Advagraf Conversion and De Novo: Clinical aspects

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Presentation aims

To discuss

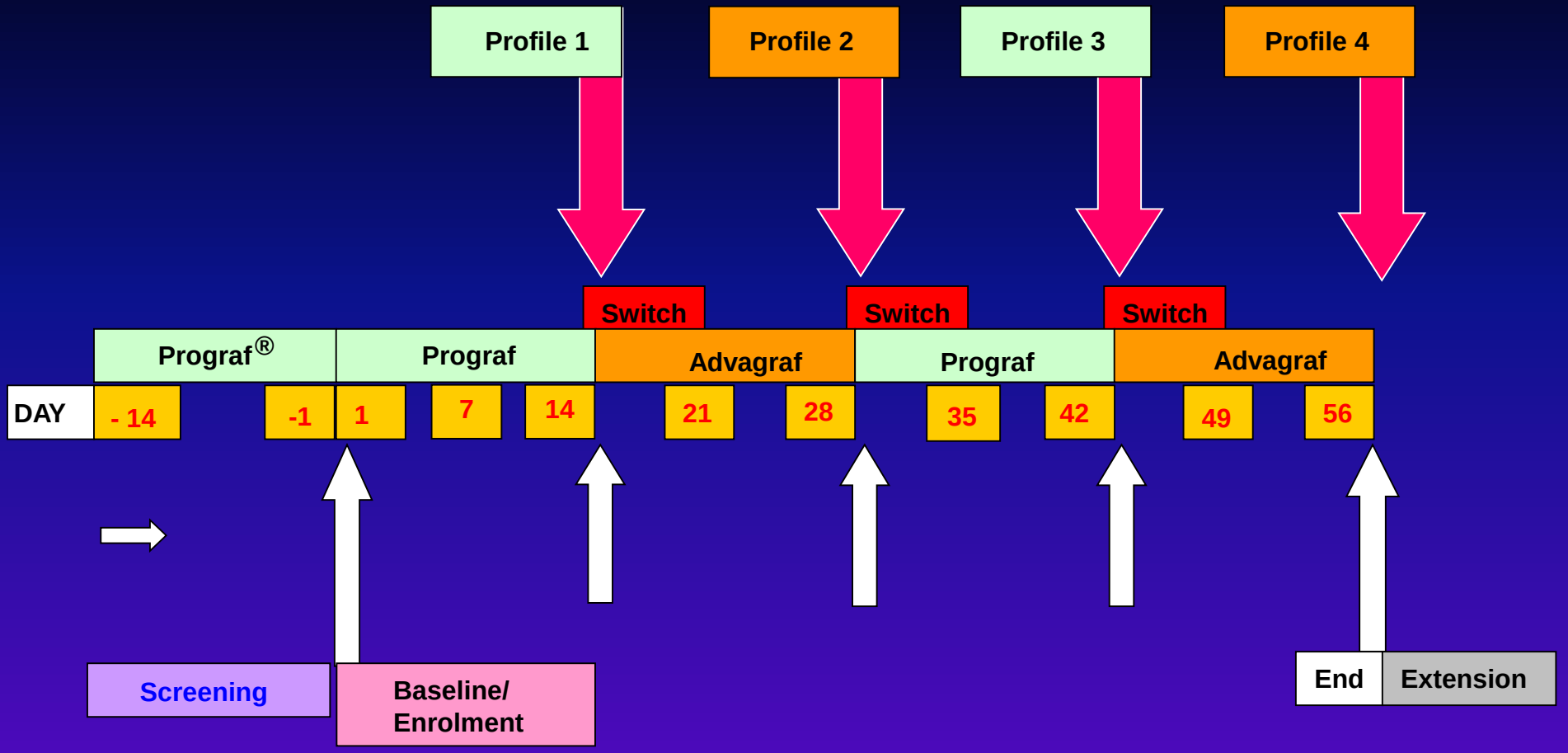
- ***Conversion*** from Prograft to Advagraf:
  - Clinical data from pivotal renal transplant studies
  - Practical recommendations for safe *conversion*

  - ***De Novo*** use of Advagraf:
  - Clinical data from pivotal renal transplant studies comparing Prograf vs Advagraf.
  - Practical recommendations for *De Novo* use of Advagraf.

