

# Late Post-Transplant Medical Complications

**Leonardo V. Riella, MD, PhD**

*Harold and Ellen Danser Chair in Transplantation*

*Director of MGH Kidney Transplant Program*

*Senior Investigator at the Center for Transplantation Sciences*

*Massachusetts General Hospital*

*Associate Professor of Medicine and Surgery, Harvard Medical School*

# Leonardo V. Riella, MD, PhD, FASN, FAST



Harold & Ellen Danser Chair in Transplantation @Harvard  
Associate Professor of Medicine & Surgery  
Director, Kidney Transplant Program @MGH

## **Clinical & Research Focus:**

Transplant immunology, glomerular disease recurrence,  
xenotransplantation



# Disclosure of Financial Relationships

Investigator-initiated research with Bristol Meyers Squibb, CareDx, Astra-Zeneca, Veloxis, and Visterra.

Industry-sponsored research from Sanofi, eGenesis, Vertex and Hansa.



# Goals of the talk



What are the most common complications late post-transplantation?



What are the underlying mechanisms involved in these complications?



What are transplant-specific treatment options?

# 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



# Case 1

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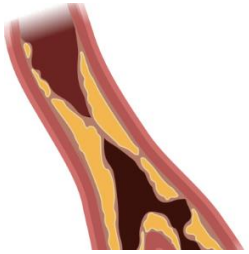
What is the most likely cause of death in kidney transplant recipients with a functioning graft?

