Long-term Dosing of Immunosuppression of Renal Transplants

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Dad usually didn't mind jokey Father's Day presents, but frankly he thought this was just sick, twisted, and morally offensive.

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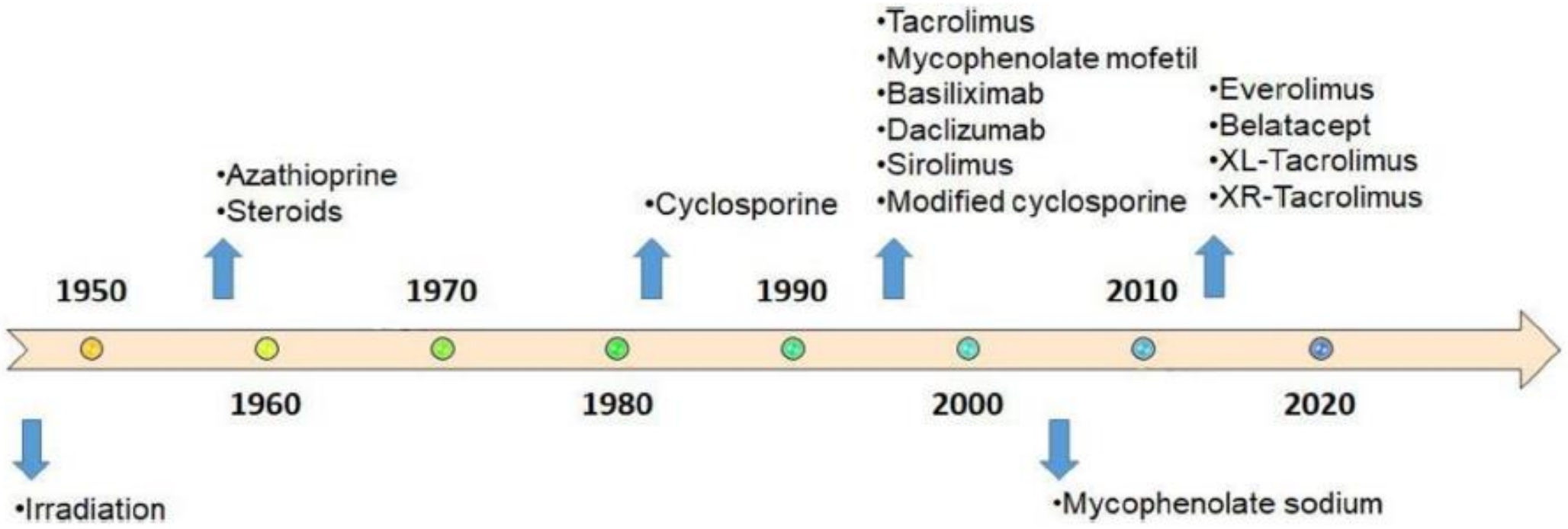
sky
HYUNDAI
2023
CHAMPION

Immunosuppression Timeline



Available IS Agents

TABLE 2 Maintenance immunosuppressive drugs

Drugs	Mechanism of action	Side effects
Corticosteroids	Bind to glucocorticoid receptors and inhibit production of cytokines, such as IL-1, IL-2, IL-3, IL-6, TNF-alpha and interferons Impair activity of B cells, T cells and macrophages	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Azathioprine	Inhibits purine synthesis	Myelosuppression, hepatotoxicity
Mycophenolic acid	Inhibits purine synthesis	Myelosuppression, diarrhoea, gastrointestinal upset
Cyclosporine	Binds to cyclophilin and inhibits IL-2 production Enhances TGF-beta expression	Hypertension, glucose intolerance, dyslipidemia, gum hypertrophy, hirsutism, neurotoxicity, nephrotoxicity
Tacrolimus	Binds to FKBP12 and inhibits IL-2 production	Similar to cyclosporine, higher incidence of glucose intolerance and neurotoxicity but lower incidence of hypertension, dyslipidemia, gum hypertrophy and hirsutism
Sirolimus/everolimus	Binds to FKBP12 and block cell cycle progression	Hyperlipidemia, thrombocytopenia, poor wound healing, oral ulcers
Belatacept	Blocks costimulation by CD28	PTLD

Abbreviations: FKBP12, FK506-binding protein 12; IL, interleukin; PTLD, post-transplant lymphoproliferative disorder; TGF, transforming growth factor; TNF, tumour necrosis factor.

Most Common Discharge IS Regimens

Organ Transplanted	Regimen
Kidney	Tacrolimus + MMF + Corticosteroids (66%) Tacrolimus + MMF (27%)
Pancreas	Tacrolimus + MMF + Corticosteroids (68%) Tacrolimus + MMF (26%)
Liver	Tacrolimus + MMF + Corticosteroids (65%) Tacrolimus + MMF (17%) Tacrolimus + Corticosteroids(6%)
Intestine	Tacrolimus + Corticosteroids (37%) Tacrolimus + MMF + Corticosteroids (30%) OTHER (18%) Tacrolimus + MMF (7%)
Heart	Tacrolimus + MMF + Corticosteroids (86%) Tacrolimus + MMF (7%)
Lung	Tacrolimus + MMF + Corticosteroids (82%) OTHER (11%)

OPTN annual data report 2019; AJT 2021

Initial IS Regimen

TABLE 1 Risk factors for acute rejection (2009 KDIGO dinical practice guidelines)

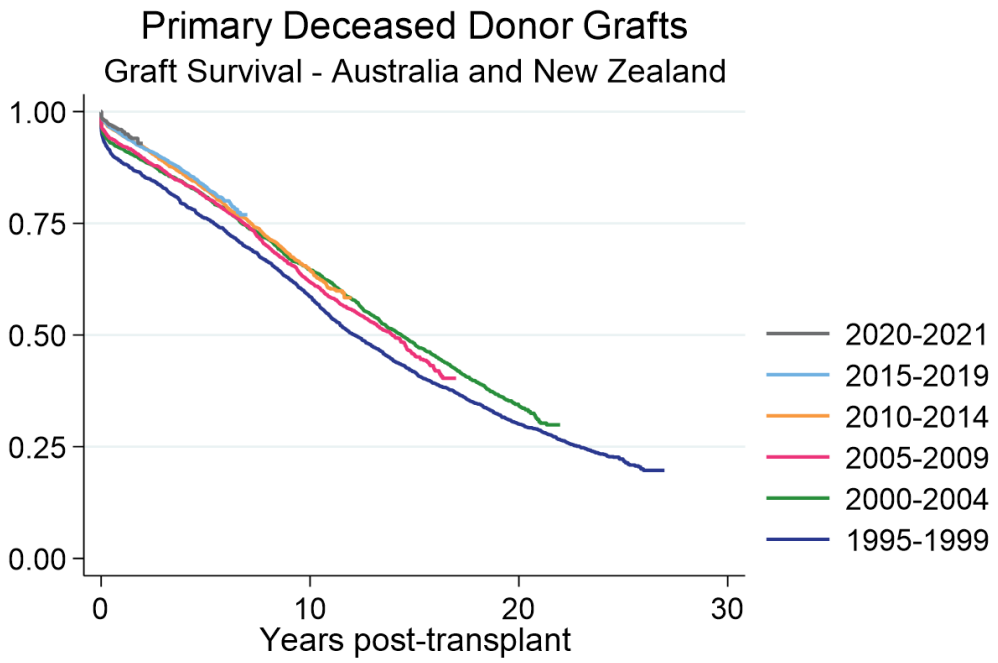
Risk factors
Younger recipient age
Older donor age
African-American ethnicity
Blood group incompatibility
Number of human leukocyte antigen mismatches
Panel reactive antibody >0%
Presence of donor-specific antibody
Cold ischemic time > 24 hours
Delayed graft function

Nephrology 2022; 27:475

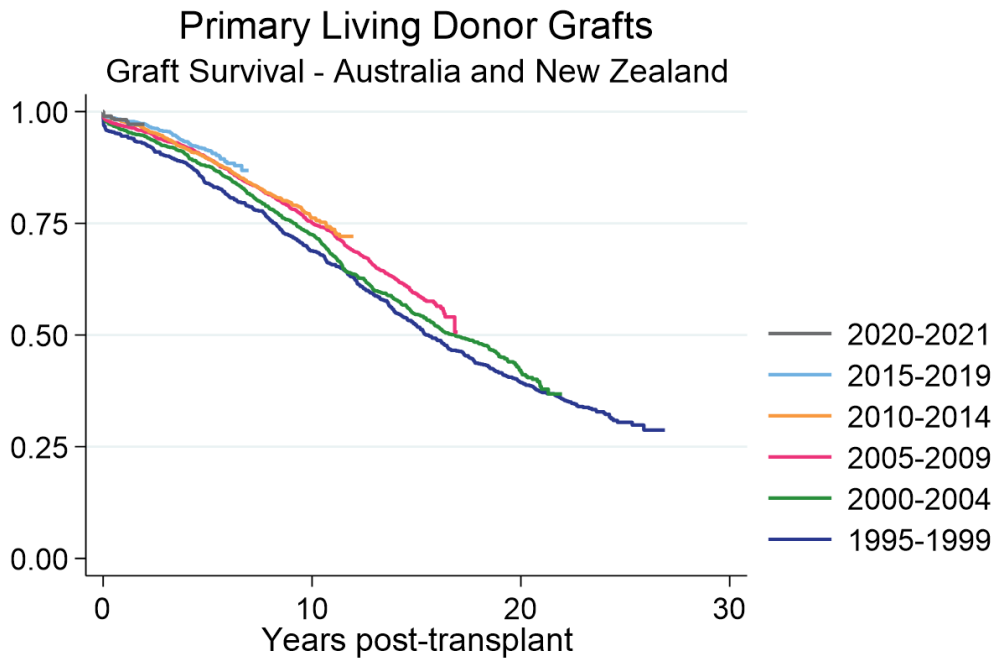
Long-term IS – Risk Stratification

- Recipient age
- Donor age
- Previous rejection
- Development of donor specific antibodies
- History/risk of malignancy
- History of infection

