Böbrek Nakilli Hastanın Dahili Sorunlarına Yaklaşım ve İlaç Kullanımı

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5. İstanbul Dahiliye Klinikleri Buluşması

Sunum Planı

- Tx öncesi yaklaşım
- Tx evresinde yaklaşım
- Tx sonrası yaklaşım
  - Erken dönem
  - Geç dönem
- İlaç kullanımı

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Kronik Böbrek Hastalığı – Tanım

1.1: DEFINITION OF CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (*Not Graded*)

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

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Kronik Böbrek Hastalığı – Evreleme

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

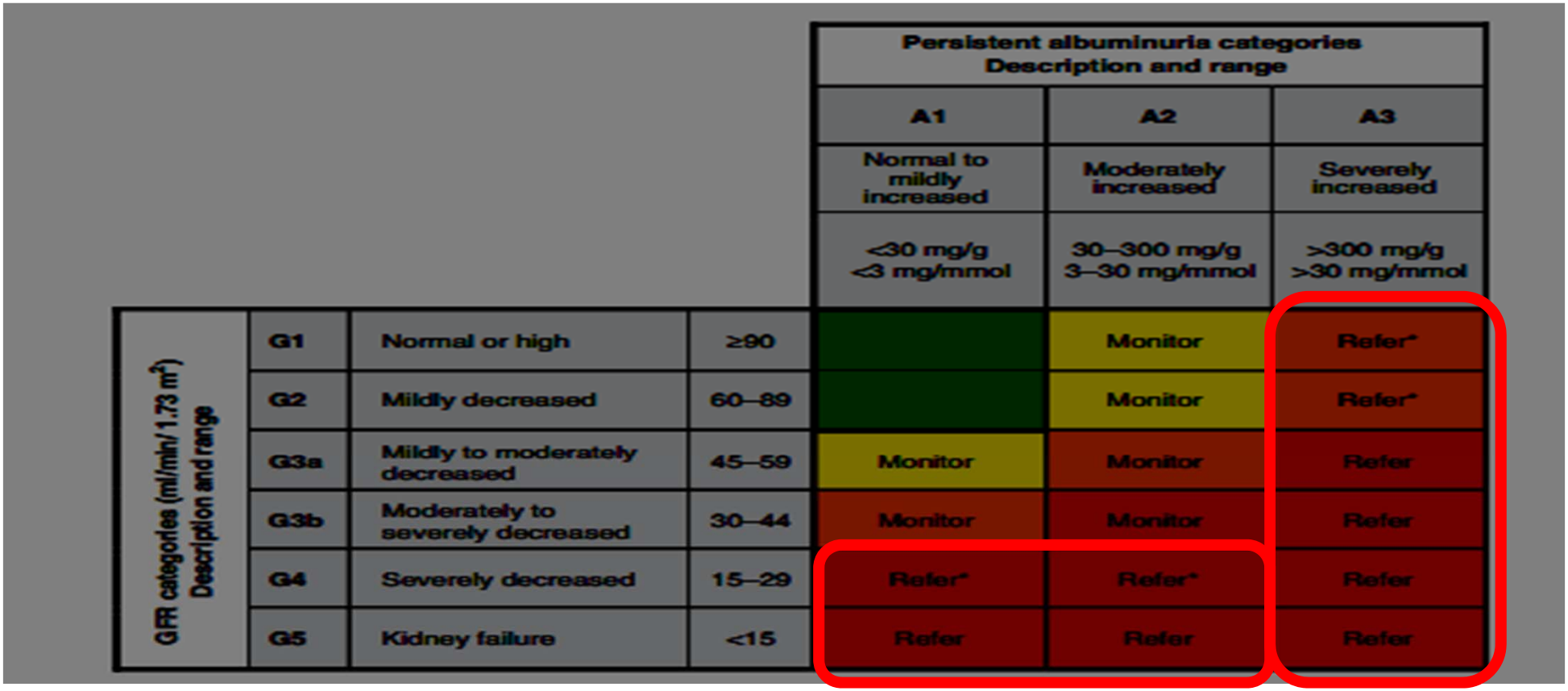
*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Kronik Böbrek Hastalığı – Evreleme

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Kronik Böbrek Hastalığı – Evreleme



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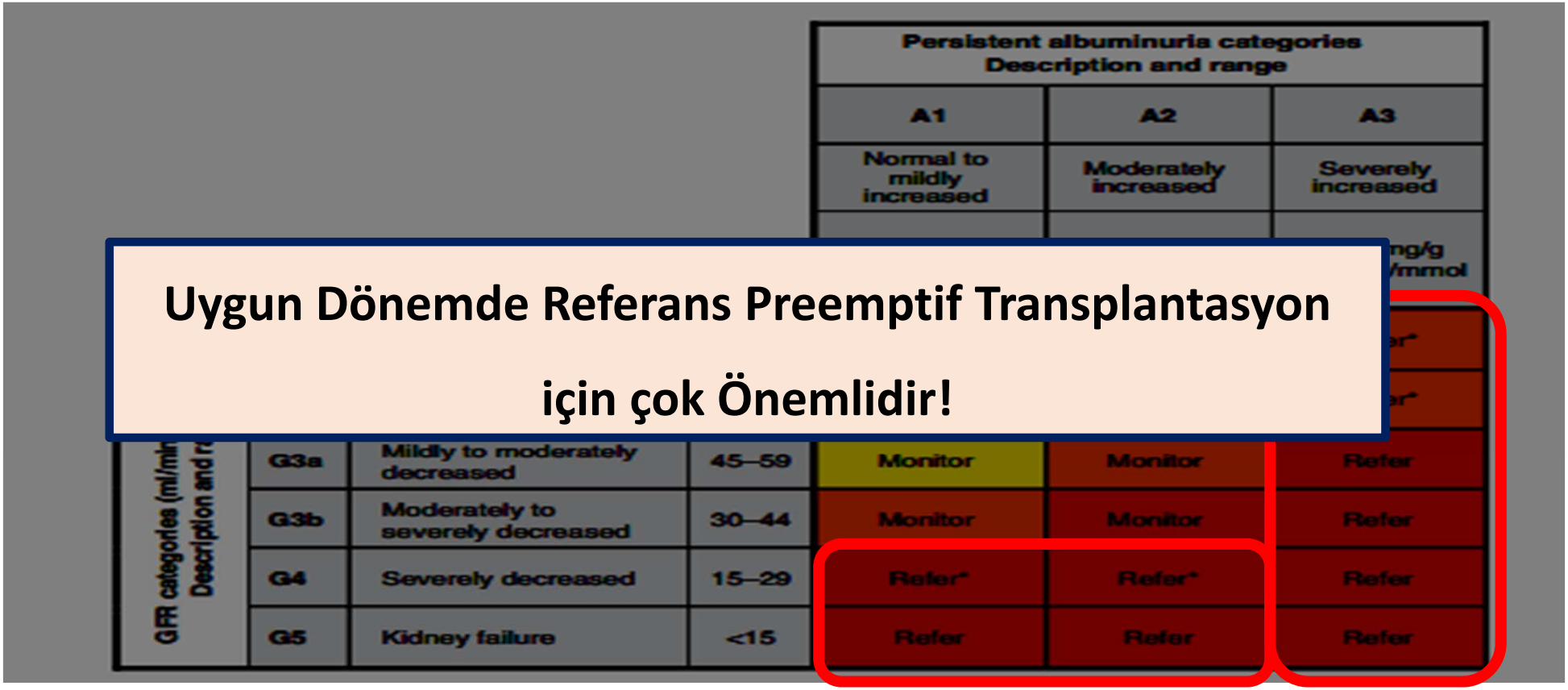

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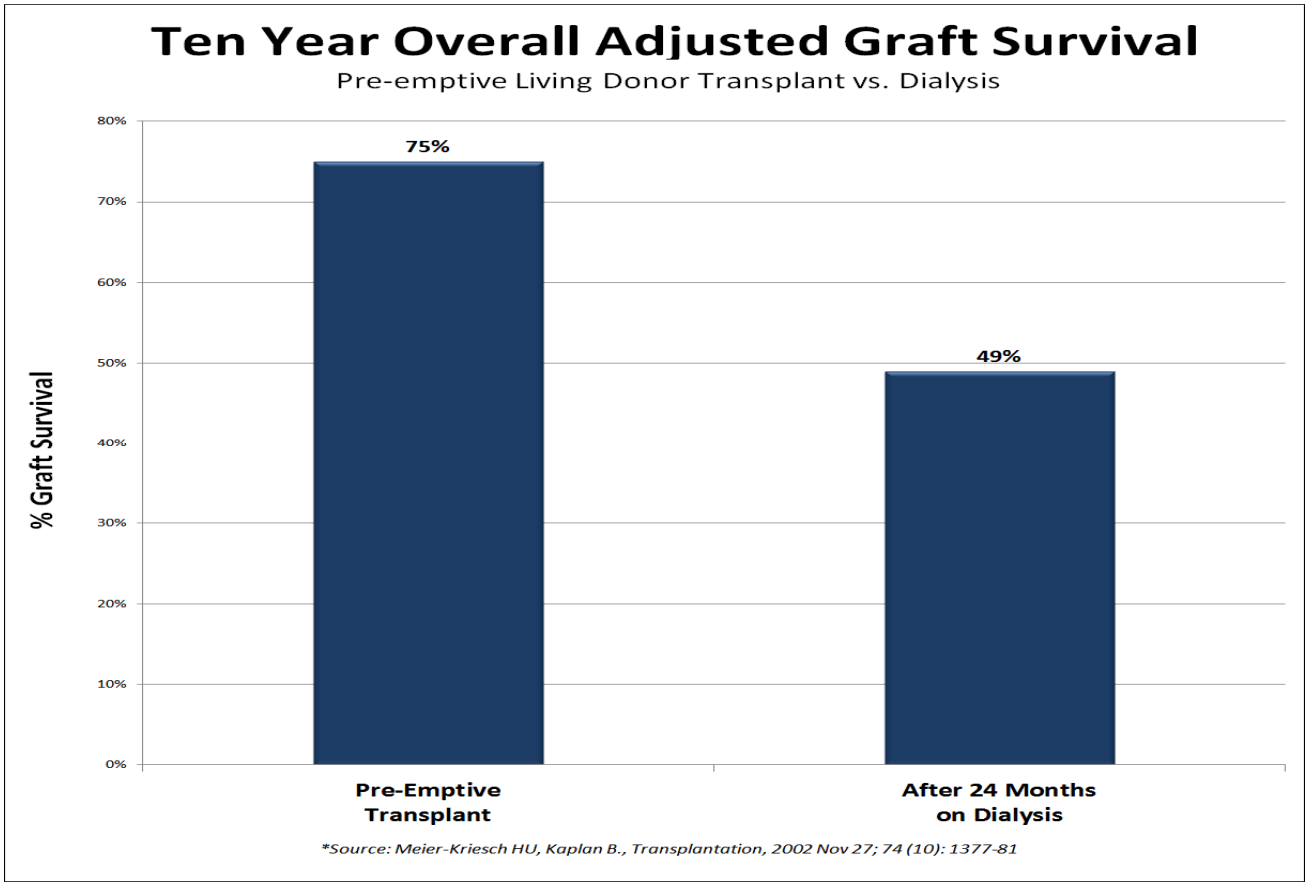
Uygun Dönemde Referans Preemptif Transplantasyon için çok Önemlidir!