- ***Longterm follow up clinical data*** of Advagraf
  - 4 year from studies
  - 10 year Maastricht data

Conversion from Prograf to Advagraf

Replicate Design (EU/SA Renal)



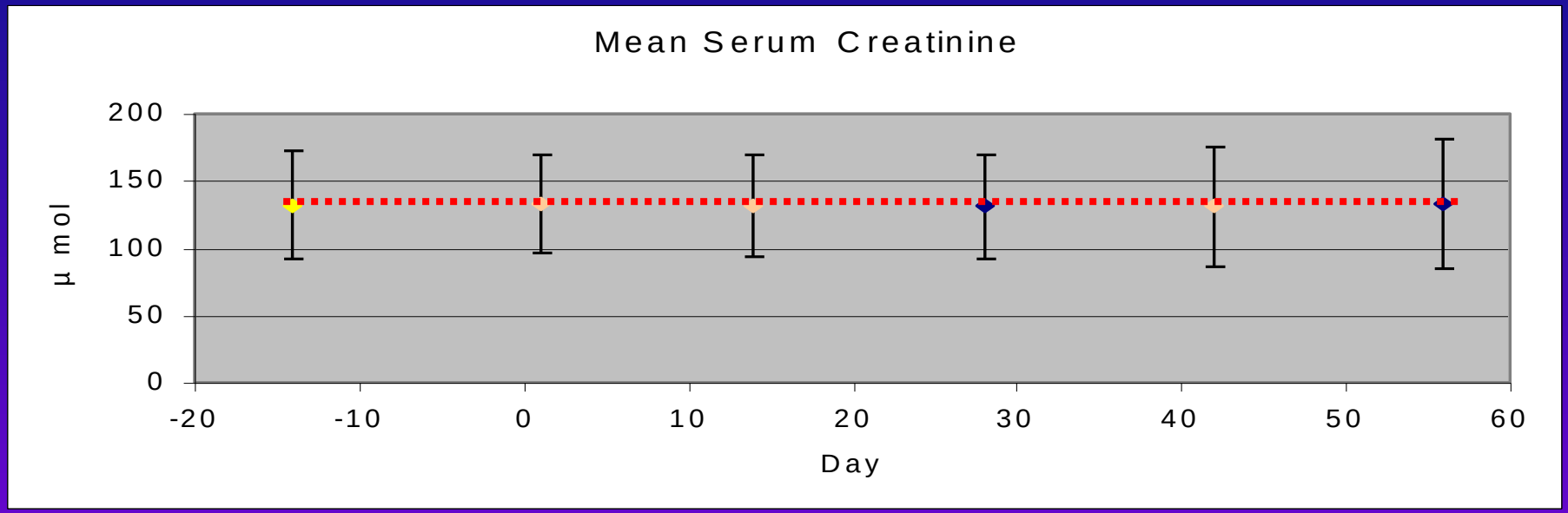
24 hours Blood Concentration-Time Profile

HOUR	0	0.5	1	2	3	4	6	8	12	12.5	13	14	15	16	18	20	24

Clinical Observations (EU Renal Conversion PRG -> ADVA)

- Not a single episode of acute rejection
- No treatment discontinuation
- No onset of PTDM or glucose intolerance after conversion to Advagraf

Gelens M, Christiaans M, Undre N, Karpf C Dackus J, van Hooff J



Spanish Experience with Conversion from Prograf to Advagraf

The EVOLUTION Study
Evaluation of Advagraf Conversion and Long-Term Use in Kidney Transplantation
(GREAT Group)

Efficacy and Safety of Conversion from Twice-daily to Once-daily Tacrolimus in a Large Cohort of Stable Kidney Transplant Recipients

American Journal of Transplantation 2011, vol 11, 1965-71.

