Massachusetts General Hospital
Founding Member, Mass General Brigham

Late Post-Transplant Medical Complications

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Clinical & Research Focus:

Transplant immunology, glomerular disease recurrence, xenotransplantation

Disclosure of Financial Relationships

Investigator-initiated research with Astra-Zeneca, Veloxis, CareDx, eGenesis and Visterra.
Industry-sponsored research from Sanofi, Vertex and Hansa.

Objectives

By the end of this lecture, you should be able to:

- recognize the major late complications after kidney transplantation
- choose evidence-based management strategies
- identify transplant-specific board pearls

Case 1

45-year old male, 3 years post-living donor transplant (ADPKD), stable creatinine 1.5 mg/dL.

What is the most likely cause of death in kidney transplant recipients with a functioning graft?

A. Malignancy
B. Infection
C. Stroke
D. Cardiovascular disease
E. Trauma

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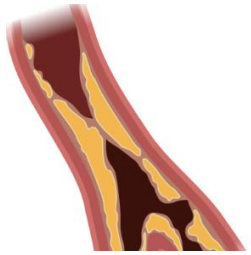
D. Cardiovascular disease ✅
E. Trauma

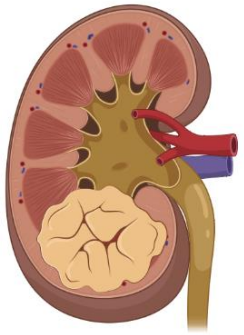
Key Point: CV disease is the leading cause of death post-transplant.

