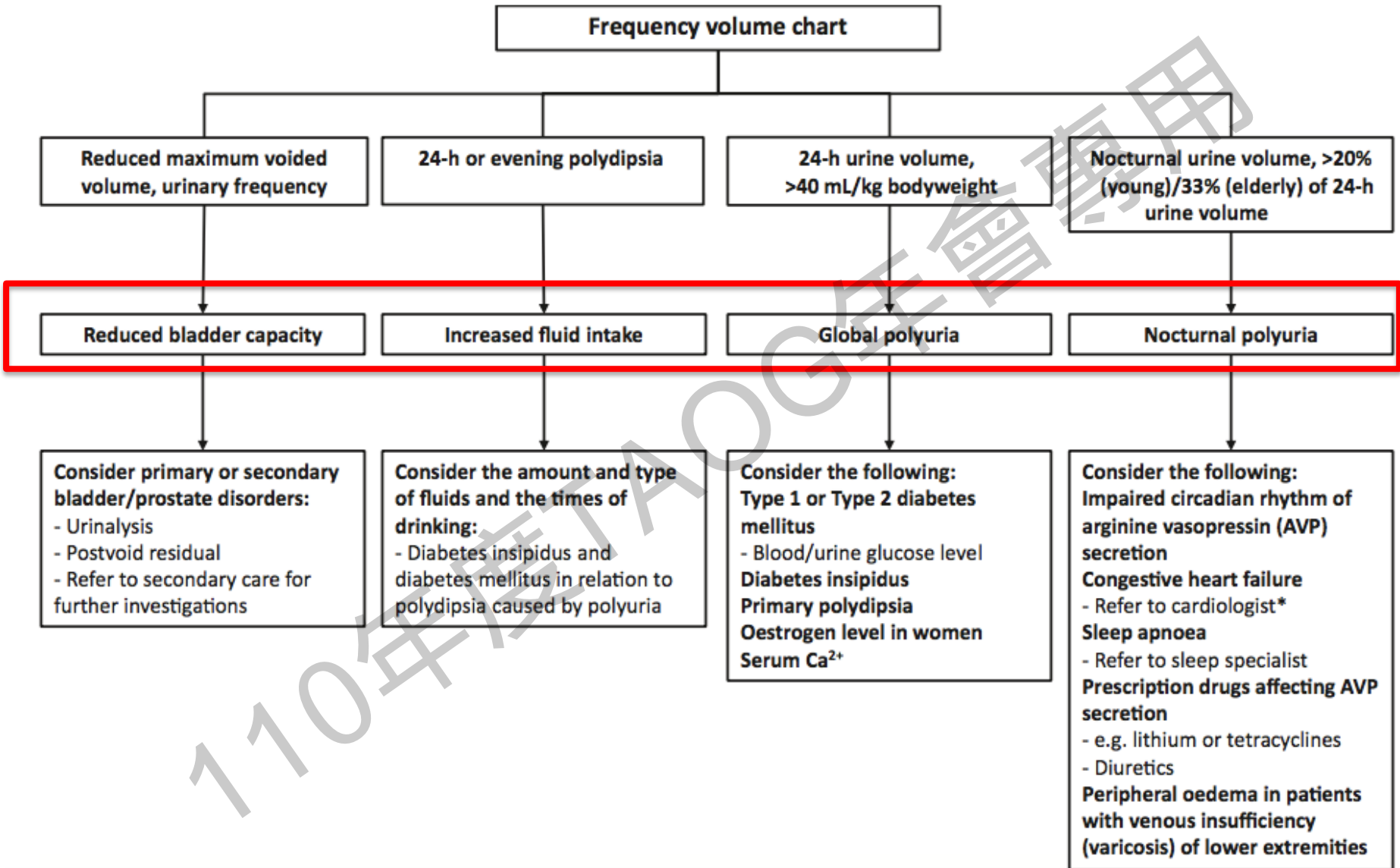
Nocturia evaluation algorithm based on frequency-volume chart