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

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



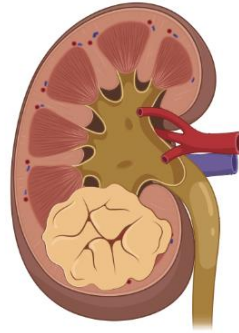
# Objectives



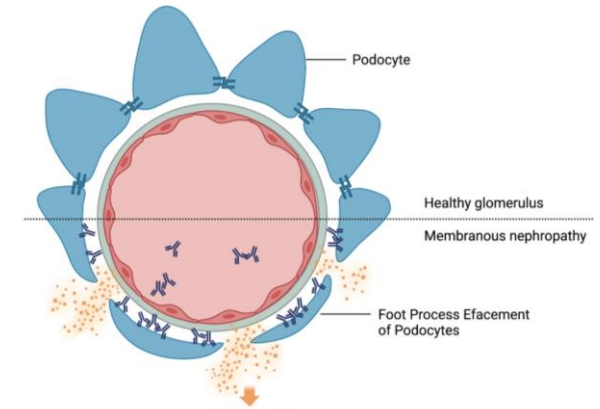
Heart  
disease



Diabetes

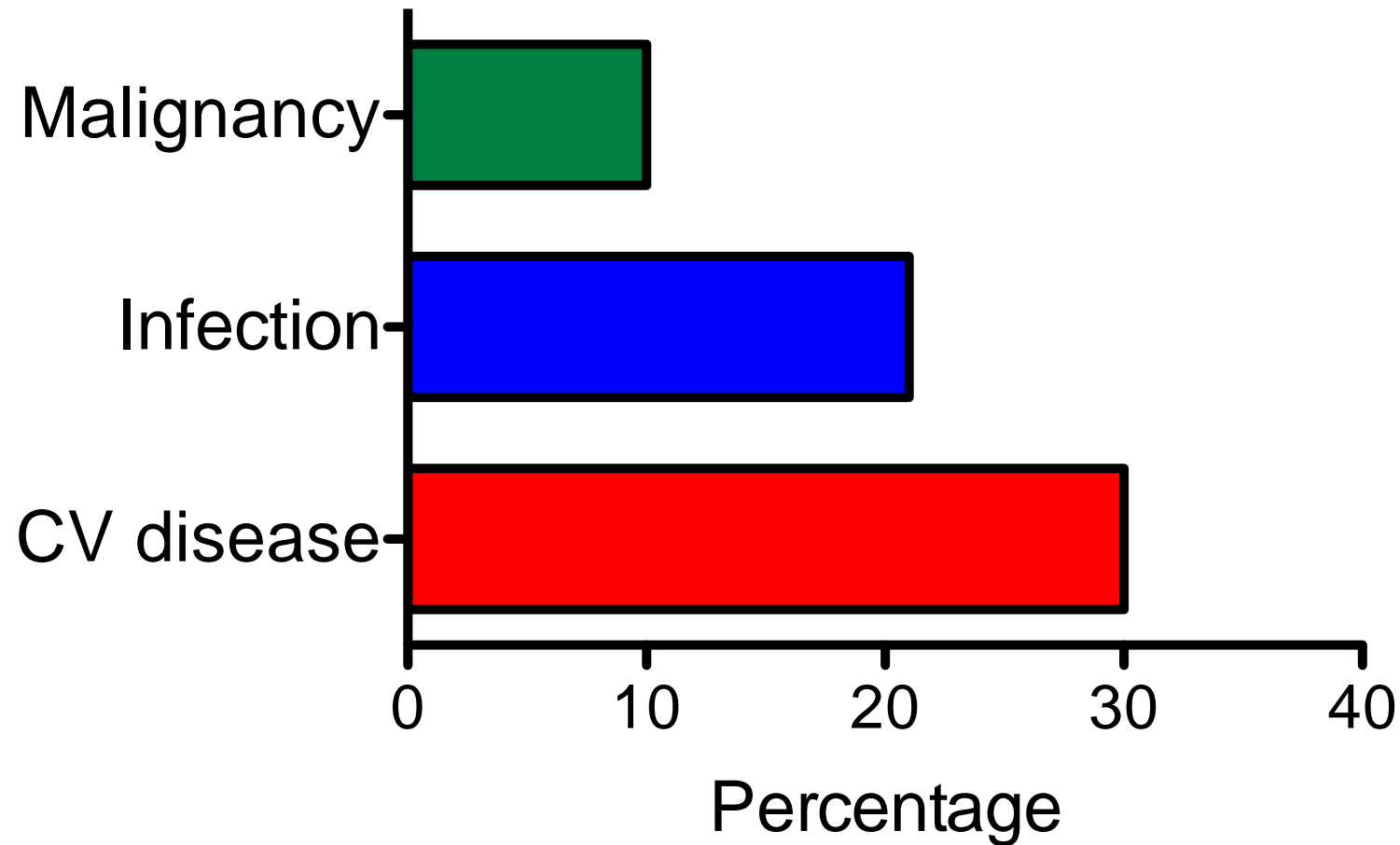


Cancer



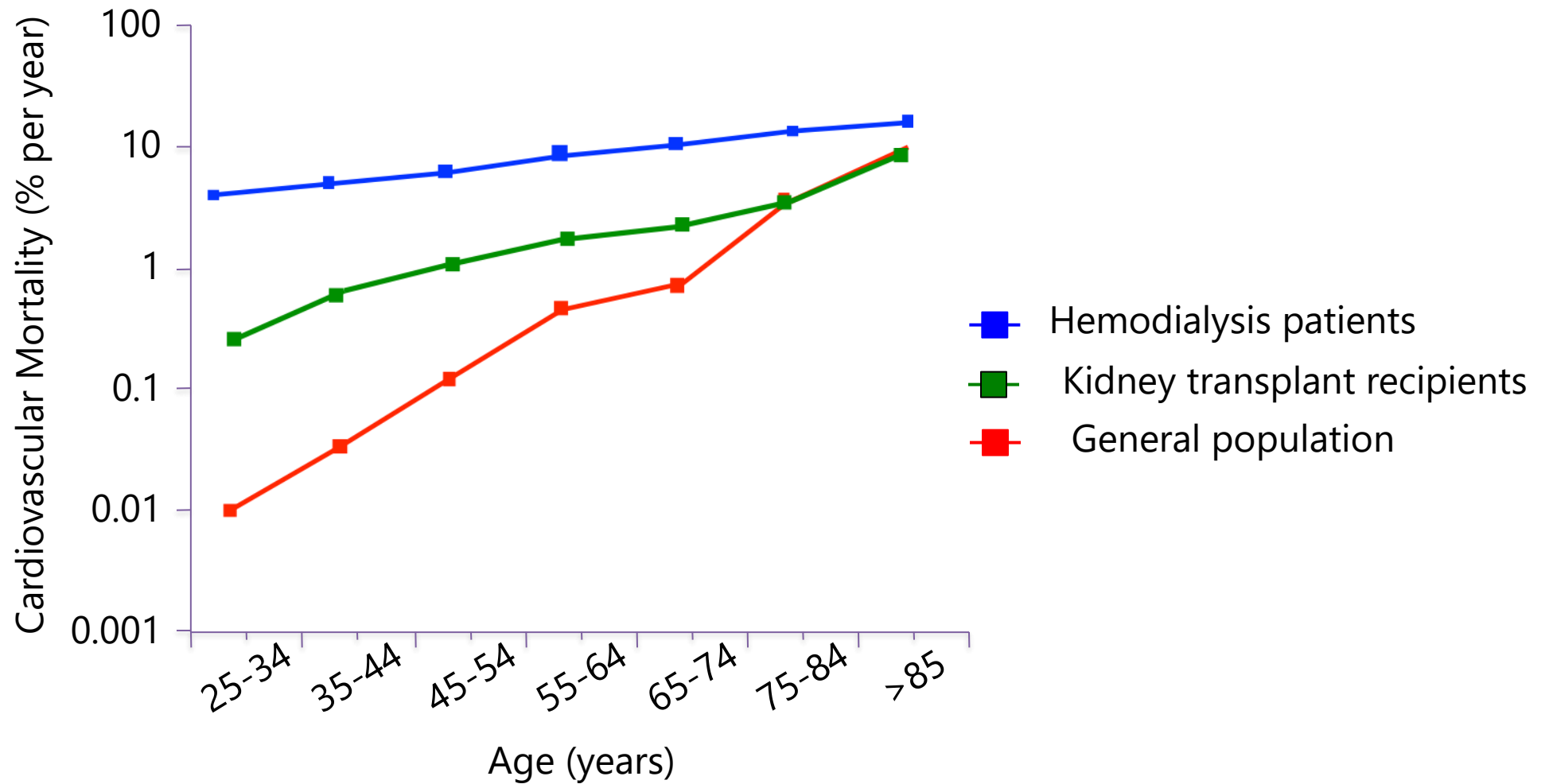
Recurrence of  
kidney disease

# Causes of death with a functioning graft

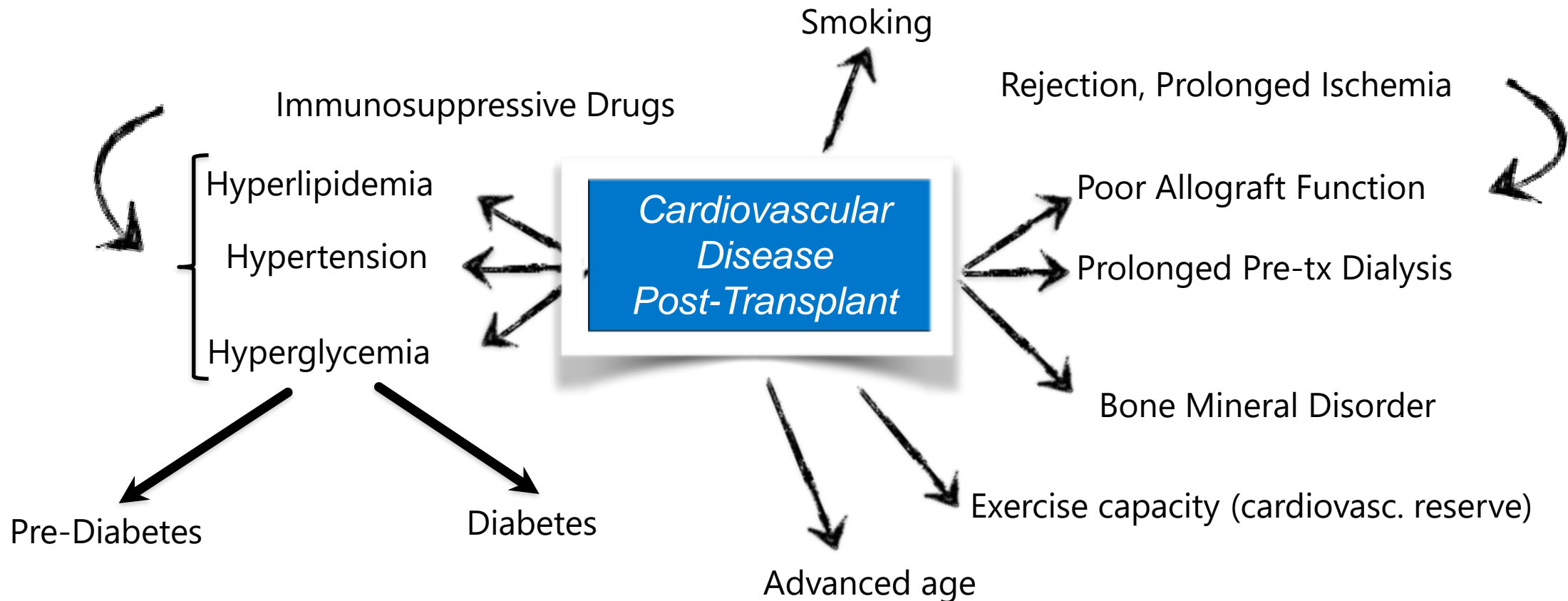




# Cardiovascular mortality by age group



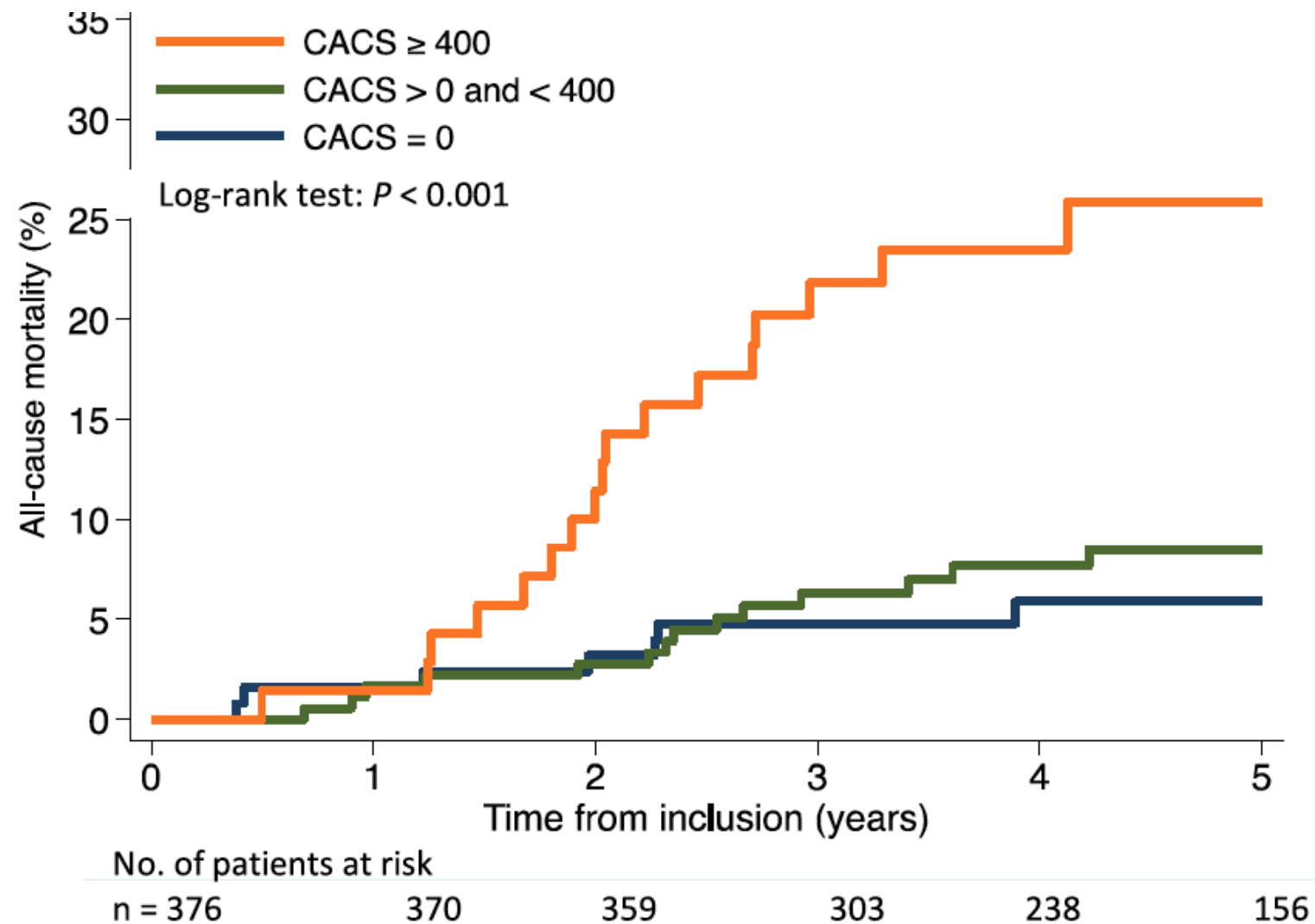
# Risk Factors for CV Disease after Kidney Transplantation



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

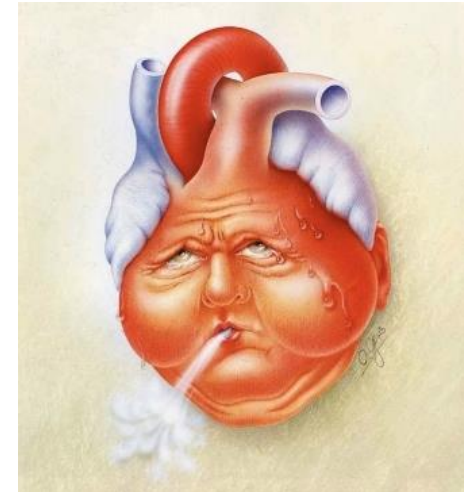
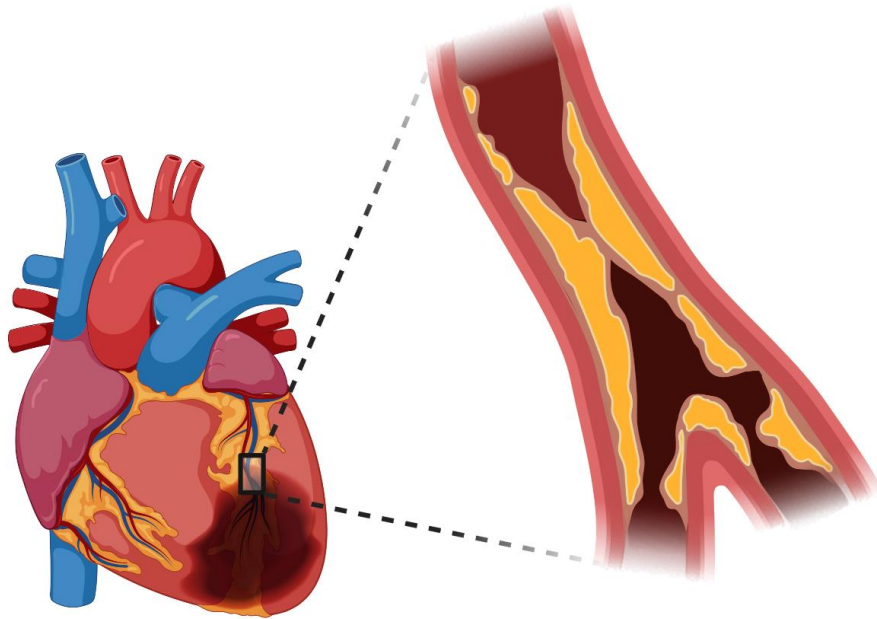


# Coronary artery calcium score and all-cause mortality



# Heterogenous Heart Disease after Kidney Transplantation

- Myocardial infarction is associated with dyslipidemia, age and diabetes
- Cardiac death is associated with severe hypertension, left ventricular hypertrophy and poor graft function.



# Immunosuppression impact on CV risk factors

Side Effects	CsA	Tacrolimus	mTOR inhibitor	Prednisone	MMF	Belatacept
<b>Hypertension</b>	++	+		++ (high dose)		
<b>Nephrotoxicity</b>	+++	++	+			
<b>Dyslipidemia</b>	++	+	+++	+		
<b>Hyperglycemia</b>	+	++	+	++		

To improve CV outcomes, we must manage complications aggressively and reduce immunosuppression when possible.  
Consider ASA and statin in high CV risk patients.