ADVAGRAF® tacrolimus prolonged release

Spanish Experience with Advagraf (Evolution study)
Conversion of stable renal transplant patients (n = 1,832)

- 62.8% men and 37.2% women
- Period of transplant: 1985–2008; Converted since September 2005
- Conversion
  - 1mg:1mg in 96% of patients
  - 1mg:1.1mg in 4% of patients (low tacrolimus levels <6ng/mL)
- Trough tacrolimus levels measured pre-conversion and at 7-14 days after

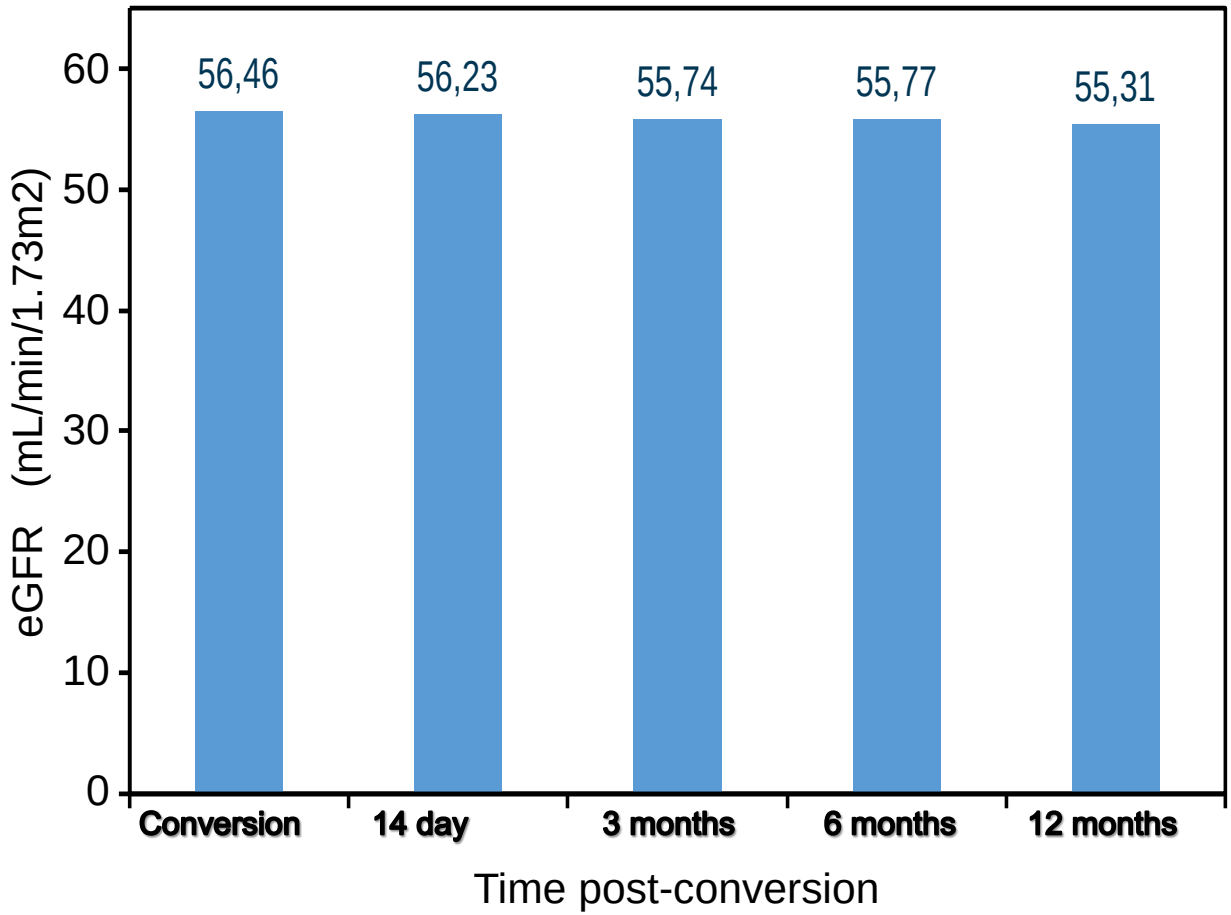
- Lower Tacrolimus mean trough levels ↓ 9.1%
- Increased dosages of tacrolimus ↑ 1.24%

- Low rate of acute rejection post-conversion 0.4%
- Conversion no effect on bloodpressure, Lipids, Hepatic profile