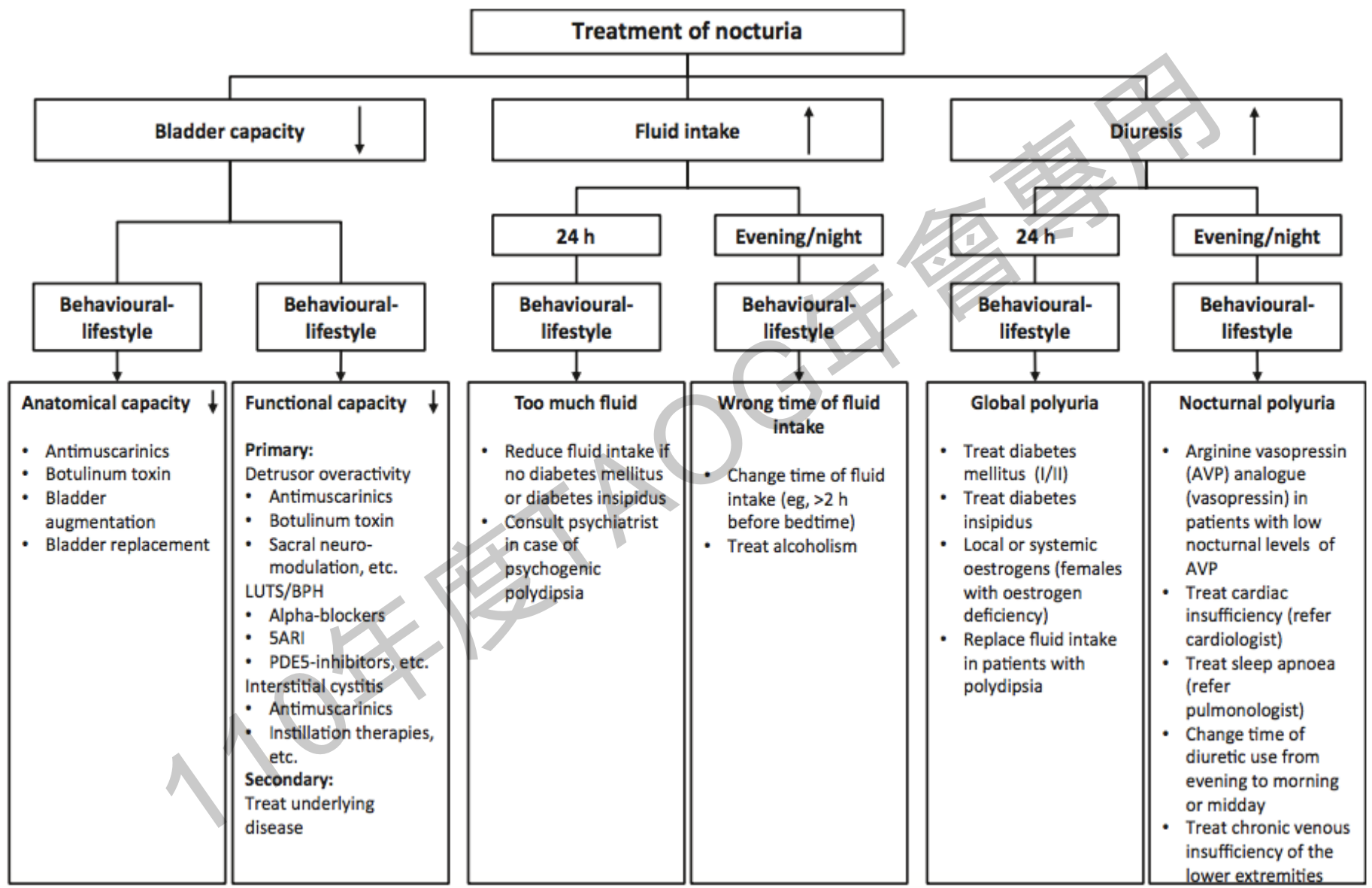


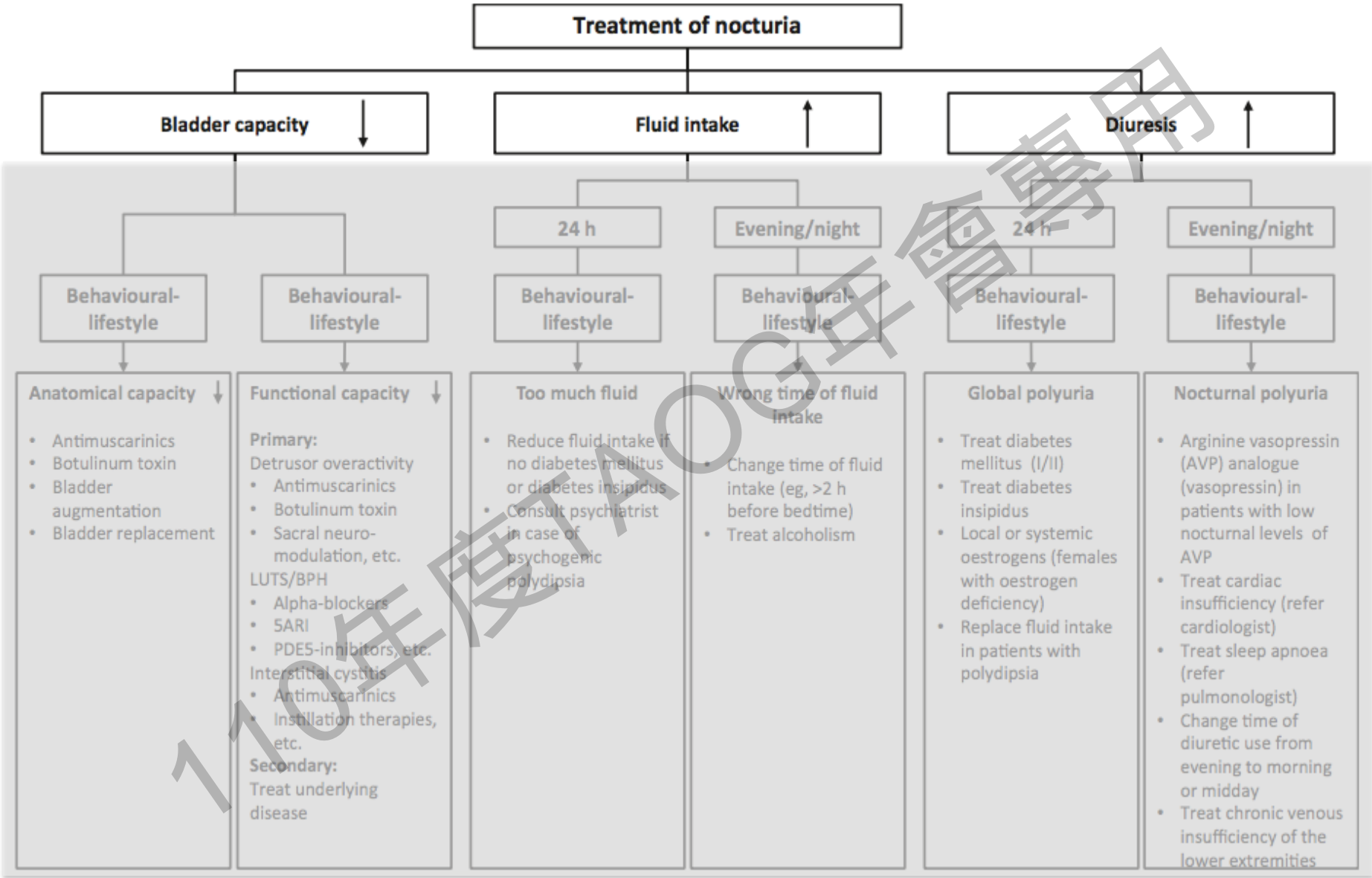
Nocturia evaluation algorithm based on frequency-volume chart