Long-term Outcomes

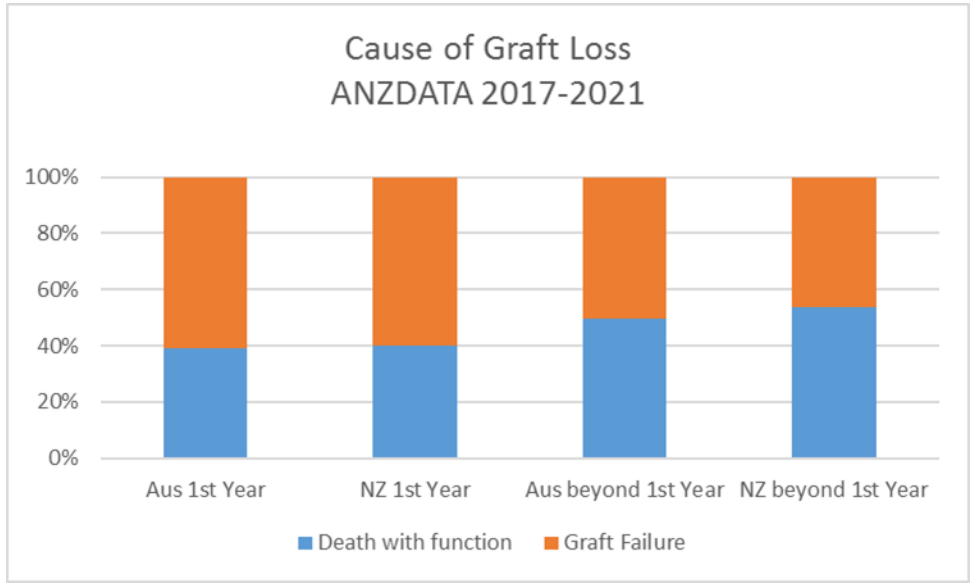


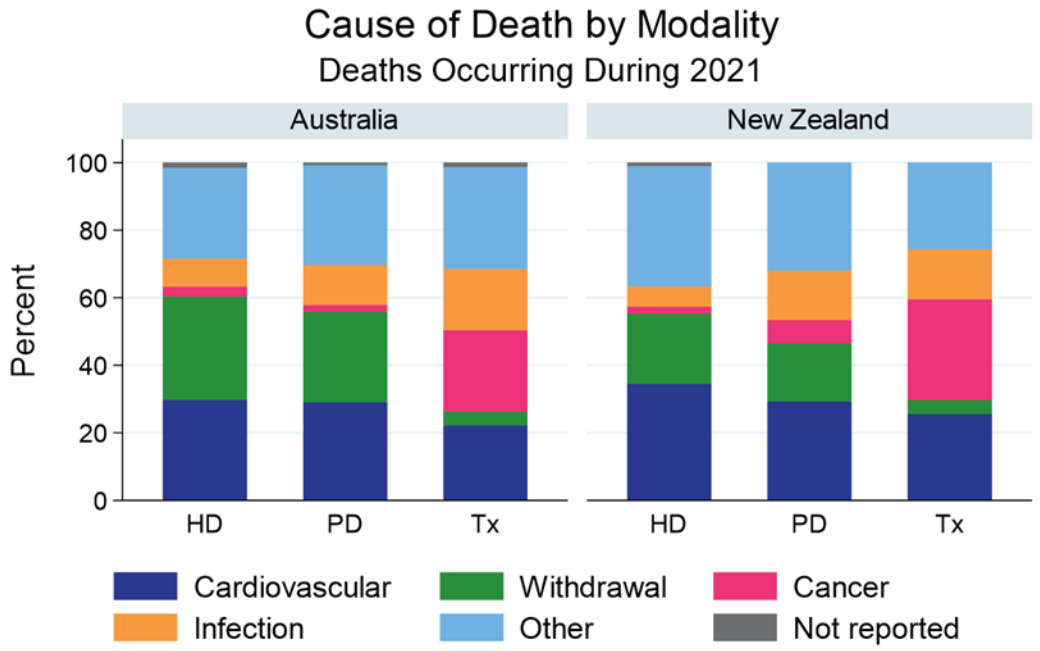
2022 ANZDATA Annual Report, Figure 7.19



2022 ANZDATA Annual Report, Figure 7.29

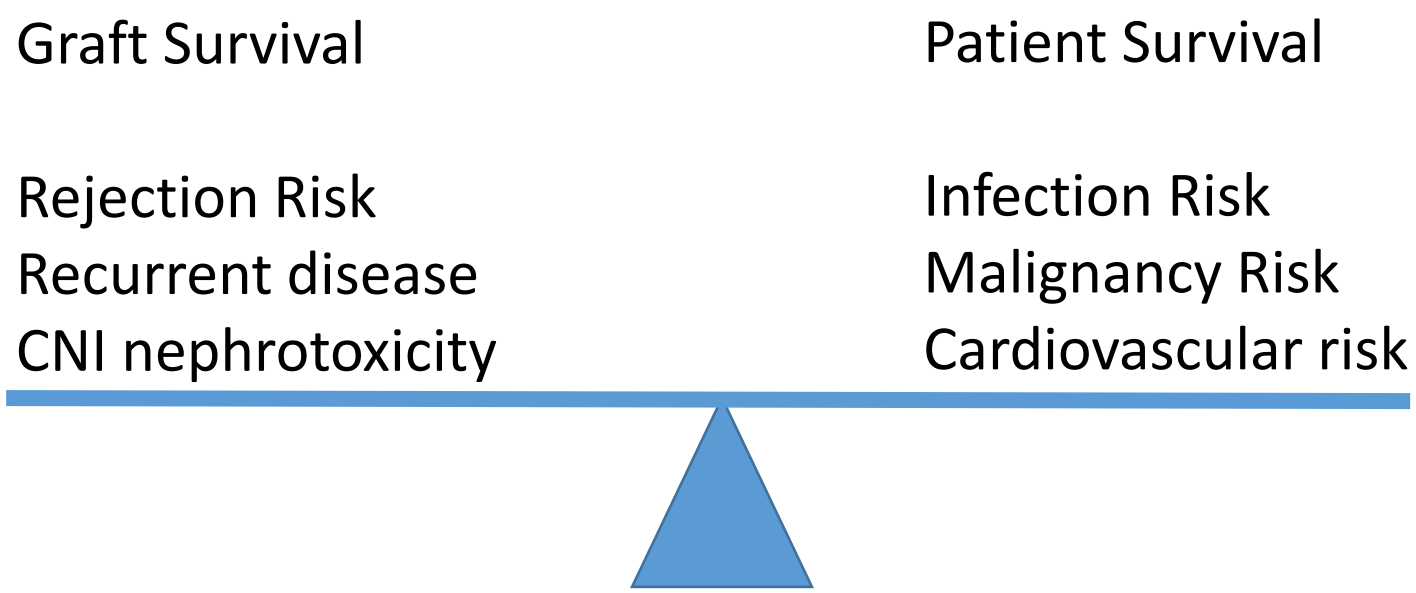
Graft Loss and Death



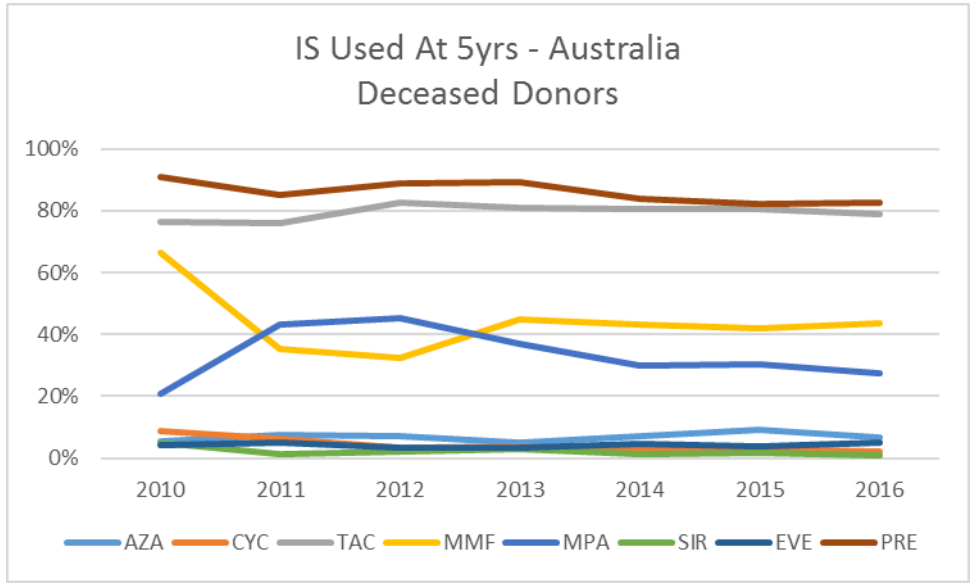


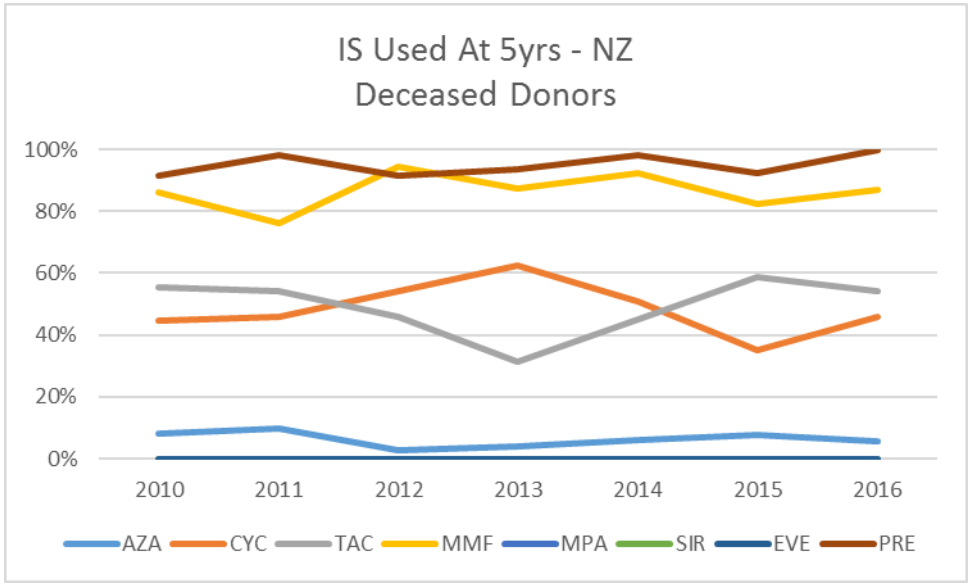