Objectives

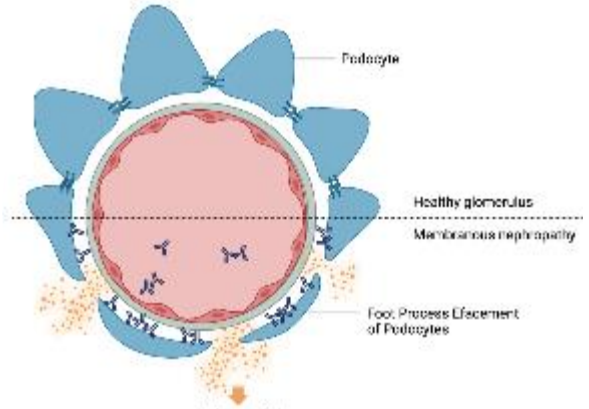


Heart disease

Diabetes

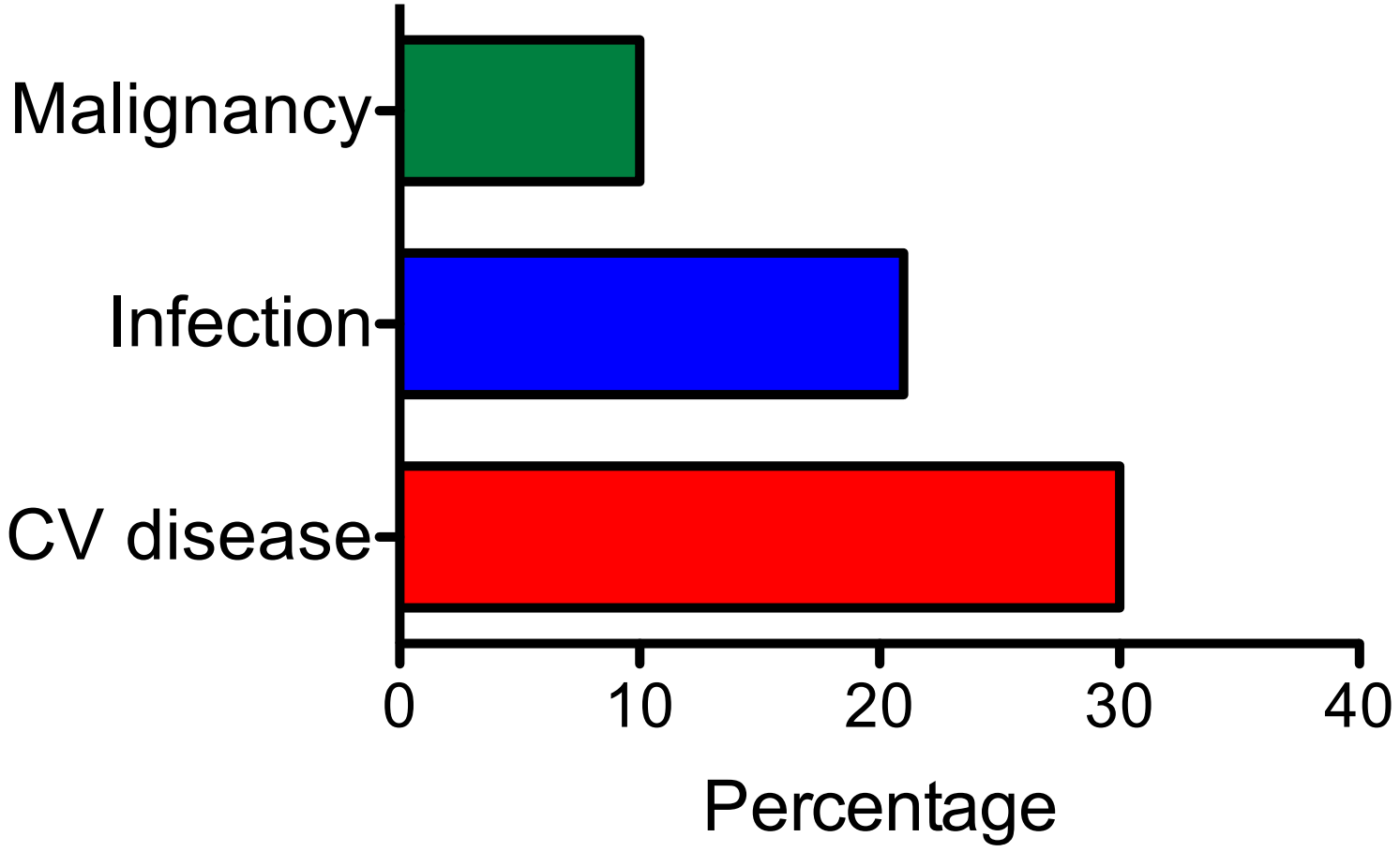


Cancer



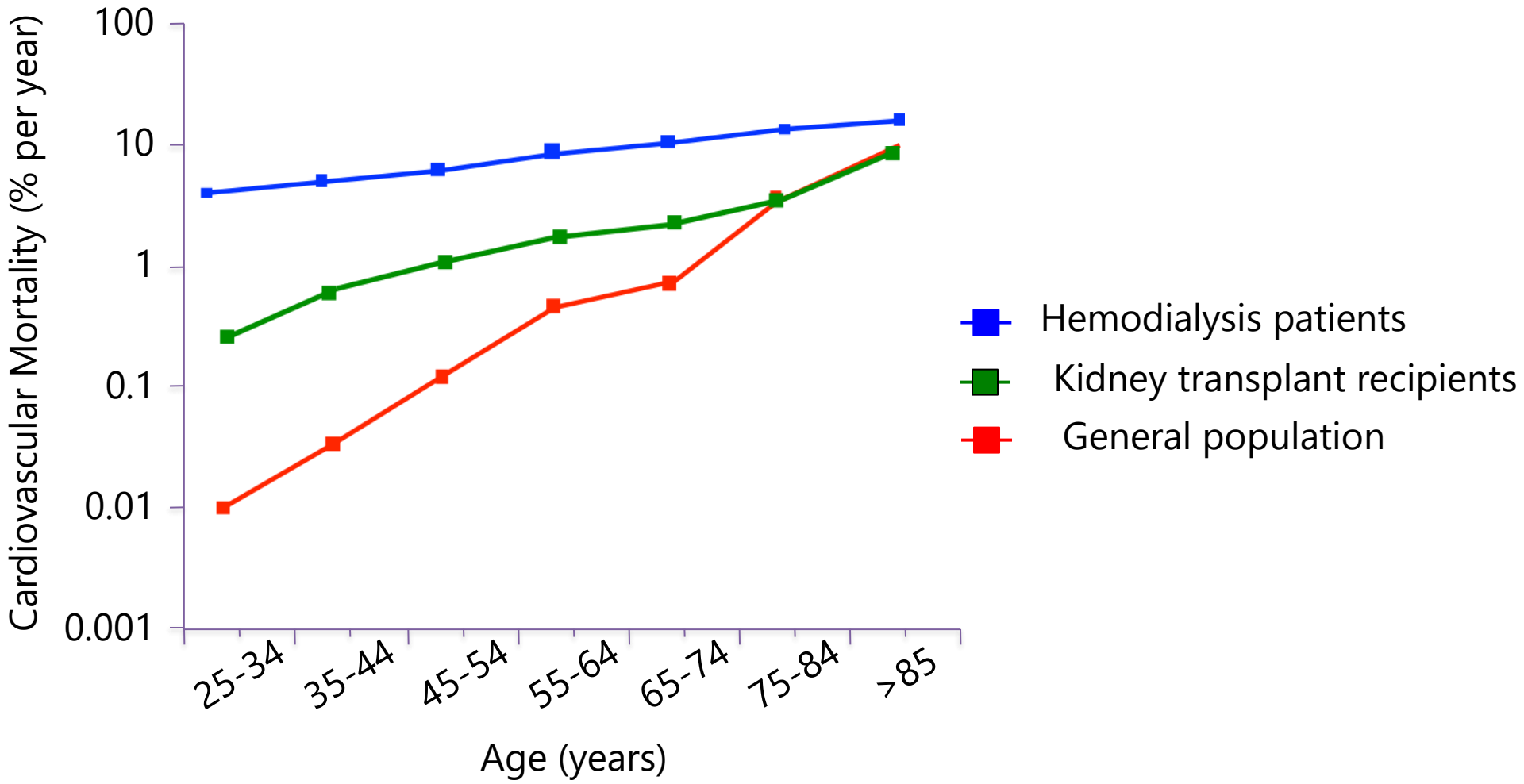
Recurrence of kidney disease

Causes of death with a functioning graft



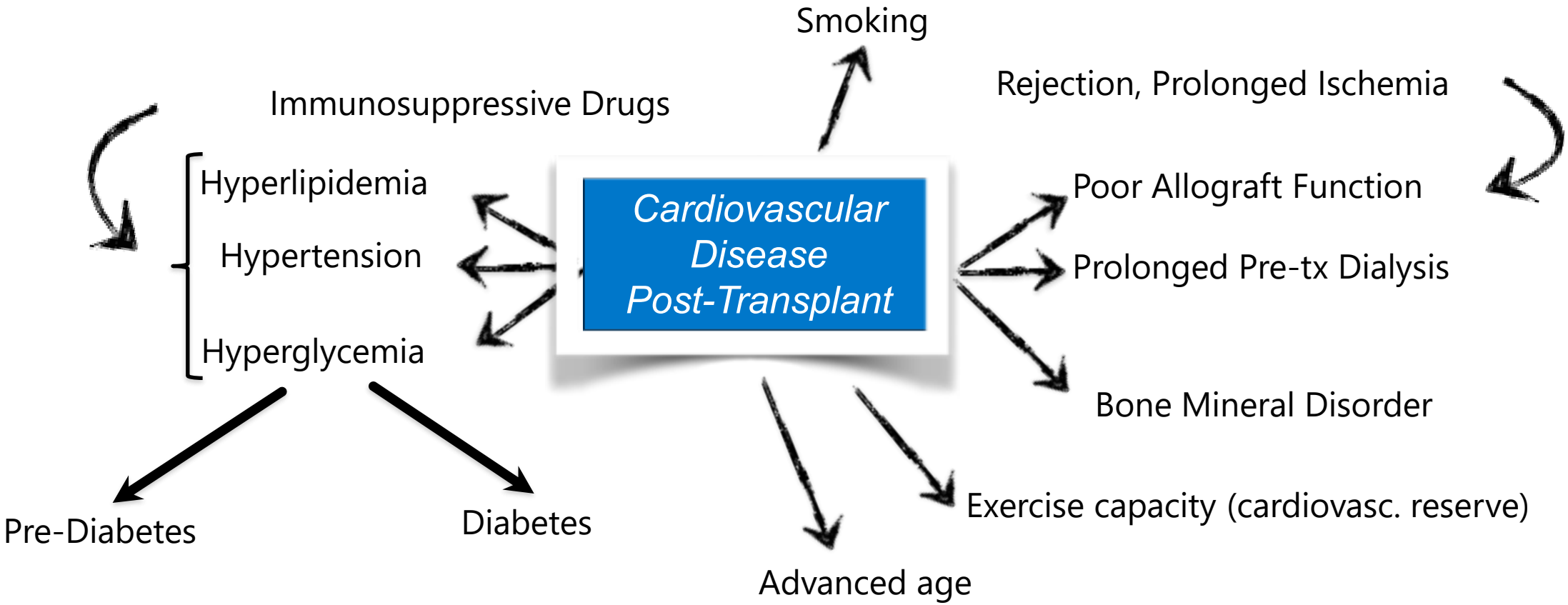
USRDS data (2004-2008)

Cardiovascular mortality by age group



Adapted from *Jardine AG, et al. Lancet 2011;378:1419*

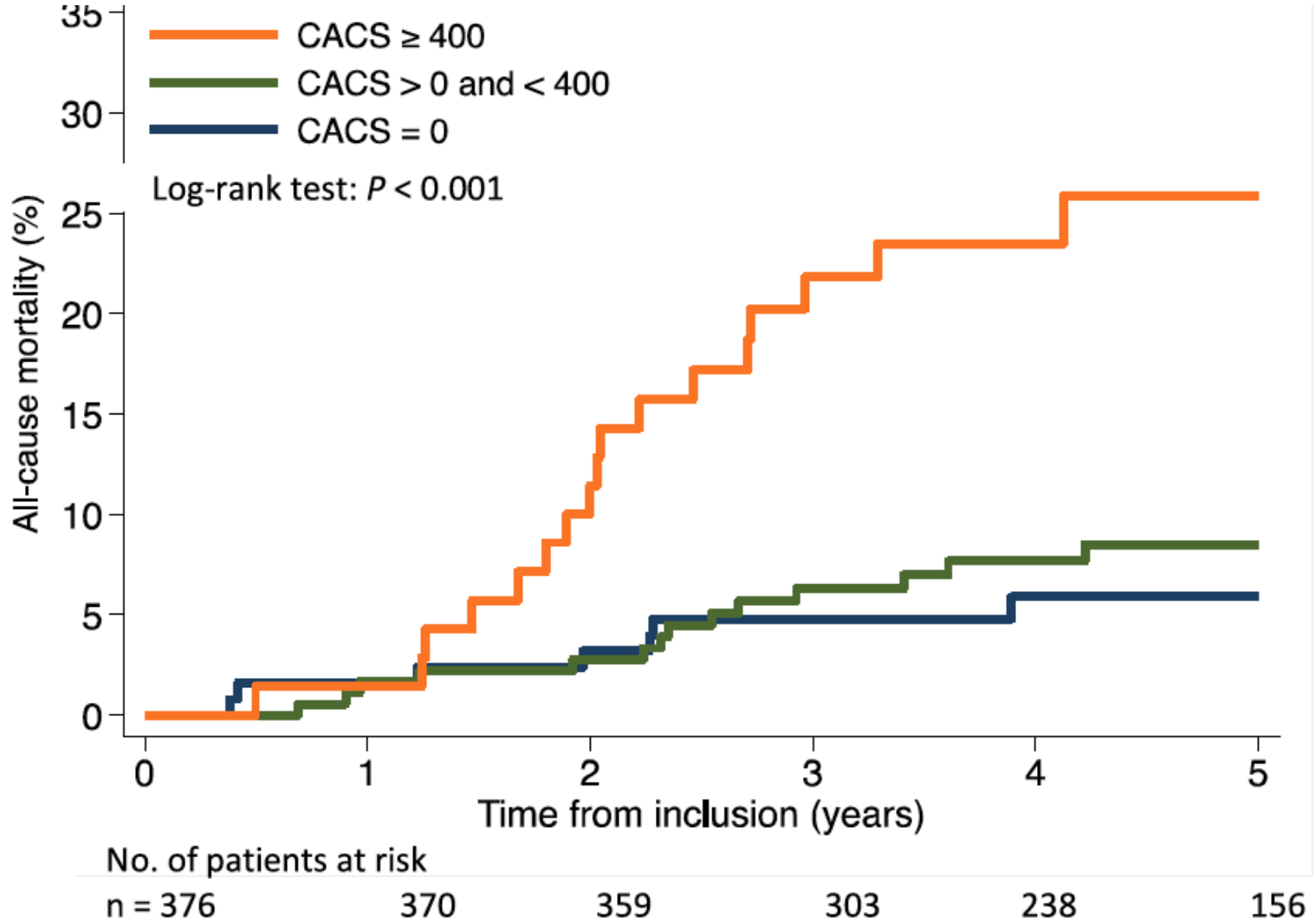
Risk Factors for CV Disease after Kidney Transplantation



*Traditional CV risk factors are poor predictors in the transplant population

Riella LV. Kidney Transplant eBook 2019

Coronary artery calcium score and all-cause mortality



Nielsen et al. Am J Transp 2023

Immunosuppression impact on CV risk factors

- Tacrolimus → diabetes
- Cyclosporine → hypertension
- mTOR → dyslipidemia
- Steroids → everything

Case 2

A 58-year-old man , 3 months post-transplant, fasting blood glucose 145 mg/dL, HbA1c 6.9%.
Meds: tacrolimus, MMF, prednisone 5 mg

What is the primary cause of post-transplant hyperglycemia?

A. Glucocorticoid-induced insulin resistance
B. Hepatic insulin resistance via IL-2
C. Calcineurin inhibitor–induced β-cell dysfunction
D. SGLT2 upregulation
E. CMV-triggered insulitis

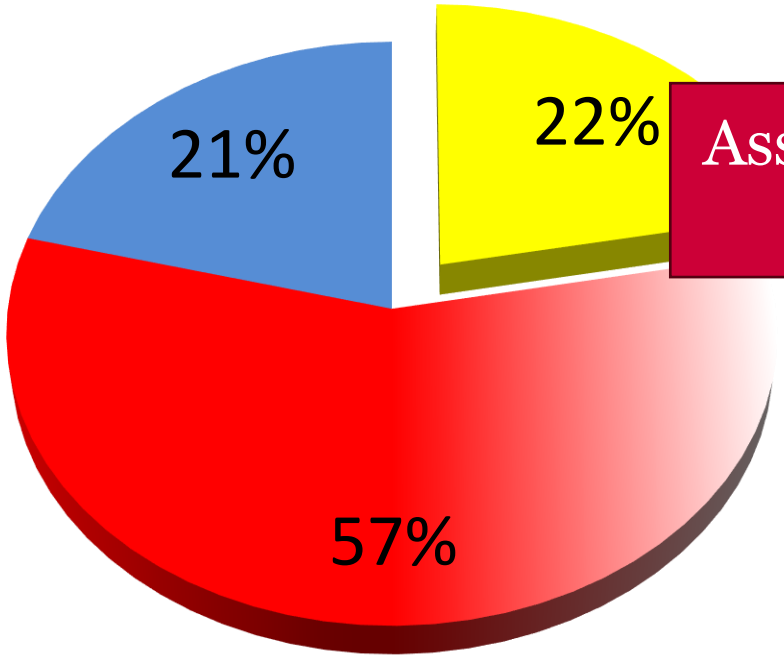
Case 2

What is the primary cause of post-transplant hyperglycemia?

A. Glucocorticoid-induced insulin resistance
B. Hepatic insulin resistance via IL-2
C. Calcineurin inhibitor–induced β-cell dysfunction ✅
D. SGLT2 upregulation
E. CMV-triggered insulitis

Key Point: Tacrolimus impairs β-cell function, leading to post-Tx diabetes.

Prevalence of Transplant-Associated Hyperglycemia (TAH)



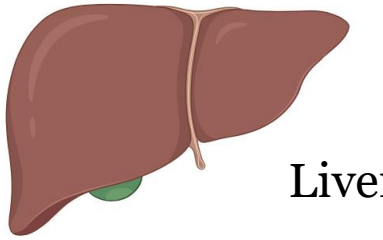
Associated with higher mortality and graft failure

Oral glucose tolerance test

n=606 kidney recipients without prior DM
1 year after transplantation

Adapted from *Porrini et al. NDT 2016*

Pathogenesis of Hyperglycemia



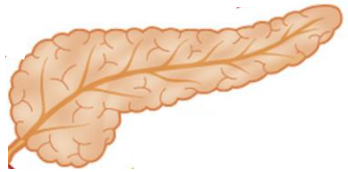
Liver

↑Hepatic Gluconeogenesis

Transplant-Associated Hyperglycemia

↓ Insulin Secretion

Pancreas

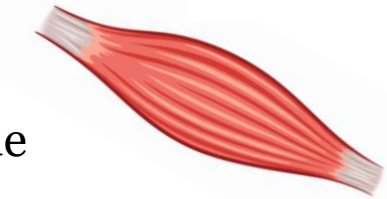


↓ Insulin Sensitivity

Adipose tissue

Adipose tissue

Skeletal muscle



Investigation: check for fasting serum glucose and HbA1c (not reliable early after transplant).