Ten Year Overall Adjusted Graft Survival
Pre-emptive Living Donor Transplant vs. Dialysis
% Graft Survival
80%
70%
60%
50%
40%
30%
20%
10%
0%
75%
49%
Pre-Emptive Transplant
After 24 Months on Dialysis
*Source: Meier-Kriesch HU, Kaplan B., Transplantation, 2002 Nov 27; 74 (10): 1377-81

Transplantasyon Ne Zaman Yapılmalıdır?

- **Erişkinde canlı Donörde Preemptive renal Transplantasyon**
  - **GFR <20 ml/dk/1.73 m2**

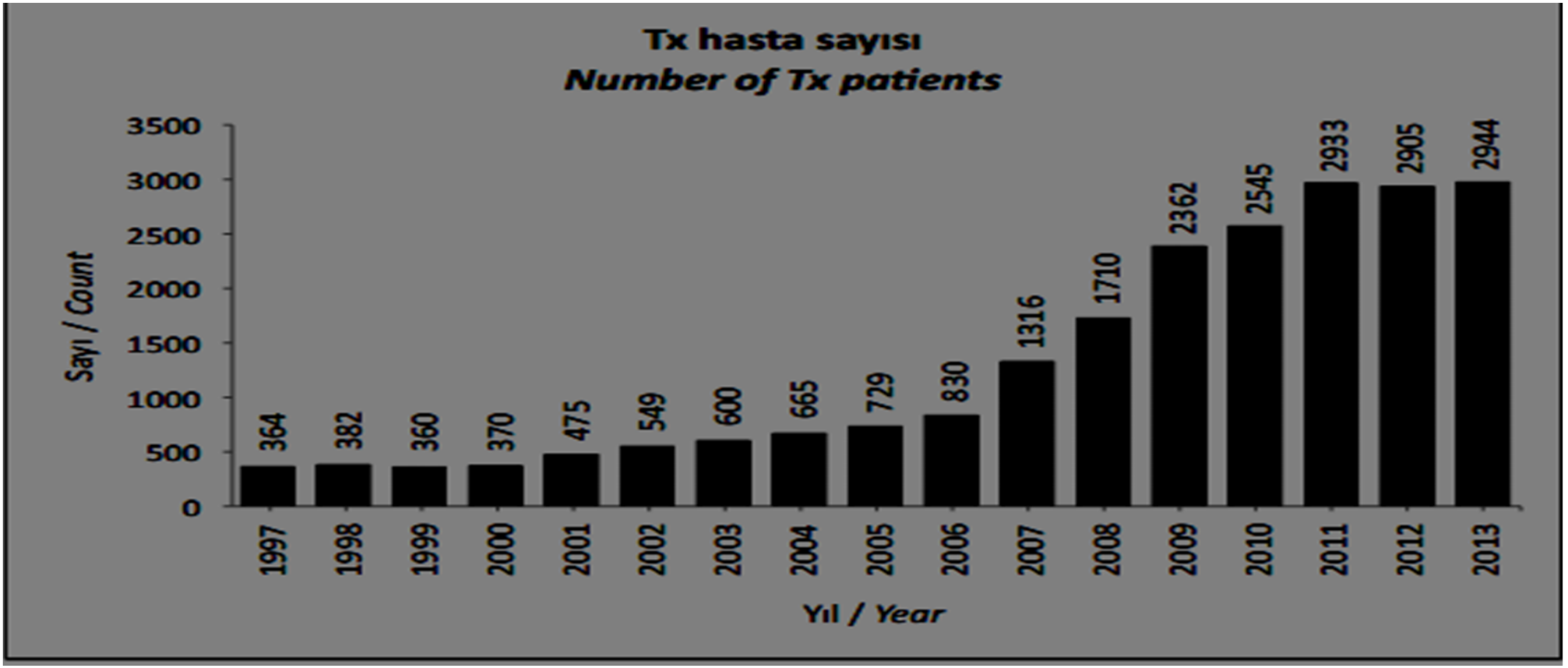
5.3.2: Living donor preemptive renal transplantation in adults should be considered when the GFR is <20 ml/min/ 1.73 m^2, and there is evidence of progressive and irreversible CKD over the preceding 6–12 months. (*Not Graded*)

Son Dönem Böbrek Yetmezliği'nin

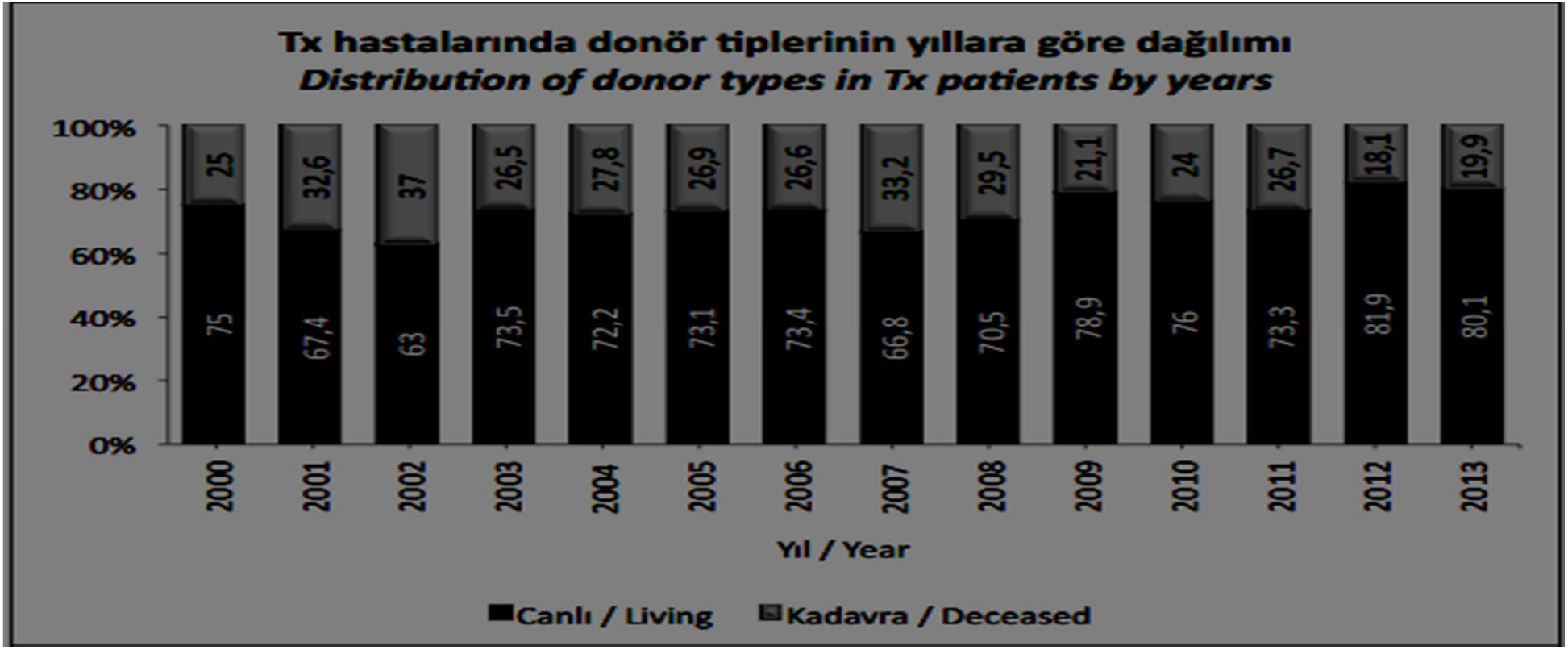
'ALTIN STANDART' tedavisi

'Renal Transplantasyondur'.