2022 ANZDATA Annual Report, Figure 3.5

Competing Risks



Real World Experience – Long-term IS





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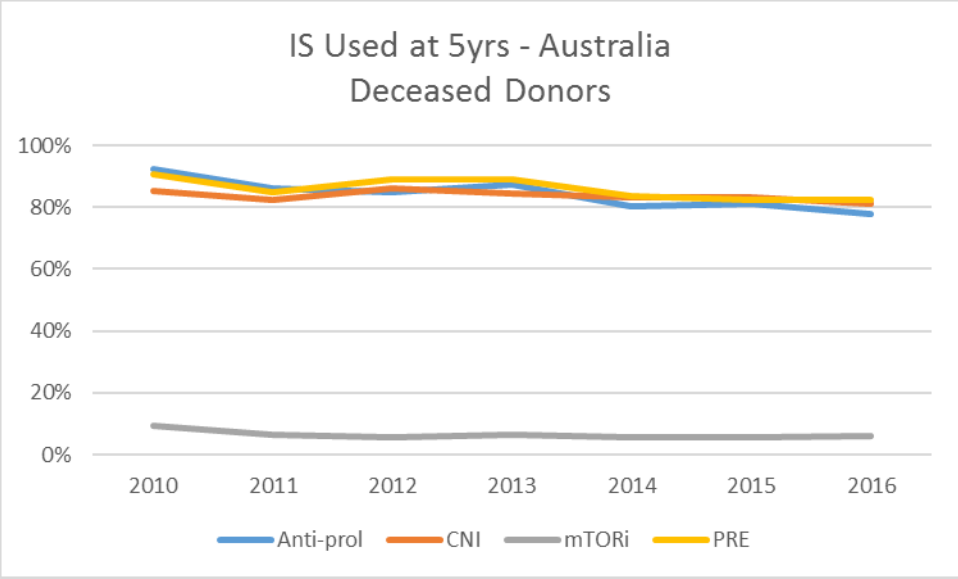
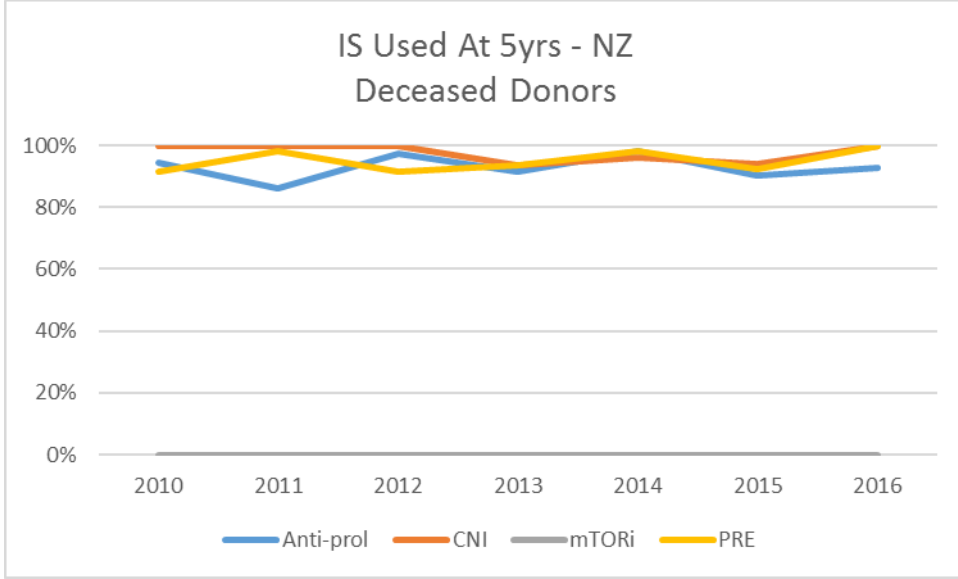
Real World Experience – Long-term IS





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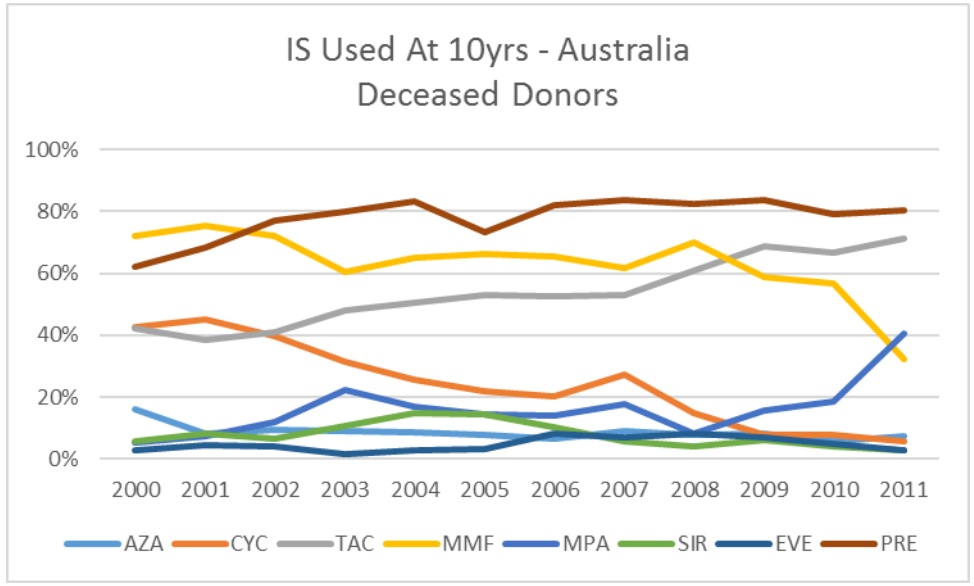