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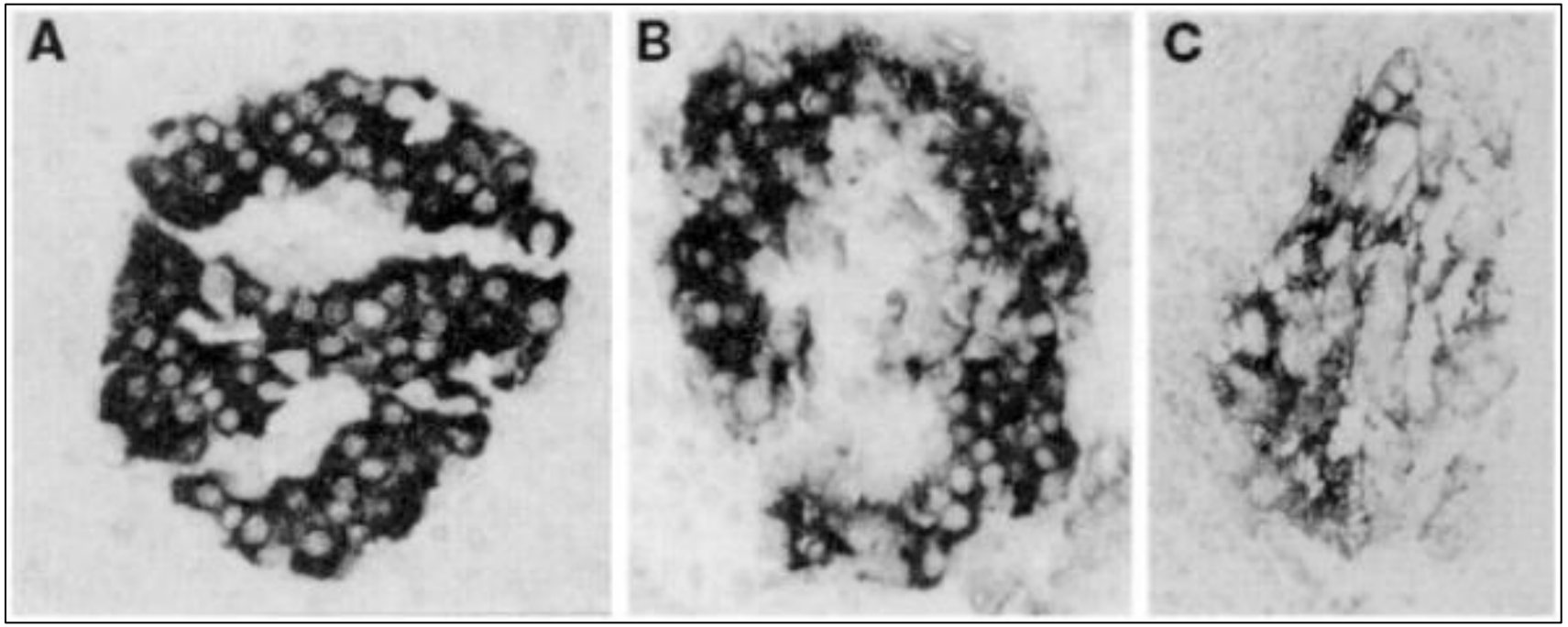
Effects of Calcineurin Inhibitors on Pancreatic β Islet Cells

Control | Cyclosporine | Tacrolimus

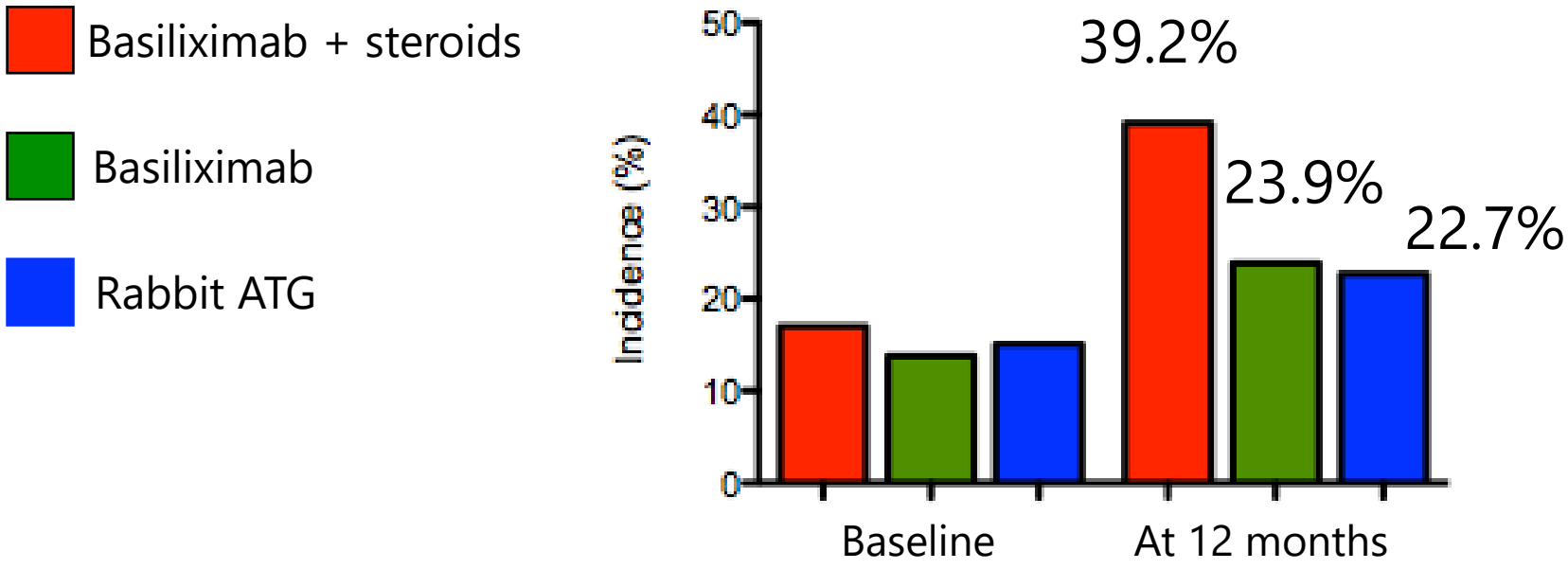


Insulin Staining (black)

Drachenberg CB et al. *Transplantation* 1999; 68: 396–402

Steroid withdrawal is associated with lower incidence of post-transplant DM

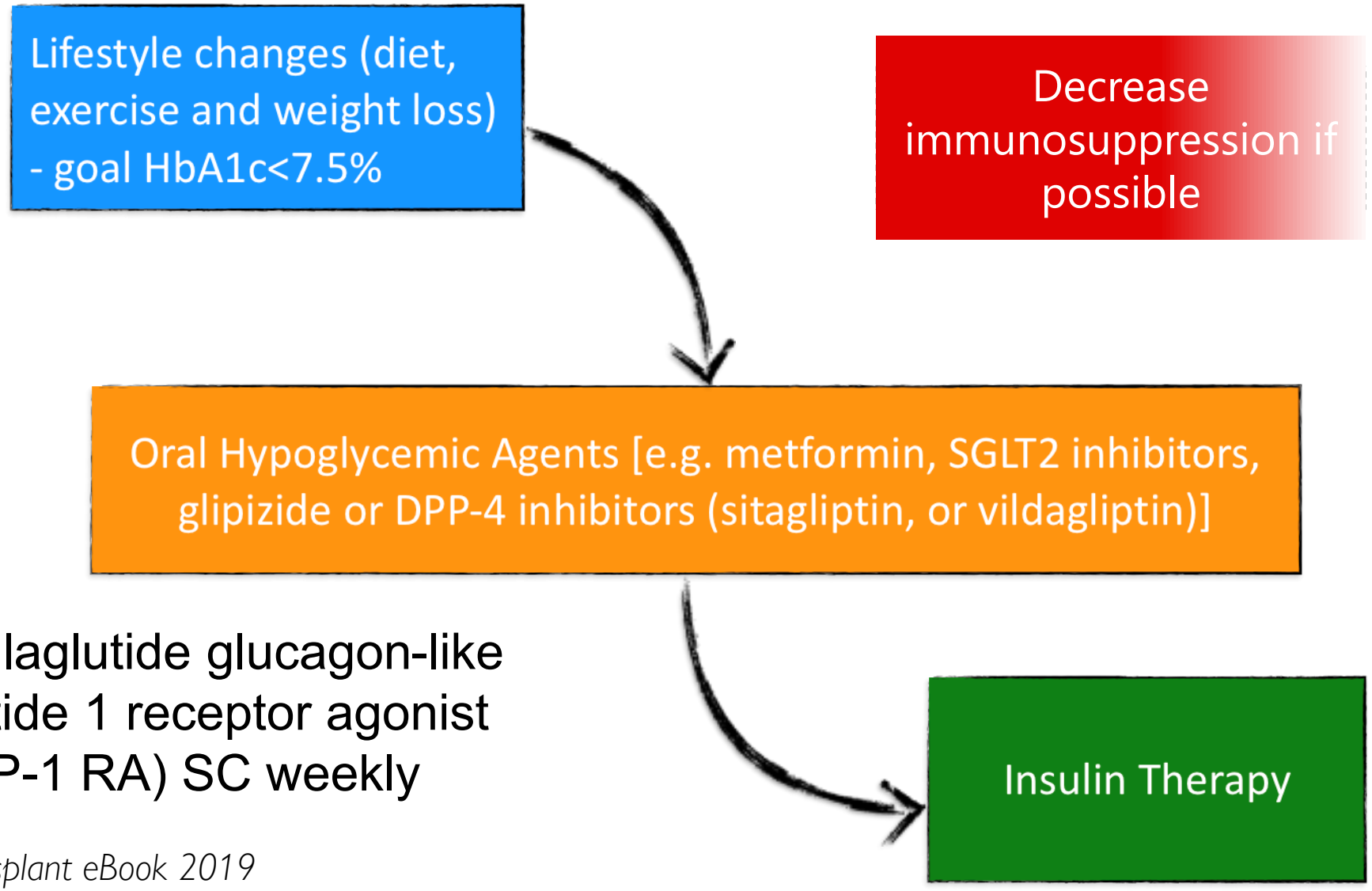
Randomized trial of different induction therapies with or without steroid withdrawal
~200 patients on each group



* All groups received high-dose steroids early after tx

Thomusch et al. Lancet 2016

Management of Post-tx DM - Stepwise Approach



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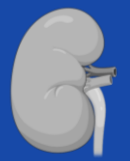
SGLT2 Inhibitors and GLP-1 Receptor Agonists in Kidney Transplantation: A Systematic Review and Meta-Analysis

AIM

Summarize current evidence on the efficacy and safety of SGLT2i and GLP-1RA in KTRs.