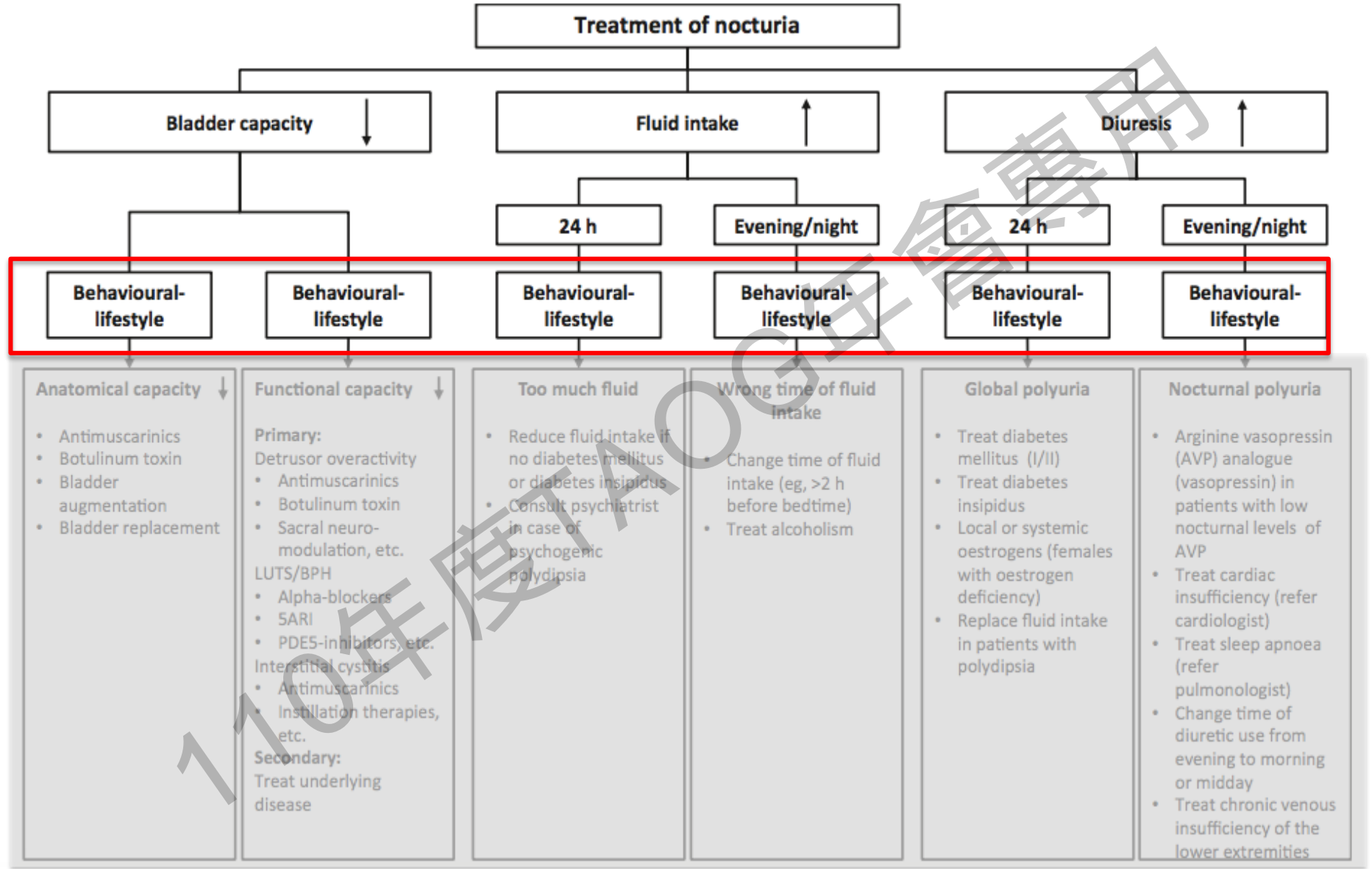


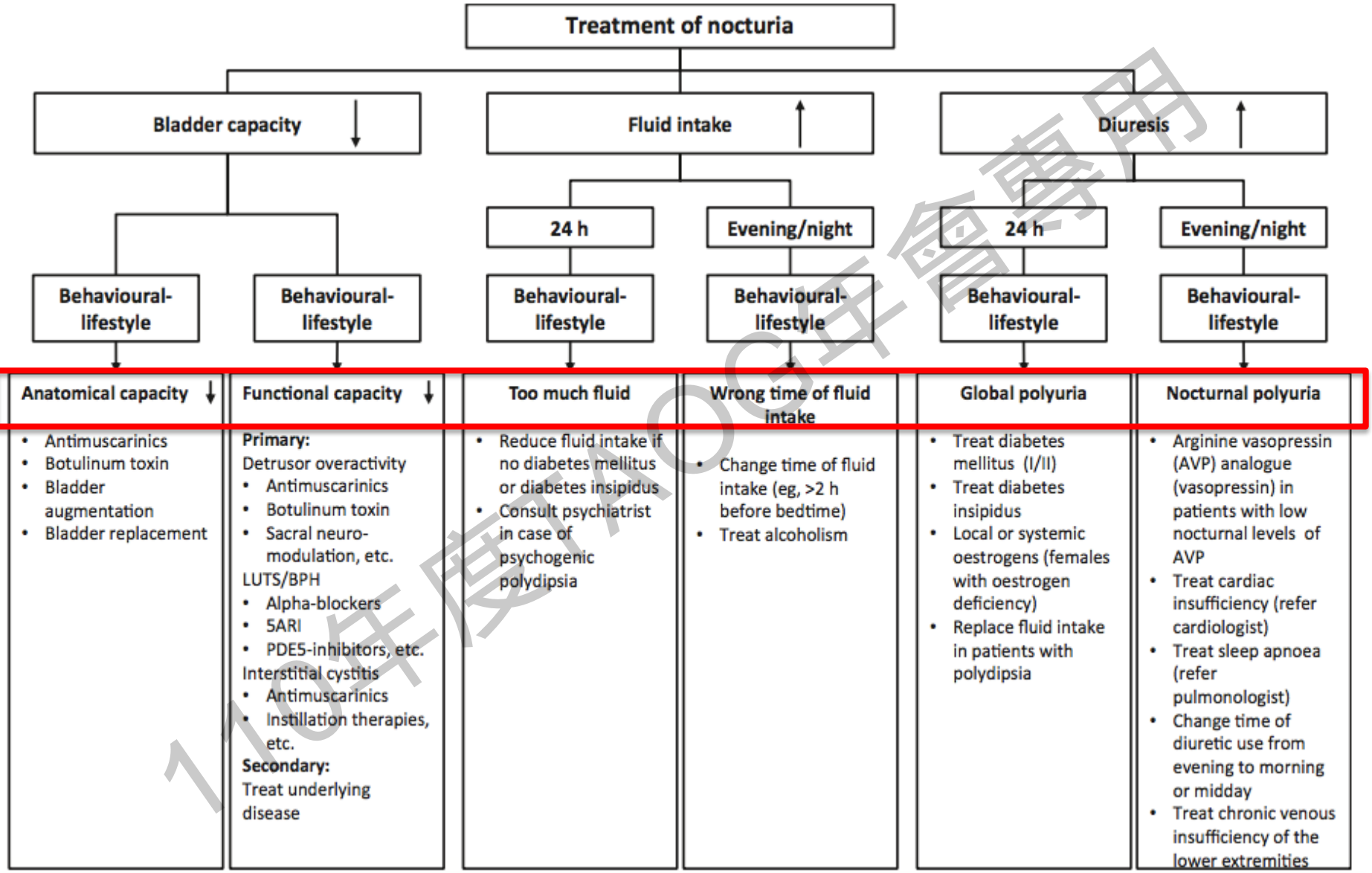
Nocturia evaluation algorithm based on frequency-volume chart