Türkiye'de Transplantasyon verileri



Türkiye'de Transplantasyon Verileri



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- **Erken dönem**

Kısa Dönem Riskler

- **Rejeksiyon**
- **Donör Faktörleri**
- **Hastanın Ölümü**
  - Operatif komplikasyonlar
  - İnfeksiyonlar
  - Maligniteler
  - Kardiyovasküler hastalıklar
- **İmmünosupressif Tedavinin Komplikasyonları**

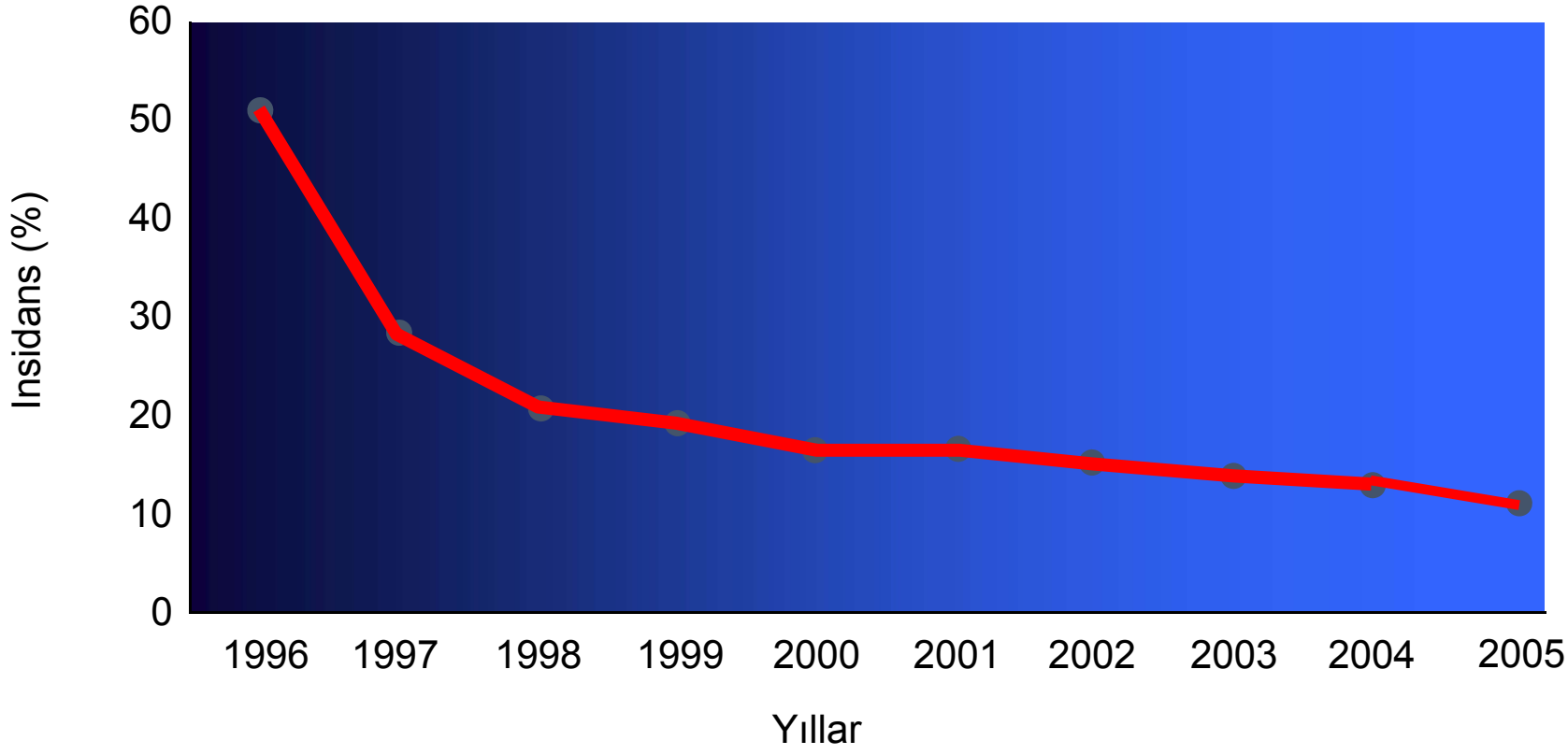
Kısa Dönem Riskler – İnfeksiyonlar

- **İlk 6 hf:** Standart postoperatif infeksiyonlar; üriner sistem, cerrahi alan, tromboflebit, solnum yolları, yara infeksiyonları, oral kandidiazis, vs

- **6. hf'dan sonra:** Fırsatçı infeksiyonlar; CMV, EBV, PJP, Listeria, aspergillus, mikobakterialar, vs...

- **Kemoproflaksi:** Kotrimoksazol, MTS, valgansiklovir

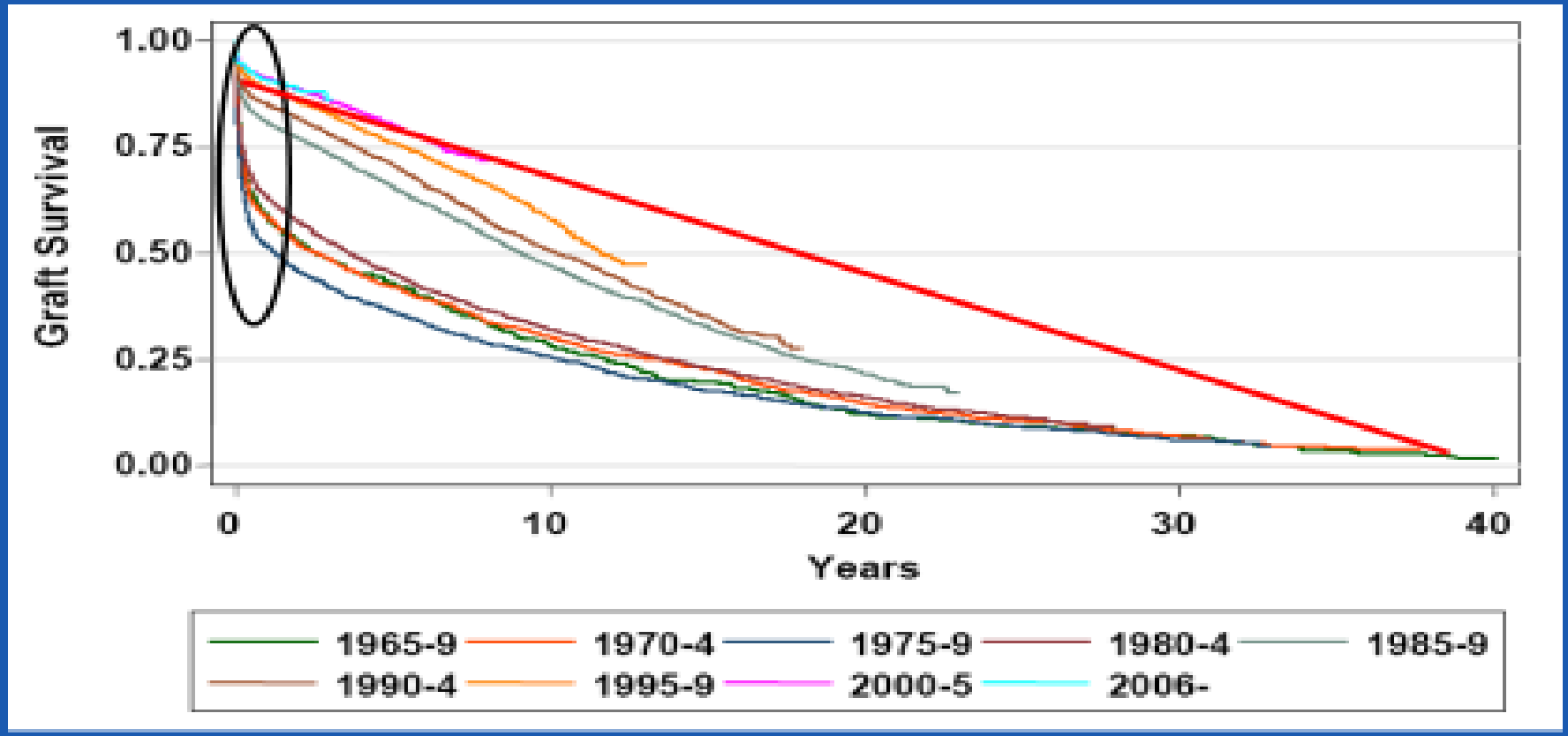
Akut Rejeksiyon Oranları Zamanla Değişmiştir!



1. OPTN/SRTR 2006 Annual Report.
2. OPTN/SRTR 2007 Annual Report.

Longer-term outcomes remain a challenge in kidney transplantation

Primary graft survival of deceased donors by year of transplant to 31/12/07: Australia and NZ

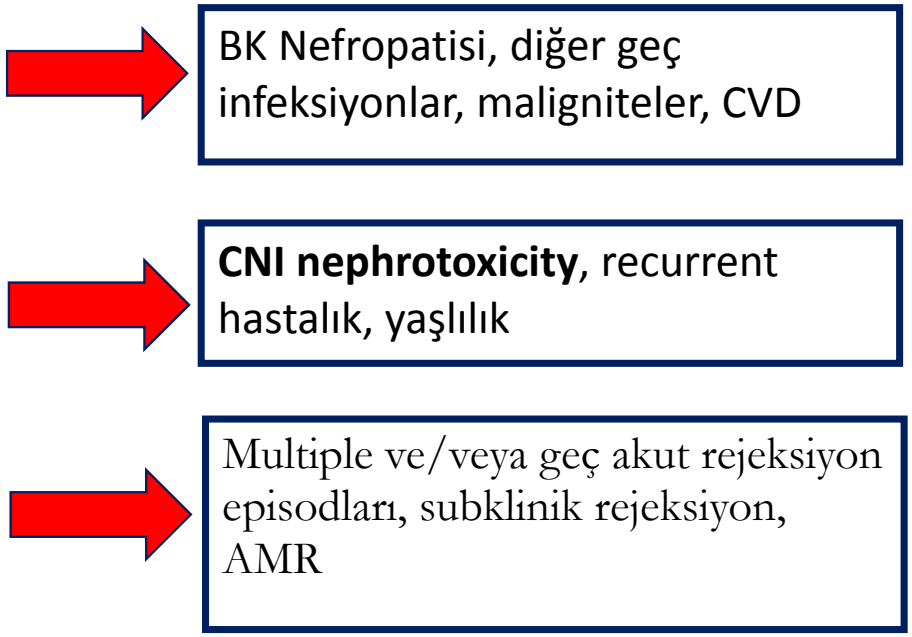


ANZDATA 31st annual report 2008 (http://www.anzdata.org.au/anzdata/AnzdataReport/31stReport/Ch08Txpart2.pdf)

Neden?

Neden?

- Immunosupresyon erken dönem yararlı olan etkileri geç dönemde olumsuz olması.
- Geç dönem graft yetmezliği immun hasarla ilişkisiz mekanizmalara bağlı olabilmesi
- Immunosupresyonun yetersiz olması veya uyum sorunu



Sunum Planı

- **Geç dönem**

'Outpatient care' izlem

- İlk 3 ay çok önemlidir; başlangıçta 1-2 hf bir kontrol, 1. yılın sonuna doğru 4 – 8 hf bir kontrol gerekebilir.
- İzlemde ayrıntılı anamnez ve fizik muayenenin yanısıra rutin idrar analizi, kan biyokimyası, tam kan sayımı, CNI düzeyi, spot idrarda ACR
  - Preemptif viral tarama ve izlem endikasyonu olan hastalarda 3 – 6 ayda bir yapılmalıdır.