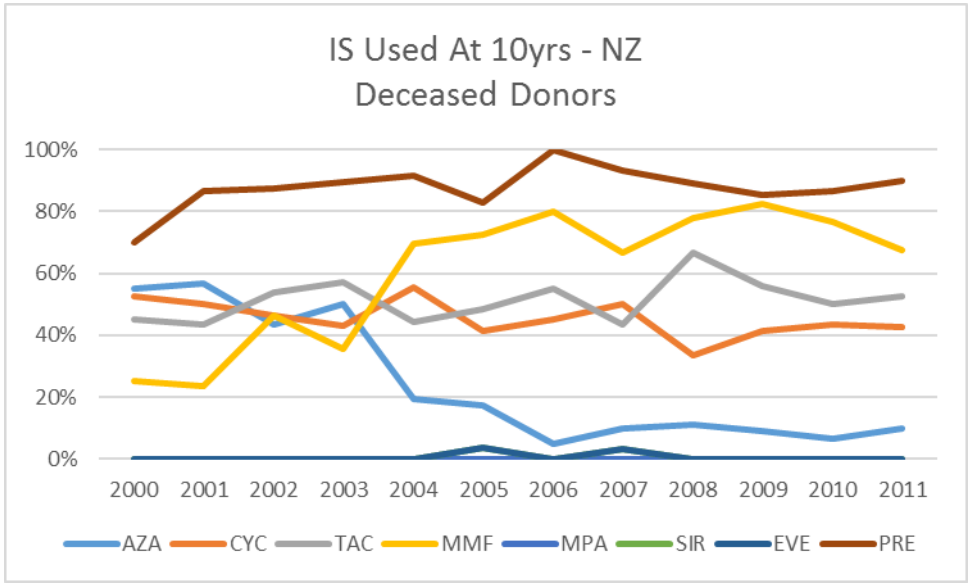

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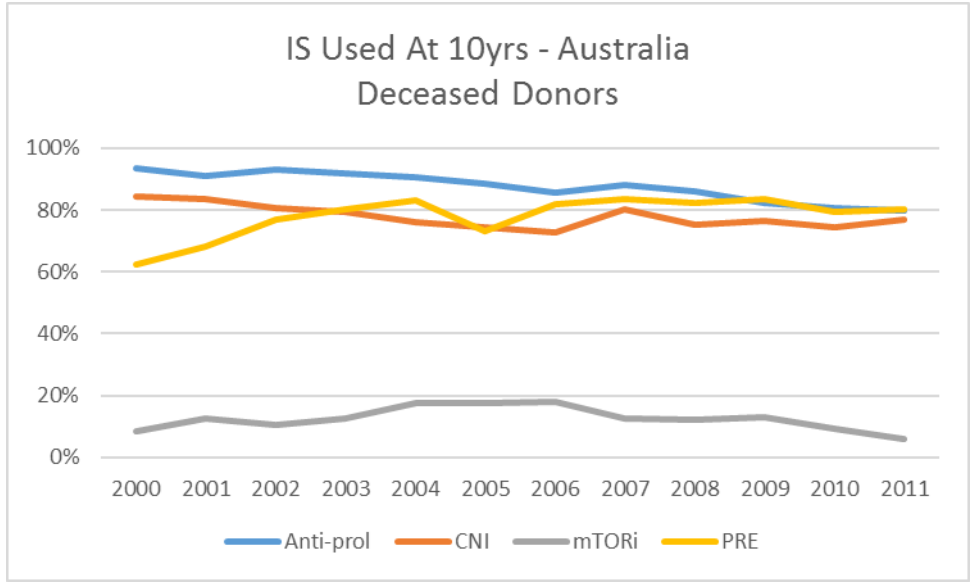
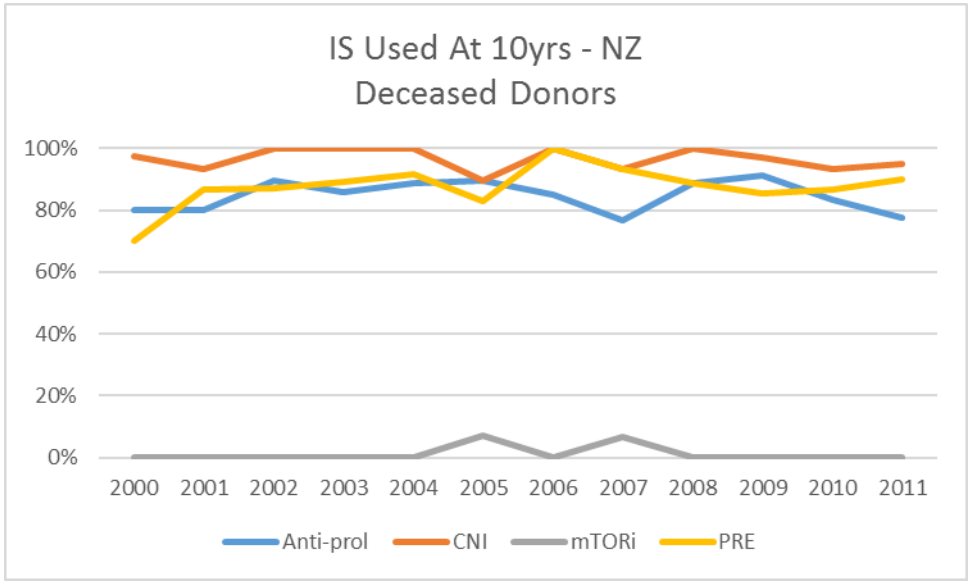
Real World Experience – Long-term IS





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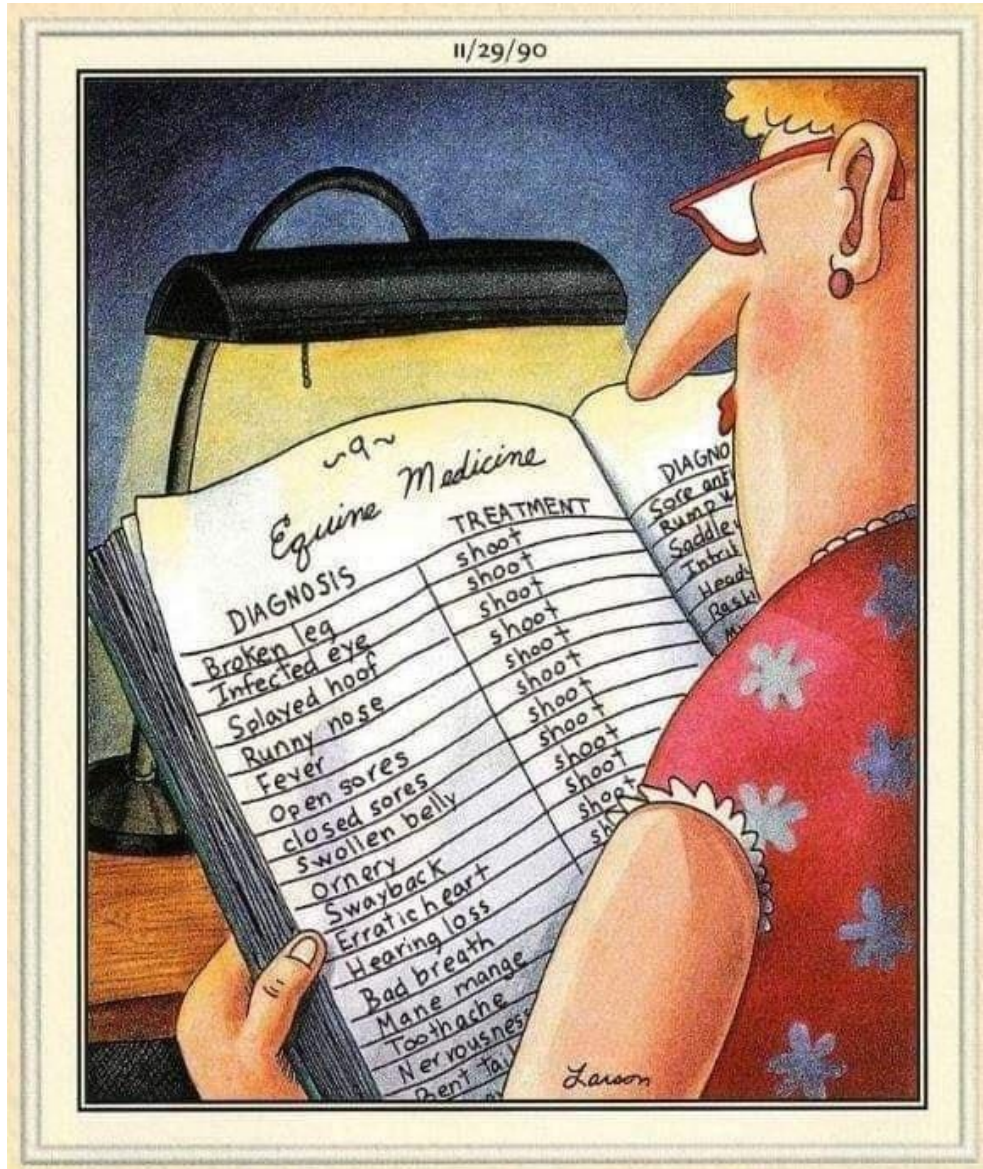


Like most veterinary students, Doreen breezes through chapter 9.

ifunny.co

Immunosuppression - Nuances

- CNI dosing
- MPA dosing
- Steroid withdrawal
- mTORi use

- Comorbidities

CNI Dosing

- Tacrolimus
  - Better efficacy
  - **Increased NODAT**
  - Increased alopecia
  - Reduced gingival hyperplasia
  - Reduced hirsutism
  - **Nephrotoxicity**
- Trough concentrations
  - 8-12 ug/L early
  - 3-8 ug/L long-term

- Cyclosporine
  - Increased acute rejection
  - Reduced graft survival
  - Gingival hyperplasia
  - Hirsutism
  - Hypertension
  - **Nephrotoxicity**
- Trough concentrations
  - 150-300 ug/L early
  - 50-150 ug/L long-term