## 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  $\beta$ -cell dysfunction
- D. SGLT2 upregulation
- E. CMV-triggered insulinitis



## Case 2

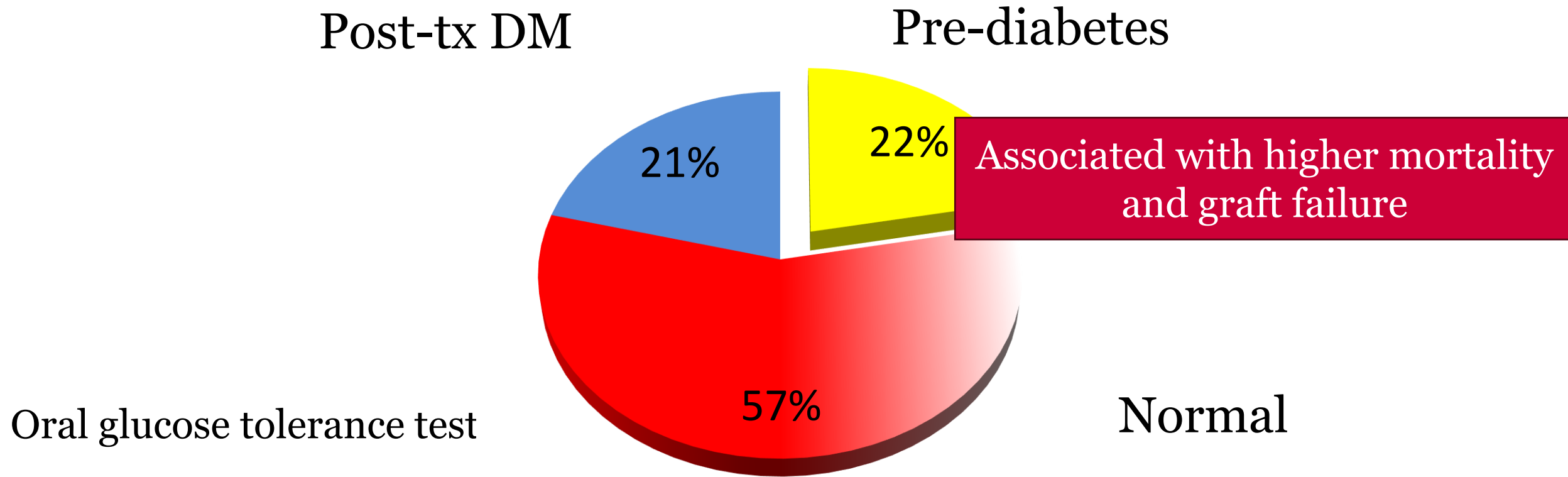
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- E. CMV-triggered insulinitis

Key Point: Tacrolimus impairs  $\beta$ -cell function, leading to post-Tx diabetes.



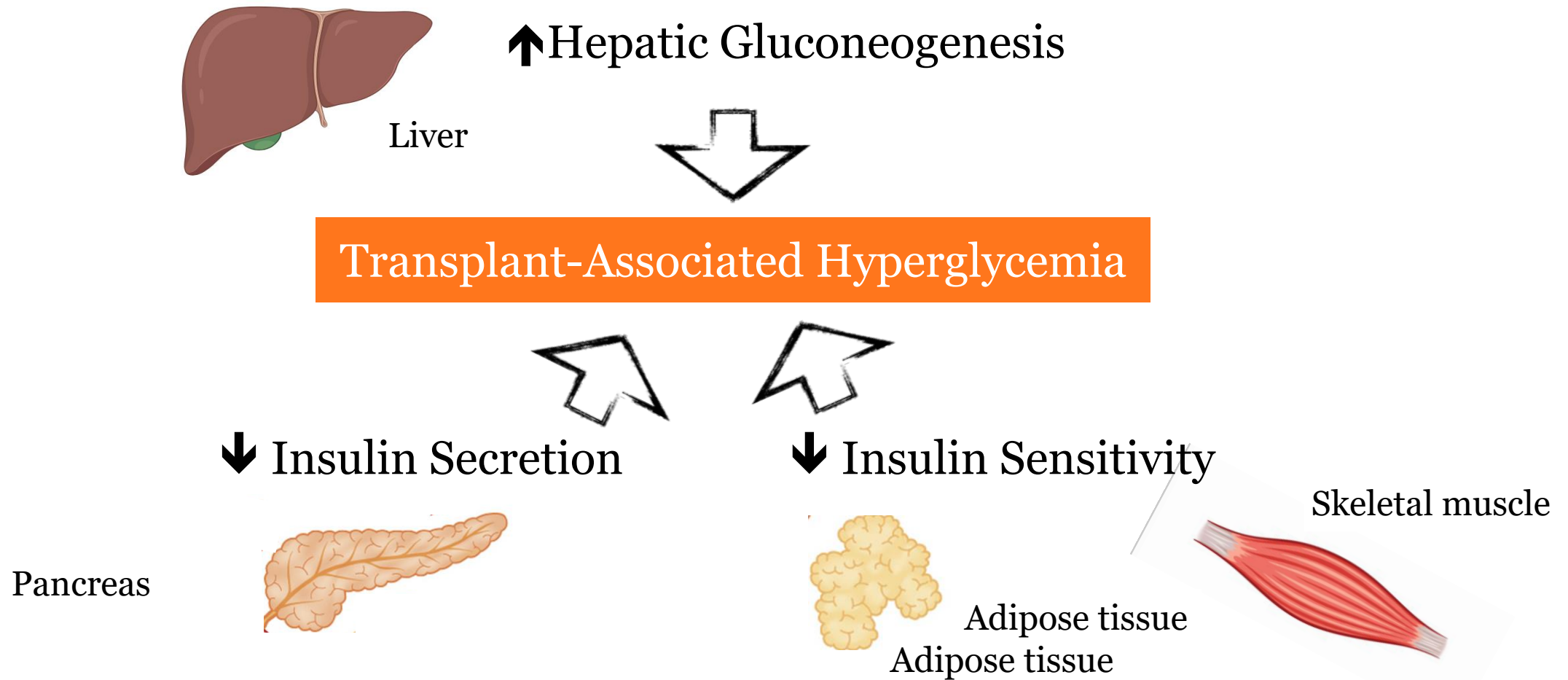
# Prevalence of Transplant-Associated Hyperglycemia (TAH)



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



# Pathogenesis of Hyperglycemia



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

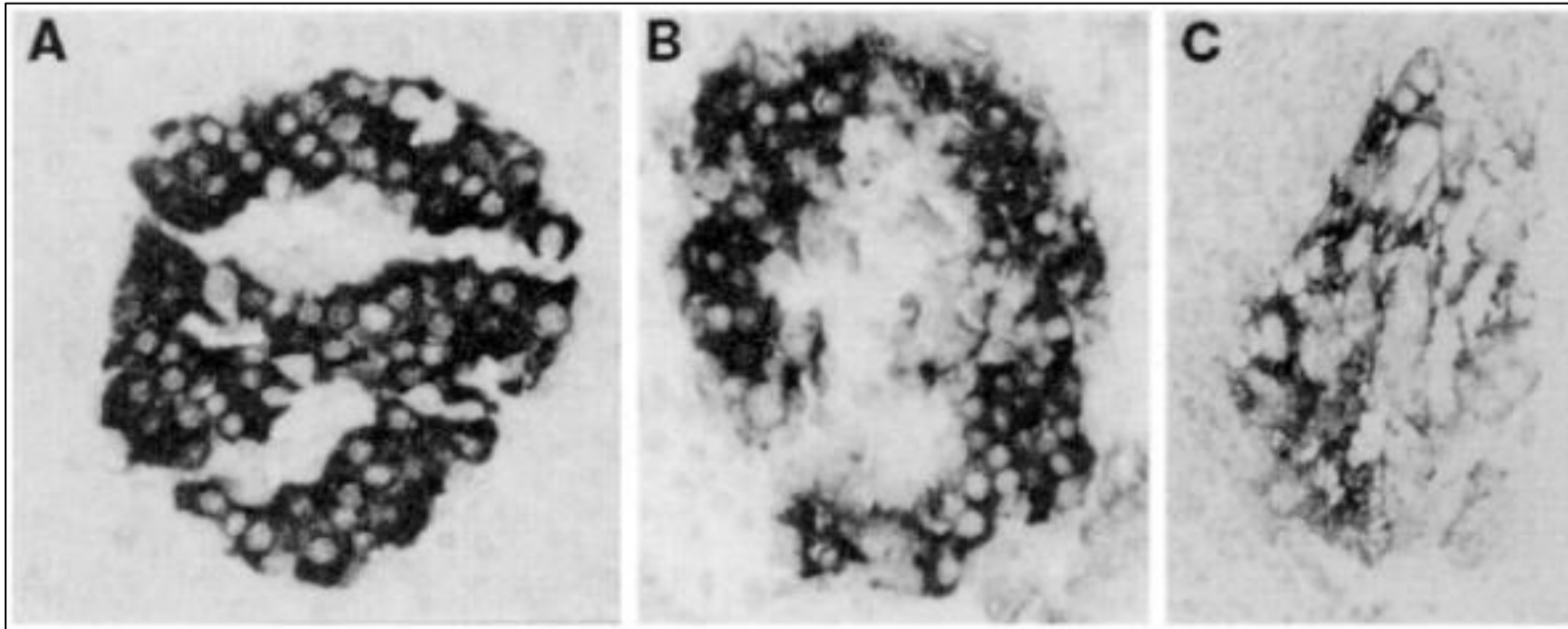


# Effects of Calcineurin Inhibitors on Pancreatic $\beta$ Islet Cells

Control

Cyclosporine

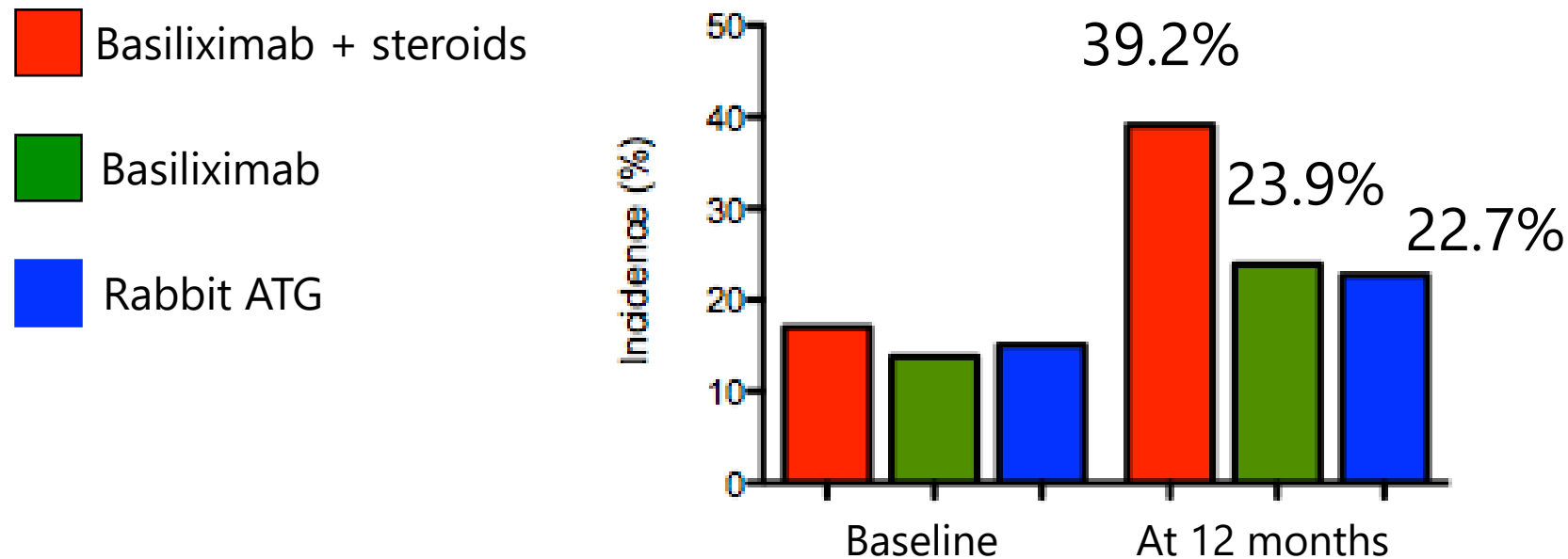
Tacrolimus



Insulin Staining (black)

