

MAGnificent Properties of Cisplatin

Mitigating Risk and Managing AKI

September 17, 2026



Memorial Sloan Kettering
Cancer Center

Disclosures

Research support from:

- National Comprehensive Cancer Network
- NCI P30 CA008748
- PKD foundation

Learning Objectives

1. Describe the burden and clinical impact of cisplatin-associated AKI.
2. Explain key mechanisms of cisplatin nephrotoxicity (tubular uptake, oxidative stress, cell death).
3. Identify risk factors and apply a validated risk-prediction approach.
4. Evaluate the role of antiemetics — balancing protection against MATE-mediated platinum accumulation.
5. Appraise magnesium as a biomarker and preventive target.
6. Summarize CKD burden after cisplatin and the role of pretreatment eGFR.

Why This Topic Still Matters

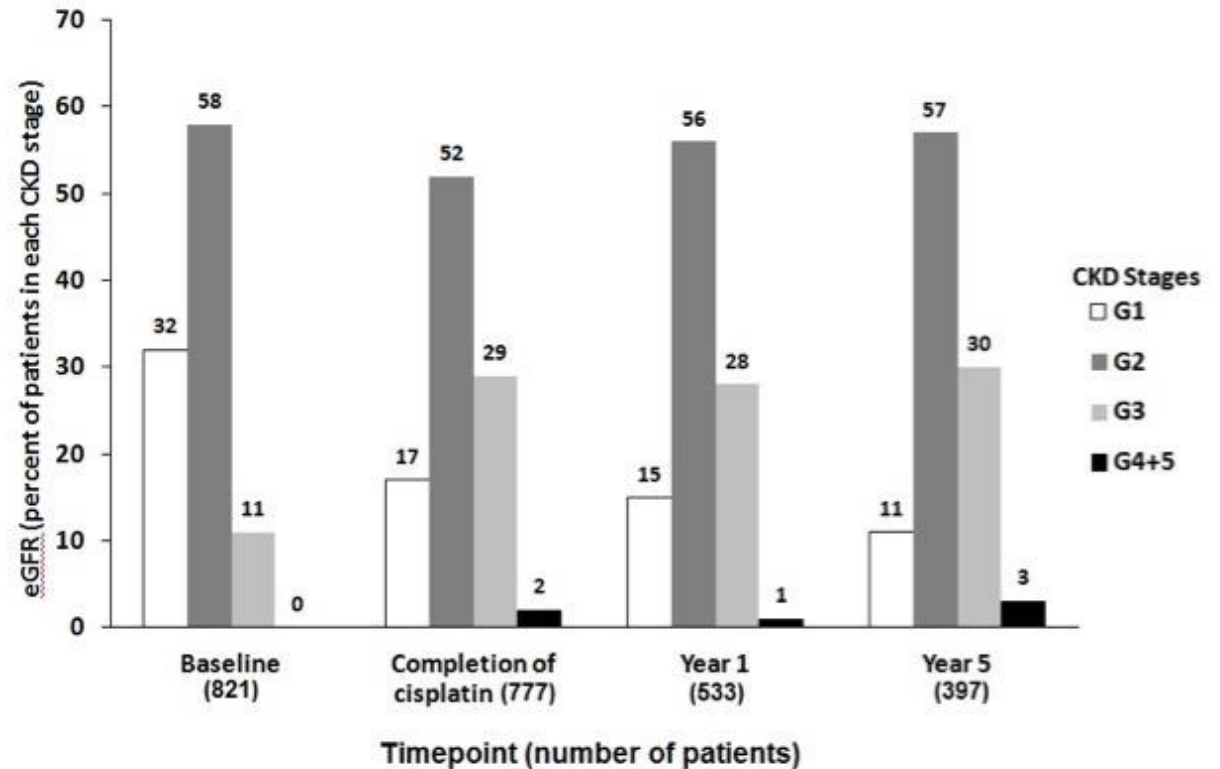
Cisplatin remains essential in:

- Germ cell tumors
- Head and neck cancer
- Bladder cancer
- Lung cancer
- Gynecologic cancers

AKI occurs in ~20–30%

Renal injury leads to:

- Treatment delays
- Dose reduction/discontinuation
- Electrolyte wasting
- CKD and survivorship burden



Clinical Phenotypes of Cisplatin Nephrotoxicity

AKI

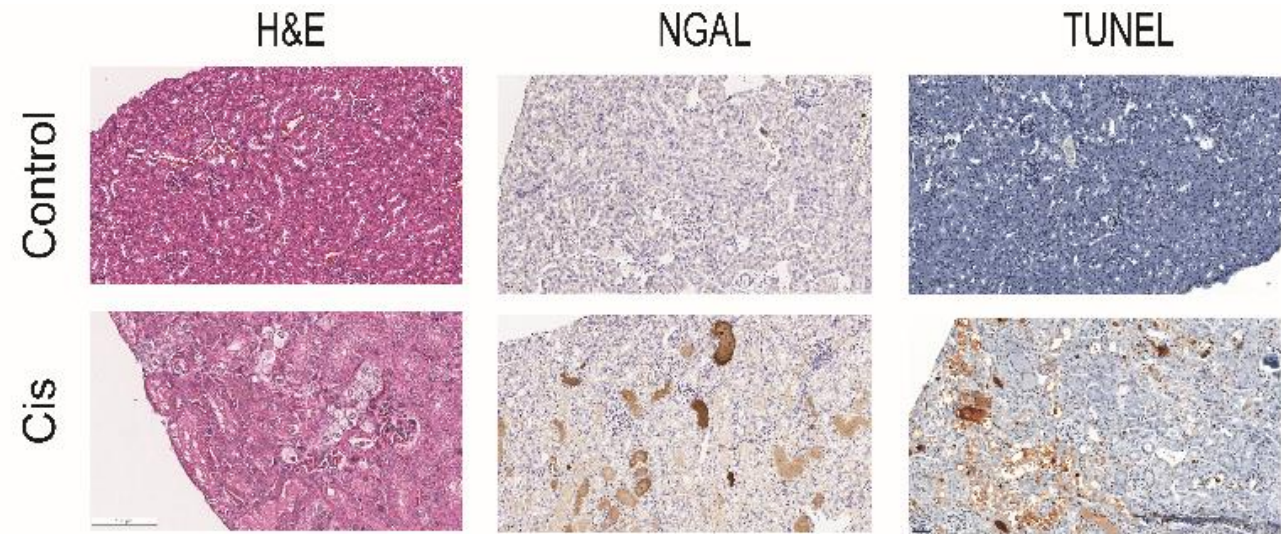
- Typically, non-oliguric
- Develops within days
- Tubular dysfunction
- Hypomagnesemia
- Hypokalemia
- Phosphate wasting
- Concentrating defect

Chronic toxicity

- Cumulative eGFR decline
- CKD

Rare:

- Thrombotic microangiopathy
- Fanconi-like syndrome
- Salt wasting

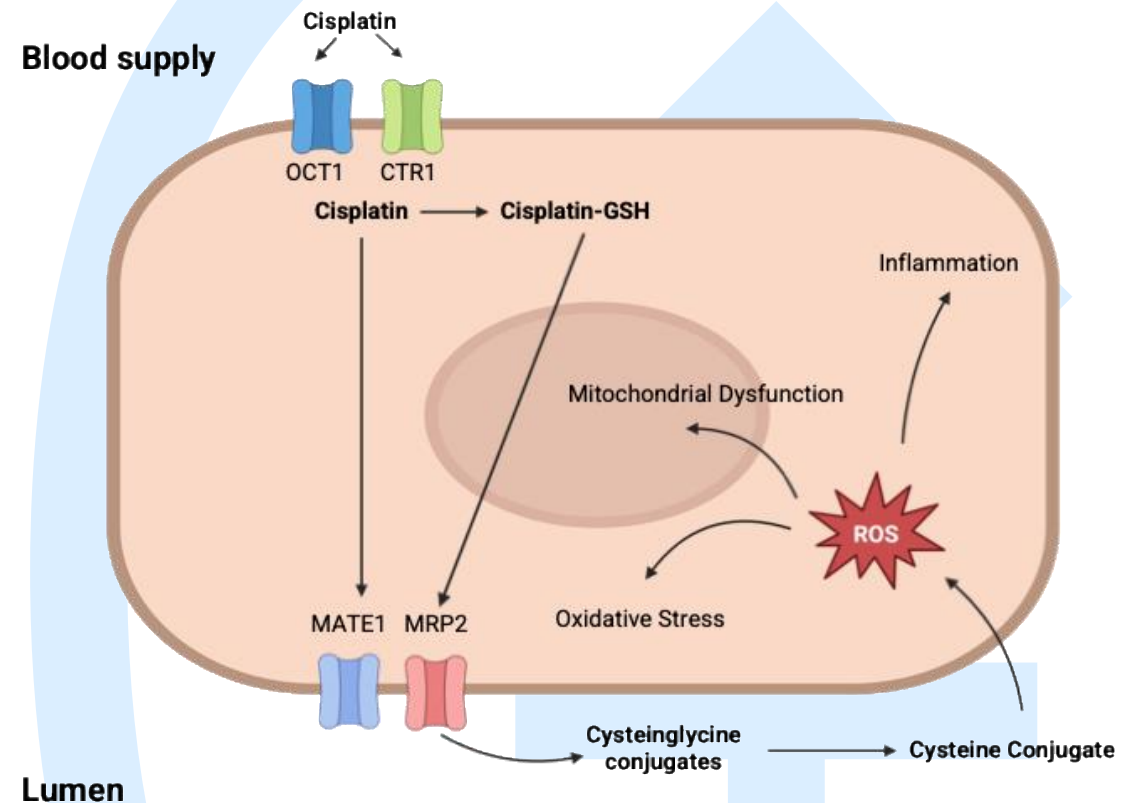


Why the Kidney Is Vulnerable

- High renal blood flow
- Tubular concentration of cisplatin
- Preferential proximal tubule uptake
- High metabolic demand of tubular cells

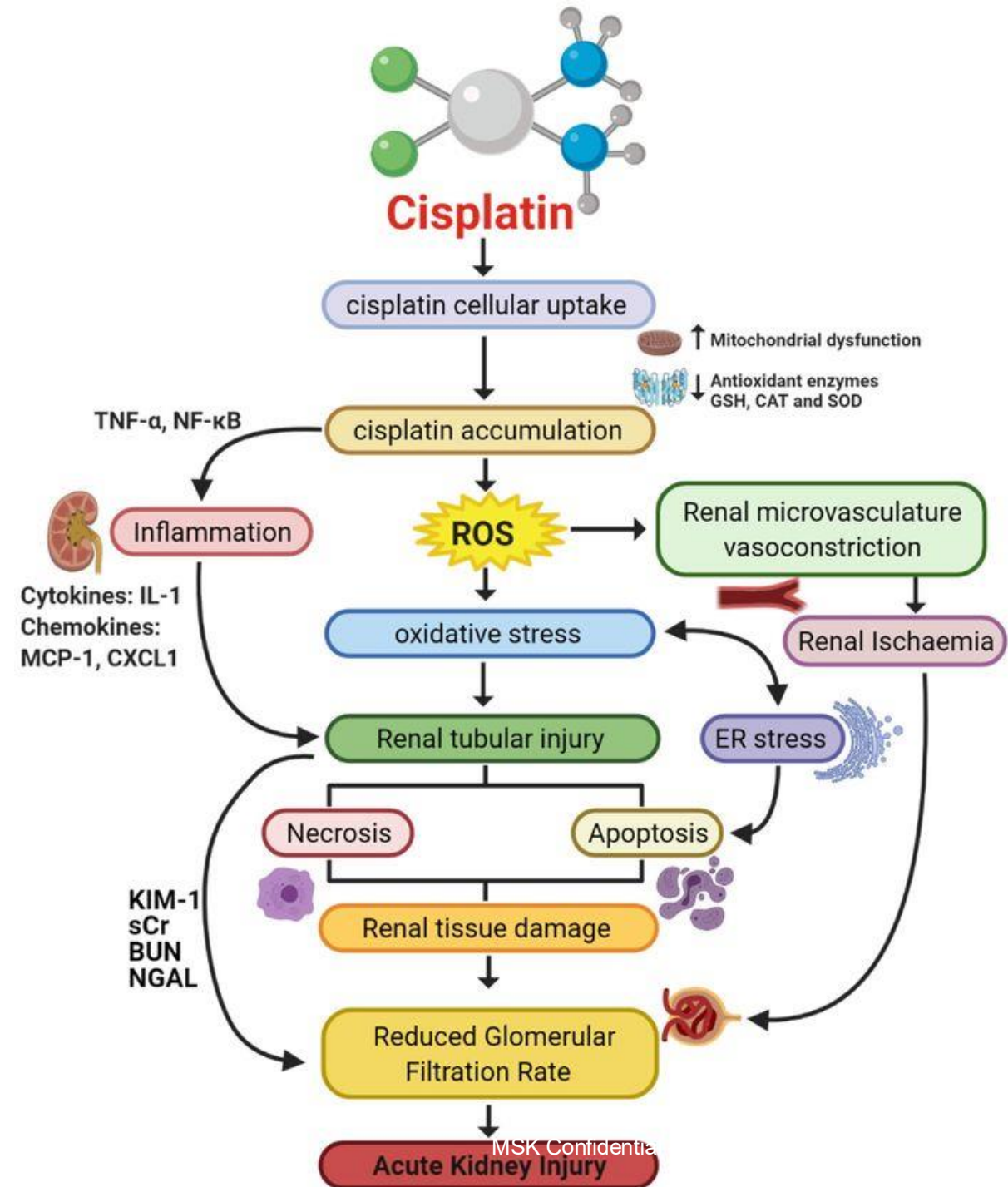
Key transporters

- OCT2
- CTR1
- MATE transporters



Mechanisms of Injury

- Tubular uptake and accumulation
- DNA damage
- Mitochondrial dysfunction
- ROS generation
- ER stress
- Inflammatory signaling
- TNF- α
- NF- κ B
- NLRP3
- Cell death pathways
- Apoptosis
- Necroptosis
- Ferroptosis-related signaling



Predicting Cisplatin-Induced AKI

Derivation and External Validation of a Simple Risk Score for Predicting Severe Acute Kidney Injury After Intravenous Cisplatin

Gupta S, Glezerman IG, Hirsch JS, et al.