ELITE – Symphony trial

NEJM 2007; 357:25

- Comparison or primary renal transplant recipients
  - Std dose CyA, MMF, Pred
  - Daclizumab, low-dose CyA, MMF, Pred
  - Daclizumab, low-dose Tac, MMF, Pred
  - Daclizumab, low-dose Siro, MMF, Pred
- Target trough concentrations
  - 150-300 ng/mL then 100-200ng/mL
  - 50-100 ng/mL throughout
  - 3-7 ng/mL throughout
  - 4-8 ng/mL throughout

ELITE – Symphony trial

NEJM 2007; 357:25

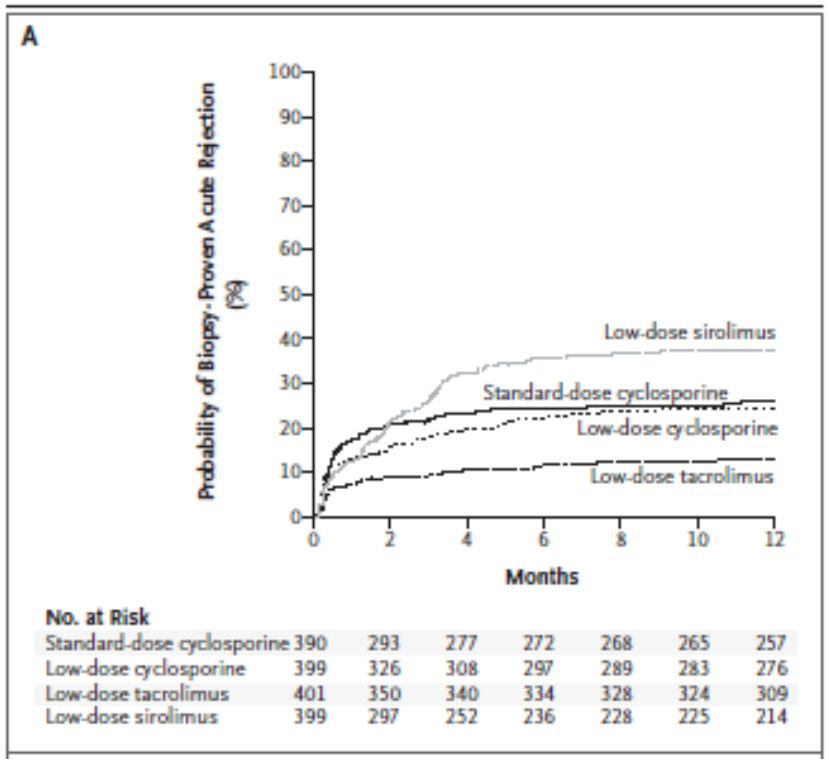
- Only 12 month follow-up

- Improved eGFR, BPAR rates and graft survival in low-dose Tac group
- Serious adverse events more common in Sirolimus group

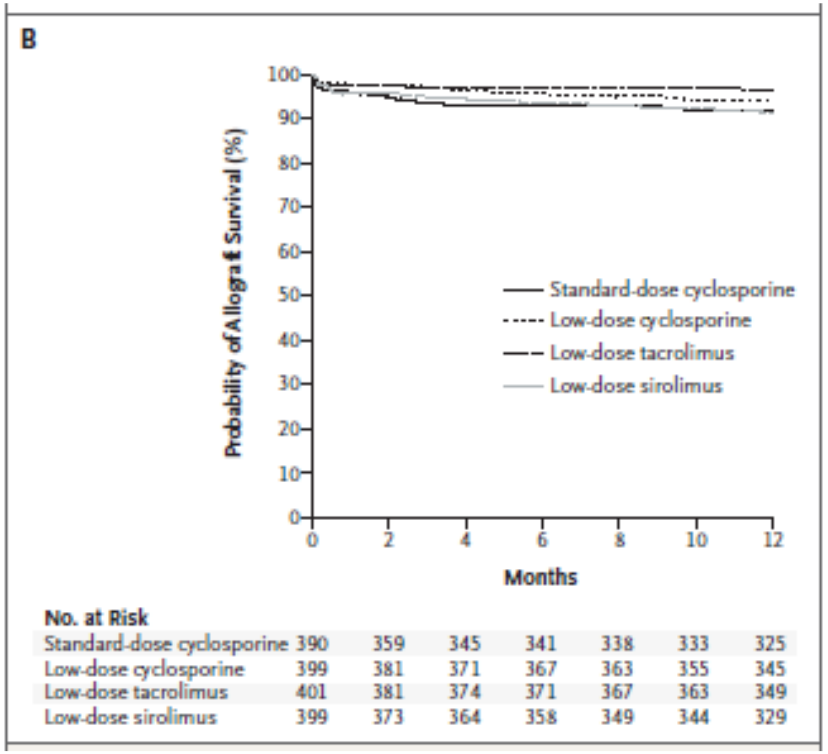
- Achieved trough concentrations were at the upper range of the target

ELITE – Symphony trial

NEJM 2007; 357:25



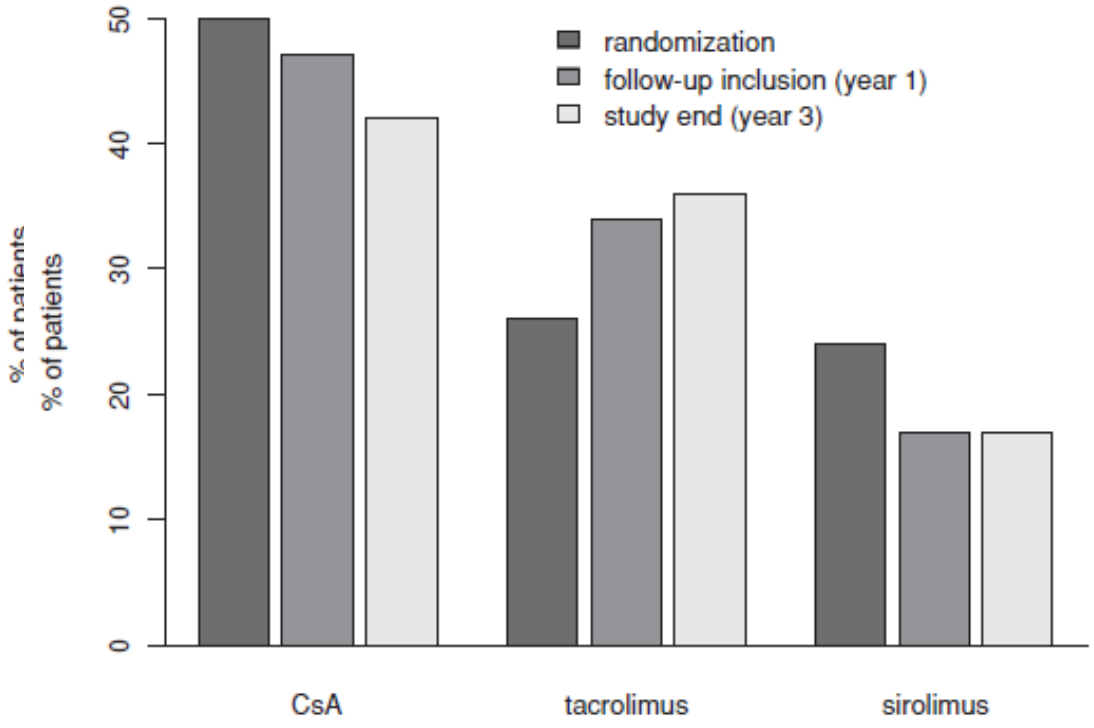
No. at Risk							
Standard-dose cyclosporine	390	293	277	272	268	265	257
Low-dose cyclosporine	399	326	308	297	289	283	276
Low-dose tacrolimus	401	350	340	334	328	324	309
Low-dose sirolimus	399	297	252	236	228	225	214



No. at Risk							
Standard-dose cyclosporine	390	359	345	341	338	333	325
Low-dose cyclosporine	399	381	371	367	363	355	345
Low-dose tacrolimus	401	381	374	371	367	363	349
Low-dose sirolimus	399	373	364	358	349	344	329