International Continence Society consensus on the diagnosis and treatment of nocturia

Diagnosis and treatment pathways



International Continence Society consensus on the diagnosis and treatment of nocturia

Diagnosis and treatment pathways

1. Intake: water, protein, sodium, obesity

2. Uro-gynecological: OAB, BOO, neurogenic bladder

3. Nephrogenical bladder: water/salt diuresis, hypercalciuria, nephrogenic DI

4. Cardiovascular: BP, metabolic syndrome, physical activity

5. Hormonal: sex hormones, DI, DM

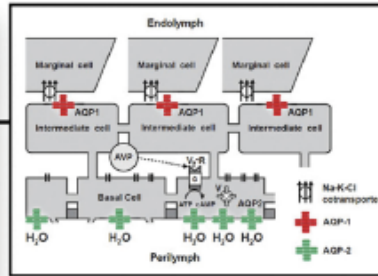
6. Sleep: OSAS, RLS, sleep disruption and shortage, low dopamine dz

Nephrological causes of nocturia

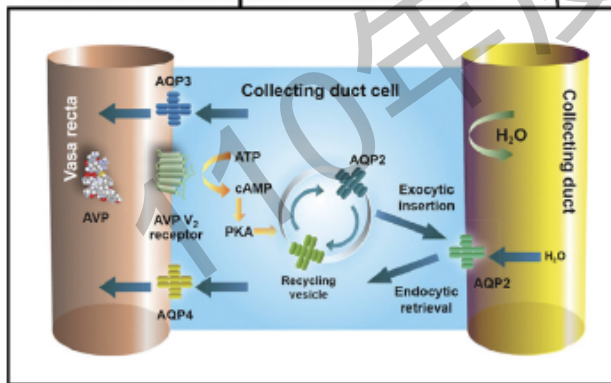
- **↑ free water clearance**
 - **Vasopressin**-related
(Antidiuretic hormone, ADH, 抗利尿激素
Arginine vasopressin, AVP, 血管加壓素)
- **↑ sodium clearance (osmotic diuresis)**
 - Salt, urea (protein), glucose (diabetes), calcium, lithium
 - Intake, leg edema, heart failure, hypertension, medication

AVP release

In the inner ear, AVP acts upon water metabolism via V2R, translocating water channels aquaporin-2 (AQP2), from the luminal epithelium of the human endolymphatic sac to the basolateral side

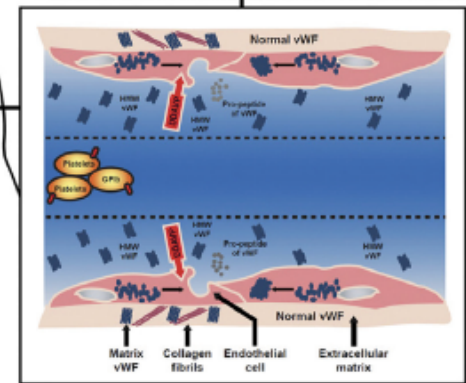


In the kidneys, upon an agonist stimulation of V2R, adenylyl cyclase and protein kinase A (PKA) are activated in a signaling cascade leading to the fusion of aquaporin-2 (AQP2) carrying vesicles with the apical membrane, which induces an increase in water permeability



AVP is secreted from the posterior pituitary gland

Extrarenal V2-receptors, primarily located in endothelial cells, have been shown to increase the circulating levels of coagulation factor VIII (FVIII), von Willebrand factor (vWF), and plasminogen activator (t-PA)