Guirado et al., AJT 2011

EVOLUTION Study: eGR by MDRD

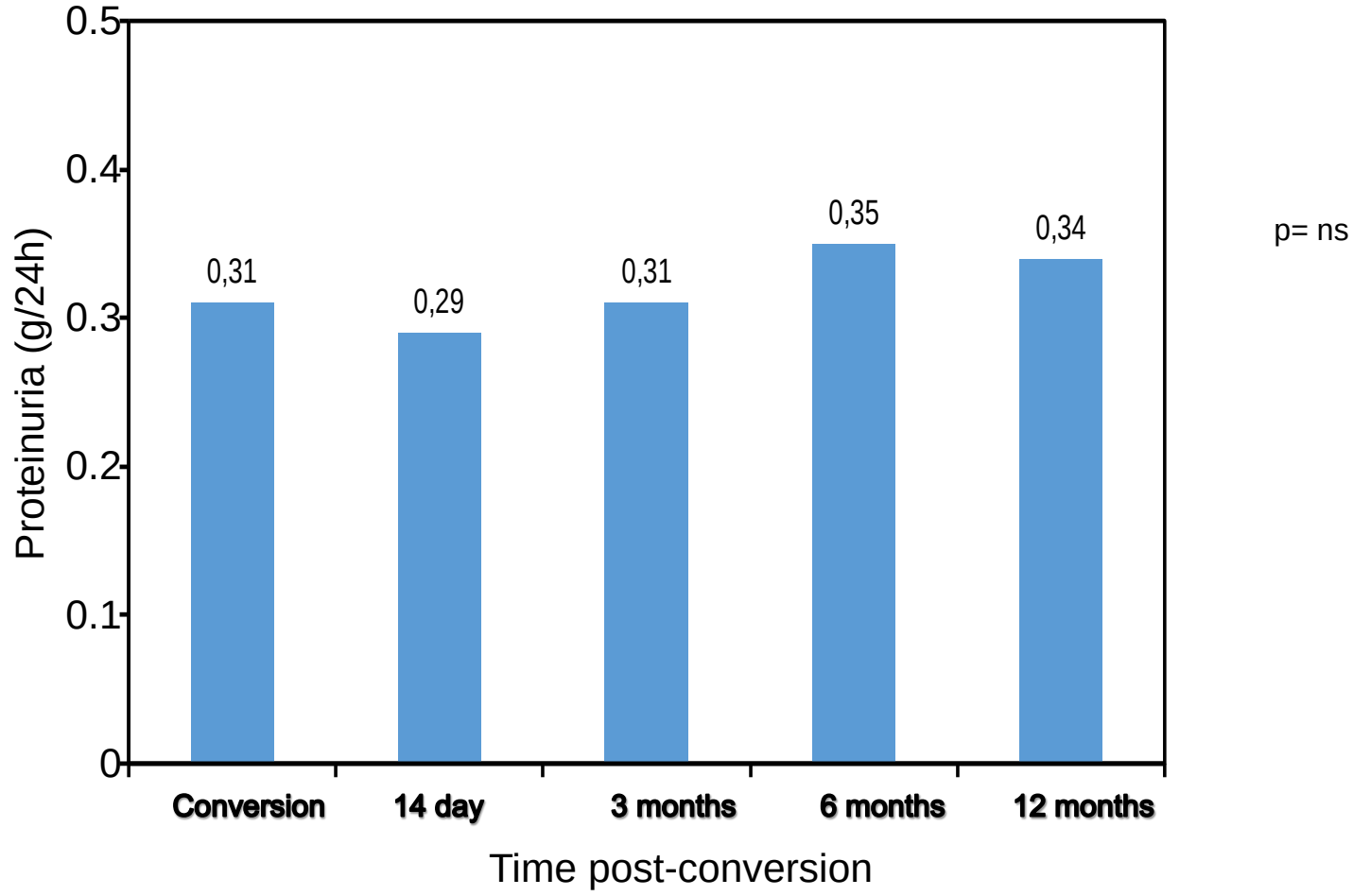
N=1,832



Guirado et al., AJT 2011, 11: 1965

EVOLUTION Study: Proteinuria (g/24h)