Systematic review and meta-analysis



Kidney transplant recipients

+

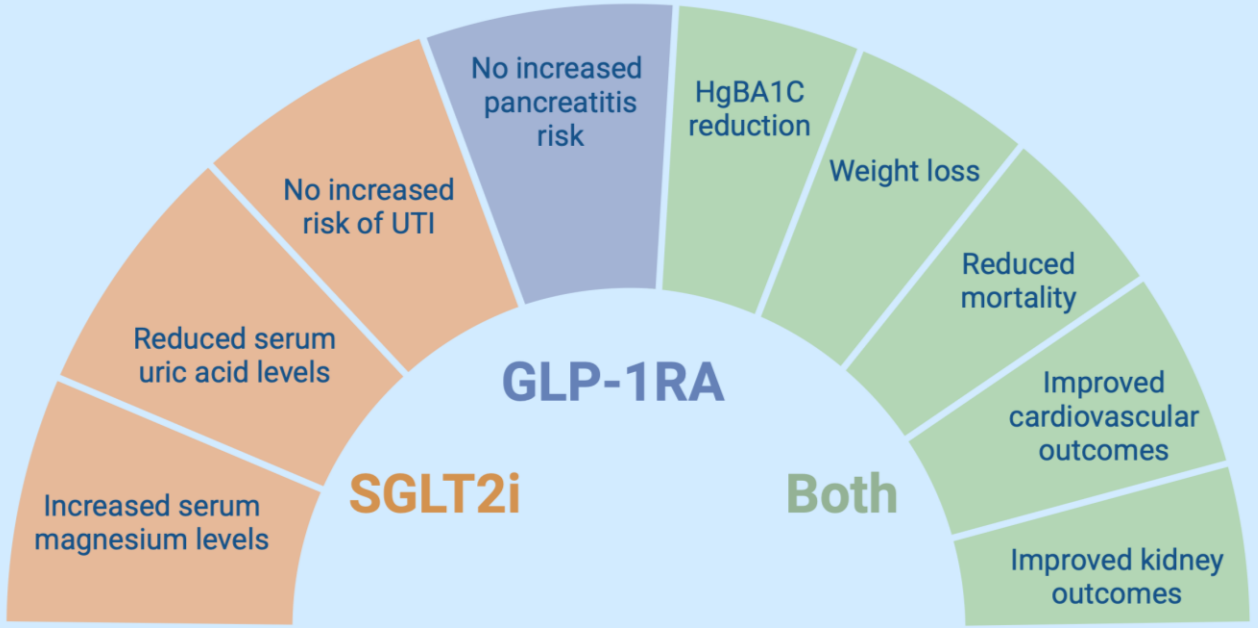
SGLT2i or GLP-1RA

COHORT

SGLT2i

GLP-1RA

RESULTS



Conclusion: The use of SGLT2i and GLP-1RA is associated with improved survival, cardiovascular, and kidney outcomes with a favorable safety profile in KT recipients.

Lee/Riella. *Transplantation*. 2025

@TransplantJrnl

Official Journal of The Transplantation Society

Transplantation®

MGH Guidelines - SGLT2 inhibitors in transplant recipients with diabetes

Use if:

- 6 months post-transplant
- eGFR >30 mL/min
- Stable immunosuppression
- No recurrent UTIs

Options: Empagliflozin 10 mg daily or Canagliflozin 100 mg daily

Monitor:

- Daily BP
- Creatinine/eGFR at 2, 4, and 8 weeks after initiation
- **Hold 3–4 days** before procedures (e.g., cath, colonoscopy); restart with normal diet

(↓ DKA risk)

If eGFR <30:

→ Consider **GLP-1 RA (e.g., dulaglutide)**

Case 3

75-year-old, 20 yrs post-transplant, 20 lb weight loss + night sweats

Exam: palpable allograft, enlarged femoral LNs

Next best step?

A) Kidney biopsy

B)PET- CT scan

C) Chest X-Ray

D) Abdominal X-Ray

E) Abdominal MRI

Case 3

75-year old, 20 yrs post-transplant, 20 lb weight loss + night

Exam: palpable allograft, enlarged femoral LNs

Next best step?

A) Kidney biopsy

B) PET- CT scan ✅

C) Chest X-Ray

D) Abdominal X-Ray

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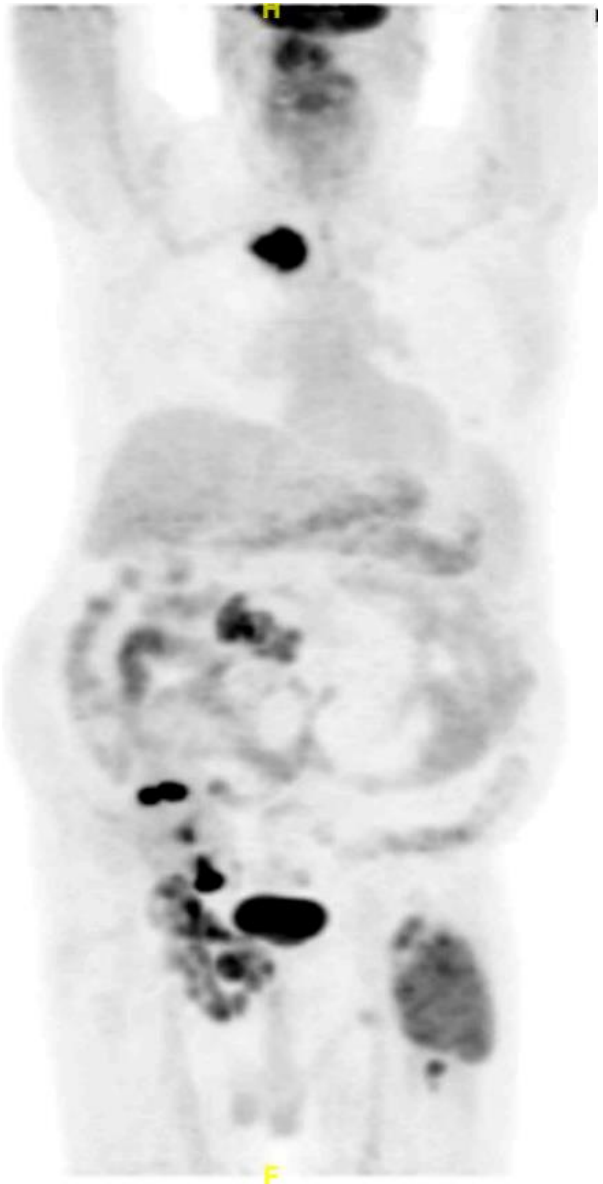
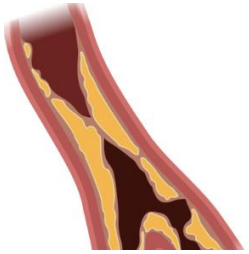


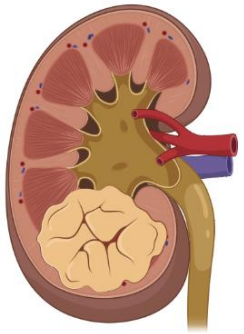
Key Point: PET-CT is best to assess suspected PTLD or other malignancy.