ELITE – Symphony trial

AJT 2009; 9:1876



ELITE – Symphony trial

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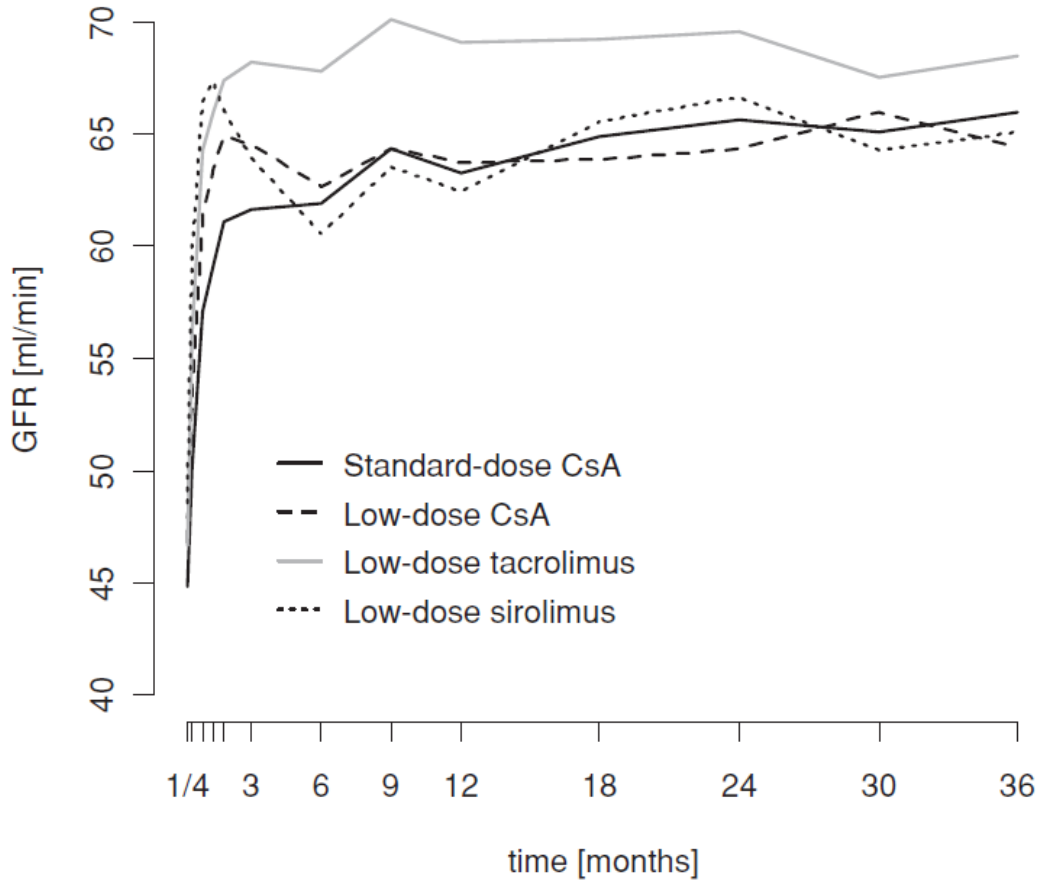
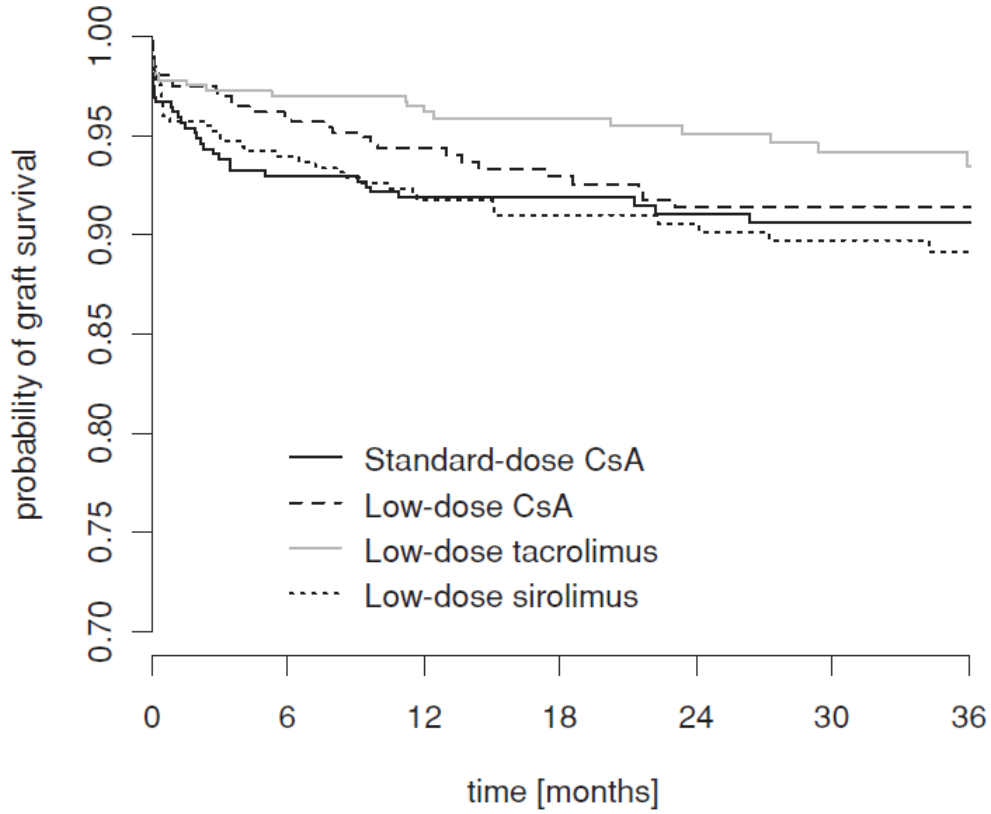


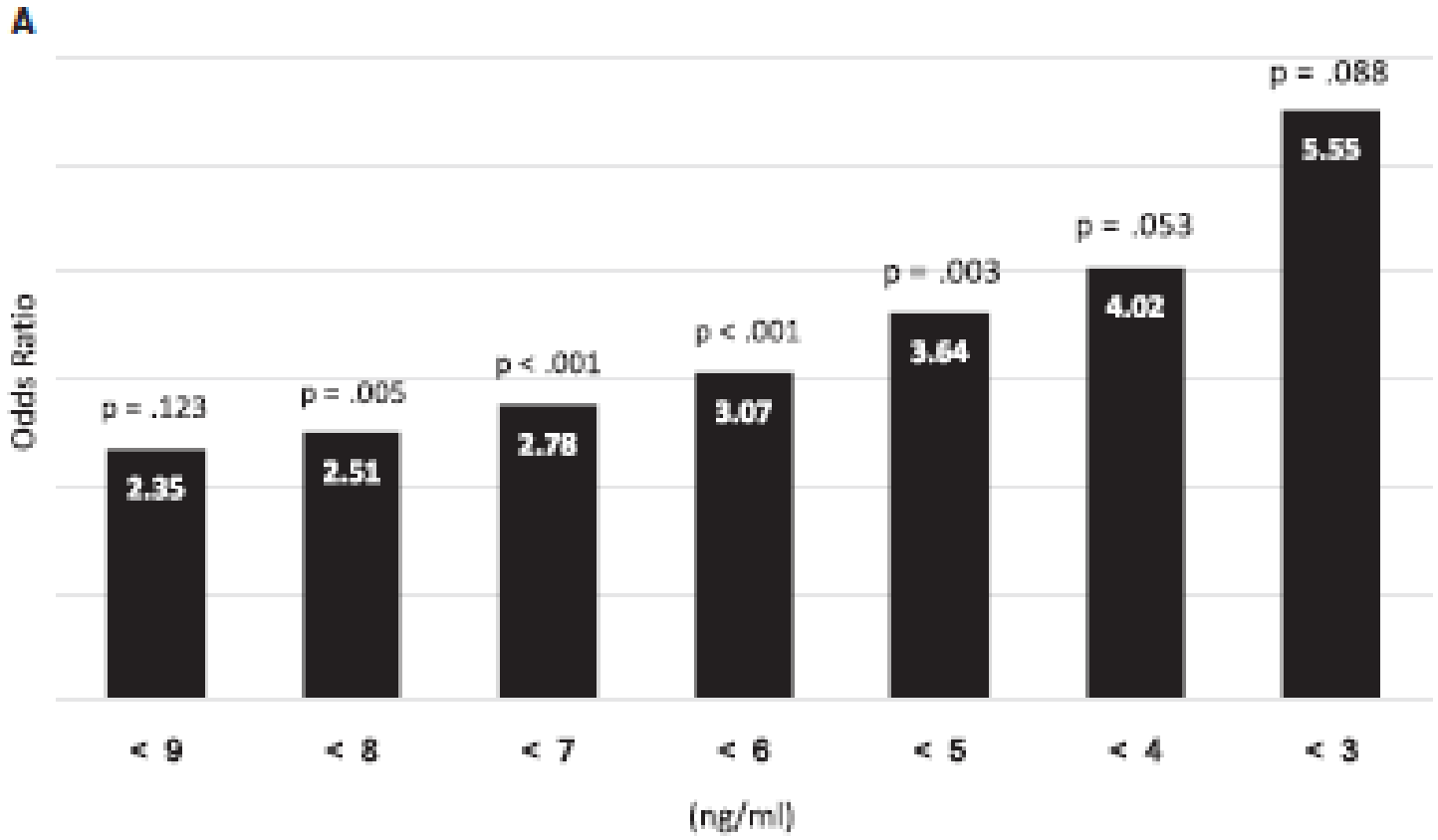


How Low Can You Go?