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

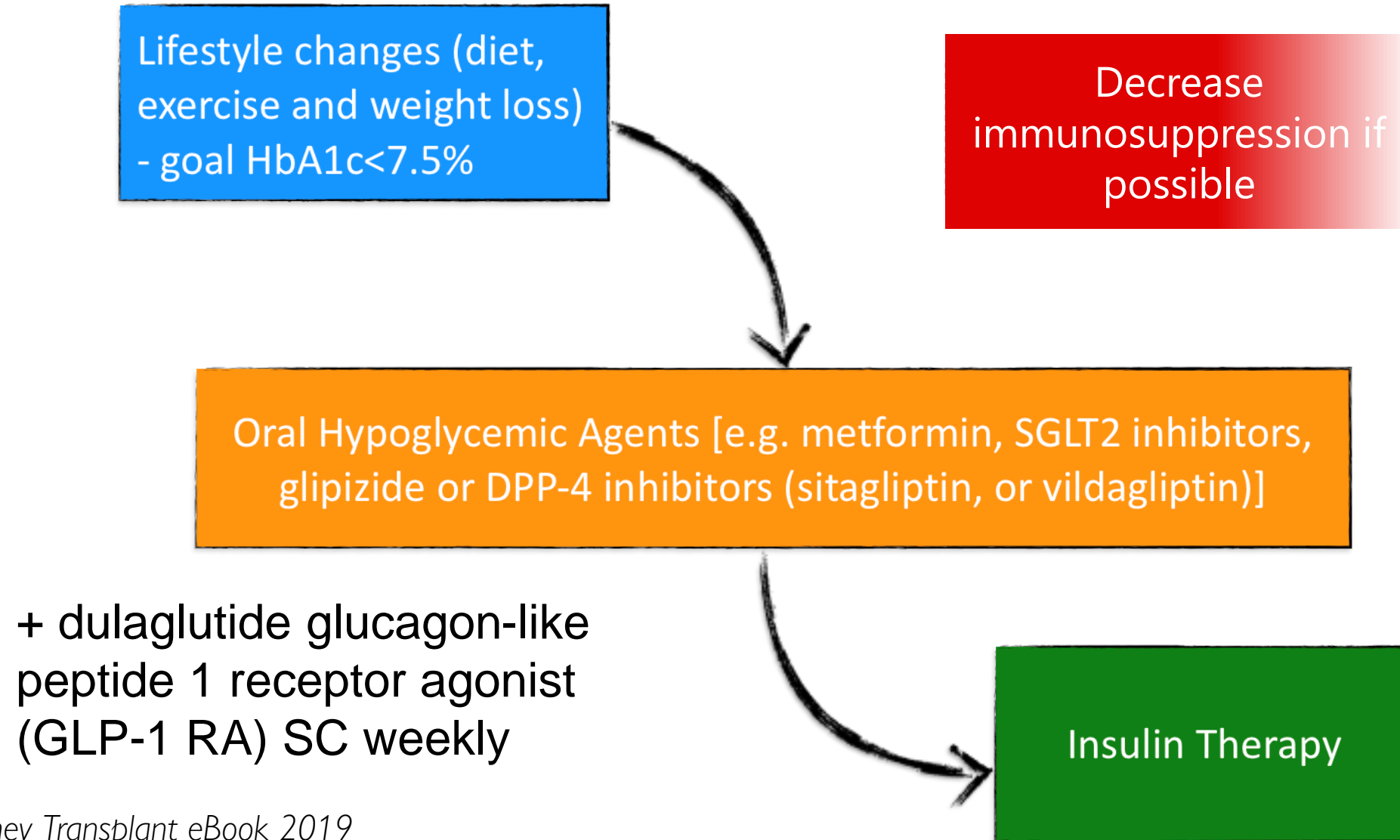
Randomized trial of different induction therapies with or without steroid withdrawal  
~200 patients on each group



\* All groups received high-dose steroids early after tx



# Management of Post-tx DM - Stepwise Approach



# 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

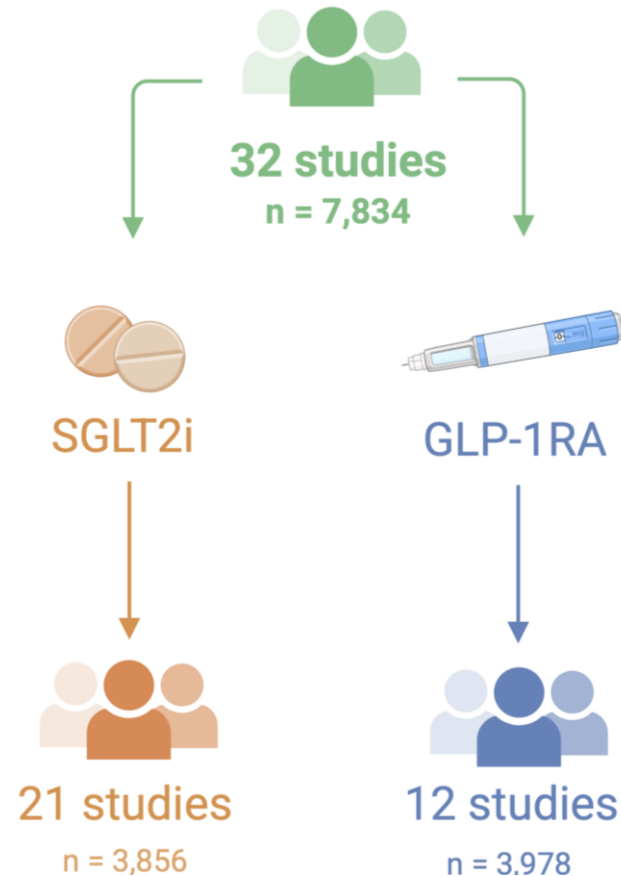


Kidney transplant recipients

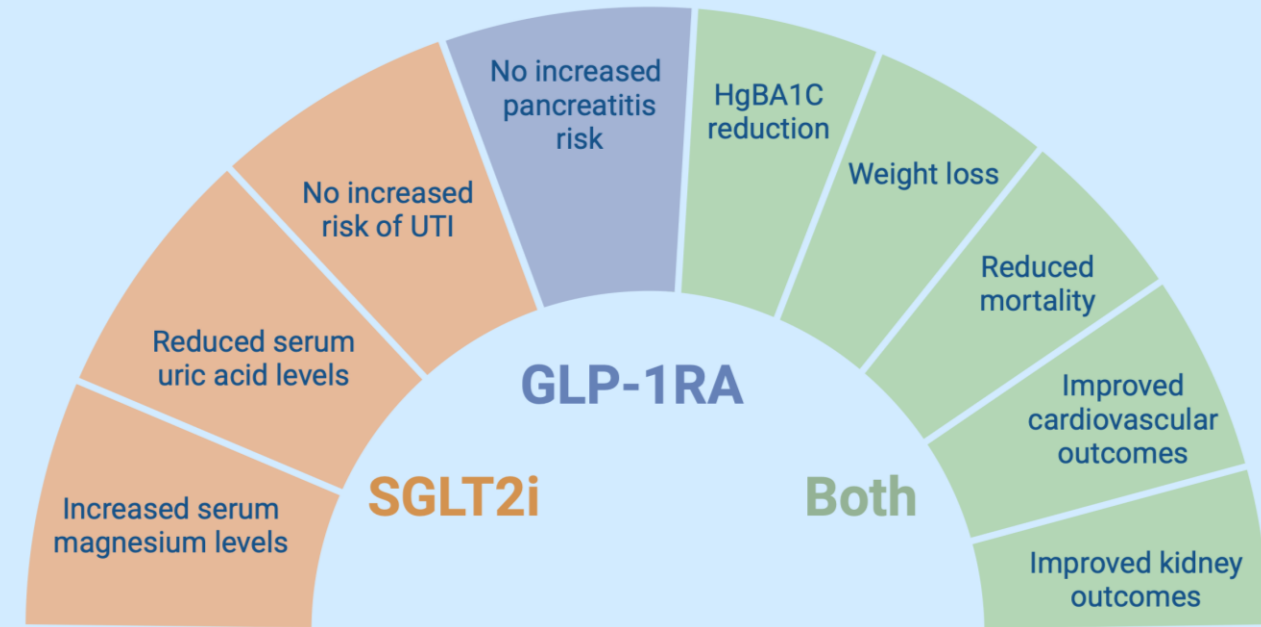


SGLT2i  
or  
GLP-1RA

## COHORT



## 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

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# 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



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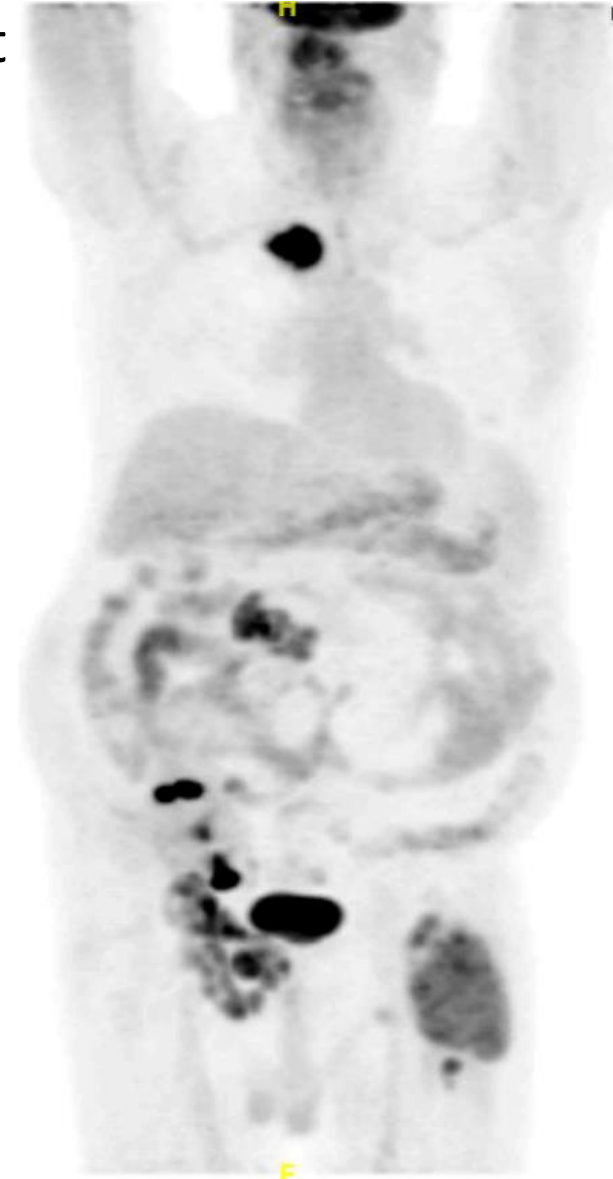
B) PET- CT scan ☒