Objectives

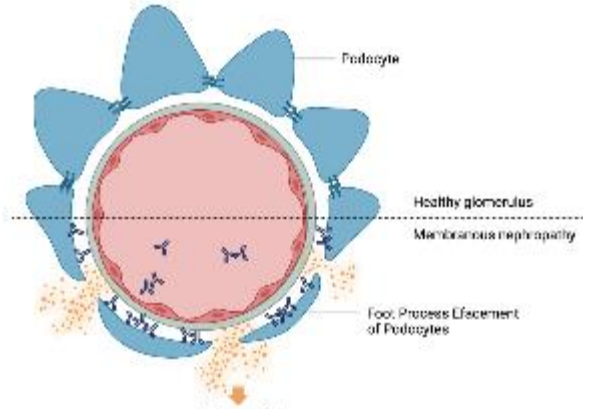


Heart disease

Diabetes



Cancer

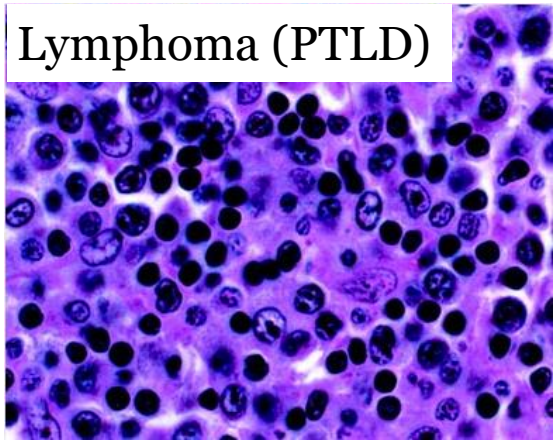


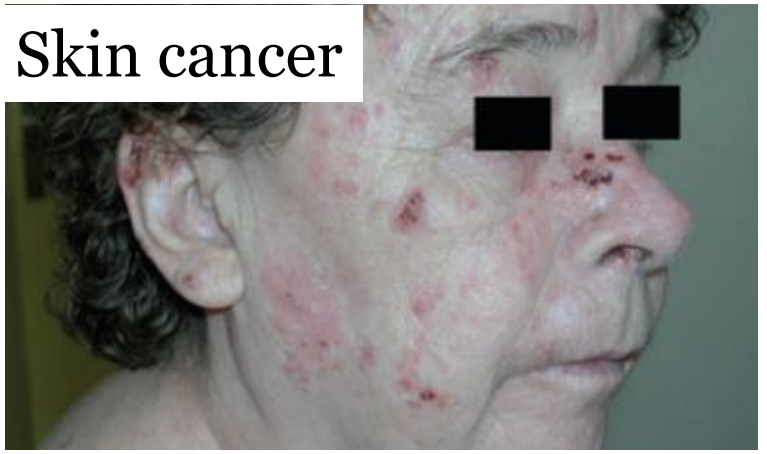
Recurrence of kidney disease

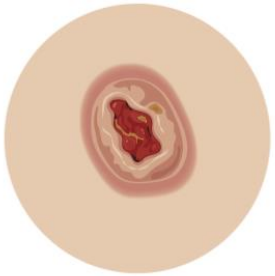
Post-Transplant Malignancies

most common malignancy after tx

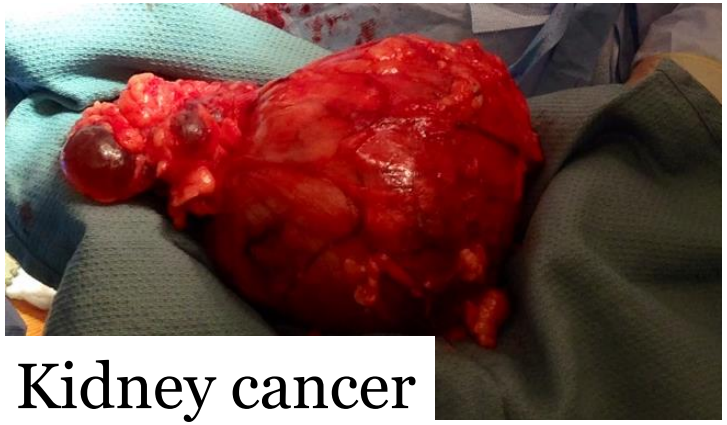
EBV

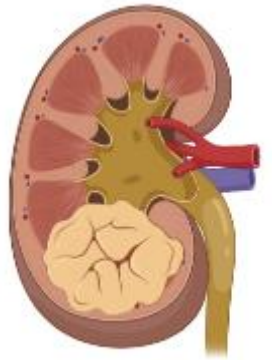






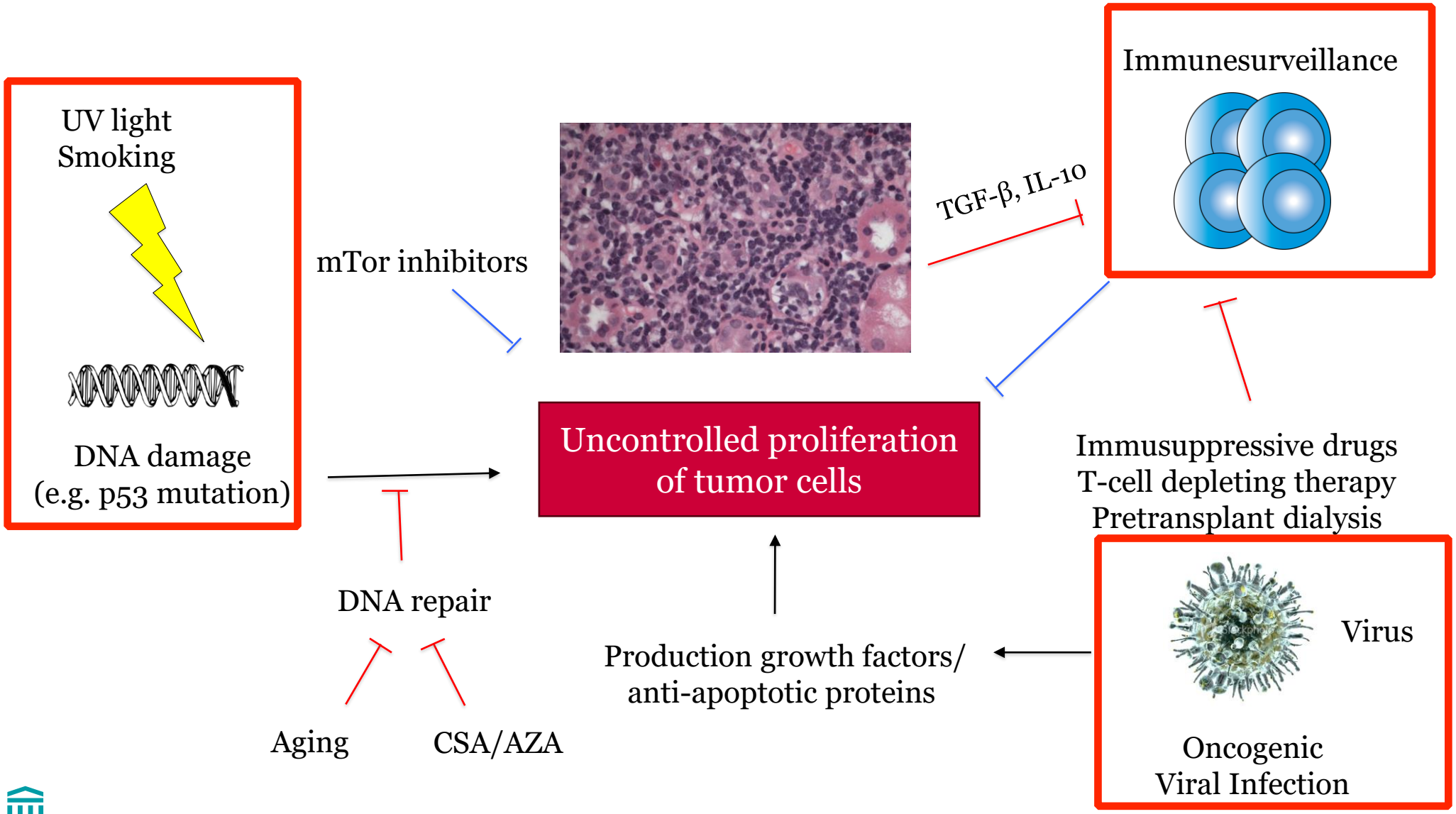
HHV-8





Engels et al. JAMA 2011; Van Leeuwen et al. BMJ 2010

Pathogenesis of Malignancy Post-Transplant



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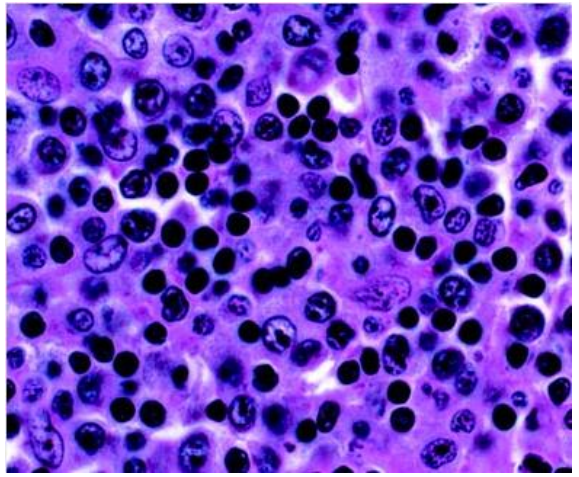
Post-Transplant Lymphoproliferative Disease (PTLD)

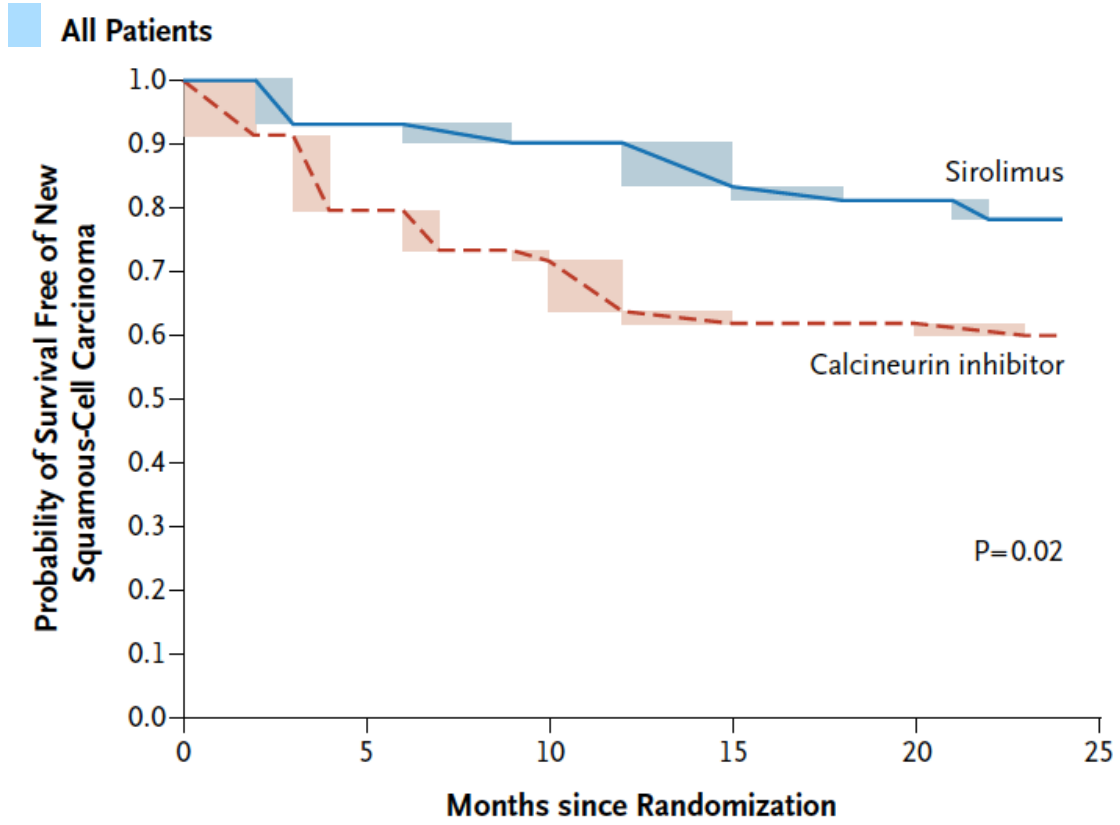


- Most common type: non-Hodgkin Lymphoma
- Peak incidence on first year after transplant
- Strong association with EBV infection (monitor VL)
- Major risk factors: EBV negative status, high degree of immunosuppression (rejection treatment) and CMV co-infection
- Treatment:
  - reduction of immunosuppression,
  - anti-CD20 therapy (rituximab) and/or chemotherapy

Nourse et al. Am J Transplant. 2011
Dhamidhark VR. Am J Transplant. 2017
Sprangers, Riella, Dierickx AJKD 2021

mTOR inhibitor in Secondary Skin Cancer Prevention

- Multicenter trial (n=120): pts on CNI and at least 1 SCC were randomized 1:1 to sirolimus or CNI continuation.
- Primary end-point: survival free of SCC at 2 years



Relative risk: 0.56 (0.32-0.98)

60 serious adverse event mTORi (lung,GI)
vs 14 in CNI group
23% discontinuation rate mTORi
Graft function stable on both groups

Euvrard et al. N Engl J Med 2012.

Case 4

Kidney transplant recipient with advanced squamous cell cancer being considered for immune checkpoint inhibitors (ICIs) therapy.

Which is most accurate about immune checkpoint inhibitors (ICIs) post-tx?