BMJ 2024;384:e077169



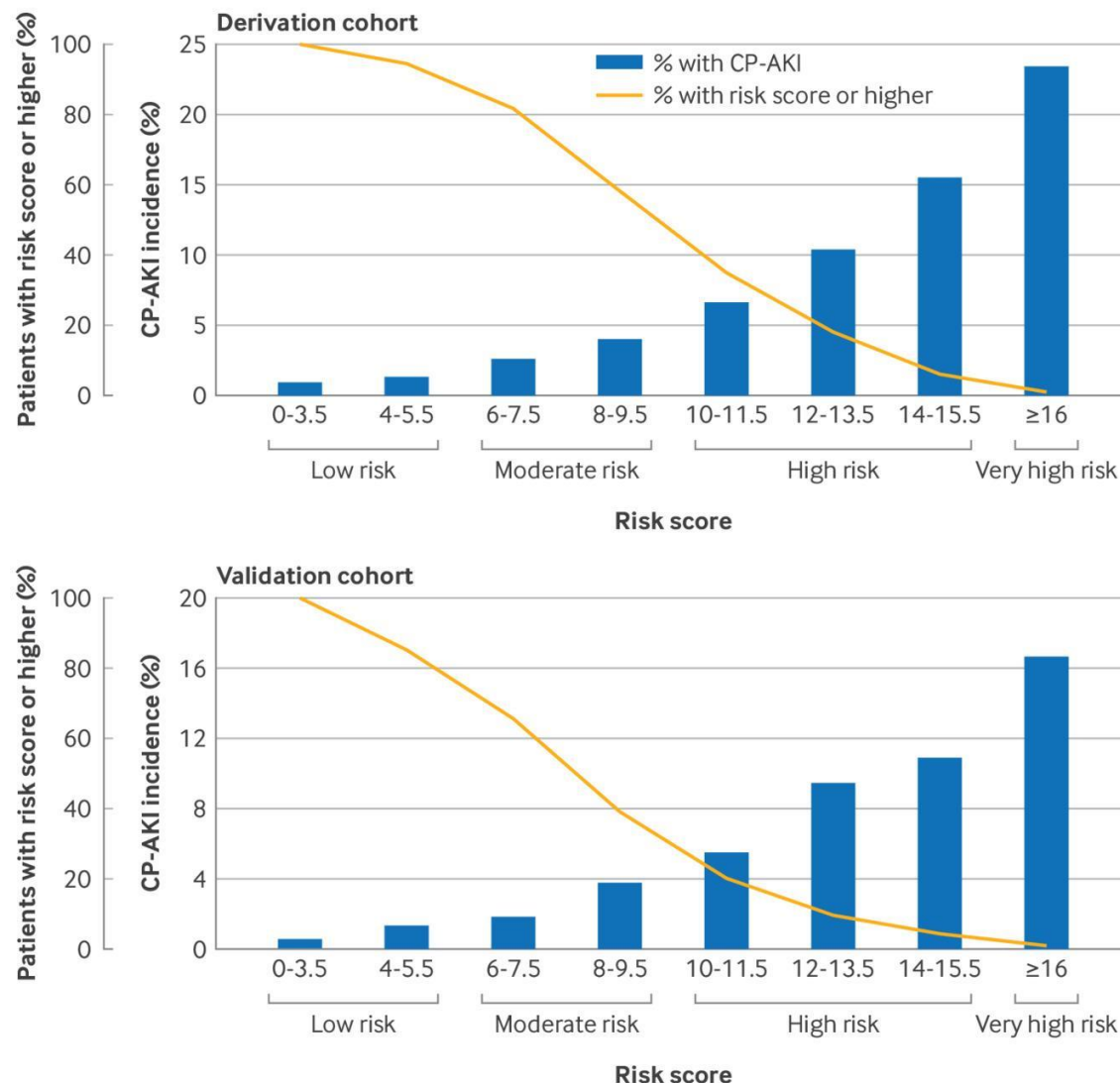
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Study Design & Population

- Included data from 6 major cancer centers
- Study Population: adults receiving first dose of IV cisplatin between 2006-2022
- Primary outcome: CP-AKI, defined as ≥ 2 -fold rise in serum creatinine or RRT in the 14 days following IV cisplatin
- Used multivariable logistic regression to identify predictors of CP-AKI in the derivation cohort
- Developed a clinically useful integer-based score
- Assessed model calibration and discrimination

A New Risk Prediction Model

Risk factor	Odds ratio (95% CI)	Score
Age (years)		
≤45	1 (reference)	0
46-60	2.90 (2.06 to 4.09)	2.5
61-70	4.12 (2.91 to 5.83)	3.5
>70	5.15 (3.49 to 7.60)	4.5
Hypertension	1.31 (1.09 to 1.58)	1
Diabetes	1.30 (1.02 to 1.64)	1
Current/former smoker	1.20 (1.00 to 1.45)	1
Hemoglobin (g/L)		
≥120	1 (reference)	0
110-119	1.41 (1.10 to 1.82)	1
<110	1.62 (1.28 to 2.05)	1.5
White blood cell count (x10 ⁹ /L)		
≤12.0	1 (reference)	0
>12.0	1.59 (1.25 to 2.02)	1.5
Serum albumin (g/L)		
>38	1 (reference)	0
33-38	1.28 (1.01 to 1.62)	1
<33	1.73 (1.30 to 2.29)	1.5
Serum magnesium (mmol/L)		
≥0.82	1 (reference)	0
<0.82	1.39 (1.14 to 1.70)	1
Cisplatin dose (mg)		
≤50	1 (reference)	0
51-75	2.16 (1.47 to 3.18)	2
76-100	3.19 (2.10 to 4.84)	2.5
101-125	3.41 (2.14 to 5.44)	3
126-150	6.40 (4.29 to 9.53)	5
151-200	8.81 (5.99 to 12.94)	7.5
>200	11.74 (7.68 to 17.94)	9.5



Risk of CP-AKI In highest vs lowest risk score category was 24-fold and 17.8-fold higher in DC and VC, respectively

Risk Factors & Model Performance

- Nine independent predictors of CP-AKI: age, hypertension, diabetes mellitus, serum creatinine, hemoglobin, white blood cell count, platelet count, serum albumin, serum magnesium, and cisplatin dose.
- Novel laboratory predictors: WBC count, hemoglobin, platelet count, creatinine, and serum magnesium.
- Strong risk stratification: Highest-risk vs. lowest-risk patients had a 17.87 to 24.00-fold higher odds of CP-AKI
- Superior discrimination