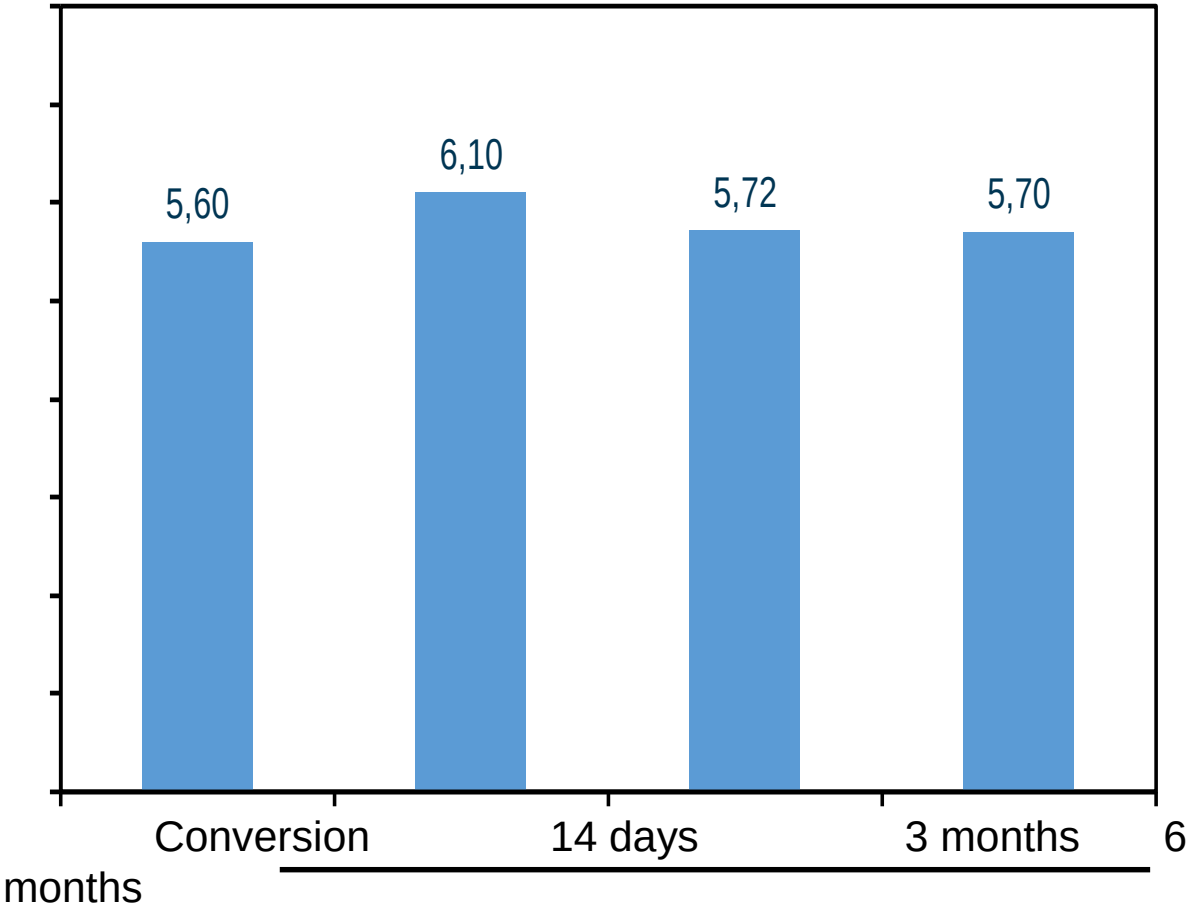
N=1,832



p= ns

Guirado et al., AJT 2011

EVOLUTION Study: Glycosylated Haemoglobin



Guirado et al., AJT 2011, 11: 1965

Conclusions from Prospective PRG ->ADVA Conversion Studies

- Exposure to tacrolimus from Advagraf ≈ 10% lower
  - *Trough levels should be measured prior to and < 2 weeks after conversion*
  - Dose adjustments should be made if necessary

- Majority of patients did not require dose adjustments

- Conversion is ***a safe procedure***.