Hormones and nocturia

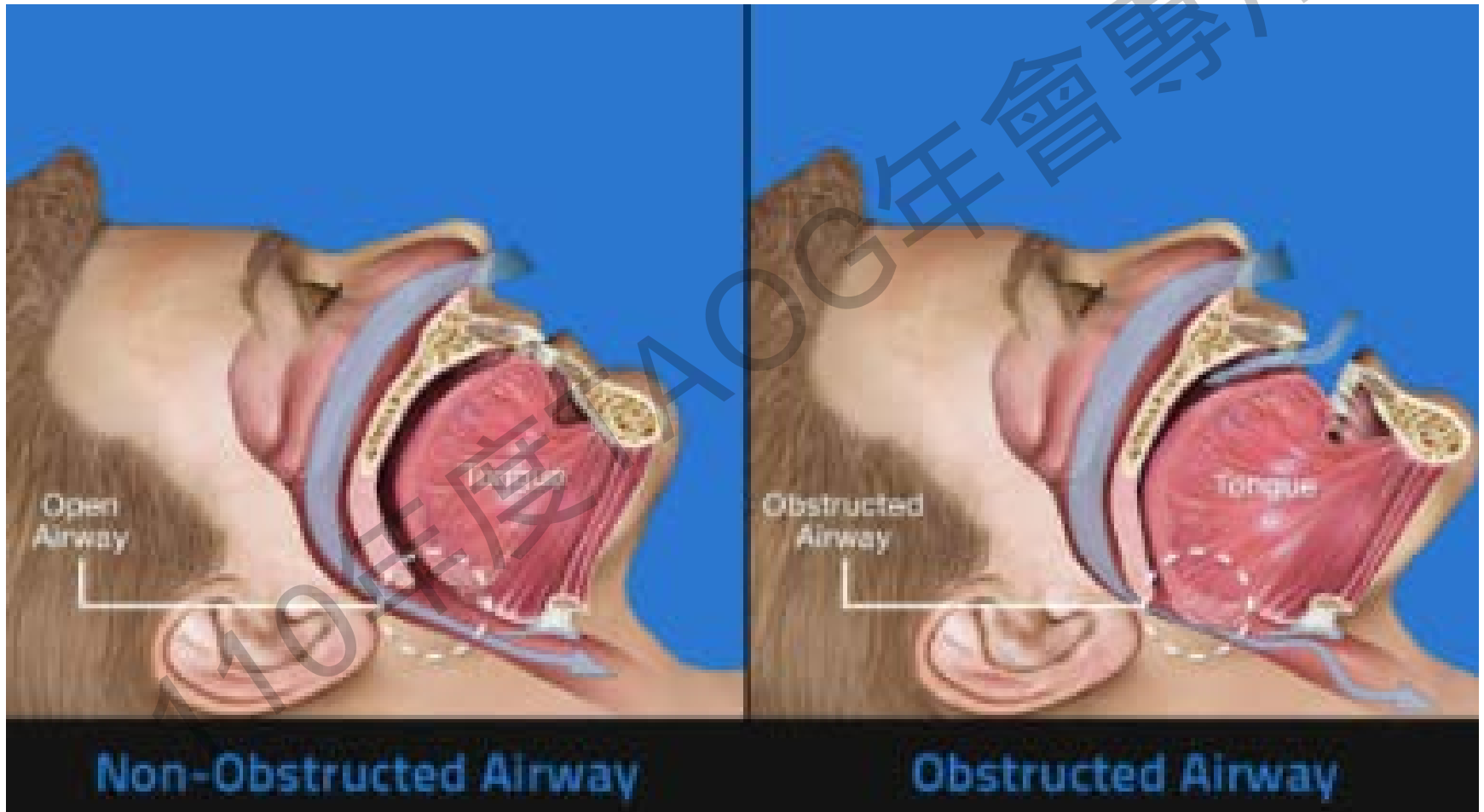
- **Vasopressin**: the main water-regulating hormone
 1. Vasopressin deficiency
 2. Vasopressin resistance of receptor origin (nephrogenic, V2 receptor)
- **Diabetes Insipidus** (rare)
 - 24-hour polyuria and polydipsia
 - Dx: a bladder diary + a low morning (fasting) serum and urine osmolarity
- **Sex hormones**: also involved in regulation diuresis
 - Estrogen, testosterone deficiency
- An **abnormal circadian rhythm of vasopressin** is the the main mechanism for **NP**

Sleep on the CNS as a cause of nocturia

- Sleep pathology, insomnia, sleep disruption
 - Obstructive Sleep Apnea Syndrome (**OSAS**)
 - Parkinson's disease (**dopamine deficiency**)
 - Restless legs syndrome (**dopamine deficiency**)
- The diagnosis of a brain- or sleep-related cause of nocturia is made clinically, patients need to be **referred to specialists.**

Obstructive Sleep Apnea (OSA)

阻塞型睡眠呼吸中止



Cardiovascular causes of nocturia

- Hypertension/nondipping hypertension
- Metabolic syndrome
- Heart failure
- Renal failure
- Cardio-renal syndrome
 - ↑ brain natriuretic peptide (BNP) with hypovolemia or as overfilling (hyponatremia)
 - A bad GFR (eGFR <50)
- Leg edema
 - Resorption of fluid when supine, immediate excess in urine output, a delayed increase in ANP-related salt diuresis

Fluid and food intake as a cause of nocturia

- High intake of **water, salt, or protein** -> increased excretion by the kidney
- Excess intake **of osmoles** -> thirst, increased fluid intake
- Excess intake of **calories** -> obesity-> higher intra-abdominal pressure. When supine -> **obstruction of the respiratory tract**