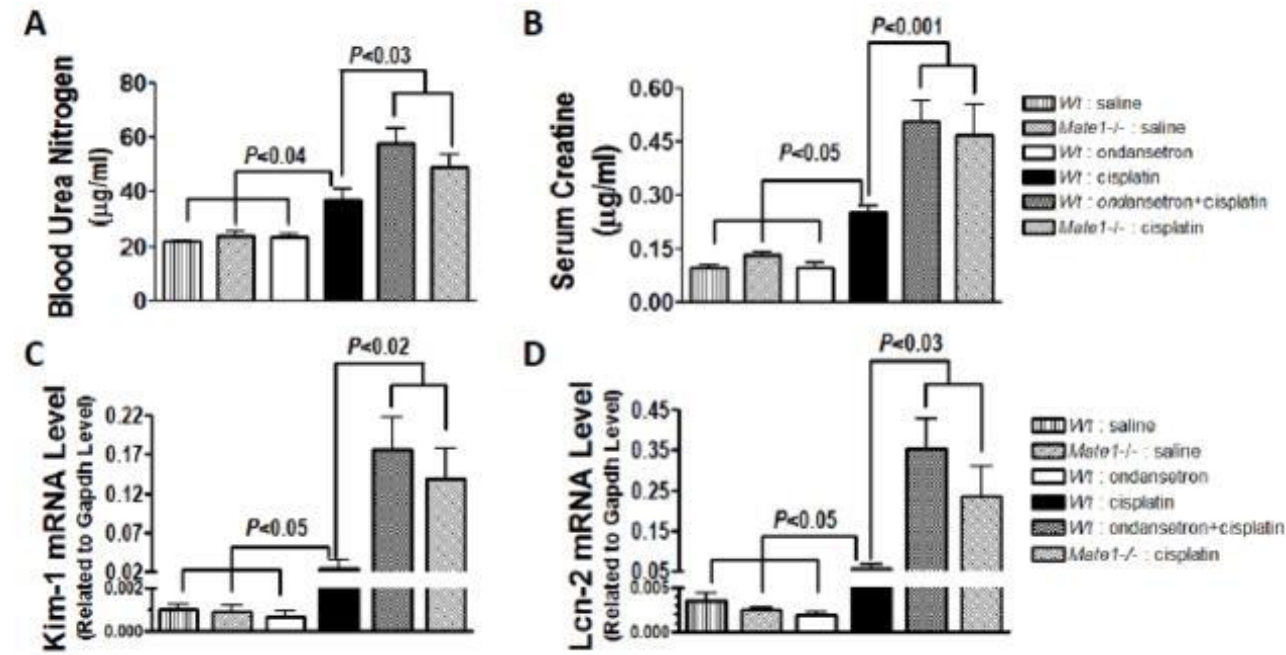
Antiemetics and cisplatin induced AKI



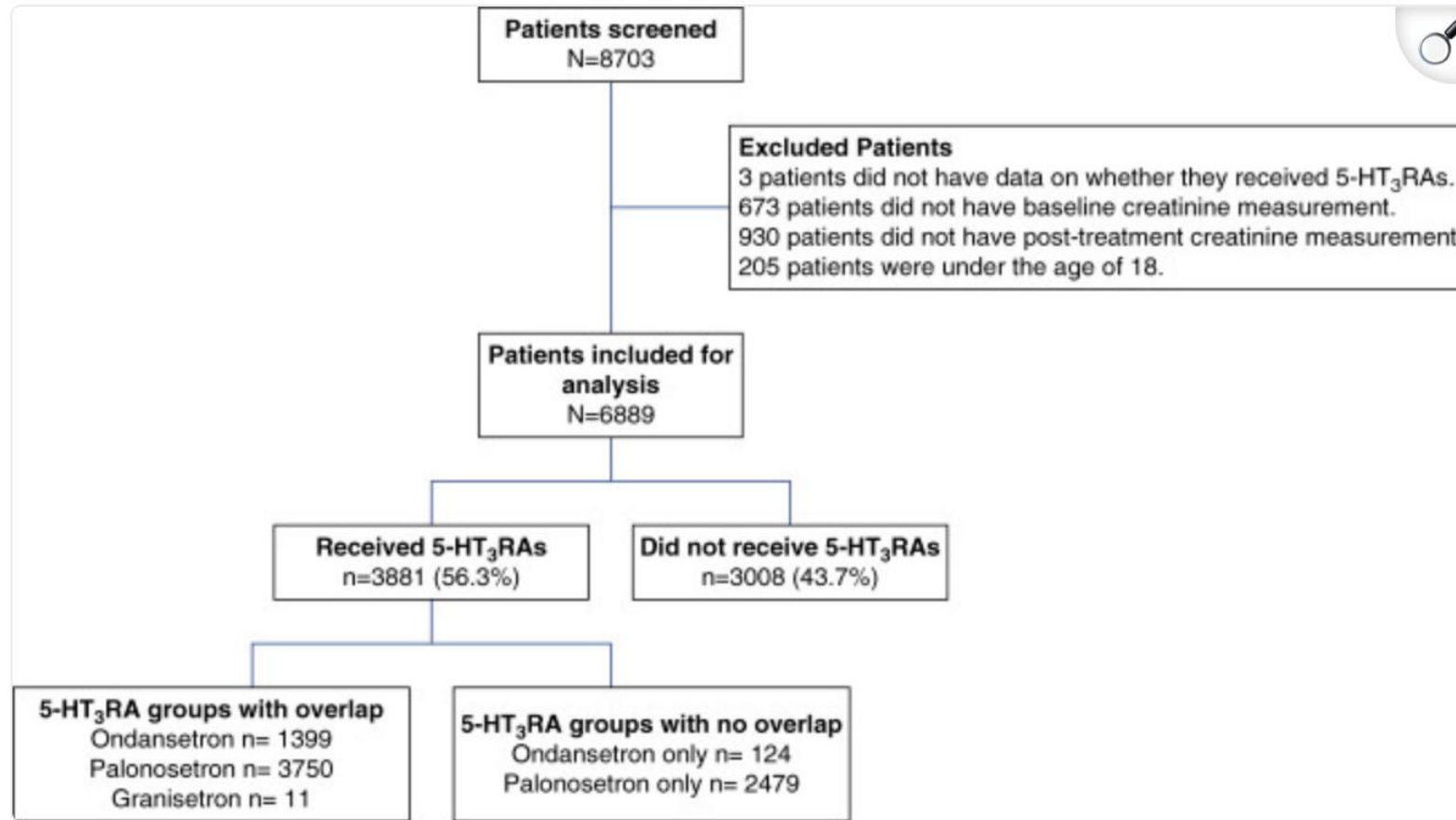
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Antiemetics and Risk for Cisplatin Induced AKI

- **Mouse cisplatin model: ondansetron co-treatment –**
 - ↑ Severity of cisplatin nephrotoxicity
- Mechanism: strong inhibition of renal MATE1/2-K → ↓ tubular secretion of cisplatin .
(Li et al. Toxicol Appl Pharmacol, 2013)
- **In vitro OCT2/MATE1 assays:**
 - Ondansetron is a potent MATE1 inhibitor → high likelihood of in-vivo transporter inhibition.
(George et al. Int J Mol Sci, 2021)



Antiemetics and AKI: Retrospective Study at MSKCC



Antiemetics and AKI: Retrospective Study at MSKCC

- 5-HT₃ receptor antagonists, as a class, reduce the incidence of AKI in cisplatin-treated patients—likely via prevention of emesis, dehydration, and prerenal injury.
- Any 5-HT₃RA is preferable to none for kidney protection during cisplatin therapy.
- New-generation 5-HT₃RA do not provide additional AKI protection over first-generation agents in this retrospective study.

Univariate analysis between 5-hydroxytryptamine type 3 receptor antagonist use and AKI

<i>5-HT₃RA Type</i>	<i>5-HT₃RA Status</i>	<i>AKI</i>	<i>P Value</i>
	<i>N=6889</i>	<i>n=1666</i>	
Any 5-HT ₃ RA	No: 3008	789 (26.2%)	0.001
	Yes: 3881	877 (22.6%)	
Ondansetron	No: 5490	1359 (24.8%)	0.03
	Yes: 1399	307 (21.9%)	
Palonosetron	No: 3139	812 (25.9%)	0.003
	Yes: 3750	854 (22.8%)	
Granisetron ^a	No: 6878	1664 (24.2%)	1
	Yes: 11	2 (18.2%)	
Combination therapy ^b	None: 3008	789 (26.2%)	0.003
	Palonosetron, only: 2479	570 (23.0%)	
	Ondansetron, only: 124	22 (17.7%)	
	Palonosetron+Ondansetron: 1267	283 (22.3%)	

Pharmacokinetic Model of Platinum Disposition in Cancer Patients Receiving Cisplatin and Randomized to 5-HT3 Antiemetic Drugs

Purpose:

Population PK model of unbound and bound platinum; assess effect of 5-HT3 antiemetics on platinum disposition.