Önemli Geç Dönem Riskler

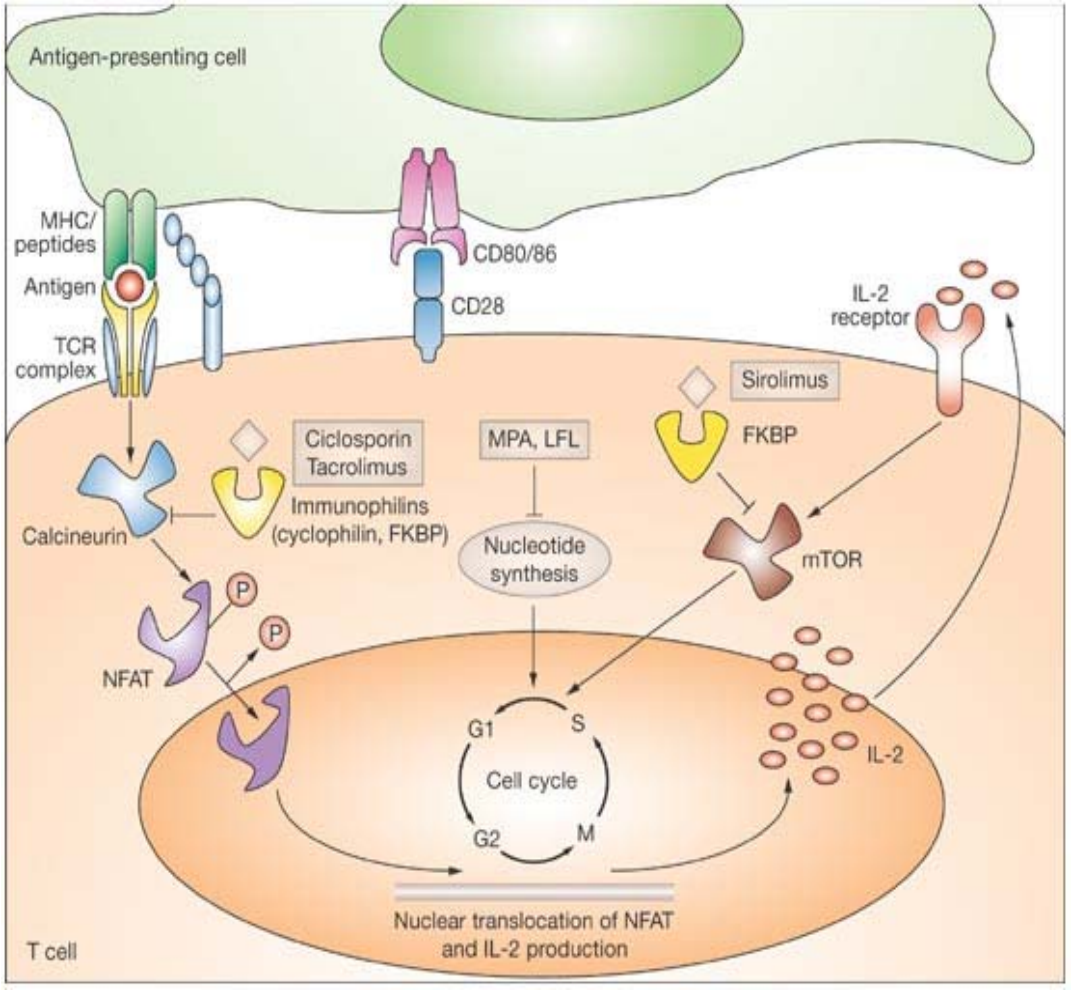
- Donör faktörleri
- Alıcının ölümü
  - Kardiyovasküler hastalıklar
  - Maligniteler
  - İnfeksiyonlar

- Geç Dönem Graft Kaybı
  - Kronik Allograft Nefropatisi
  - Subklinik ACR veya AMR
  - İnfeksiyonlar

İmmunosupresyon

Renal Tx kilit noktasıdır.

- Protokoller
- Uzun dönem dozajlama ve izlem
- Yan etkiler ve ilaç etkileşimleri



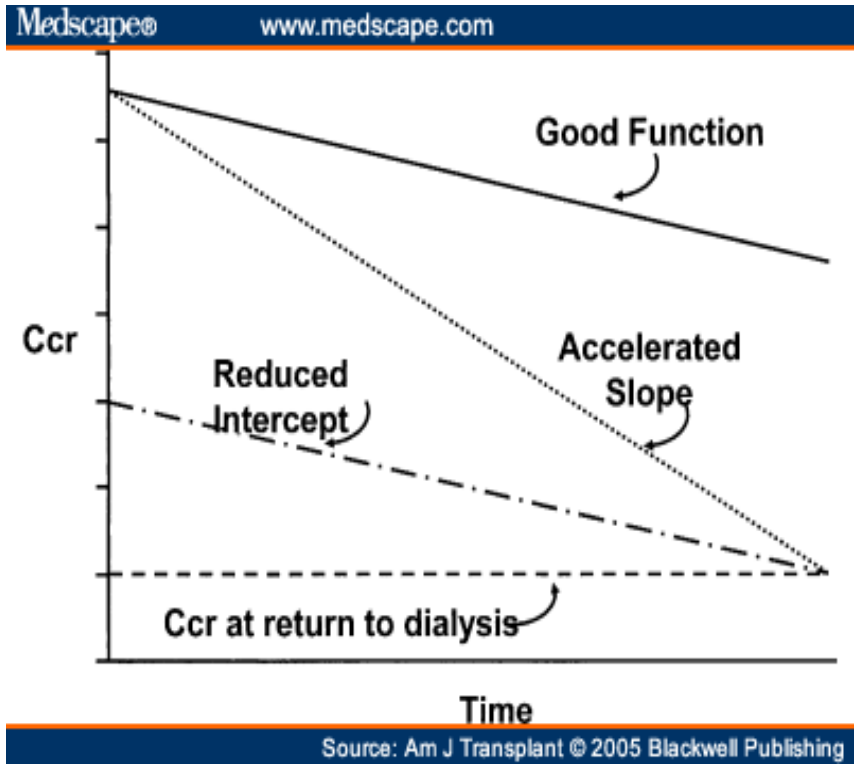
İmmunosupresyon

Induction Agents	Thymoglobulin
	Basiliximab
	Daclizumab
	Alemtuzumab
	Rituximab
Maintenance Agents	Tacrolimus
	Cyclosporine
	Sirolimus
	Mycofenolate Mofetil
	Azathioprine
	Corticosteroids
	Belatacept
	Leflunomide

Increases CNI level by inhibition of P450	Decreases CNI level by induction of P450
* Verapamil	Rifampin
Amlodipine	Rifabutin
* Diltiazem	Barbiturates
Nicardipine	Phenytoin
* Ketoconazole	Carbamazepine
Fluconazole	
Itraconazole	
Voriconazole	
Erythromycin	
Ritonavir	

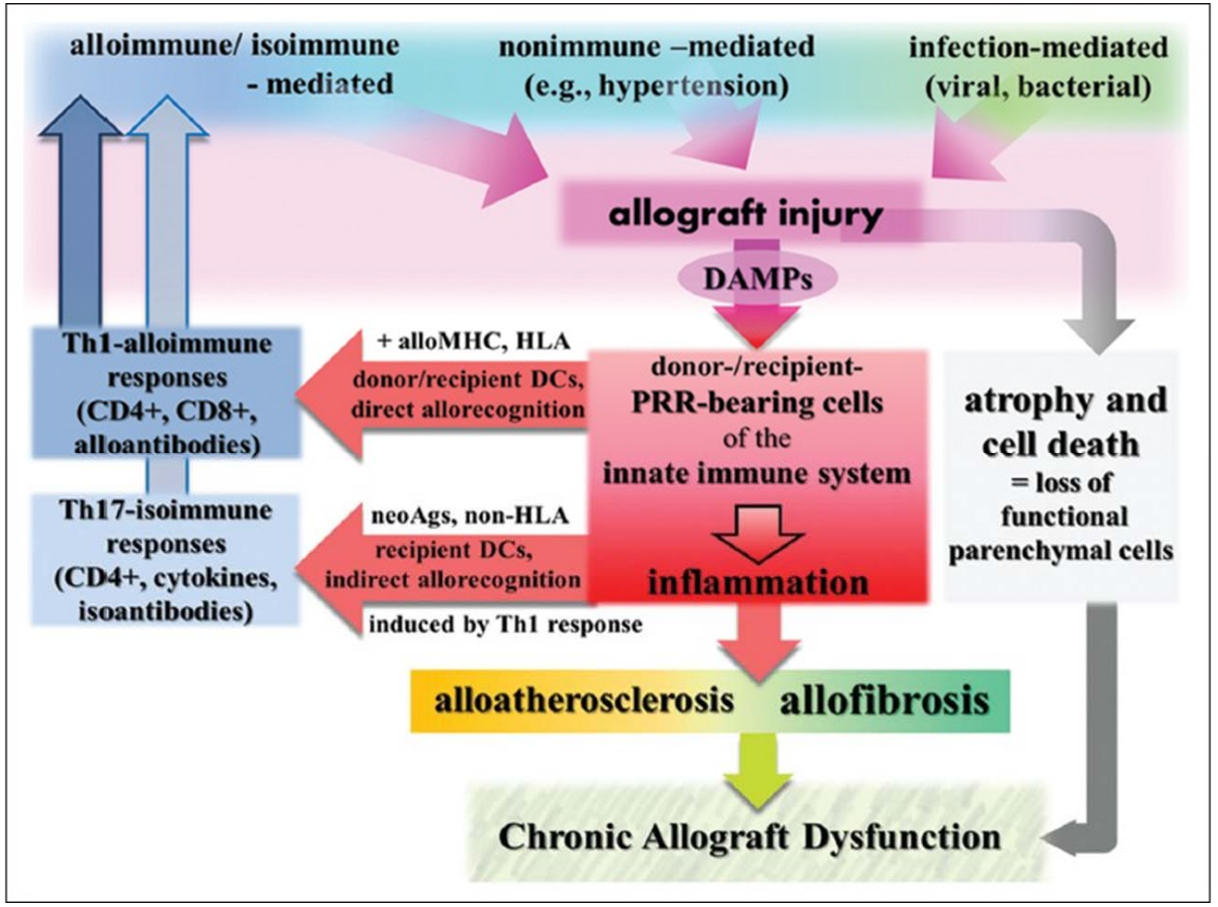
Allograft Disfonksiyonu

1. **Hiperakut Rejeksiyon:** dakikalar ile saatler
   - Donör HLA antijenlerine karşı antikor varlığı
   - Kompleman aktivasyonu, makrofajlar
2. **Akselere Rejeksiyon**
3. **Akut Rejeksiyon:** 10 – 30 gün
   - Sellüler mekanizma
4. **Kronik Rejeksiyon;** aylar – yıllar !!
   - Mikst sellüler ve humoral mekanizmalar