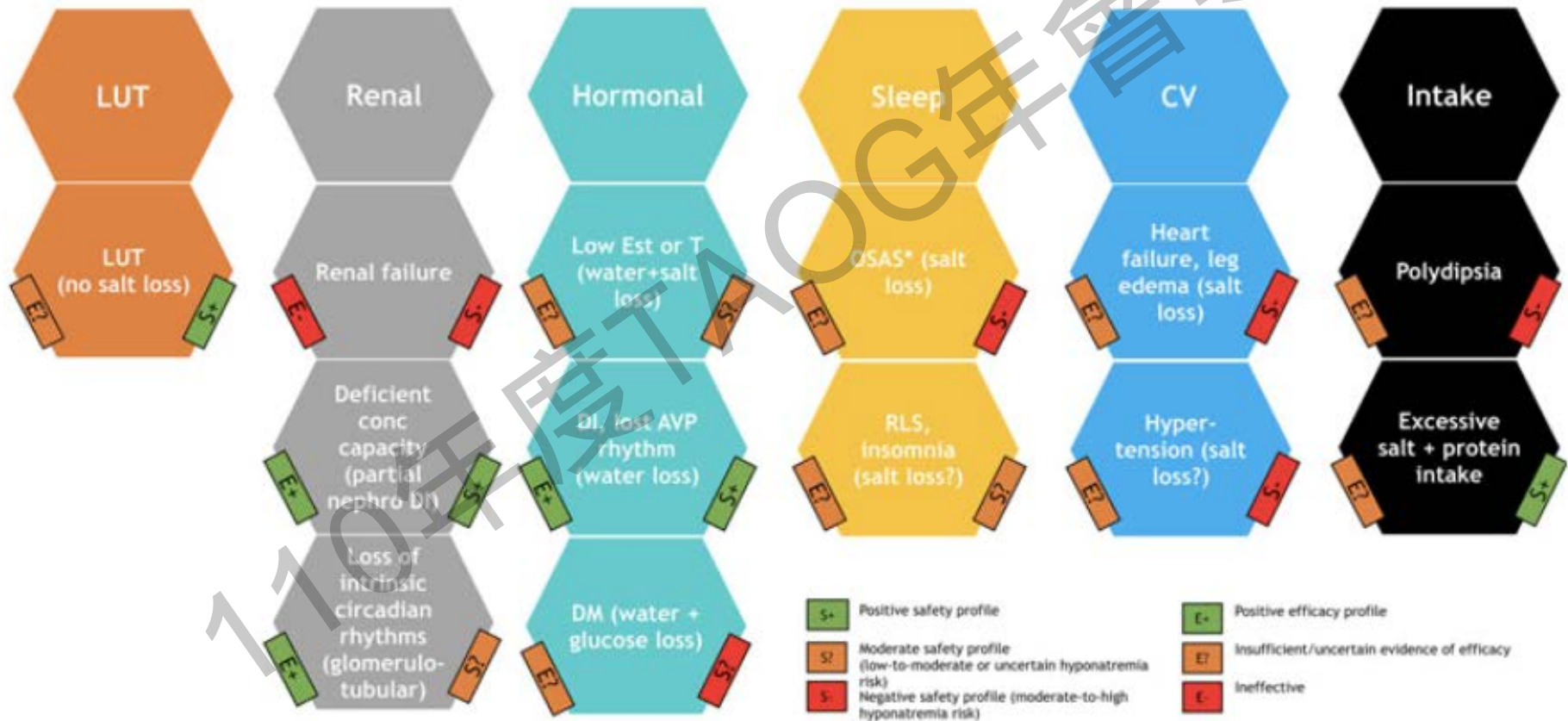
Concomitant medication leading to nocturia

- Increasing or decreasing diuresis, changing bladder function, interfering with sleep
- The timing/mode of administration, formulation
 - **Increase diuresis:** diuretics, all antihypertensive medication, progesterone, melatonin, lithium
 - **Decrease diuresis:** antidepressants, antiepileptics, estrogens, testosterone, corticoids, NSAIDs
 - **Cause leg edema:** antidepressants, antihypertensives, antivirals, hormones, NSAIDs...

Lifestyle interventions



Phenotyping nocturia for uncontrolled causalities when prescribing **desmopressin**



Therapeutic packages

- There is only good evidence for **desmopressin** and **CPAP (for OSA)**
- For other therapies, the evidence is moderate or weak
 - **The safe candidates for desmopressin** can be phenotyped as **no** polydipsia, heart/kidney failure, severe leg edemas, or OSAS.