Design:

33 adult cancer patients on cisplatin (first or second cycle ≥ 25 mg/m²), randomized to ondansetron, granisetron or palonosetron

Sampling & PK Modeling:

Plasma collected pre-dose and up to 10 days (0.5–240 h) post-cisplatin.

Total and unbound platinum measured by ICP-MS

Effect of 5-HT₃ Antagonists on Platinum Exposure

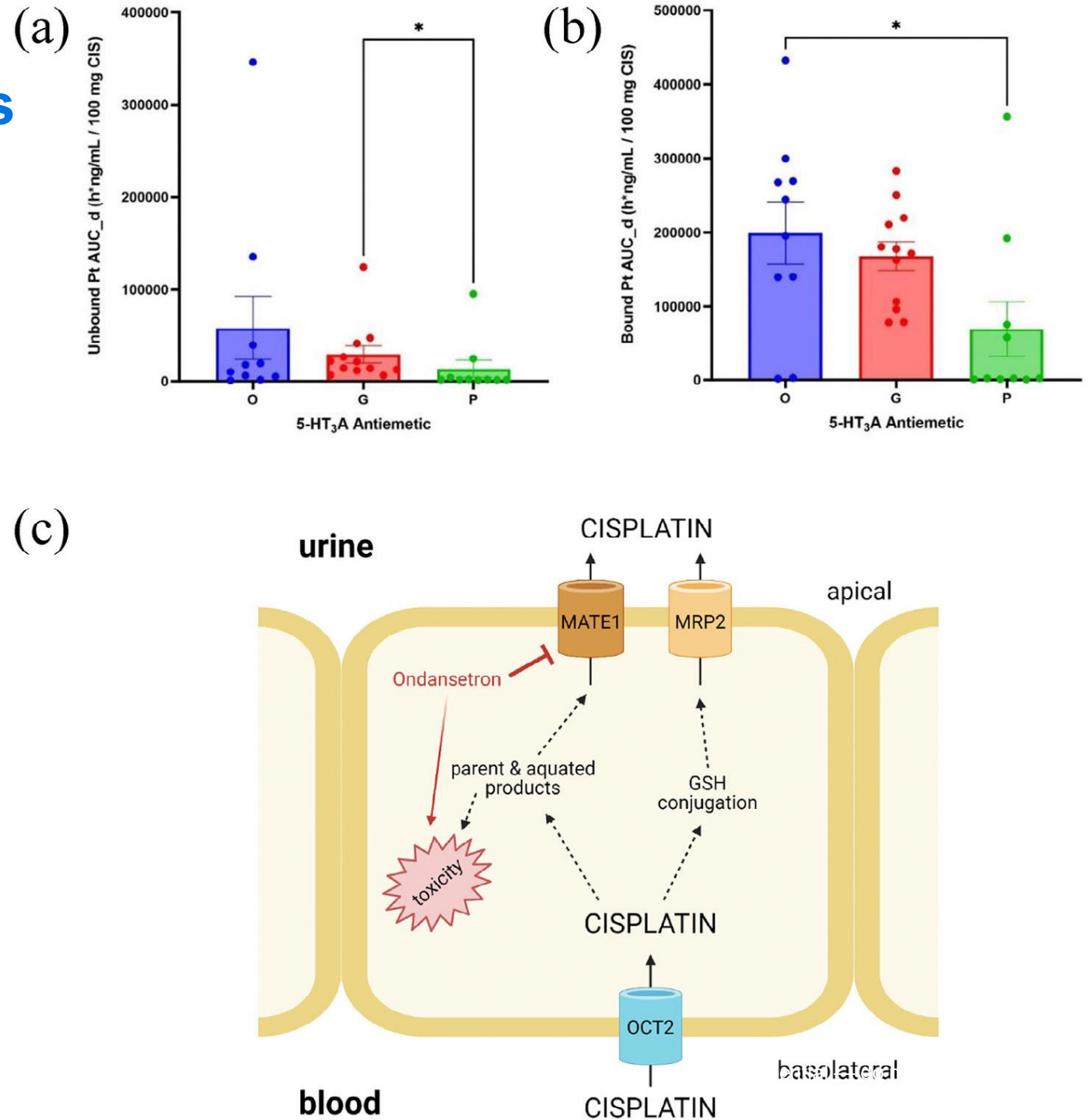
Compared with palonosetron:

- **Ondansetron:**

- Unbound Pt AUC (dose-normalized) ↑ ~331%.
- Bound Pt AUC ↑ ~188%.
- Strong MATE1 inhibition → reduced renal secretion, higher systemic and renal platinum.

- **Granisetron:**

- Unbound Pt AUC ↑ ~114%.
- Bound Pt AUC ↑ ~143%.



Summary: Antiemetics and Cisplatin Nephrotoxicity

Key Takeaways: 5-HT3 Antagonists

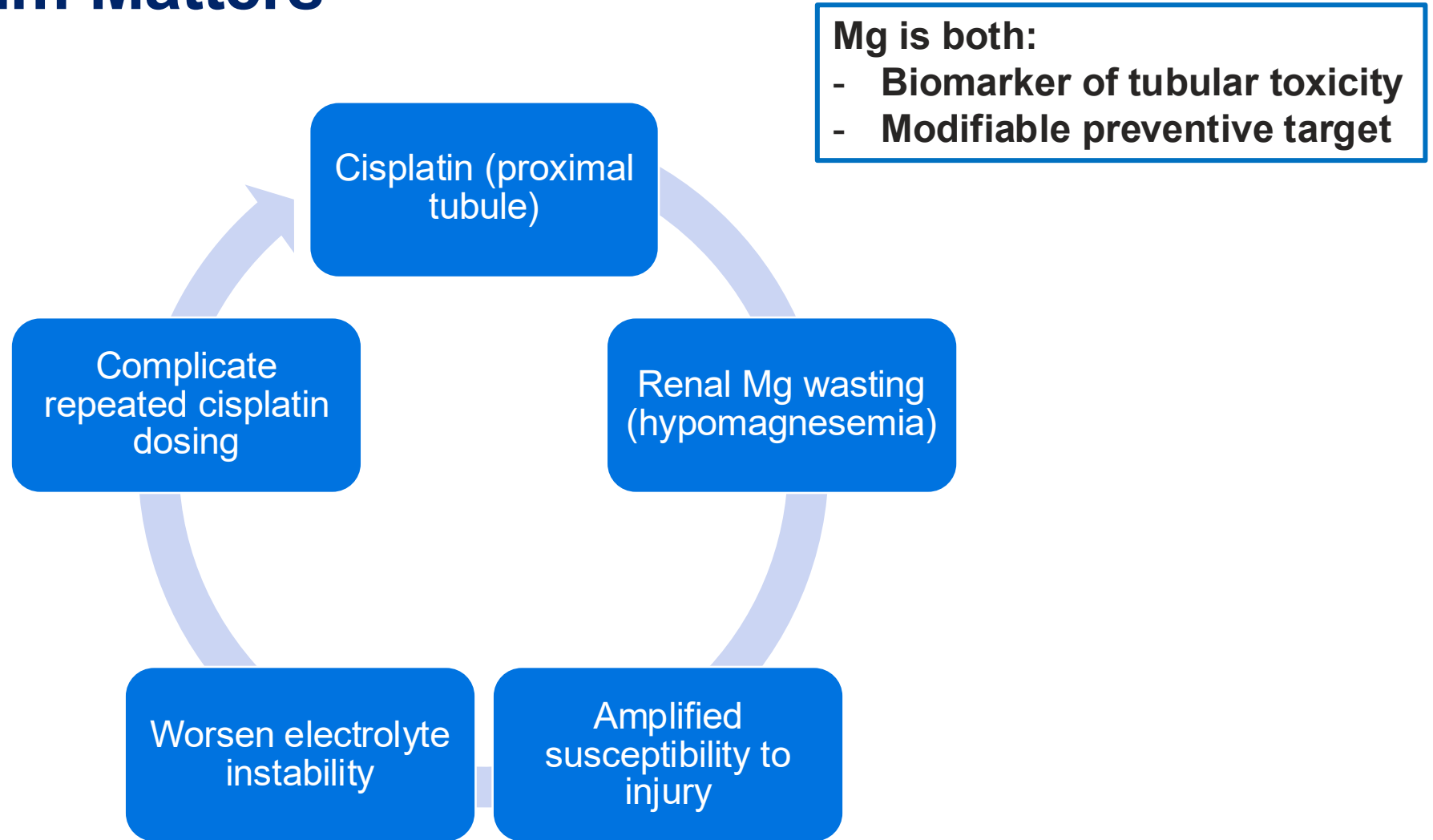
- Class benefit: Any 5-HT3RA reduces AKI vs. none (26.2% → 22.6%; $P=0.001$).
- No advantage to newer agents over first-generation.
- Caution with ondansetron/granisetron: potent MATE1 inhibition → higher intrarenal platinum.
- Clinical dilemma: antiemetic protection vs. transporter-mediated platinum accumulation.