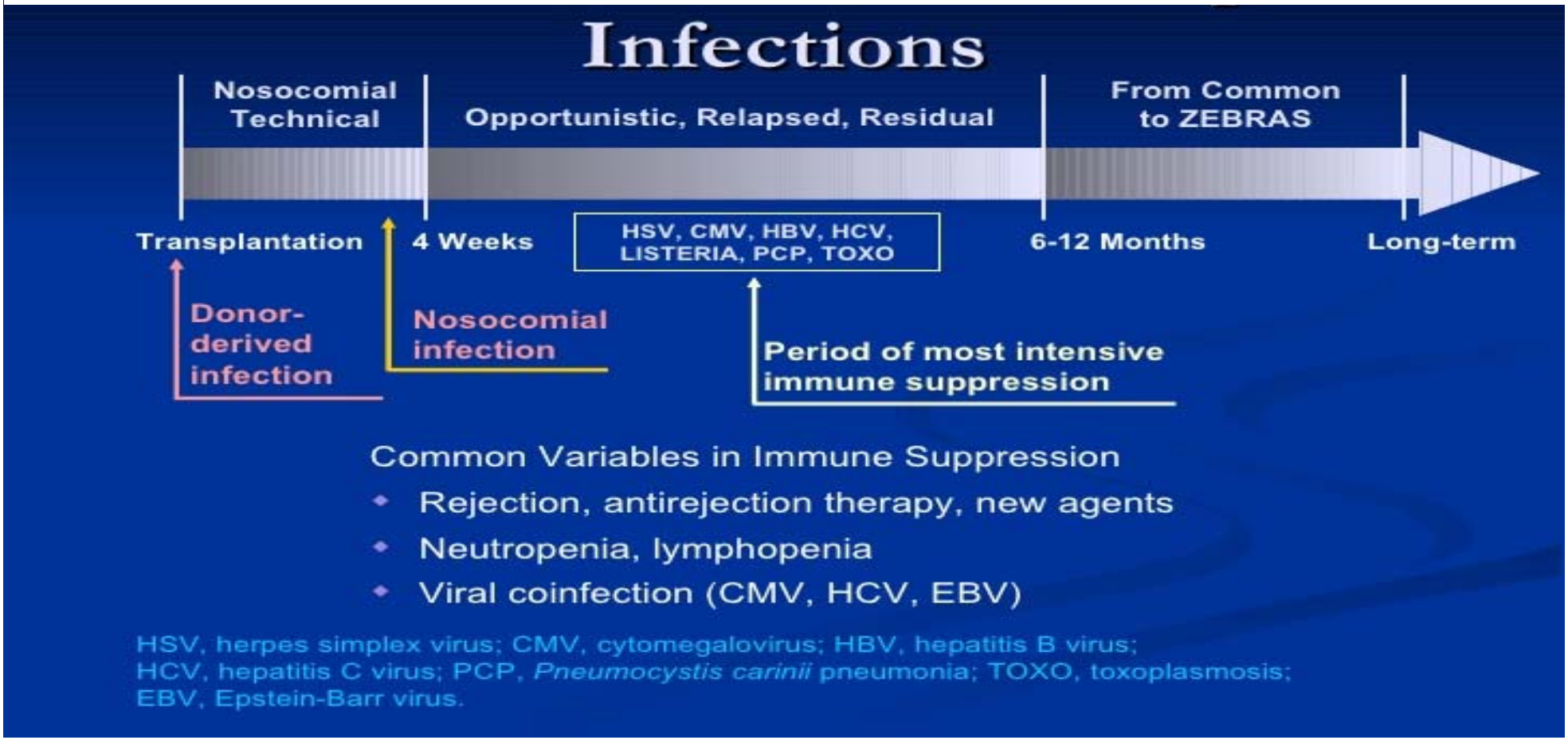


Allograft Disfonksiyonu

- **Kronik Allograft Disfonksiyonu**
  - Renal fonksiyonlarda azalma; progressif GFR
  - Agrave olmuş hipertansiyon
  - Proteinüride artış



İnfeksiyöz Komplikasyonlar



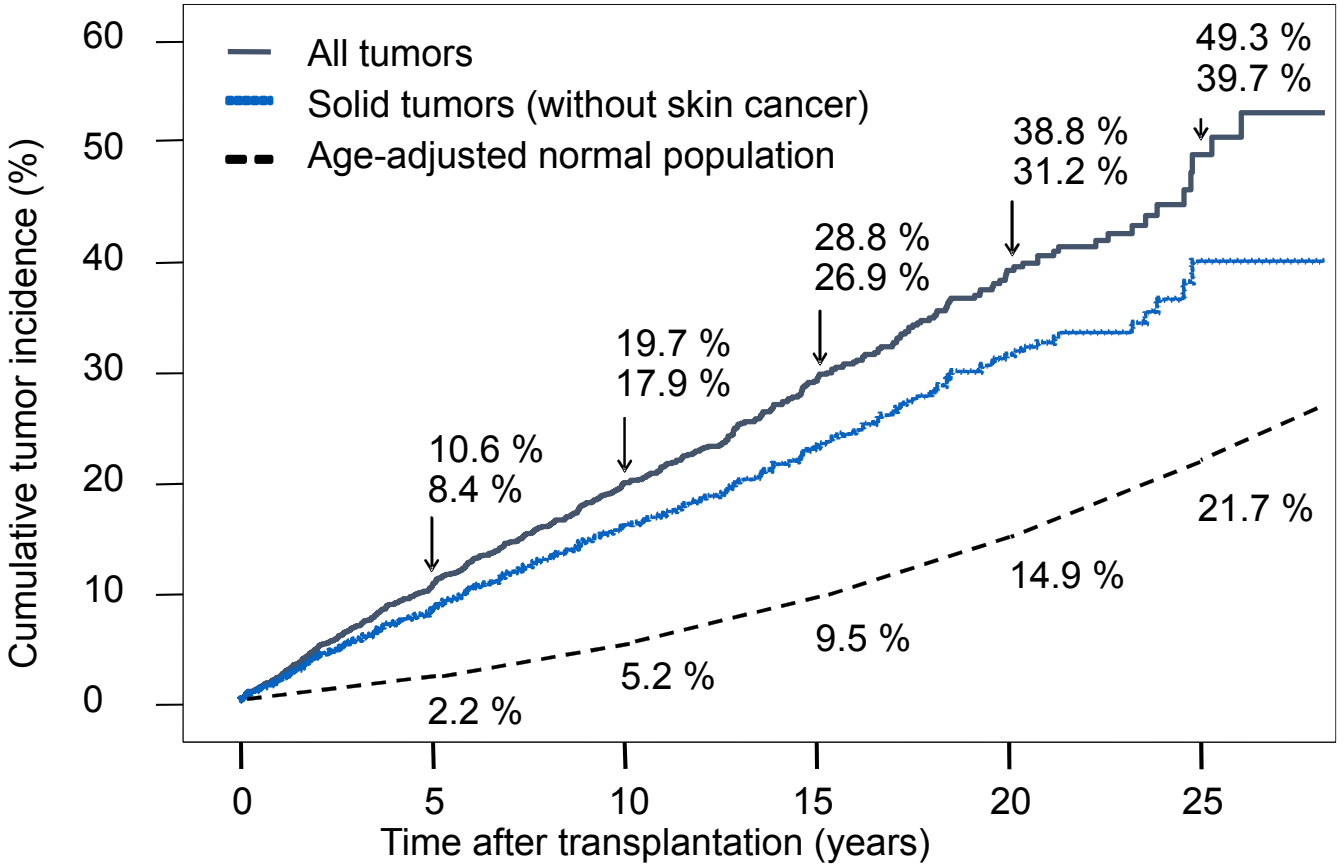
Hematolojik Komplikasyonlar

Hematolojik Komplikasyon	Nedenler
Anemi	Allograft disfonksiyonu Kan kaybı ESA resistansı İlaçlar; immunosupresifler, diğerleri İnfeksiyonlar; CMV, parvovirüs B19, polyomavirüs BK, tb, vs Hemolitik anemi Komorbid durumlar
Lökopeni	İmmunosupresif ve diğer ilaçlar
Trombositopeni	İmmunosupresif ve diğer ilaçlar İnfeksiyonlar HUS/TTP Otoimmun

Posttransplant Maligniteler

- **RTx malignite riskini arttırmaktadır.**
  - Viral ajanların aracılık ettiği maligniteler sıktır; EBV, CMV, HHV8
- **Risk Faktörleri**
  - İleri yaş
  - Beyaz ırk
  - Erkek cins
  - Kanser öyküsü
- **Tarama**: Normal popülasyon gibidir