A. ICIs contraindicated in all cases
B. 40% risk of rejection with ICI use
C. Safe without immunosuppression change
D. Rejection not a concern if EBV-negative
E. Combine with CNI to reduce tumor growth

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Key Point: ICI therapy poses high rejection risk; requires careful selection.

A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant

Retrospective cohort study (2010-2020)

International Multi-center (23 institutions)

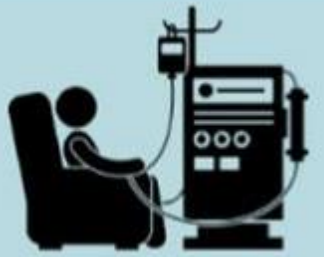
Kidney transplant recipients (n=69)

ICI therapy for advanced cancer (aPD-1, aPD-L1, aCTLA-4)

Safety

Acute rejection **42%**

Time to rejection **24 days**



Graft loss **65%** of rejection

Efficacy: Tumor response to ICI therapy (complete response + partial response)

Skin squamous cell carcinoma (n=24) **36%**

Melanoma (n=22) **40%**

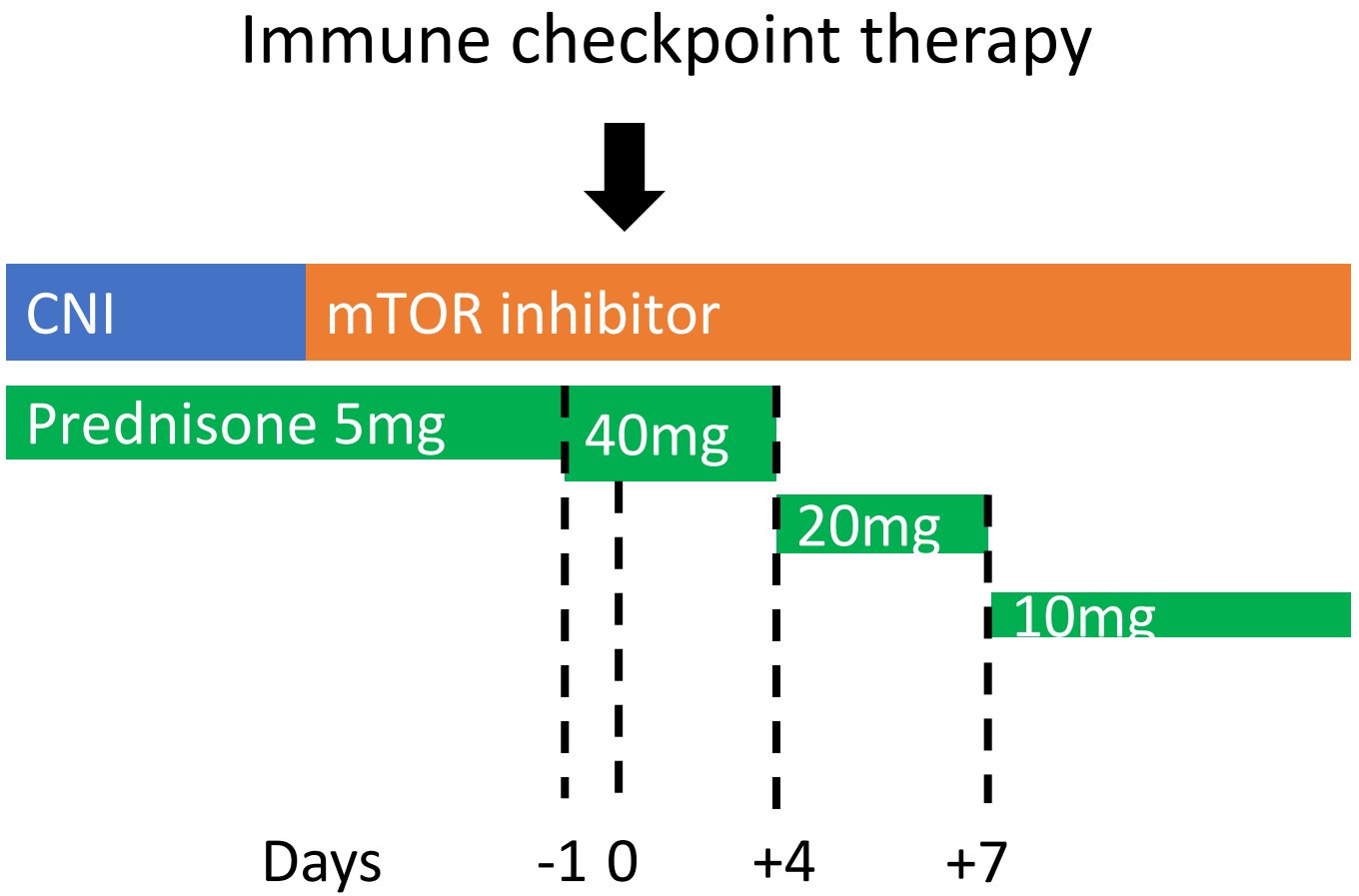
CONCLUSION:

Immune checkpoint inhibitors are associated with high acute rejection rate but result in reasonable tumor response.

kidney INTERNATIONAL ISN

Murakami et al, 2020

Rejection Preventive Strategy for ICI in advanced skin cancer

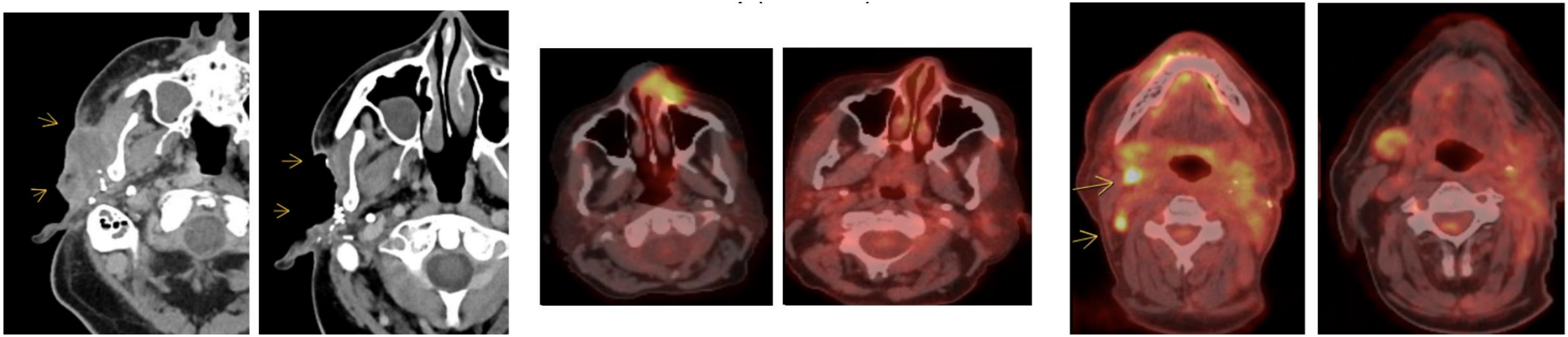


Maintain on pred 10mg while receiving cycles

Clinical trial: Hanna (Dana Farber) and Riella (BWH)

Phase 1 study of cemiplimab for kidney transplant recipients with advanced cutaneous squamous cell cancer (aSCC)

12 patients were treated with anti-PD1 antibody for aSCC.
No kidney rejection or loss was observed.
A response to cemiplimab was observed in 5 of 11 evaluable patients (45%; 90% confidence interval [CI], 22- 78) including 2 with durable responses beyond a year.

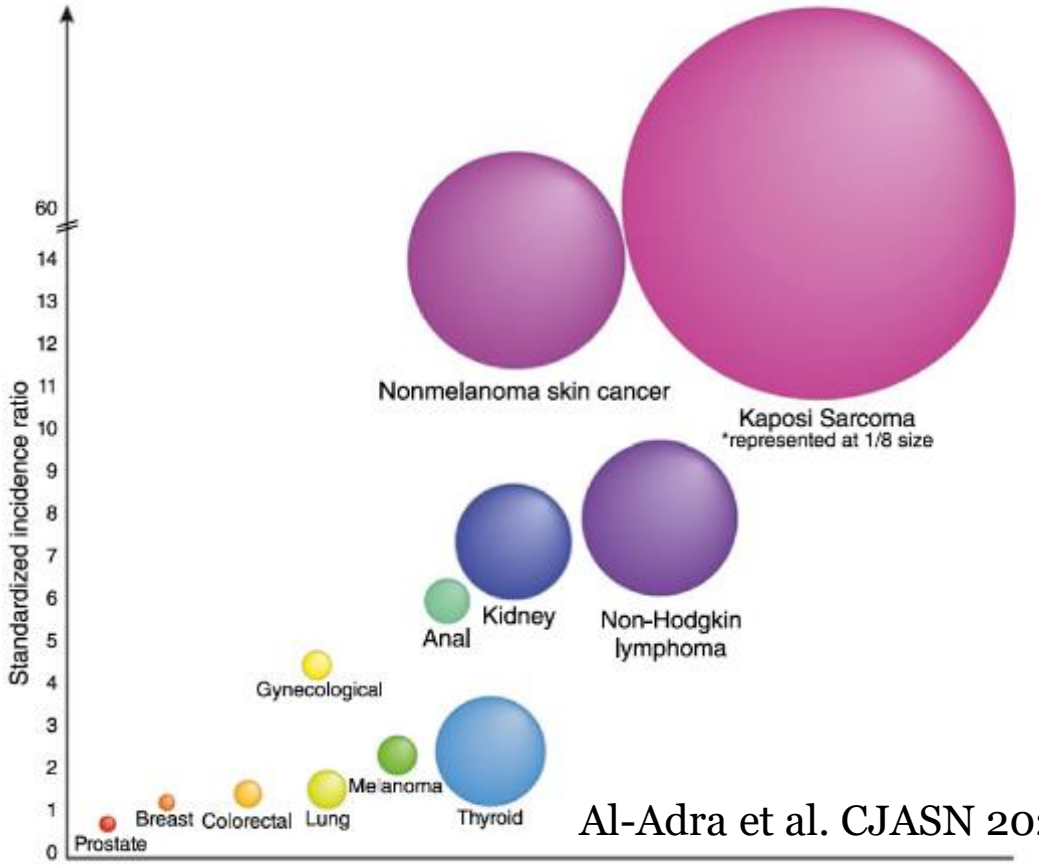


Hanna … Riella, Sik. Journal of Clinical Oncology 2024

Adjusting Immunosuppression in Cancer

- Tailor based on **cancer type and stage**
- **Never fully stop immunosuppression**
- Some cancers are more sensitive to immunosuppression.
- **Hold MMF** during cytotoxic chemotherapy
- **mTOR inhibitors** may help in:
  - Squamous cell carcinoma
  - Kaposi sarcoma
  - Kidney cancer

SIR of different cancers in kidney recipients compared to age and sex-matched gen pop.