Role of Magnesium

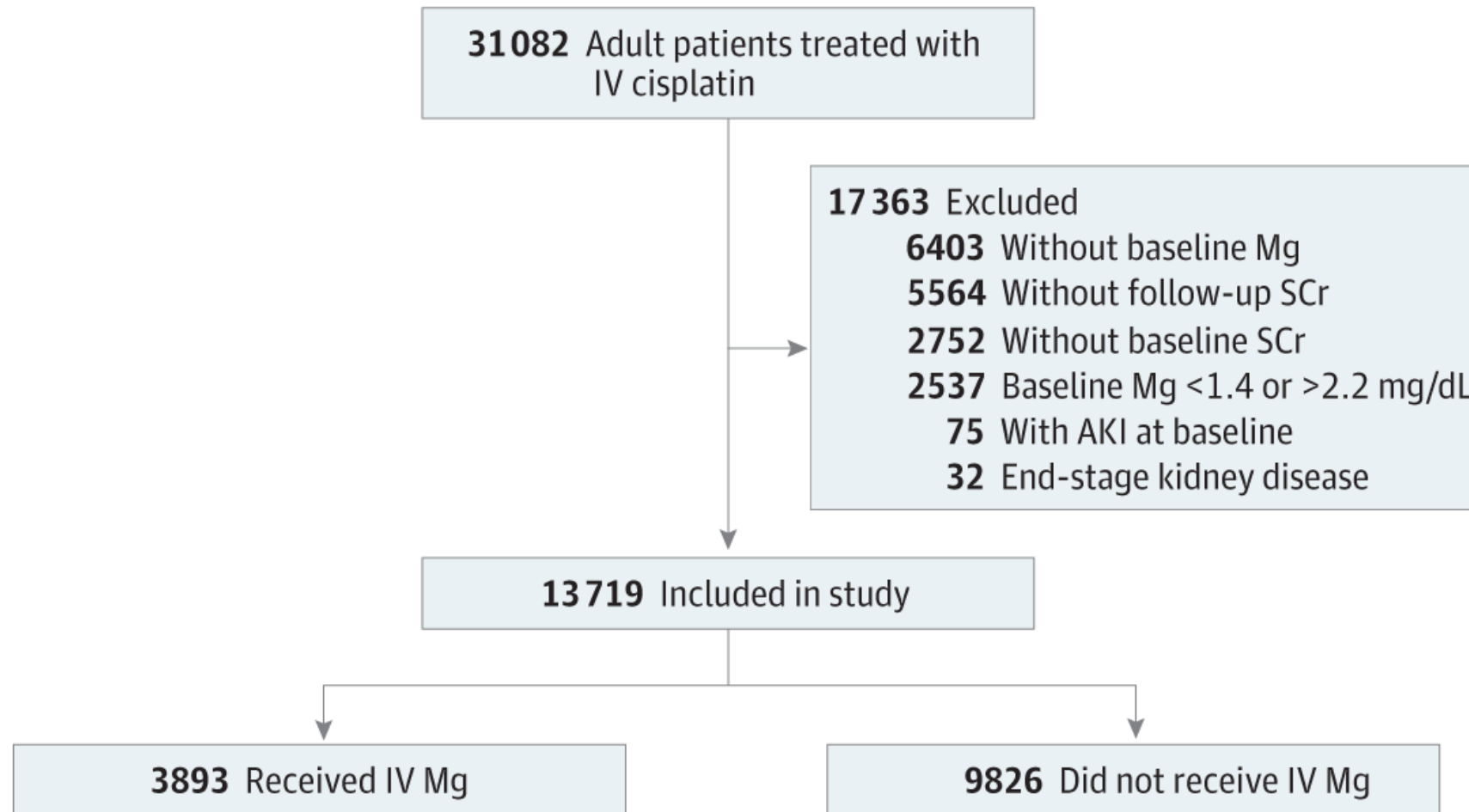


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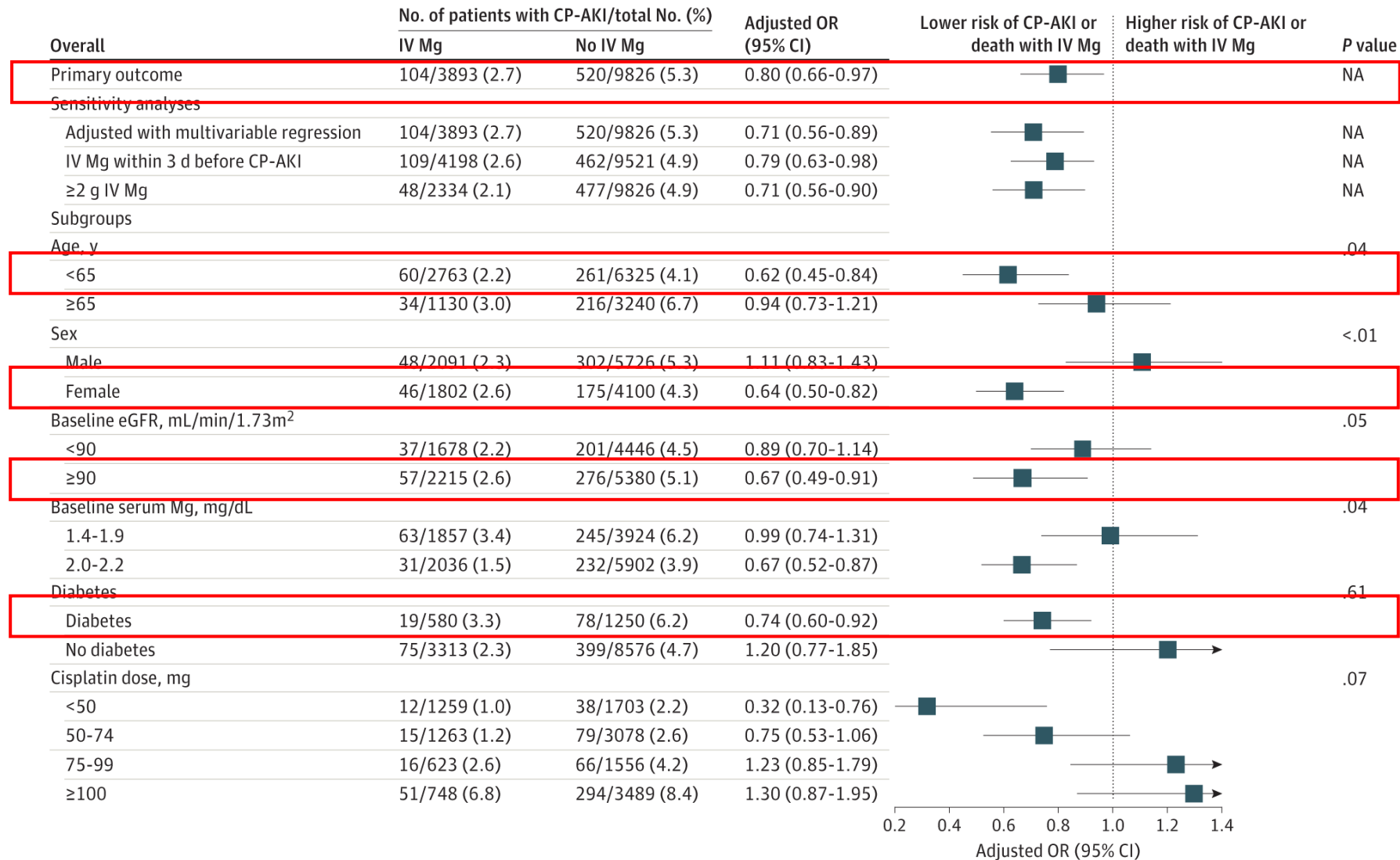
Why Magnesium Matters



Intravenous Mg and cisplatin-associated AKI



Cisplatin-Associated Acute Kidney Injury (CP-AKI) or Death in Intravenous Magnesium-Treated (IV Mg) vs Nontreated Patients



Key Takeaways

Magnesium in Cisplatin Nephrotoxicity

- Cisplatin causes renal Mg wasting — both a biomarker and a modifiable target.