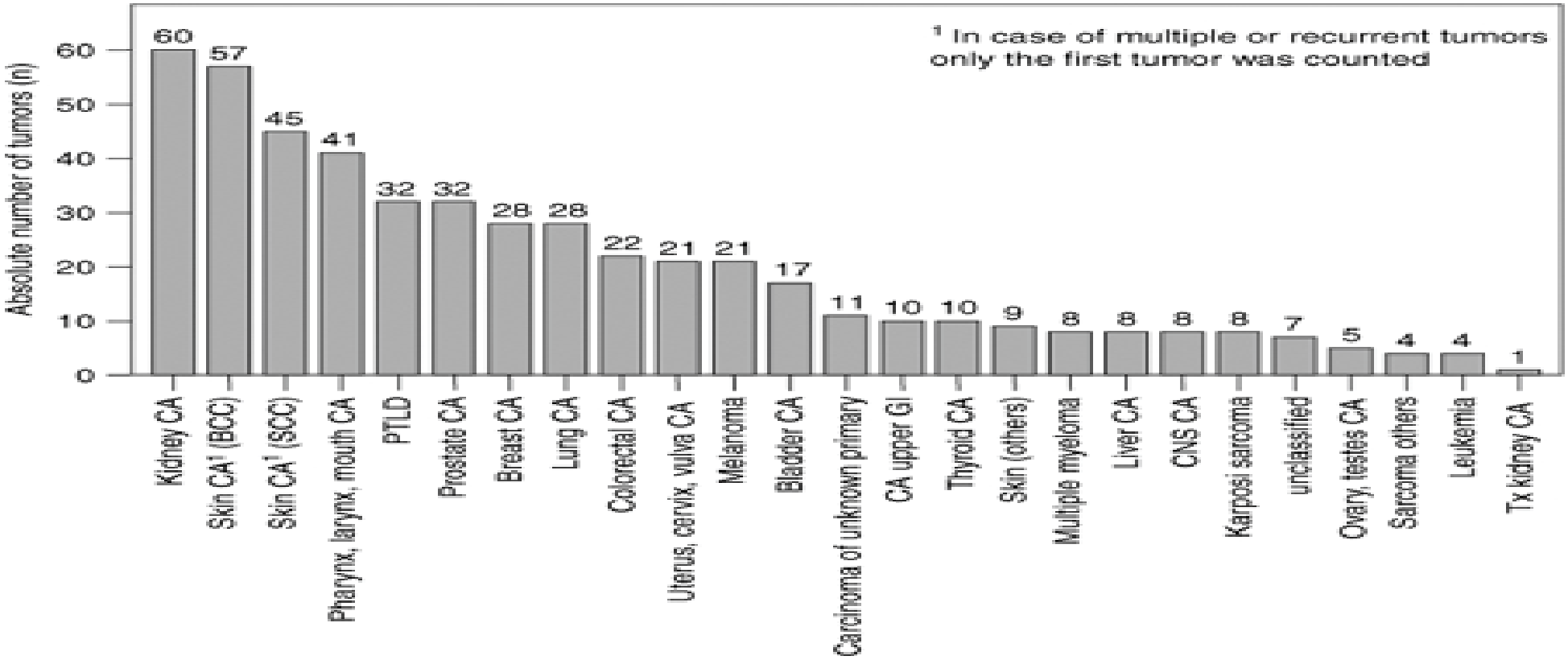
Renal Tx & Kümülatif İnsidans



Based on 2419 renal transplant recipients from the Munich Großhadern transplantation center

Wimmer CD, et al. Kidney Int. 2007;71:1271–1278.

Posttransplant Maligniteler



The increased risk of malignancy in kidney transplant patients

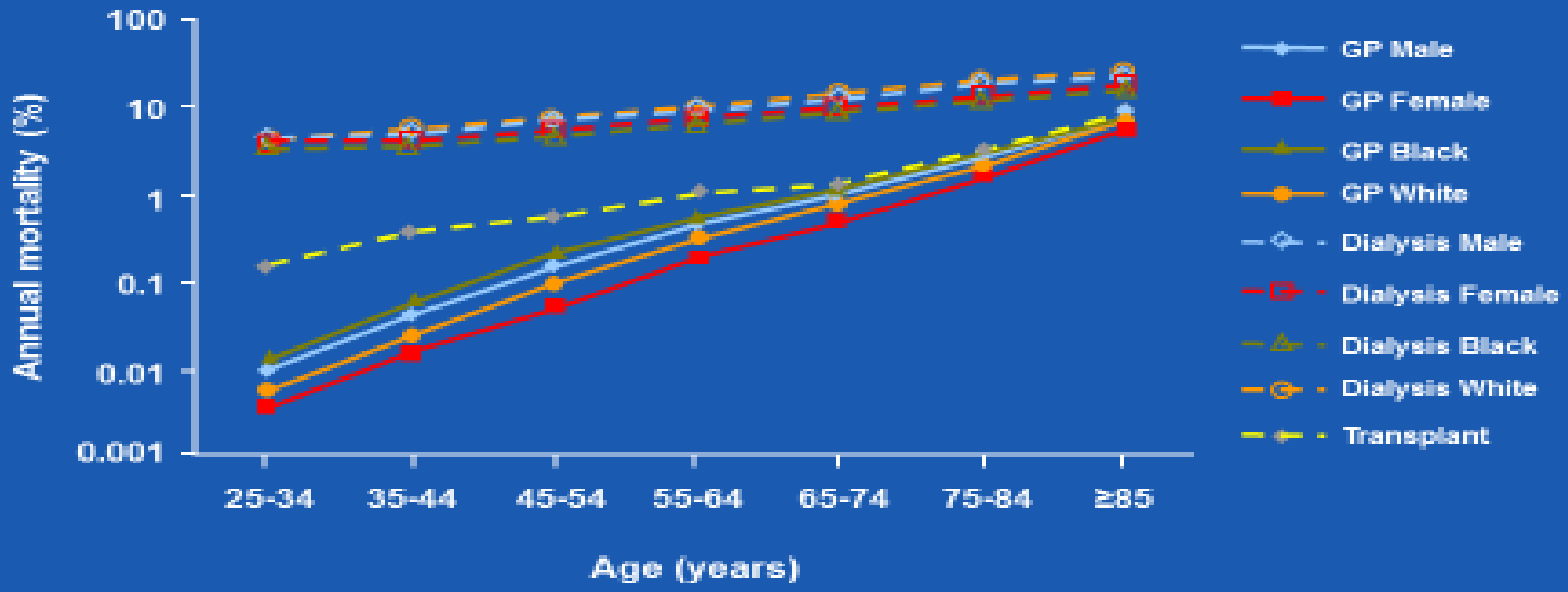
		Cancer rates vs. general population
Moderate Risk	Colon, lung, prostate, gastric, esophagus, pancreas, ovary and breast	2
	Testes and urinary, bladder	3
	Cutaneous melanoma, leukemia, liver and gynecological tumors	5
High risk	Kidney	15
	Kaposi sarcoma, PTLD, skin cancer	>20

Kasiske BL, et al. *Am J Transplant.* 2004;4:905–913.

Kardiyovasküler Risk faktörleri

- Metabolik Sendrom
- Obezite
- Hipertansiyon
- Dislipidemi
- Diyabet (NODAT)

Cardiovascular Mortality Is Higher in Patients With ESRD



Adapted from Foley RN et al. *Am J Kidney Dis.* 1998;32(5 Suppl 3):S112–S119.

Traditional and Nontraditional Risk Factors Increase CVD Event Risk in Patients With CKD[1]

Traditional Risk Factors	Non-Traditional Risk Factors
Older age	Anemia
Male sex	Volume overload
Hypertension	Abnormal mineral metabolism
High LDL-C	Electrolyte imbalances
Low HDL-C	Albuminuria
Diabetes	Lipoprotein(a) and Apo(A) isoforms and lipoprotein remnants
Smoking	Homocysteine
Physical inactivity	Oxidative stress/inflammation
Menopause	Malnutrition
Family history of heart disease	Thrombogenic factors
Left ventricular hypertrophy	Sleep disturbances
White race	High sympathetic tone
	Altered nitric oxide/endothelin balance

Particular to individuals with CKD

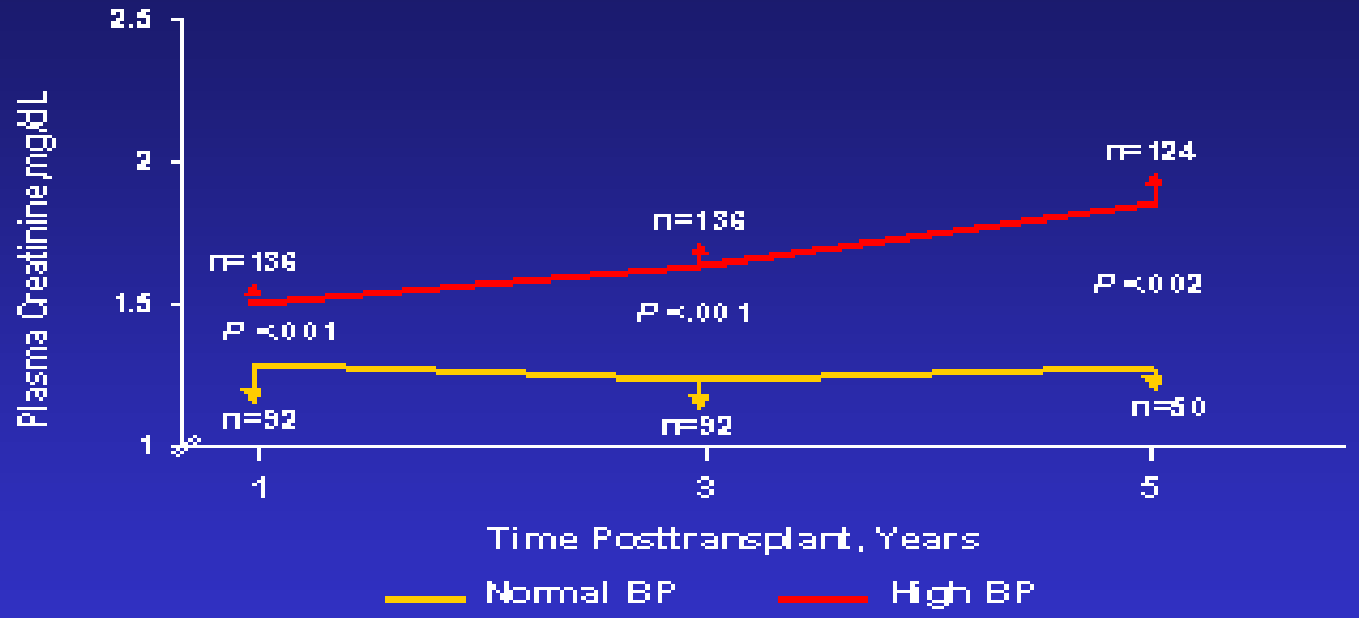
CVD = cardiovascular disease; CKD = chronic kidney disease;
LDL-C = low-density lipoprotein cholesterol;
HDL-C = high-density lipoprotein cholesterol; Apo = apolipoprotein.