Al-Adra et al. CJASN 2022

Riella LV. Kidney Transplant iBook 2019

Case 5

Which best predicts recurrence of membranous nephropathy after transplant?

A. Proteinuria pre-transplant
B. Time on dialysis
C. Anti-PLA2R antibody >150 RU/mL pre-transplant
D. HLA-DR mismatch
E. Donor-specific antibodies

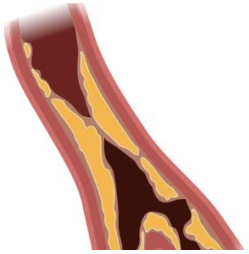
Case 5

Which best predicts recurrence of membranous nephropathy after transplant?

A. Proteinuria pre-transplant
B. Time on dialysis
C. Anti-PLA2R antibody >150 RU/mL pre-transplant ✅
D. HLA-DR mismatch
E. Donor-specific antibodies

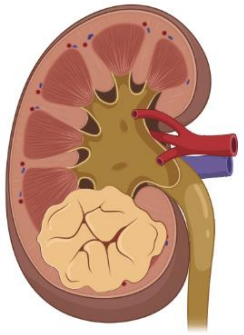
Key Point: Anti-PLA2R levels guide recurrence risk stratification.

Objectives

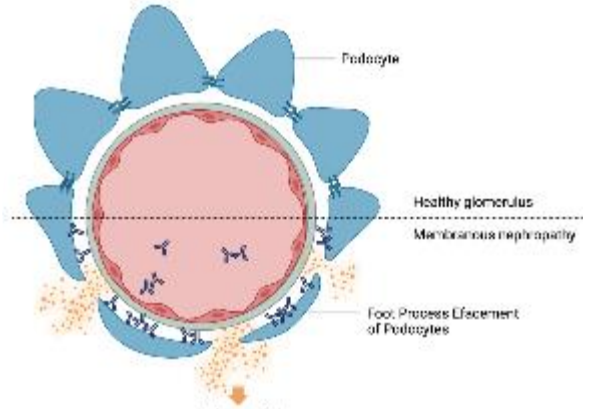


Heart disease

Diabetes

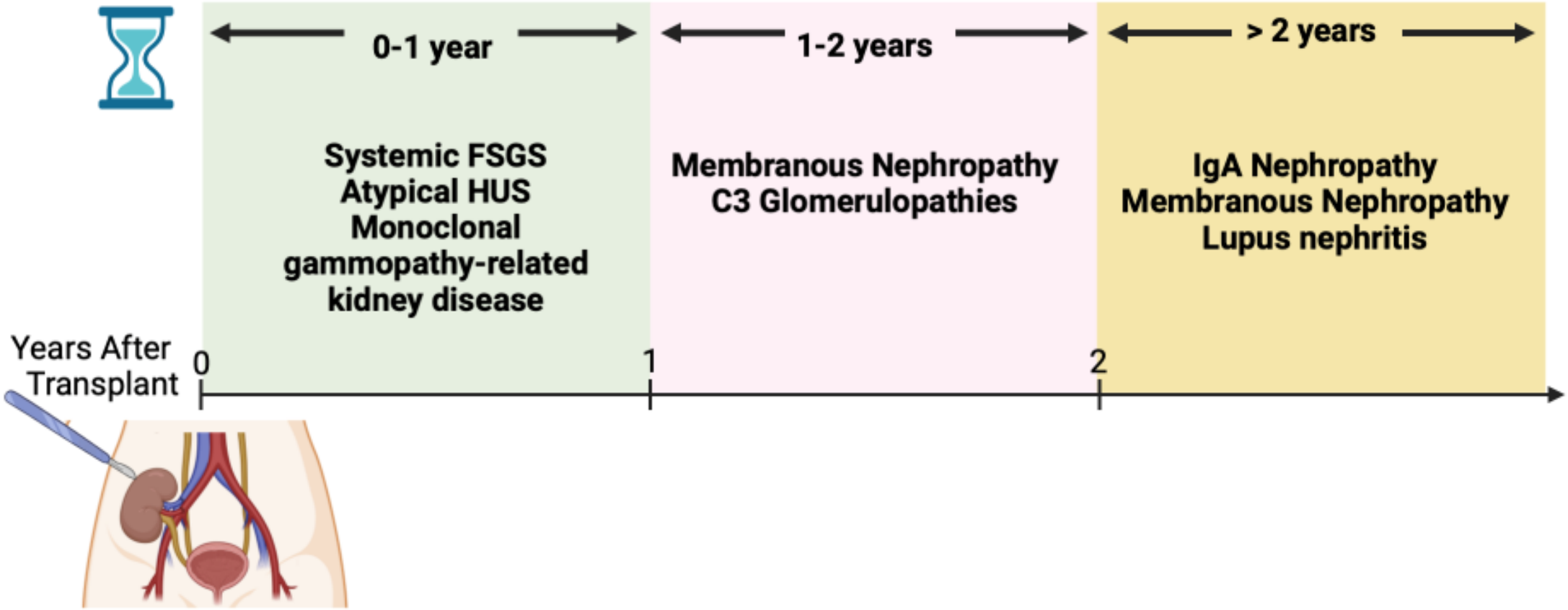


Cancer



Recurrence of kidney disease

Recurrence of glomerular diseases post-transplantation



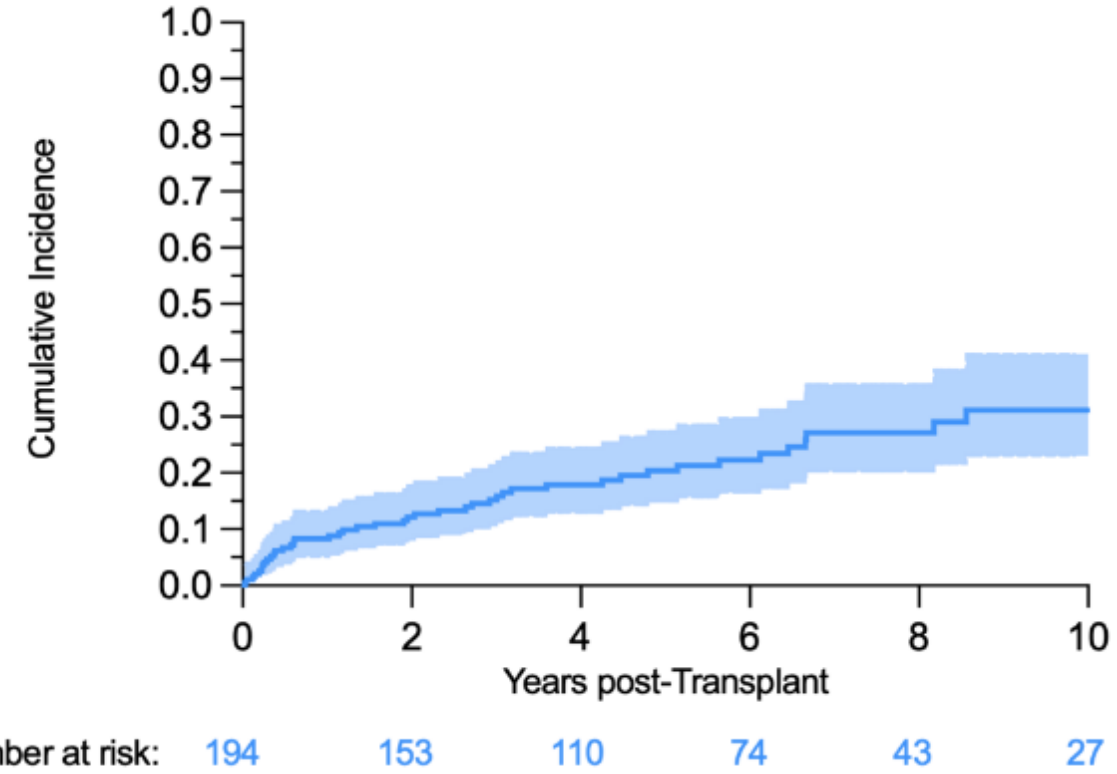
Efe, Riella LV. Kidney Transplant iBook 2019
Uffing, Hullekes, Riella CJASN 2021

Rate of Membranous Nephropathy Recurrence

Incidence of recurrence: 31% (95% CI: 0.23-0.41) at 10 years post-transplant

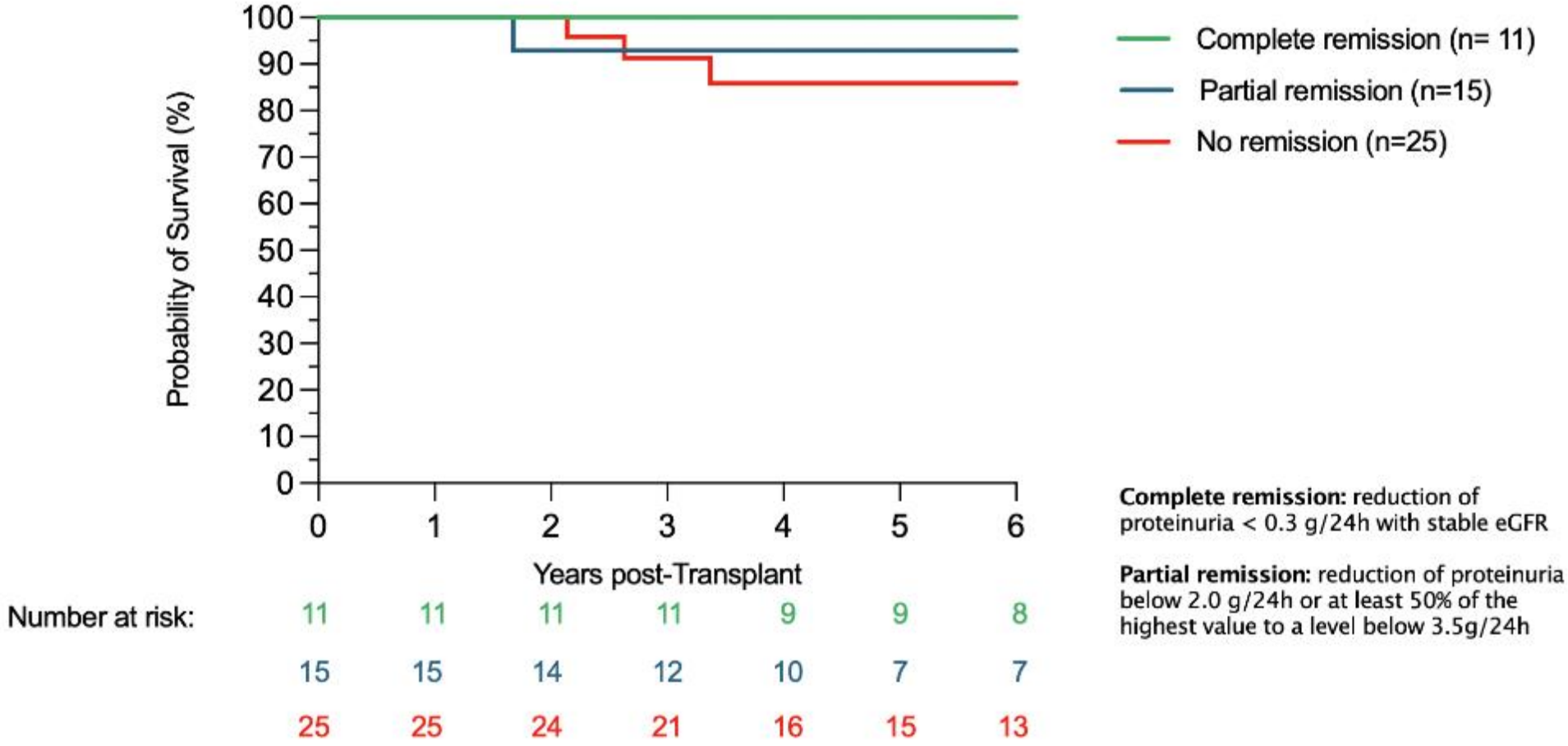
22,921 patients screened
Across 18 transplant centers