- Some studies suggest that lowering Tac doses too far may increase rates of de-novo DSA formation
- May influence graft outcomes

Tacrolimus Exposure and dnDSA

Davis et al; Am J Transplant 2018; 18:907



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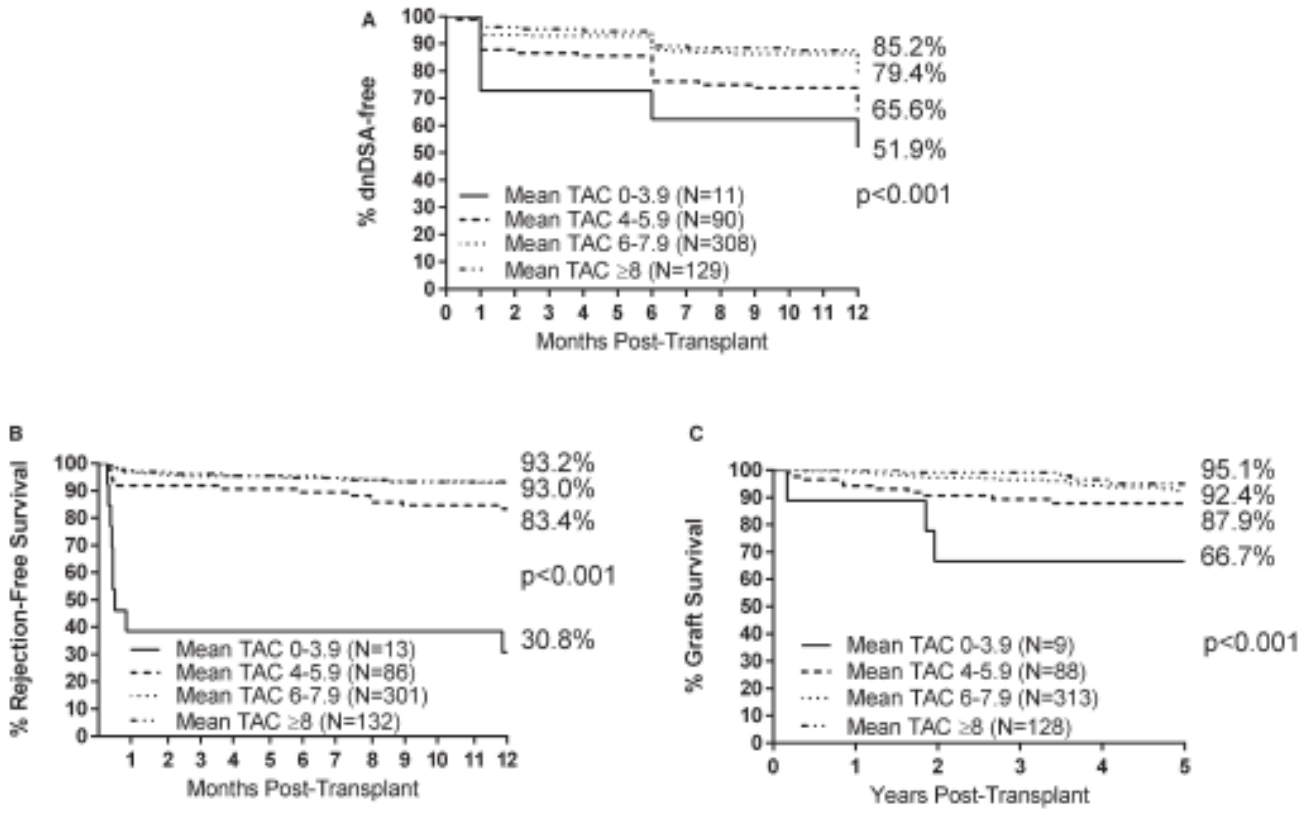

FIGURE 2 Kaplan-Meier plot for mean TAC C_0 ranges (ng/mL) and (A) percent dnDSA-free survival by 12 months, (B) percent acute rejection-free survival by 12 months, and (C) percent death-censored graft loss by 5 years

CNI Dosing - Summary

- Tacrolimus more efficacious
- Different side effect profiles
  - Increased diabetogenesis
  - Reduced hypertension

- In low risk population trough concentrations < 10 ug/L adequate
- Caution with lowering Tac concentrations < 5 ug/L too quickly

Anti-Proliferative Agents

- Mycophenolate likely more effective than Azathioprine, with an acceptable side-effect profile
- Risk of tissue invasive CMV disease higher
- GI side-effects more prevalent

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Mycophenolate mofetil (MMF) versus azathioprine (AZA) for primary immunosuppression in kidney transplant recipients

MMF compared to AZA for primary immunosuppression in kidney transplant recipients

Patient or population: patients with kidney transplant recipients
Settings: primary immunosuppressive regimens (RCTs)
Intervention: MMF
Comparison: AZA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk AZA	Corresponding risk MMF				
Death, all cause Follow-up: 0.5 to 5 years	**49 per 1000**	**47 per 1000** (34 to 63)	**RR 0.95** (0.7 to 1.29)	2987 (16)	⊖⊖⊖⊖ **moderate** [1]	No evidence for difference due to low precision
Graft loss, censored for death Follow-up: 0.5 to 6 years	**11 per 100**	**9 per 100** (7 to 11)	**RR 0.78** (0.61 to 0.98)	2540 (17)	⊕⊕⊕⊕ **high** [2]	Statistically significant risk reduction of meaningful magnitude (˜20%) with MMF treatment
Malignancy, any Follow-up: 1 to 6 years	**10 per 100**	**8 per 100** (6 to 11)	**RR 0.81** (0.6 to 1.09)	1735 (5)	⊕⊖⊖⊖ **very low** [3,4,5]	Statistically not significant favourable point estimate (˜20%) with MMF treatment, but very low quality evidence
Acute rejection, steroid resistant/antibody treated As reported in the articles Follow-up: 0.5 to 3 years	**11 per 100**	**5 per 100** (4 to 7)	**RR 0.48** (0.36 to 0.65)	2914 (15)	⊕⊕⊕⊕ **high**	Statistically significant risk reduction of meaningful magnitude (˜50%) with MMF treatment
Infection, CMV tissue invasive As reported in the articles Follow-up: 0.5 to 3 years	**4 per 100**	**7 per 100** (5 to 11)	**RR 1.7** (1.1 to 2.61)	1510 (7)	⊕⊕⊕⊕ **high** [3,6]	Statistically significantly increased risk of meaningful magnitude (1.7 fold) with MMF treatment
Acute rejection, total Any treated acute rejection, including biopsy-proven Follow-up: 0.5 to 5 years	**35 per 100**	**23 per 100** (20 to 26)	**RR 0.65** (0.57 to 0.73)	3301 (22)	⊕⊕⊕⊕ **high**	Statistically significant risk reduction of meaningful magnitude (˜35%) with MMF treatment

Comparison: AZA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk AZA	Corresponding risk MMF				
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Anti-proliferative Agents

- MMF
  - 1gm BD early
  - 500-750mg BD long-term (lower with Tac)

- Azathioprine
  - 1.5-2.5mg/kg

- MMF contraindicated in pregnancy and therefore of concern in women of child-bearing age.
- Safe for men to take

- MMF in Covid era

Steroid Reduction or Withdrawal

- Early steroid withdrawal popular in US in up to 30% of patients
  - Low immunologic risk
  - Induction with depleting antibodies
  - Increased risk of rejection if delayed graft function

- Late withdrawal
  - Increased rates of rejection
  - Possibly reduced long-term graft survival

- Long-term dosing
  - 5mg/day

Role of mTORi

- Enthusiasm as means to reduce CNI nephrotoxicity
- Used as either replacement for CNI or in combination at low dose

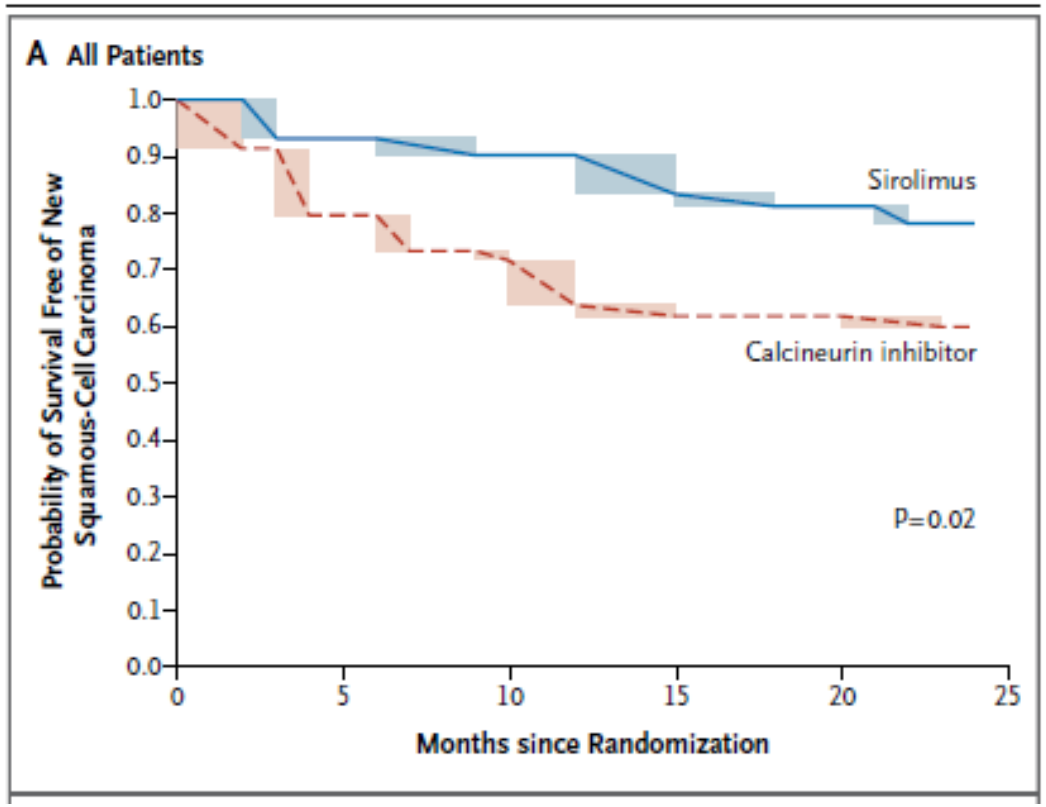
- Generally improved GFR
- Increased rates of acute rejection
- No benefit on patient or graft survival