1. Shastri S et al. *Am J Kidney Dis.* 2010;56:399-417.

Hipertansiyon & Patogenez

- Esensiyel hipertansiyon varlığı
- Genel-populasyon risk faktörleri
  - Obesite, sigara, alkol, tuz tüketimi
- Renal disfonksiyon/rejeksiyon
- Renal-transplant artery stenosis
- Native böbreğin etkileri
- Hipertansive donör
- Immunosupresif ilaçlar

Hypertension and Renal Graft Failure[8]



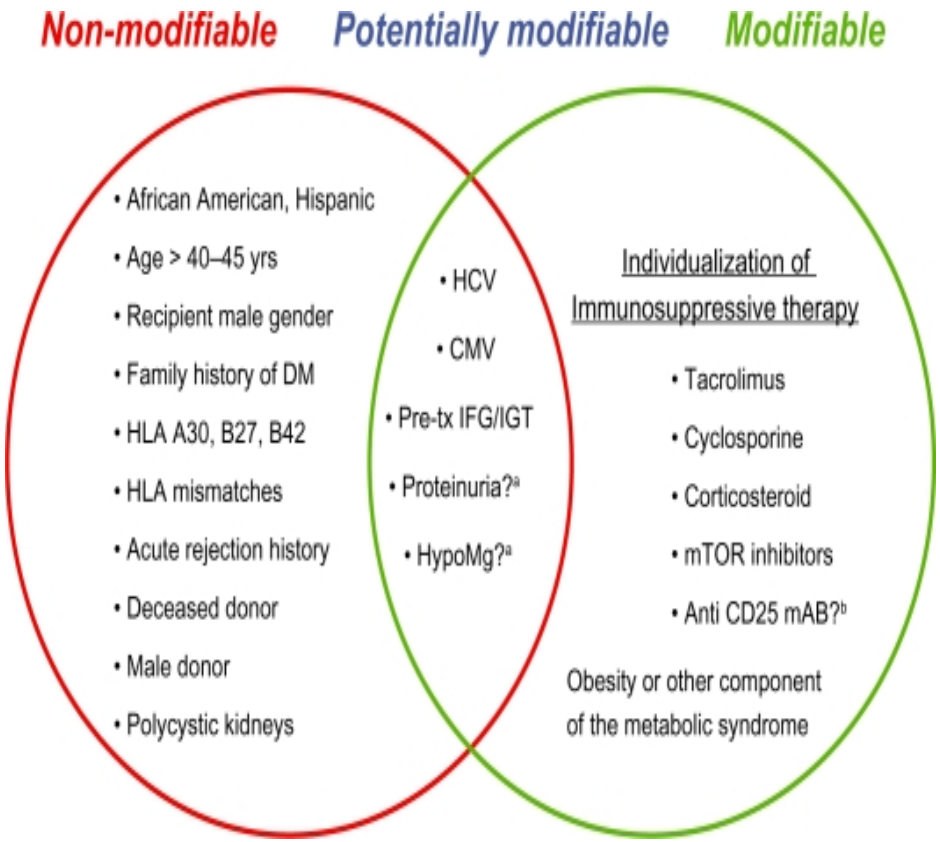
BP = blood pressure

Hipertansiyon & Tedavi

- Konsensus yok
    - Kişiselleştirilmiş tedavi
- KKB öneren ekoller var

New Onset Diabetes After Transplantation (NODAT)

- Sıktır; %4 – 25
- Yakın izlem ve tedavi modifikasyonları gerektirebilir.

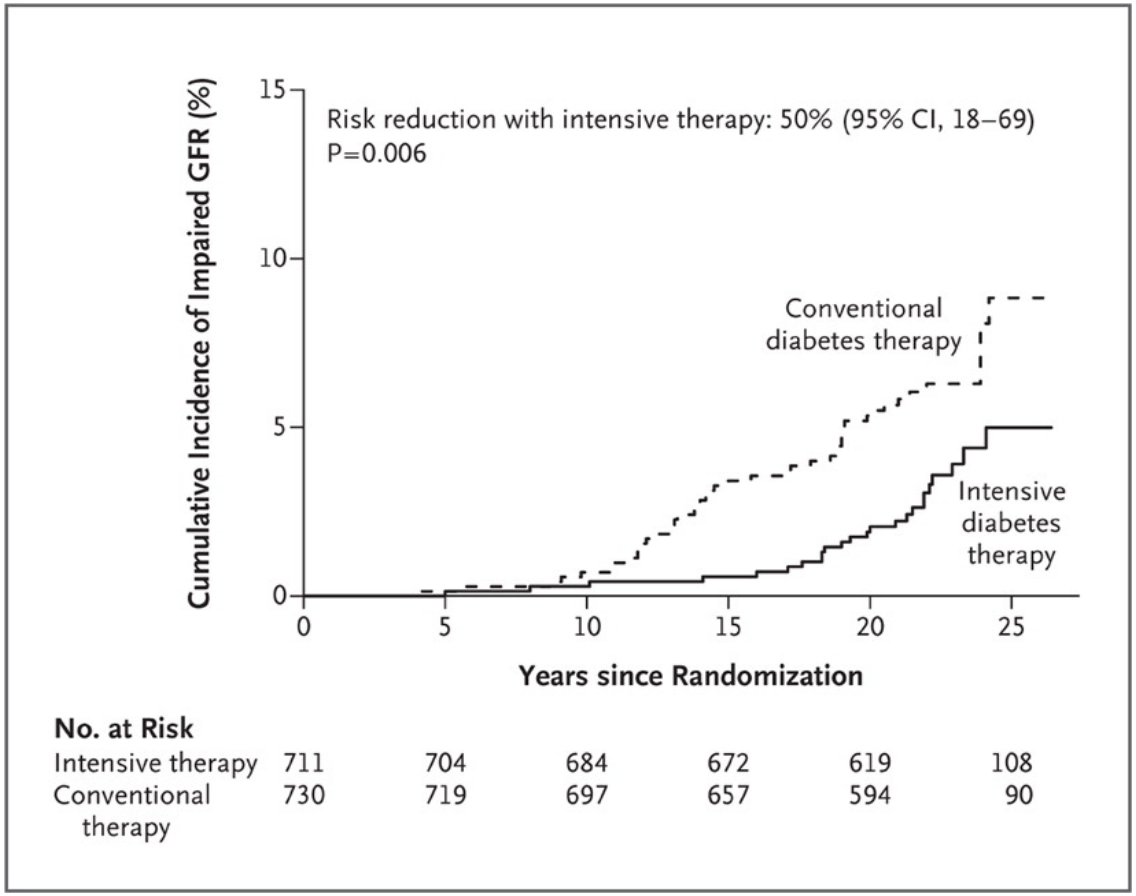


New Onset Diabetes After Transplantation (NODAT)

Immunosuppressive agent	Pathogenic mechanism(s)	Comments
Corticosteroids	• ↓Peripheral insulin sensitivity • Inhibit pancreatic insulin production & secretion • ↑Hepatic gluconeogenesis • Promote protein degradation to free amino acids in muscle, lipolysis	•Dose-dependent •Impact of complete withdrawal of chronic low-dose steroids unclear •Potential ↓NODAT risk in steroid-free regimens
Cyclosporine	• ↓insulin secretion (CsA < Tac) • ↓insulin synthesis • ↓β-cell density	•Dose-dependent, •Diabetogenic effect ↑ with ↑ steroid dose*
Tacrolimus	• ↓insulin secretion (Tac > CsA) • ↓insulin synthesis	•Dose-dependent, •Diabetogenic effect ↑ with ↑ steroid dose*
Sirolimus	•↑Peripheral insulin resistance • Impair pancreatic β-cell response	↑Diabetogenicity when use with CNIs

Abbreviations: CNI: calcineurin inhibitors
* Demonstrated in some but not all studies

Glisemik Kontrol & Graft sağkalımı



No. at Risk

Intensive therapy	711	704	684	672	619	108
Conventional therapy	730	719	697	657	594	90

NODAT & Sonuçlar

Kısa Dönem Sonuçları

- Akut Metabolik Komplikasyonlar; DKA, Laktik asidoz, hipoglisemi, vs
- Rejeksiyon
- Akut infeksiyonlar; majör infeksiyonlar

Uzun Dönem Sonuçları

- Kardiyovasküler Hastalık
- Nefropati
- Retinopati
- Diyabetik Ayak

KVH Düzeltici Stratejiler

- KB <130/80 mmHg
- Dislipideminin tedavisi
- Mijkroalbuminuri/proteinuri düzeltilmesi?
- Tuz ve sature yağ kısıtlanması
- Sıkı glisemik kontrol
- Aneminin kontrol edilmesi
- Ca, P dengesinin düzenlenmesi
- Anti-platelet tedavi