C) Chest X-Ray

D) Abdominal X-Ray

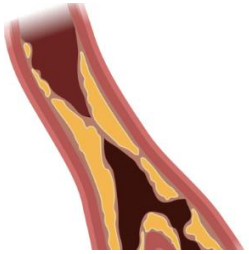
E) Abdominal MRI

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





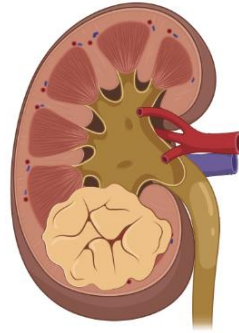
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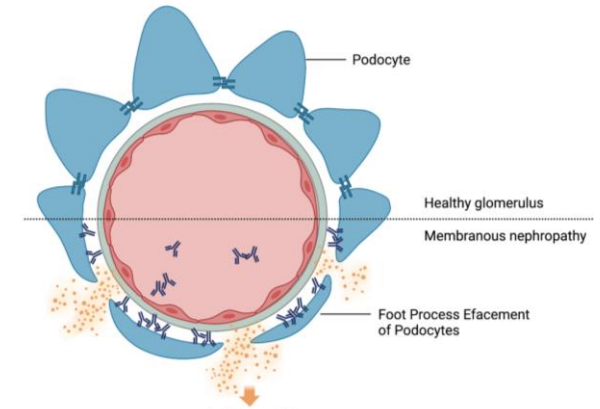
Heart  
disease



Diabetes



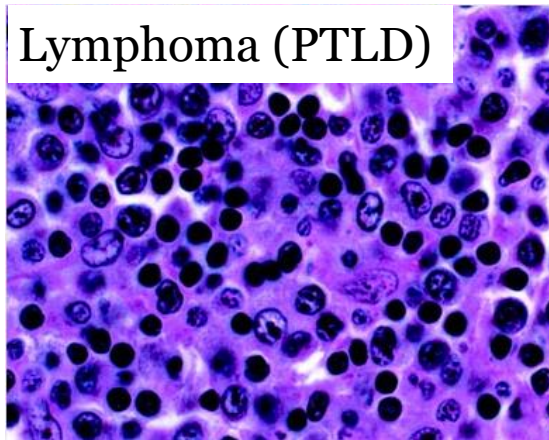
Cancer



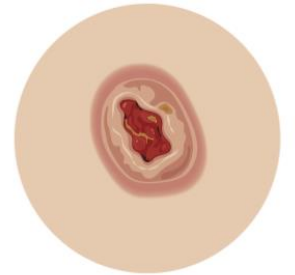
Recurrence of  
kidney disease

# Common Post-Transplant Malignancies

EBV



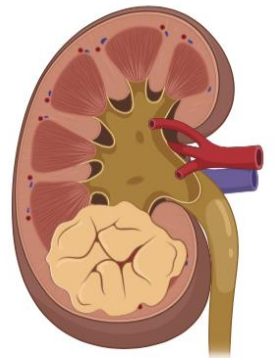
Skin cancer



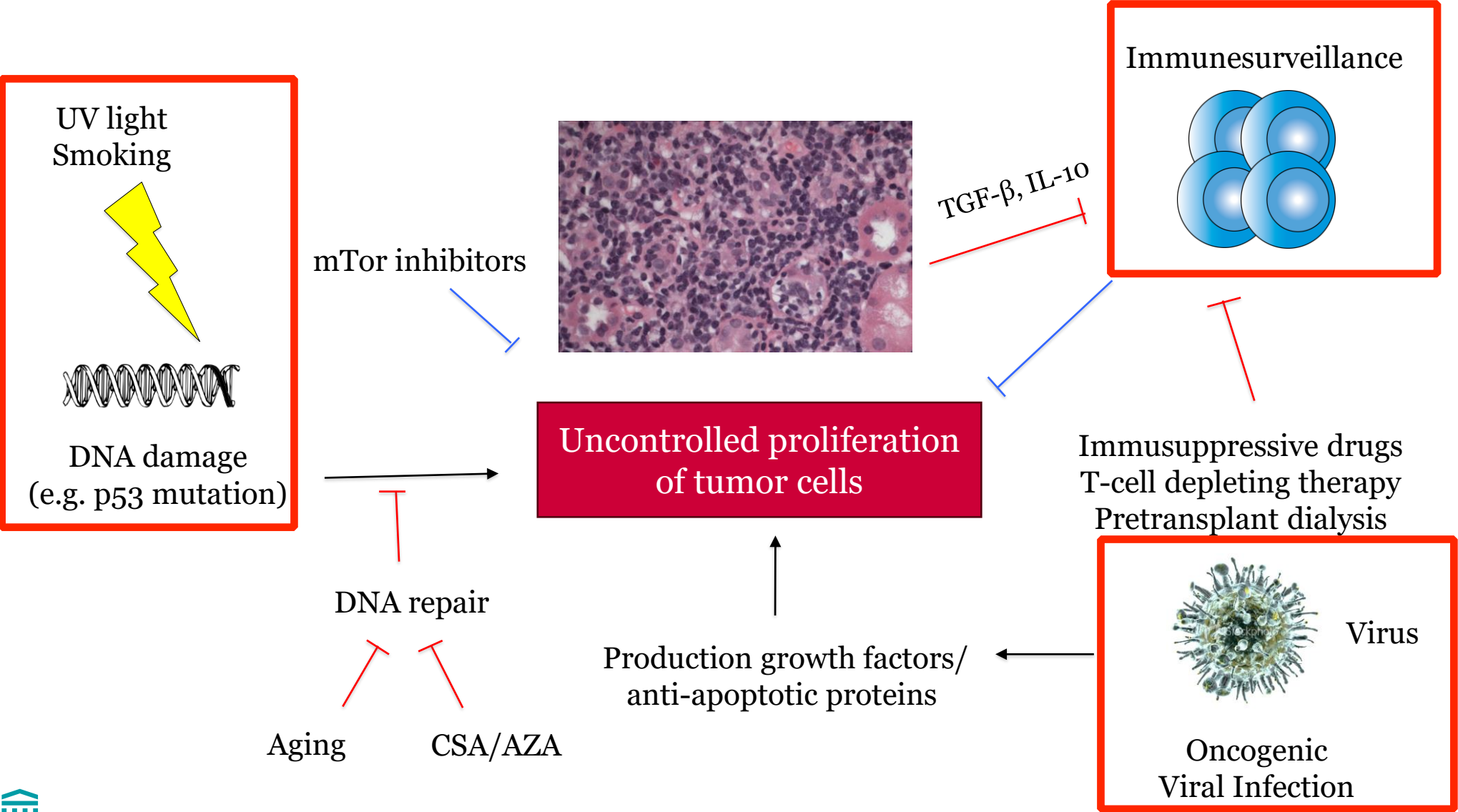
HHV-8



Kidney cancer

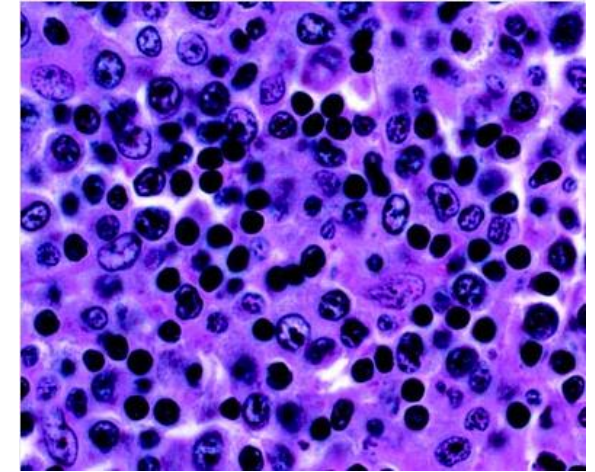


# Pathogenesis of Malignancy Post-Transplant



# 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

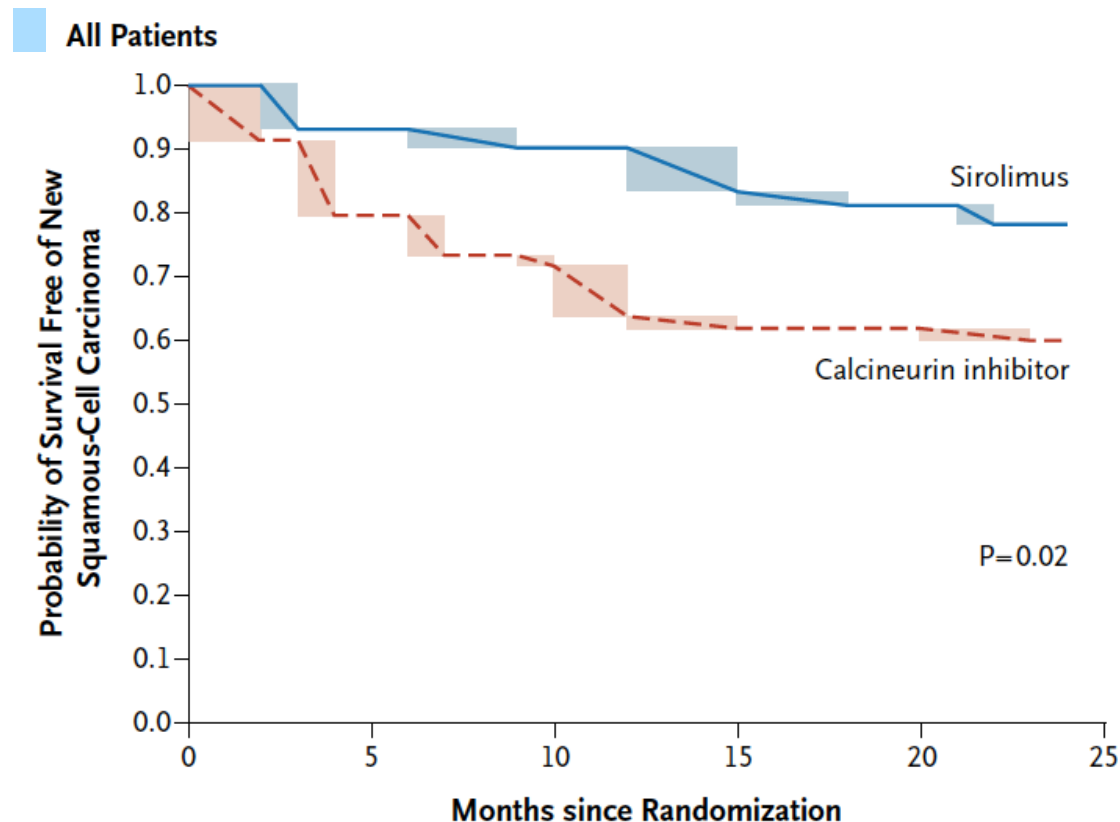


*Nourse et al. Am J Transplant. 2011*  
*Dhamidhark VR. Am J Transplant. 2017*  
*Sprangers, Riella, Dierickx AJKD 2021*<sup>28</sup>