- IV Mg reduces CP-AKI and death (primary outcome adjusted OR 0.80; consistently <1.0 across outcomes).
- Benefit consistent across subgroups (age, sex, baseline eGFR, cisplatin dose).
- Practical approach: check Mg each cycle, include IV Mg in hydration, continue replacement after treatment..

SGLT2 Inhibitors: An Emerging Strategy for CP-AKI Prevention?

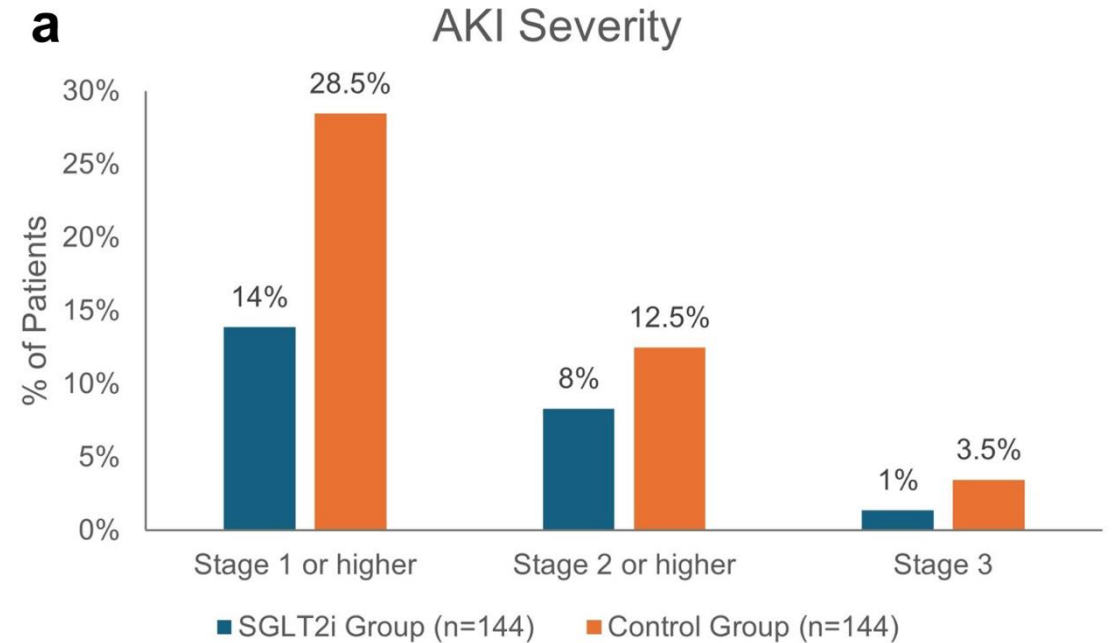
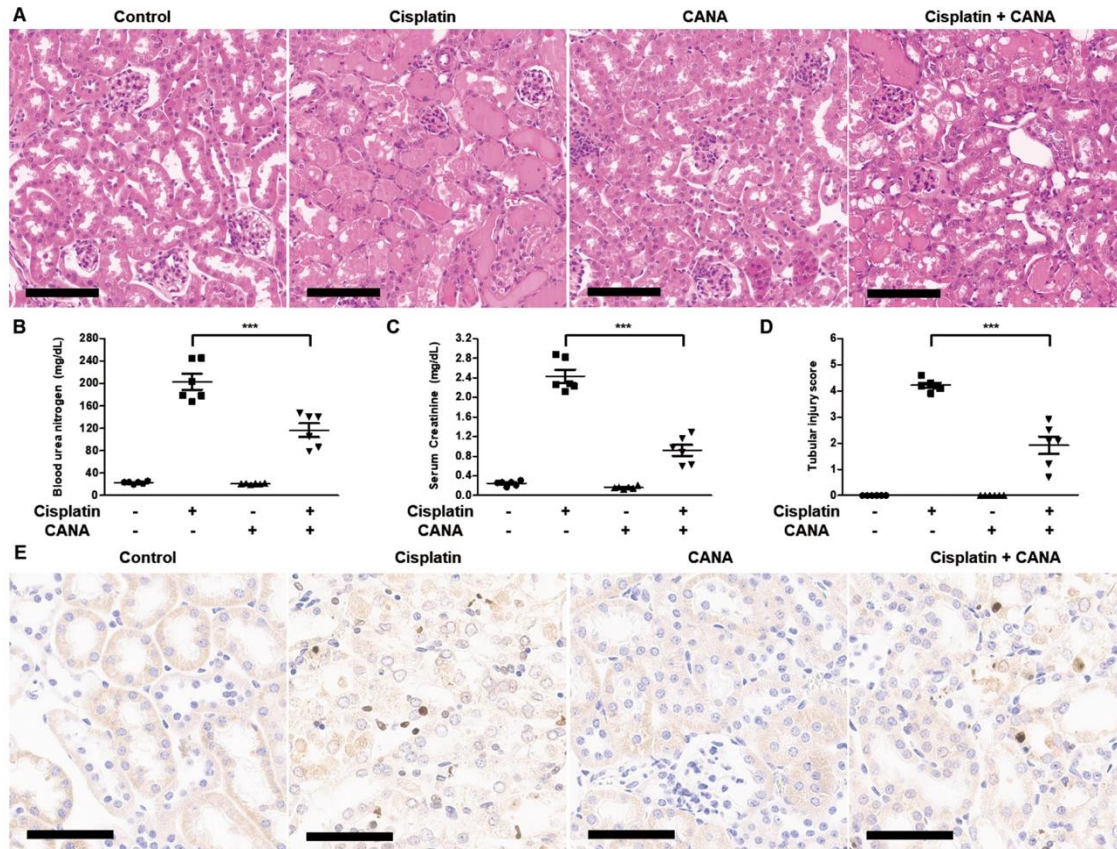
➤ Rationale / Preclinical Signal