194 patients with biopsy-proven MN were included



Hullekes et al. AJT 2024

Graft survival after Membranous Recurrence



19 patients received rituximab and complete/partial remission 68%
17 patients only received ACEI/ARB and complete/partial remission 29%

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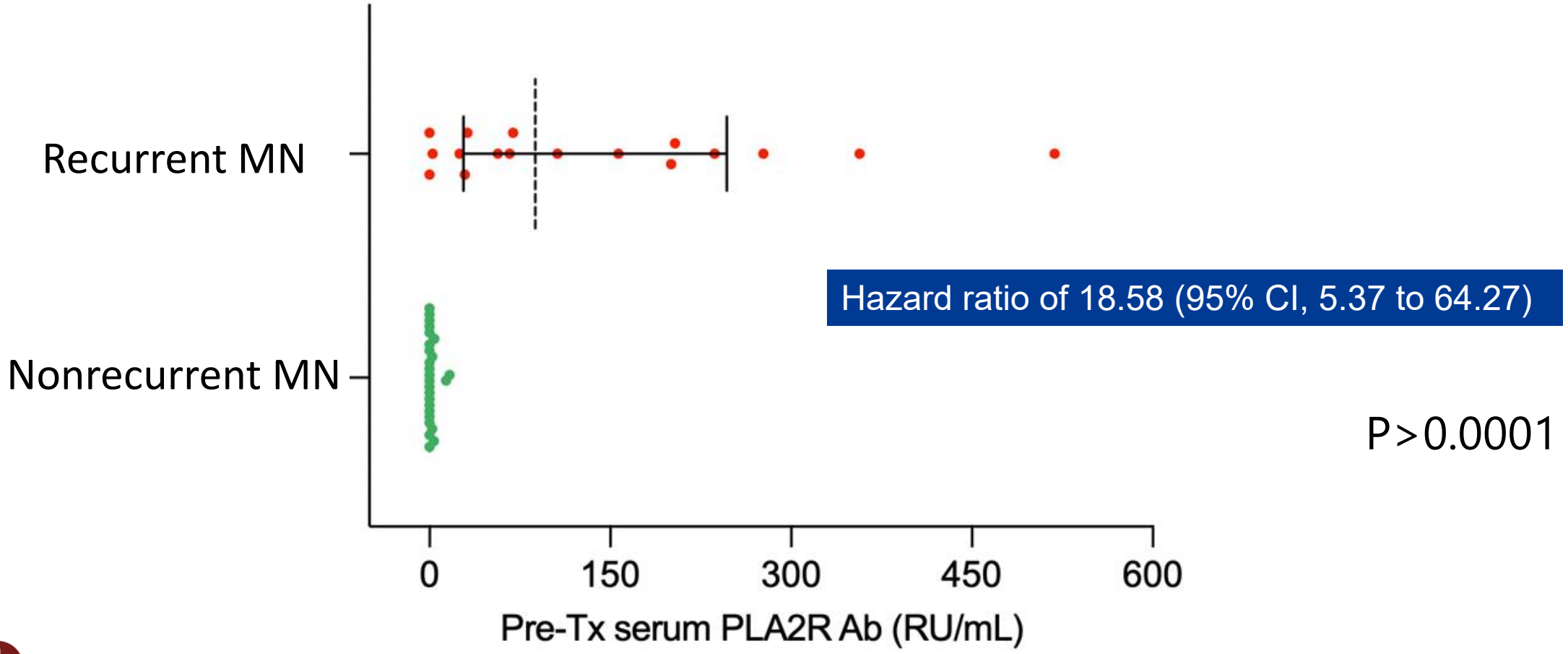
Positive anti-PLA2R antibodies at time of transplant were strongly associated with recurrence



- Bernie (PLA2R assay)

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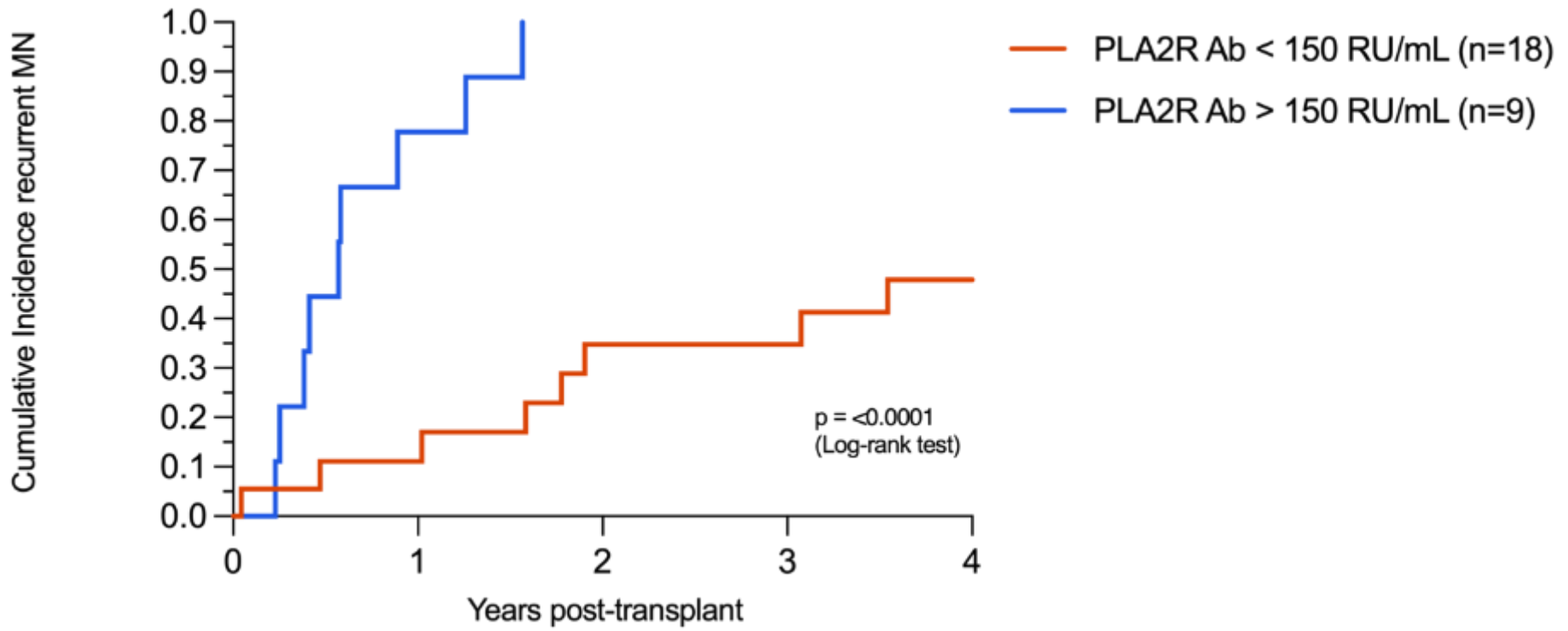
Patients with pre-Tx PLA2R Ab > 150 were earlier diagnosed with recurrence



Group	Median Timing Post-Tx (years)	IQR (25-75%)
PLA2R Ab > 150 (n=18)	0.57 years	0.38 to 0.89 years
PLA2R Ab < 150 (n=9)	1.77 years	0.75 to 3.31 years

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Take Home Messages

- Leading cause of death → cardiovascular disease
- Tacrolimus → diabetes
- Cancer post-transplant → association with viral infection and immunosuppression
- Immune checkpoint inhibitors → ~40% of kidney recipients.
- Anti-PLA2R antibody predicts recurrence risk

Top References

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Clinical Trials

Clinical Trials	Change in Management
Vincent et al. NEJM 2016	Belatacept is associated with improved kidney function and lower mortality – consider belatacept in recipients EBV IgG+
Euvrard et al. N Engl J Med 2012	mTOR inhibitors reduces recurrence of SCC – consider mTOR inhibitor conversion
Thomush et al. Lancet 2016	Steroid withdrawal associated with lower rate of post-transplant DM – consider steroid withdrawal in patients at risk of diabetes post-transplant
Lim et al .Transplantation 2022	Favorable outcomes of SGLT2 inhibitors in diabetics post-transplantation
Hanna, … Riella, Sik. Journal of Clinical Oncology 2024	Consider mini-pulse of steroids with immune checkpoint inhibitor treatment after transplantation
Hullekes et al. Am J Transp 2024	Anti-PLA2R antibody testing at time of transplant may help stratify risk of membranous nephropathy recurrence after transplantation

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Abbreviations

ACEI = ACE inhibitor
AVN = avascular necrosis
AZA = azathioprine
CCB = calcium channel blocker
CMV = cytomegalovirus
CNI = calcineurin inhibitors
CSA= cyclosporine
CV = cardiovascular
EBV = Epstein Bar Virus
FGF-23 = fibroblast growth factor 23
HTN = hypertension
IS = immunosuppression
MMF= mycophenolate mofetil
NODAT= new onset diabetes after tx
PTH = parathyroid hormone
RAS = renal artery stenosis
RCC= renal cell carcinoma
TAH= transplant-associated hyperglycemia
Tx = transplantation
VL = viral load