# 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

Euvsard 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 CNIs to reduce tumor growth





## Case 4

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- E. Combine with CNI to reduce tumor growth

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%**

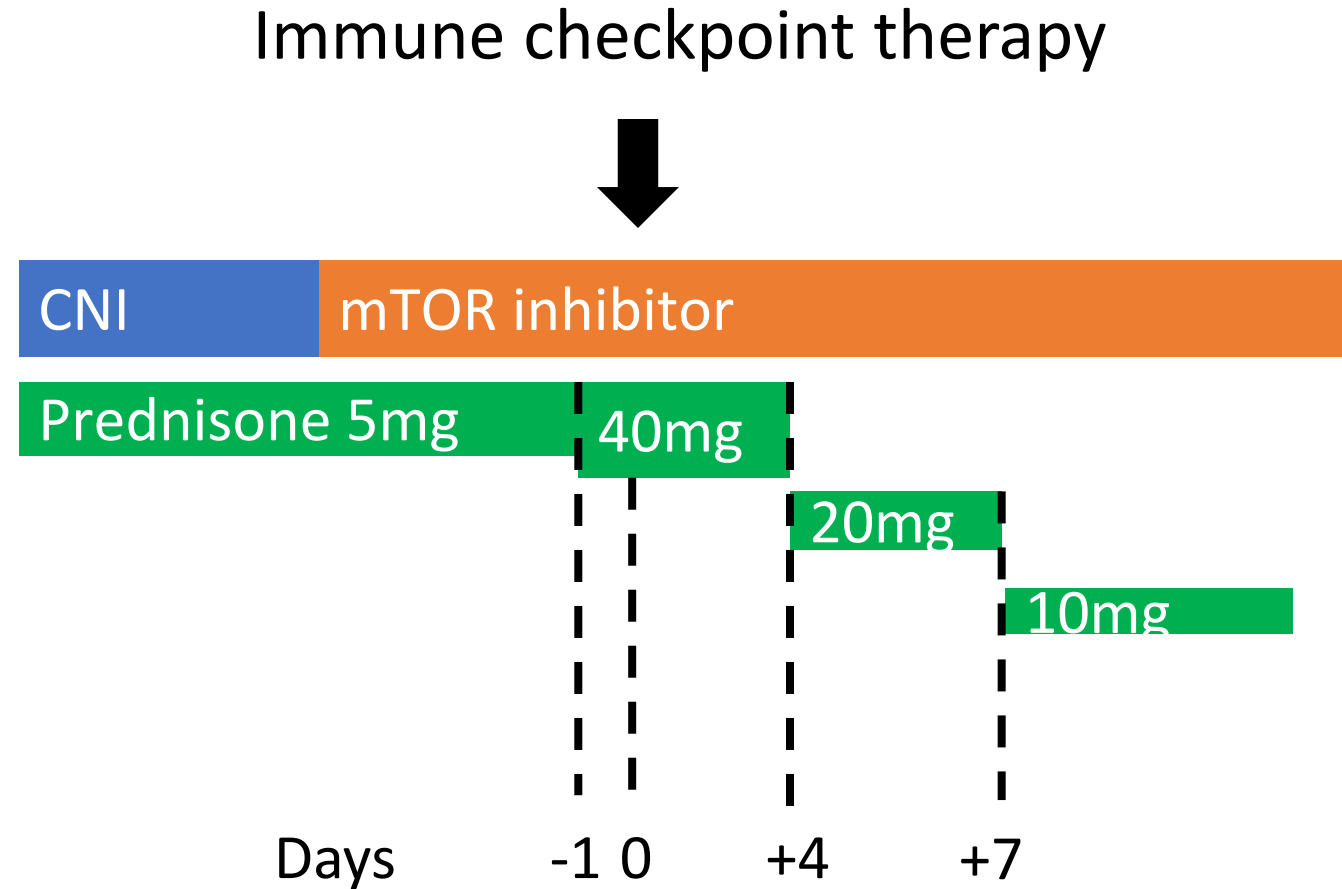
Melanoma (n=22)  
**40%**

### CONCLUSION:

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



# Rejection Preventive Strategy for ICI in advanced skin cancer



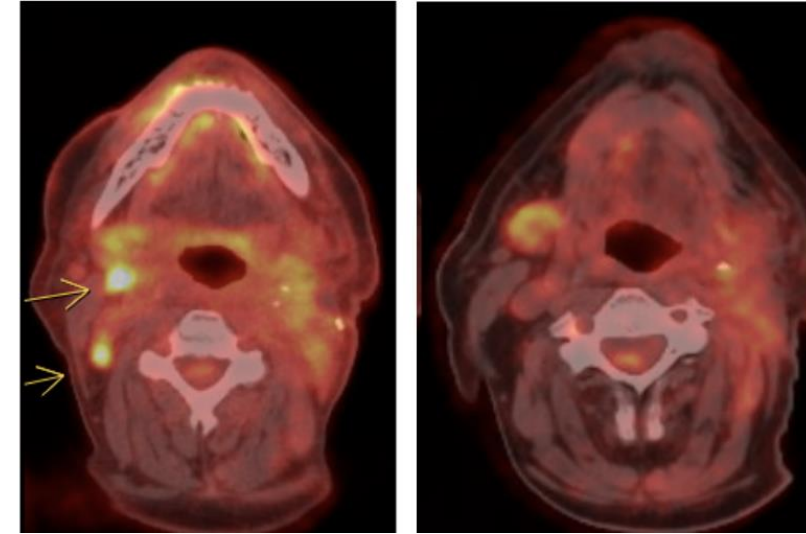
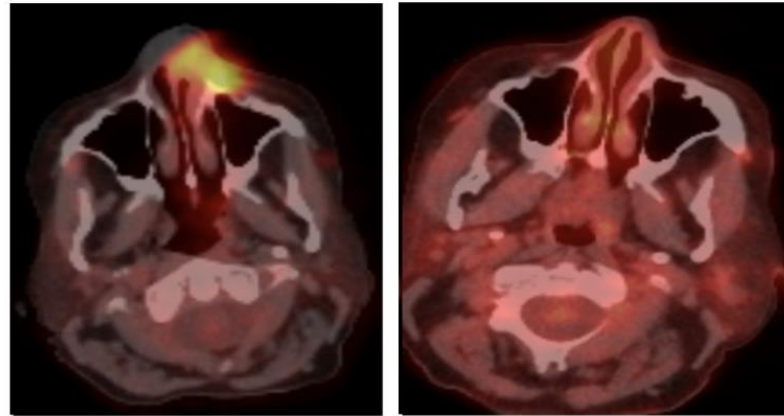
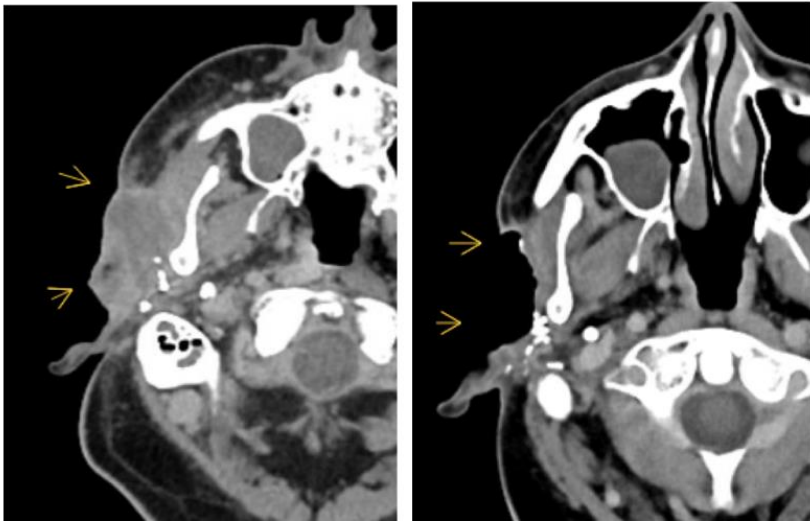
Clinical trial: Hanna (Dana Farber) and Riella (BWH)