- SGLT2 inhibitors may protect the kidney by reducing tubular cell uptake of cisplatin
- In cisplatin-treated mice, canagliflozin attenuated tubular damage and rises in BUN and serum creatinine

➤ Emerging Clinical Evidence

- Single-center retrospective study; 288 patients (144 per group); IV cisplatin July 2017–Jan 2024
- **Lower AKI incidence with SGLT2i: 13.9% vs. 28.5% (OR 0.42; 95% CI 0.23–0.76)**

SGLT2 Inhibitors: An Emerging Strategy for CP-AKI Prevention?



CKD After Cisplatin: Population-Level Burden

- Study: Population-based prognostic study of adults receiving outpatient cisplatin for nonhematologic cancers
 - Cohort: 9521 patients
 - Among 9010 patients without pretreatment CKD:
 - 13.6% developed CKD
 - 4.2% developed grade 3b or worse CKD
 - 0.9% developed grade 4 or worse CKD
 - 0.18% required dialysis
 - Mean eGFR decline: 8.1 mL/min/1.73 m²
- AKI occurred in 26.2% of patients
- Of those with AKI, 23.2% later developed CKD

Grant, Latcha et al, JAMA Oncology, 2025

Characteristic at baseline	Development, July 1, 2014 to June 30, 2017 (n = 4914)	Temporal test, July 1, 2017 to June 30, 2020 (n = 4607)
Age, median (IQR), y	63 (55-70)	64 (56-70)
Sex		
Female	2401 (48.9)	2279 (49.5)
Male	2513 (51.1)	2328 (50.5)
Recently immigrated	582 (11.8)	534 (11.6)
Rural residence	662 (13.5)	712 (15.5)
Chronic kidney disease	221 (4.5)	290 (6.3)
Diabetes	809 (16.5)	723 (15.7)
Hypertension	2342 (47.7)	2213 (48.0)
Cancer topography (top 3)		
Bronchus and lung	1773 (36.1)	1462 (31.7)
Cervix	353 (7.2)	403 (8.7)
Stomach	415 (8.4)	180 (3.9)
Treatment regimen (top 3)		
Weekly cisplatin with radiotherapy	851 (17.3)	985 (21.4)
Cisplatin and etoposide over 3 d	847 (17.2)	581 (12.6)
Cisplatin every 3 wk with radiotherapy	560 (11.4)	537 (11.7)

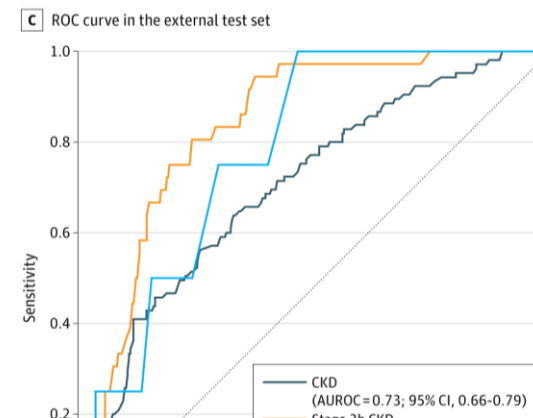
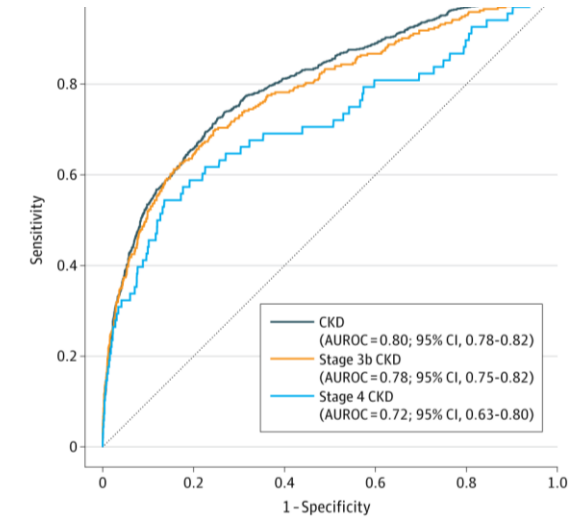
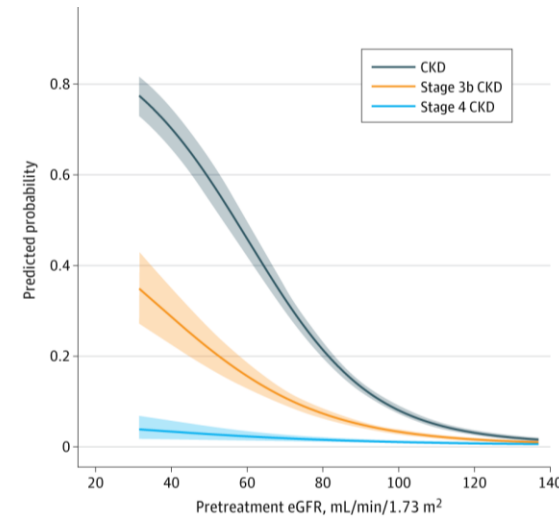
^a Data are presented as the No. (%) of patients unless indicated otherwise.

What Best Predicted CKD? Pretreatment eGFR

A simple spline-based model using pretreatment eGFR alone predicted post-cisplatin CKD well

Model performance:

- Lower baseline eGFR was associated with a steep increase in CKD risk
- More complex machine learning models using many clinical features did not meaningfully improve prediction
- Cisplatin was associated with higher CKD risk than non-cisplatin controls
- Most kidney decline appeared to occur within 3 months after treatment



Summary: CKD After Cisplatin

CKD as a Long-Term Consequence

- 13.6% developed CKD; 4.2% grade 3b+; dialysis rare (0.18%).
- AKI drives CKD: occurred in 26.2%; of those, 23.2% later developed CKD.
- Pretreatment eGFR is the strongest predictor (AUROC 0.80); complex ML models added little.
- Early window matters: most decline within 3 months, without clear later progression.

Summary & Conclusions: A Practical Approach

- Cisplatin-associated AKI is common (~20–30%) with magnesium wasting a hallmark
- Saline hydration is essential and magnesium supplementation is the most compelling adjunct
- 5-HT3RAs reduce AKI as a class, but some increase intrarenal platinum via MATE inhibition
- ~13.6% develop CKD; pretreatment eGFR is the best predictor

Before Cisplatin	During Cisplatin	After Cisplatin
Asses eGFR, Mg	Saline hydration	Early sCr and lytes assessment
Hydrate and replace Mg	Mg supplementation	Mg and K replacement
Review nephrotoxins	Potassium as needed	Modify schedule if evidence of toxicity
Identify high risk patients		