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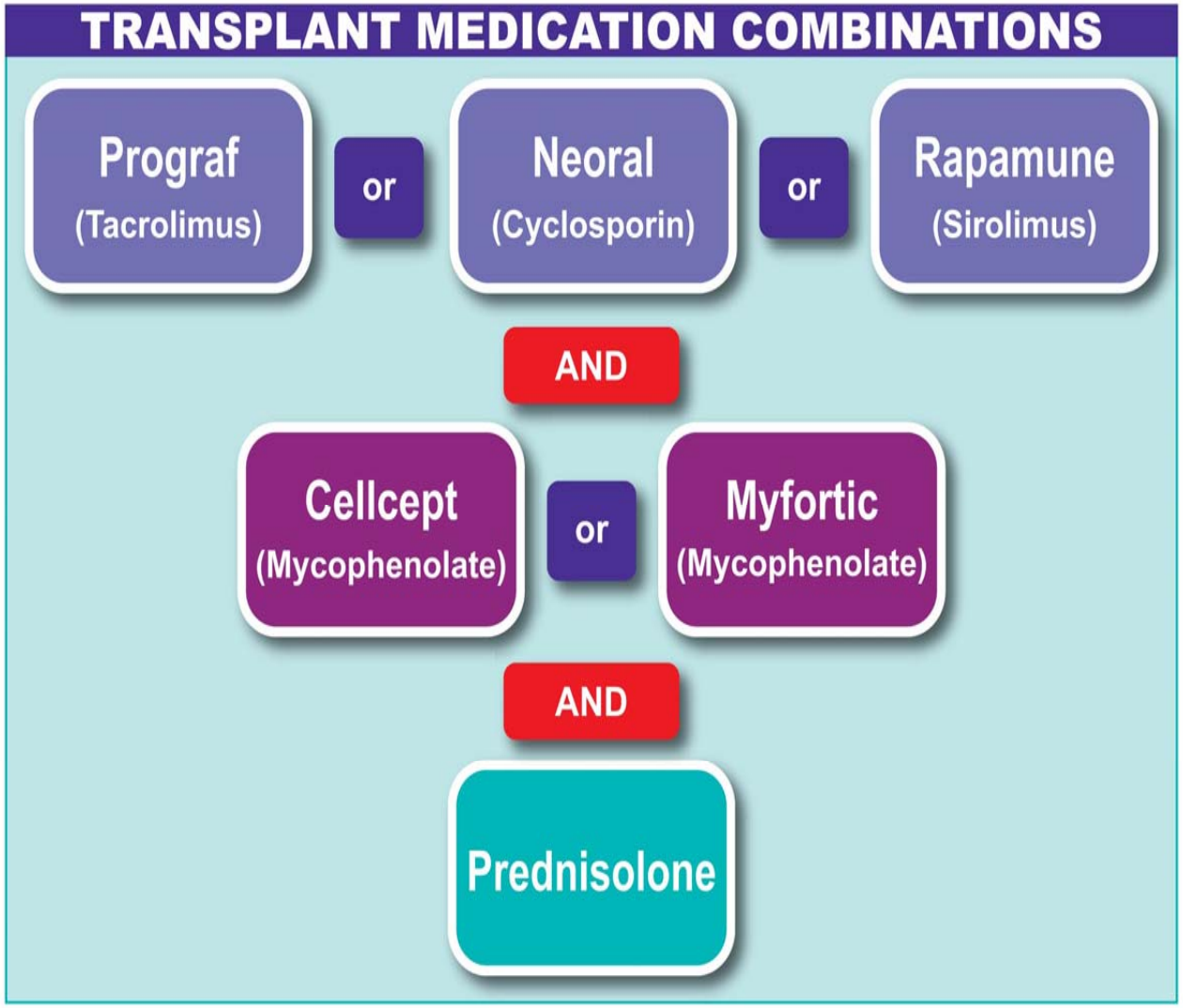

Drugs	Common side effects
Prednisolone	Weight gain, high blood pressure, gastric irritation, increased appetite, increased risk of diabetes, osteo porosis, cataract
Cyclosporine	High blood pressure, mild tremor, excess hair growth, swelling of gum, increased risk of diabetes, kidney damage
Azathioprine.	Bone marrow suppression, increased risk of infection
MMF	Abdominal pain, nausea, vomiting and diarrhea
Tacrolimus	High blood pressure, diabetes, tremor, headache, kidney damage
Sirolimus	High blood pressure, low blood cell count, diarrhea, acne, joint pain, increased cholesterol, triglycerides

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Etkileşen Ajan	Etkileşen ajanların rolü	Öneri/İzlem
Calcineurin Inhibitors		
Antifungals		
Anidulafungin	No significant effect	
Amphotericin B	Increased risk of nephrotoxicity	Appropriate hydration; monitor renal function closely
Caspofungin	Increased hepatic enzymes with cyclosporine	Monitor transaminases closely; Consider alternatives if elevation in hepatic enzymes occurs
Fluconazole	Inhibits metabolism	Monitor CNI levels closely
Ketoconazole	Inhibits metabolism	Monitor levels closely; Decrease CNI dose by 50-75%
Micafungin	No significant effect	
Posaconazole	Inhibits metabolism	Monitor CNI levels closely; Decrease cyclosporine by 25% and tacrolimus by 66%
Voriconazole	Inhibits metabolism	Monitor levels closely; Decrease CNI dose by 50-75%

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Antibiyotikler		
Azithromycin	Little effect	
Clarithromycin	Inhibits metabolism	Empiric dose reduction; monitor CNI levels closely
Erythromycin	Inhibits metabolism	Empiric dose reduction; monitor CNI levels closely
Rifampin	Induces metabolism	Increase in dose; monitor CNI levels closely
Antiretroviraller		
Antikonvulsanlar		
Barbiturates	Induces metabolism	Increase in dose; monitor CNI levels closely
Benzodiazepines	No effect	
Carbamazepine and Oxcarbazepine	May induce metabolism	Monitor CNI levels; may require increase in dose
Levertiracetam	No effect	
Modafanil	Induces metabolism	Dose reduction; monitor CNI levels
Phenytoin	Induces metabolism	Dose reduction; monitor CNI levels closely
Valproic acid	No direct effect	Monitor levels

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Antihipertansif İlaçlar		
ACEIs/ARBs	May increase risk of hyperkalemia	Monitor Potassium
Beta-blockers	Carvedilol may inhibit	Monitor CNI levels
Diltiazem, verapamil, and nifedipine	Inhibit metabolism	Decrease CNI dose by 25%; monitor CNI levels closely
Dihydropyridine calcium channel blockers	No effect	
Colchicine ve NSAIDS		
Colchicine	Inhibition of colchicine metabolism; competitive inhibition of cyclosporine metabolism	Dose adjustment of colchicine per package labeling required
NSAIDS	Increased risk of nephrotoxicity	Avoid if possible; use for short period of time if necessary with close monitoring
Lipid Lowering Agents		
HMG Co-A reductase inhibitors	Increased statin exposure with cyclosporine No effect with tacrolimus	Significant dose reductions of statin; monitor CPK

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Lipid Lowering Agents		
HMG Co-A reductase inhibitors	Increased statin exposure with cyclosporine No effect with tacrolimus	Significant dose reductions of statin; monitor CPK
Psychiatric Drugs		
Citalopram	No reports	Monitor CNI levels
Desvenlafaxine	No reports	Caution due to CYP 3A4 metabolism of desvenlafaxine
Duloxetine	No reports	Monitor CNI levels
Fluvoxamine	Inhibits metabolism	Monitor CNI levels closely; dose reductions may be necessary
Fluoxetine, paroxetine, and citalopram	Little effect	Monitor CNI levels
Haloperidol	QT prolongation	Monitor QTc interval
Lithium	Increased risk of nephrotoxicity	Monitor renal function closely
Nefazodone	Inhibits metabolism	Avoid if possible
Quetiapine and olanzapine	QT prolongation	Monitor QTc interval
Sertraline	May inhibit metabolism	Conflicting reports-monitor levels closely
Venlafaxine	Little effect	Monitor CNI levels

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Antimetabolites MMF and MPA		
Calcineurin inhibitors		
Cyclosporine	Reduction in MPA AUC	Dose adjustment may be necessary
Antivirals		
Acyclovir	Possible Increase in AUC	Monitor for adverse events
Ganciclovir	Decreased clearance of ganciclovir	Monitor for adverse events
Gastrointestinal Drugs		
Antacids	Decrease in AUC and Cmax	Avoid concomitant administration if possible
Proton Pump Inhibitors	MMF-decrease in Cmax and Tmax MPA—no effect	Caution with MMF
Phosphate Binders		
Calcium-free phosphate binders	Decrease in AUC and Cmax	Administer 2 hours after MMF

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Diğer İlaçlar		
Cholestyramine	Decrease in AUC	Concomitant use not recommended
Oral contraceptives	Decrease in levonorgestrel AUC	Caution with levonorgestrel
Anti-infectives		
Ciprofloxacin and amoxicillin/ clavulanic acid	Decrease in trough levels	Caution
Norfloxacin and metronidazole	Decrease in AUC	Concomitant use not recommended with combination
Trimethoprin/ Sulfamethoxazole	Small reduction in AUC	Does not appear clinically significant
Rifampin	Increase in exposure	Monitor for adverse events
Xanthine Oxidase Inhibitors		
Allopurinol	Increase in 6-mercaptopurine	Avoid concomitant use

İmmunosupresif İlaçlarla Etkileşen İlaçlar

Mammalian Target of Rapamycin Inhibitors		
Calcineurin Inhibitors		
Cyclosporine	Increase in sirolimus AUC	Monitor levels; if given concomitantly, give sirolimus 4 hours after cyclosporine
Antifungals		
Ketoconazole	Increase in Cmax, Tmax, and AUC	Monitor levels; significant dose reduction required
Voriconazole	Increase in Cmax and AUC	Monitor levels; significant dose reduction required
Calcium Channel Blockers		
Non-dihydropyridine calcium channel blockers	Increase in Cmax and AUC	Monitor levels; dose reduction may be required
Antibiotics		
Erythromycin	Increase in Cmax and AUC	Monitor levels; consider azithromycin as an alternative
Rifampin	Decrease in Cmax and AUC	Monitor levels; significant dose increase required
Antiretrovirals		
HIV protease inhibitors	Increase in AUC	Monitor levels: dose reduction may be required

İmmunosupresif İlaçlar

- Kullanılacak İlaçlarının etkileşip etkileşmedikleri
- İmmunosupresif İlaçların kan düzeyi ölçülmesi
- Kan düzeyine göre doz ve uygulamanın düzenlenmesi hayati öneme haizdir.

Sonuç

- Birçok Renal Tx hastası İç Hastalıkları pratiğindedir
- Transplantasyon Merkezi ile Nefrolog ile yakın ilişki hasta ve graft sağkalımı için önemlidir
- Şüpheli durumlarda mutlaka yardım ve destek gerekirse sevk işlevi işletilmelidir.

…..sabrınız için teşekkürler!