# 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.

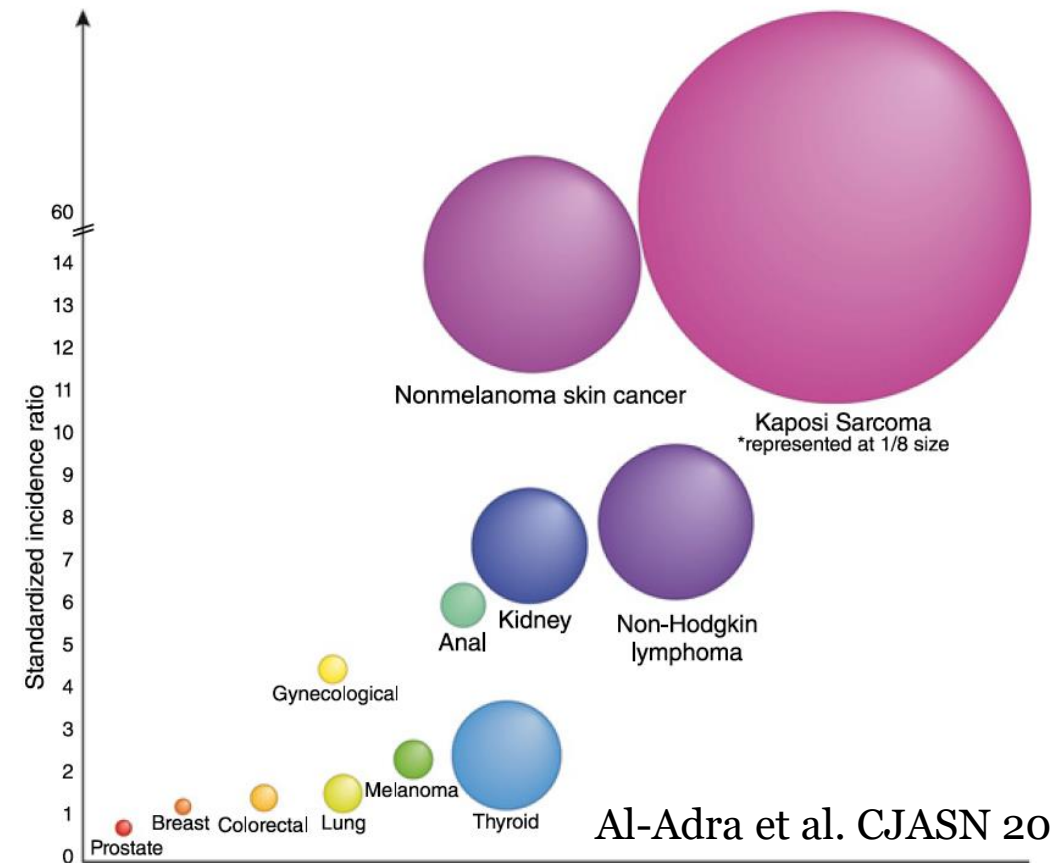
A response to cemiplimab was observed in 5 of 11 evaluable patients (45%; 90% confidence interval [CI], 22- 78) including 2 with durable responses beyond a year.



# 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



## 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

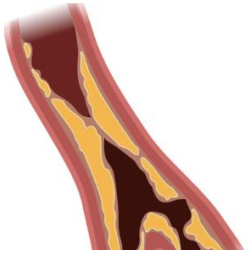
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Key Point: Anti-PLA2R levels guide recurrence risk stratification.



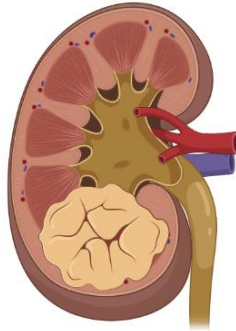
# Objectives



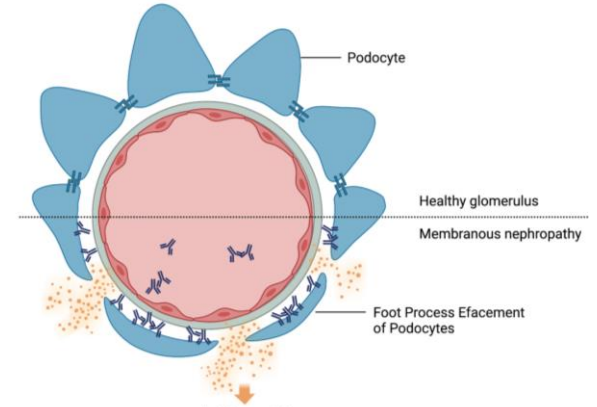
Heart  
disease



Diabetes

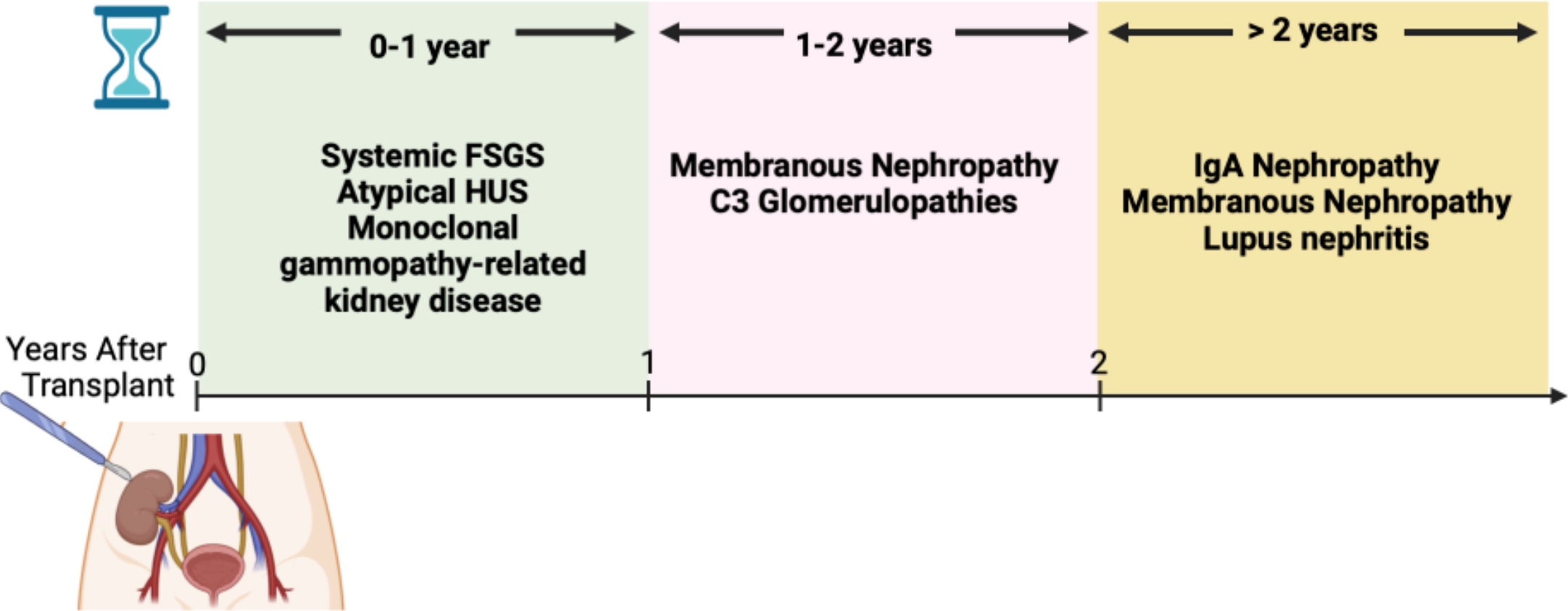


Cancer



Recurrence of  
kidney disease

# Recurrence of glomerular diseases post-transplantation







Aim: creating a large international network of centers to study glomerular disease recurrence after renal transplantation



THE **TANCO** STUDY

Post-Transplant Glomerular Diseases

1,253 patients enrolled



Audrey Uffing, MD  
PhD Candidate

Harvard Medical School, Massachusetts  
General Hospital, Boston MA



Frank Hullekes, MD  
PhD Candidate

Harvard Medical School, Massachusetts  
General Hospital, Boston MA



  
Registry Data



Biorepository



Clinical Trial Network



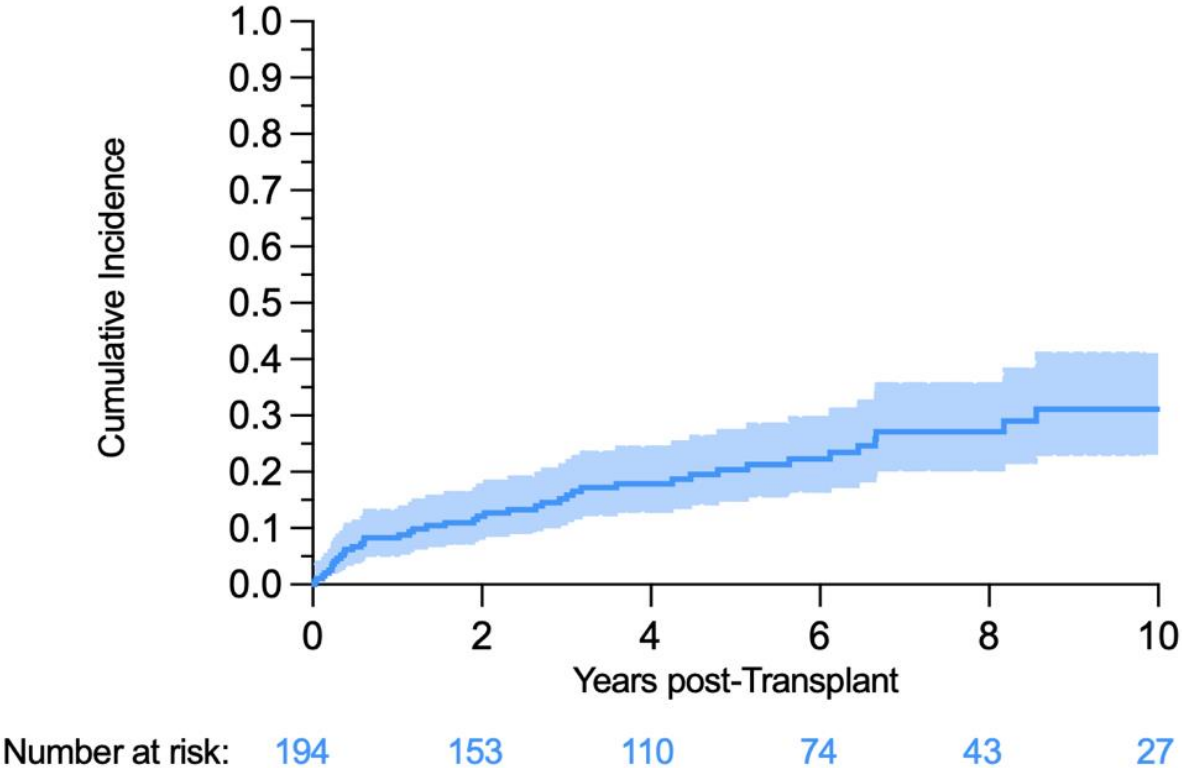
# Rate of Membranous Nephropathy Recurrence