- Increased adverse events esp. wound healing, infection and lymphocoeles
- Contraindicated if moderately reduce GFR or proteinuria

Conversion to mTORi with SCC

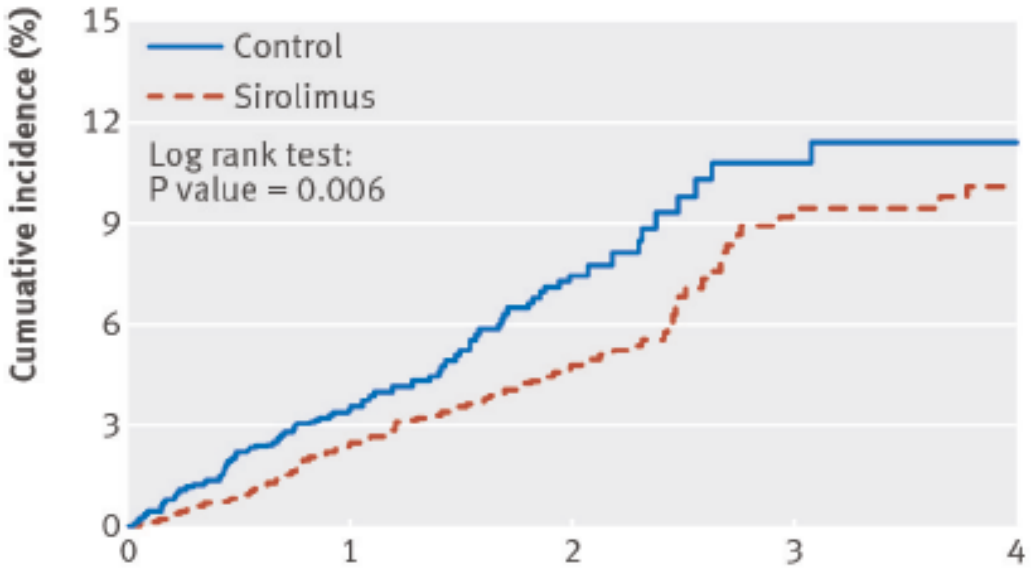
TUMORAPA Study NEJM 2012

- New SCC 22% v 39%
- SAE 60 vs 14
- Drug discontinuation 23 vs 11
- Similar graft function



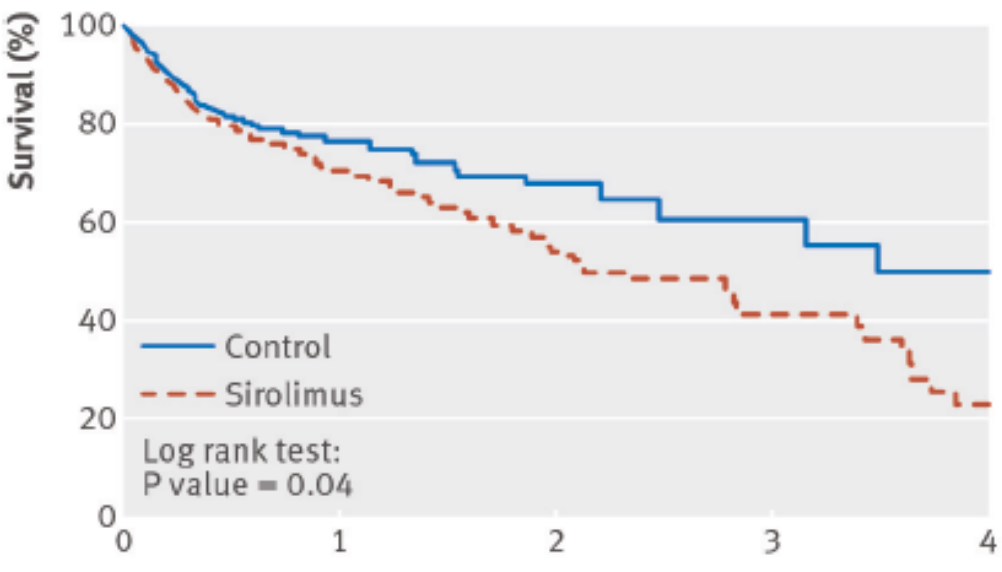
mTORi in Kidney Transplantation

BMJ 2014



No at risk

Control	2600	1741	571	157
Sirolimus	3276	2318	1314	333

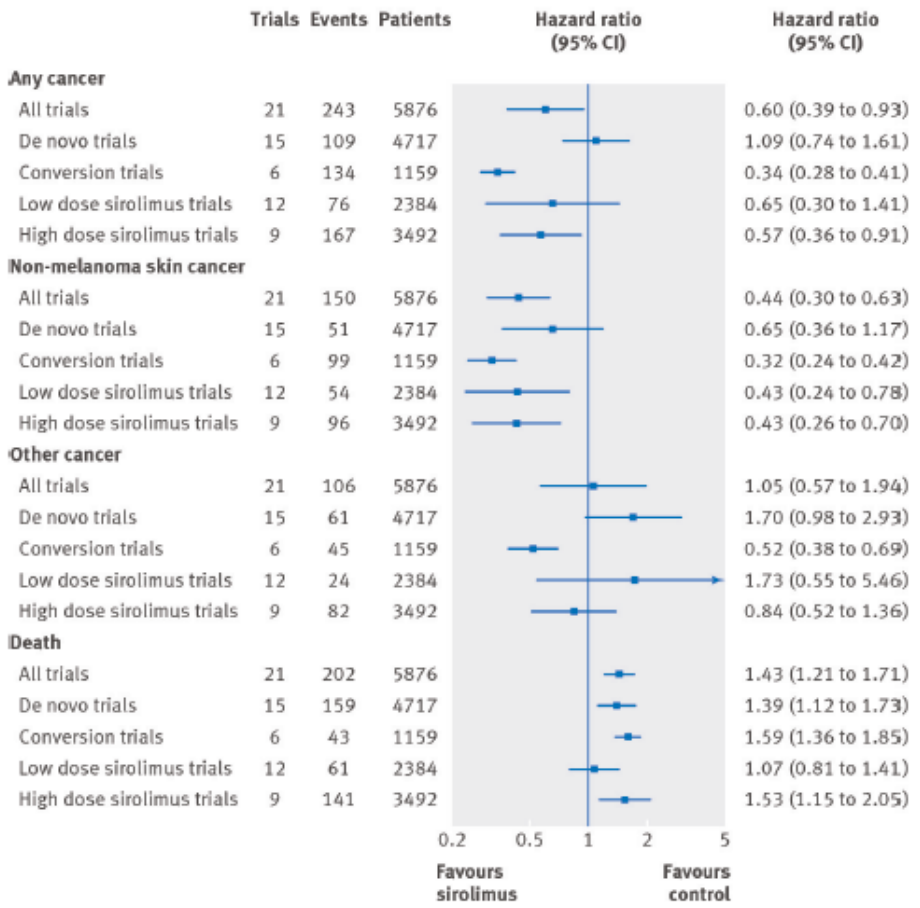


No at risk

Control	2600	1809	613	184
Sirolimus	3276	2375	1362	363

mTORi in Kidney Transplantation

BMJ 2014



- Reduced risk of malignancy
- 43% increased mortality risk

Role of mTORi

- Conversion limited by
  - Graft factors - CKD & proteinuria
  - Tolerability

- May have role
  - High risk of recurrent malignancy
  - Documented CNI nephrotoxicity
  - Development of CNI induced TMA

- Standard dosing of Sirolimus conversion for maintenance
  - 2-4mg daily
  - Trough concentrations 4-6 ug/L

BK Viraemia

- Reflection of overall state of immunosuppression

- Scant data to govern response:

    1. Reduction in dose of anti-metabolite
    2. Cessation of anti-metabolite
    3. Reduction in dose of CNI

M-IS Summary

- CNI, MMF, Pred remains the cornerstone of M-IS in Aus/NZ
  - Tac trough 3-8 ug/L but caution with excessive reduction early
  - MMF 500-750mg BD (lower with Tac)
  - Pred 5mg/day
- Steroid withdrawal not popular but possible if early and in low-risk transplants
- mTORi most useful in replacing CNIs due to nephrotoxicity, malignancy or TMA