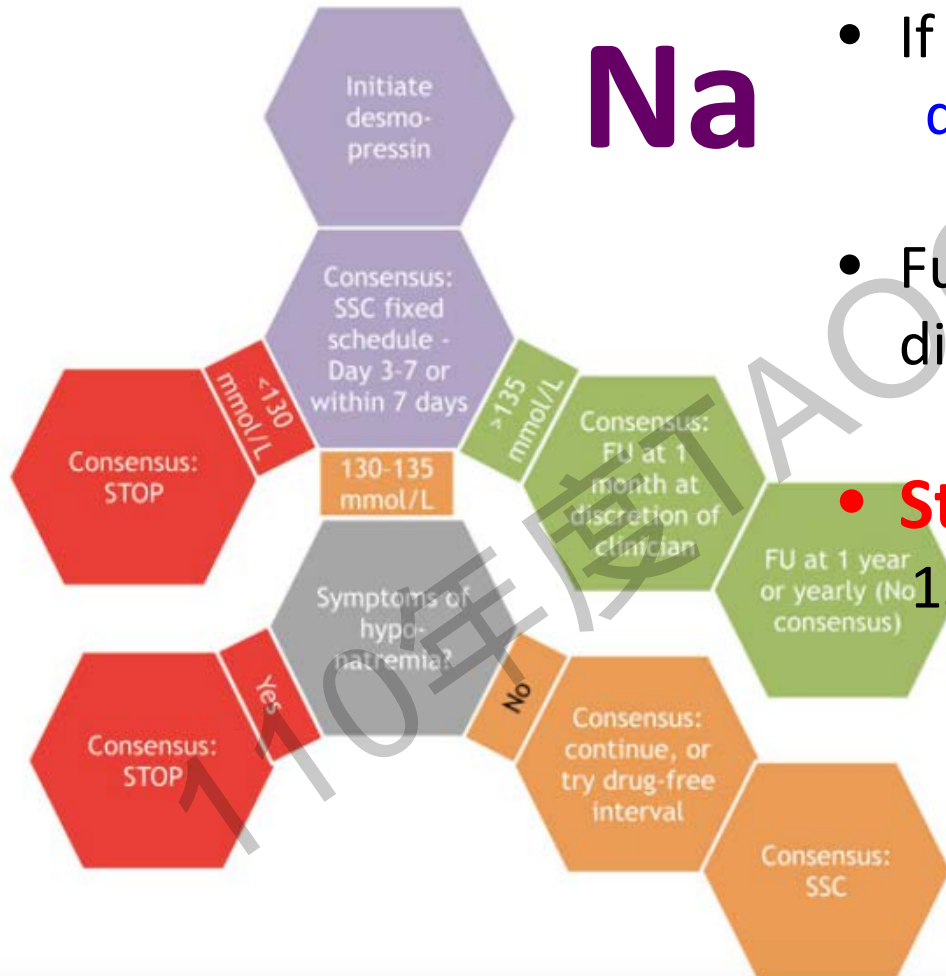
Initiating Desmopressin Tx

- NP due to reduced nocturnal vasopressin
- Bothering nocturia should be treated
- Risk management consensus on classification into three clinical pictures:
 1. Symptoms of hyponatremia
 2. Serum sodium check (SSC)
 3. Contraindications
- Low-dose formulations preferred in patients needing SSC (Na)

Follow-up after desmopressin prescription

Na

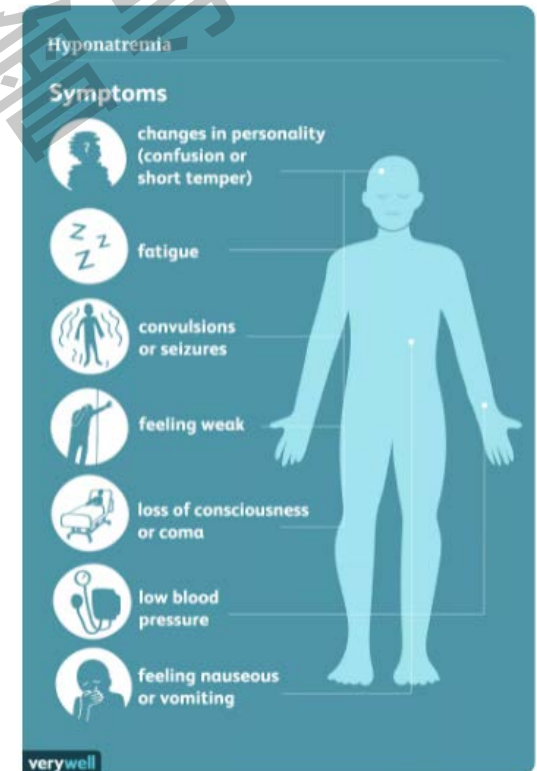
- If **SCCs** are necessary, F/U on day 3 to 7 and 1 month
- Further checks at clinician discretion



- **Stop** therapy if Na < 130 mmol/L, 130-135 with symptoms

Symptoms of hyponatremia

- Nausea and vomiting
- Headache
- Confusion
- Loss of energy
- Drowsiness
- Fatigue
- Restlessness and irritability
- Muscle weakness, spasms or cramps
- Seizures
- coma



Hyponatremia risk

- **Women:** higher sensitive to desmopressin, more prone to hyponatremia
 - X-linked V2R gene
 - Higher expression of V2 receptor
- High-risk medications
 - Carbamazepine, lithium, thiazide diuretics
- The frail elderly (\neq older persons)
- Heart failure (NY class II-IV)

Take Home Message

- **Diagnostic packages:**
 - Hx, intake and bladder diary, PV, SSC(Na), renal function, endocrine screening
- **Therapeutic packages:**
 - The safe candidates for desmopressin can be phenotyped as no polydipsia, heart/kidney failure, severe leg edema or OSAS.
 - Lifestyle interventions
- **Initial desmopressin:** risk management

Thank You for Your Attention