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

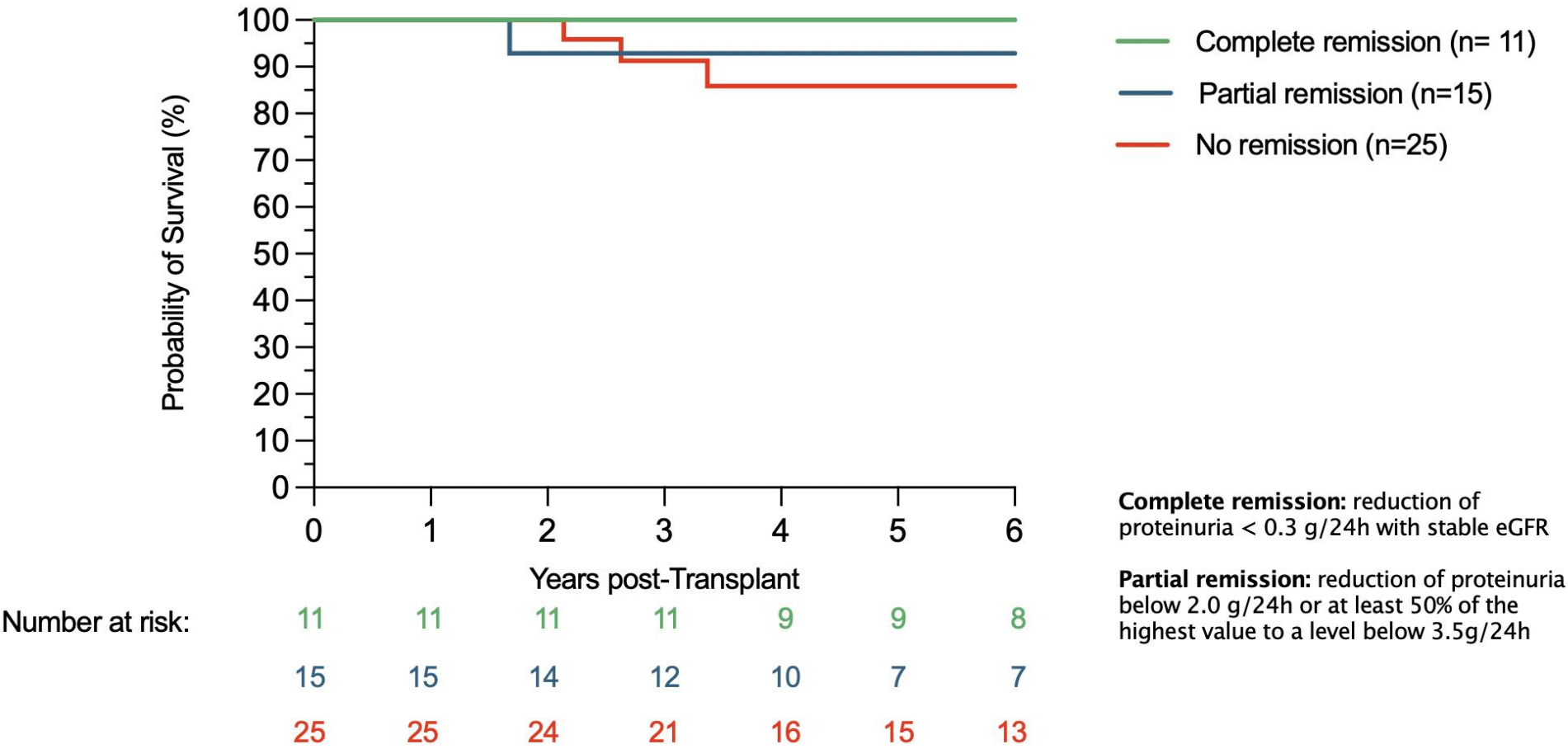
22,921 patients screened  
Across 18 transplant centers



194 patients with biopsy-proven  
MN were included



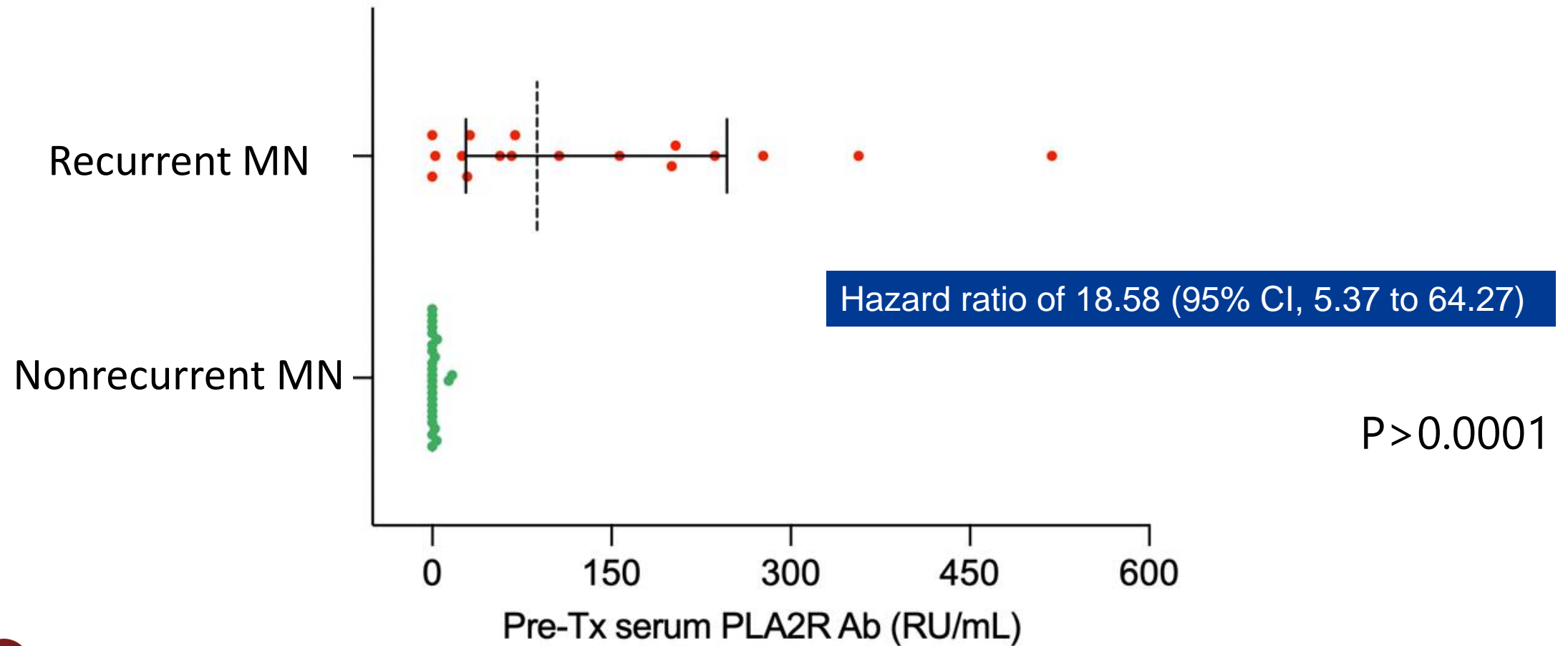
# Graft survival after Membranous Recurrence



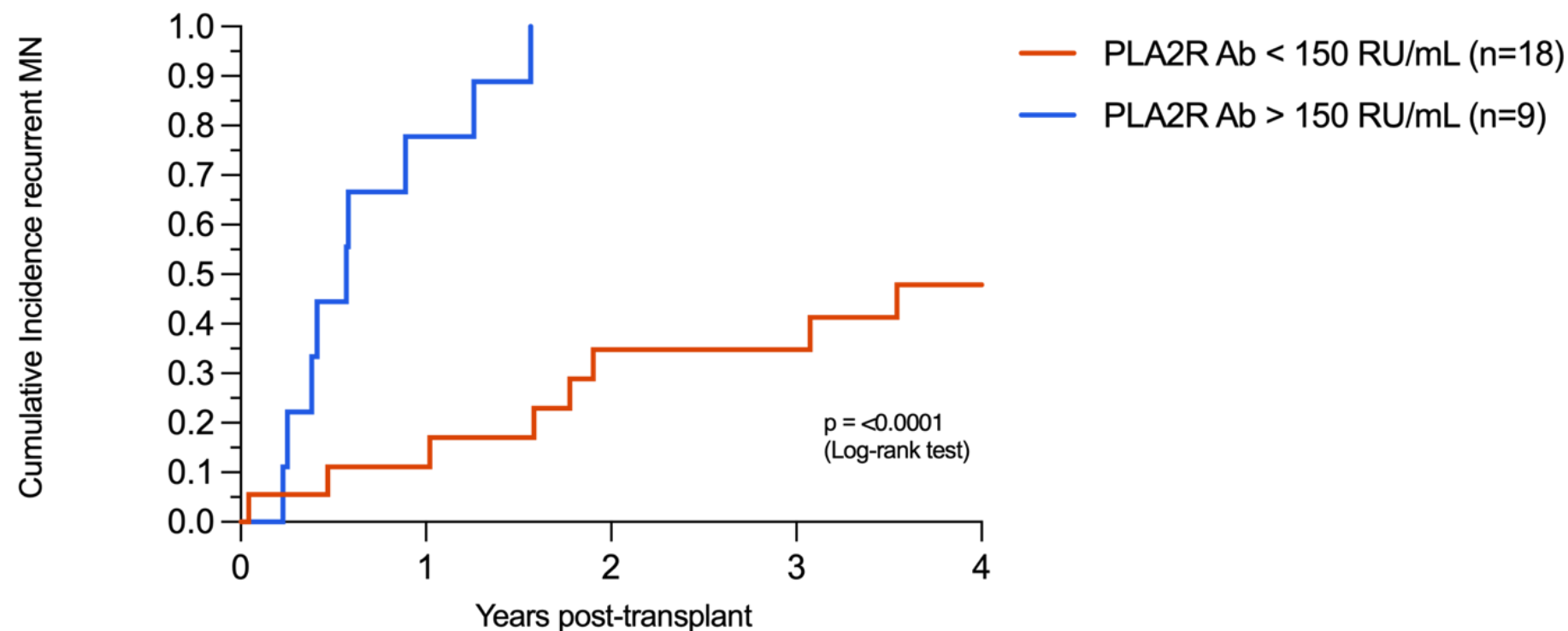
19 patients received rituximab and complete/partial remission 68%  
 17 patients only received ACEI/ARB and complete/partial remission 29%



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



# 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



# Take Home Messages

- Cardiovascular disease is the leading cause of death with functioning graft
- CNIs impair insulin secretion → post-transplant diabetes
- Cancer post-transplant has a strong association with viral infection and degree of immunosuppression
- Immune checkpoint inhibitors use is associated with rejection in ~40% of kidney recipients.
- Anti-PLA2R antibody testing help stratify membranous nephropathy recurrence risk



# Top References

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7. Lee et al. SGLT2 Inhibitors and GLP-1 Receptor Agonists in Kidney Transplantation: A Systematic Review and Meta-Analysis. *Transplantation* 2025 (in press)
8. Hullekes et al. Recurrence of membranous nephropathy after kidney transplantation: A multicenter retrospective cohort study. *Am J Transplant.* 2024, Feb 8



# 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







[www.leoriella.com](http://www.leoriella.com)

Leonardo V Riella, MD, PhD  
[Iriella@mgh.harvard.edu](mailto:Iriella@mgh.harvard.edu) (email)  
[@LVRiella](https://twitter.com/LVRiella) (twitter)



MASSACHUSETTS  
GENERAL HOSPITAL  
TRANSPLANT CENTER



HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL





# 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