- Improved patient compliance (heart, kidney, liver)

- Lower **within-patient variability** with Advagraf in stable renal transplant patients compared to Prograf

Stifft TDM 2014

Opinion of the recipient ?

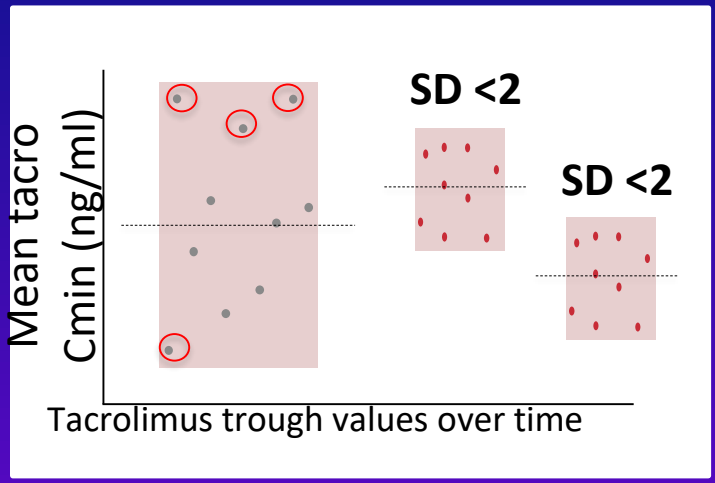
Written questionaire all 130 patients renal Tx in 2005-2007

Response 89% (n= 116)

Conversion	%	Male (%)	Age	% on 1 IS
Yes	**58**	60	59	81
No	42	47	60	82
No response	11	64	50	100

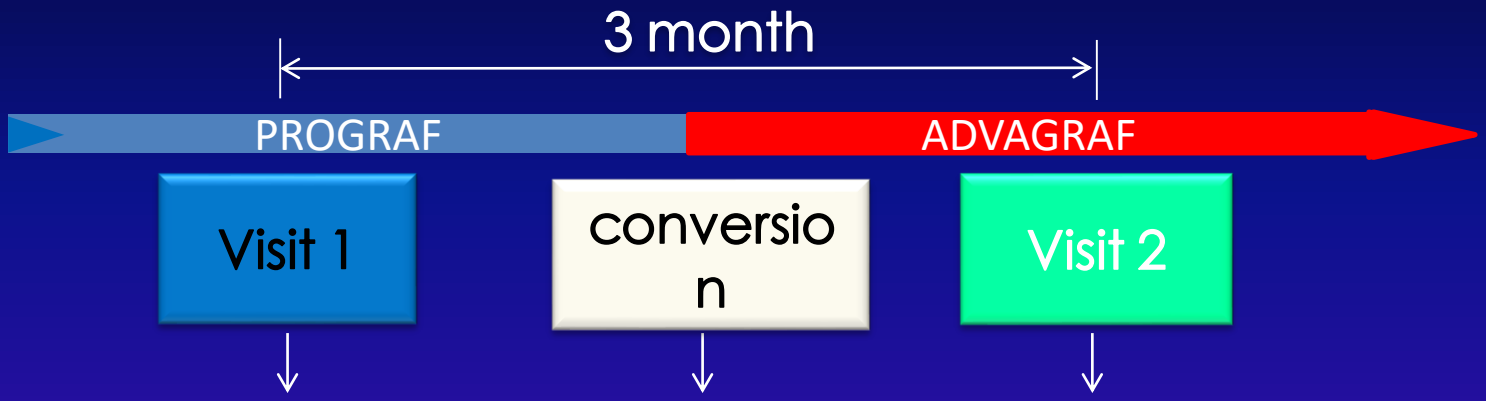
Who may benefit from conversion Prograf to Advagraf?

Reduction # dosing times # pills
Large variance in trough levels[1,2]
Suspected non-adherence[1,3]
Large doses of Prograft to achieve target trough levels[1]
Aiming at lower (or higher) trough levels: lower acceptable margin of variability[1]



1. Cervelli M, Russ G. *Aus J Pharmacy* 2012;93:83–86
2. Wu MJ et al. *Transplantation* 2011;92:648−652
3. Kuypers DRJ et al. *Transplantation* 2013;95:333−340

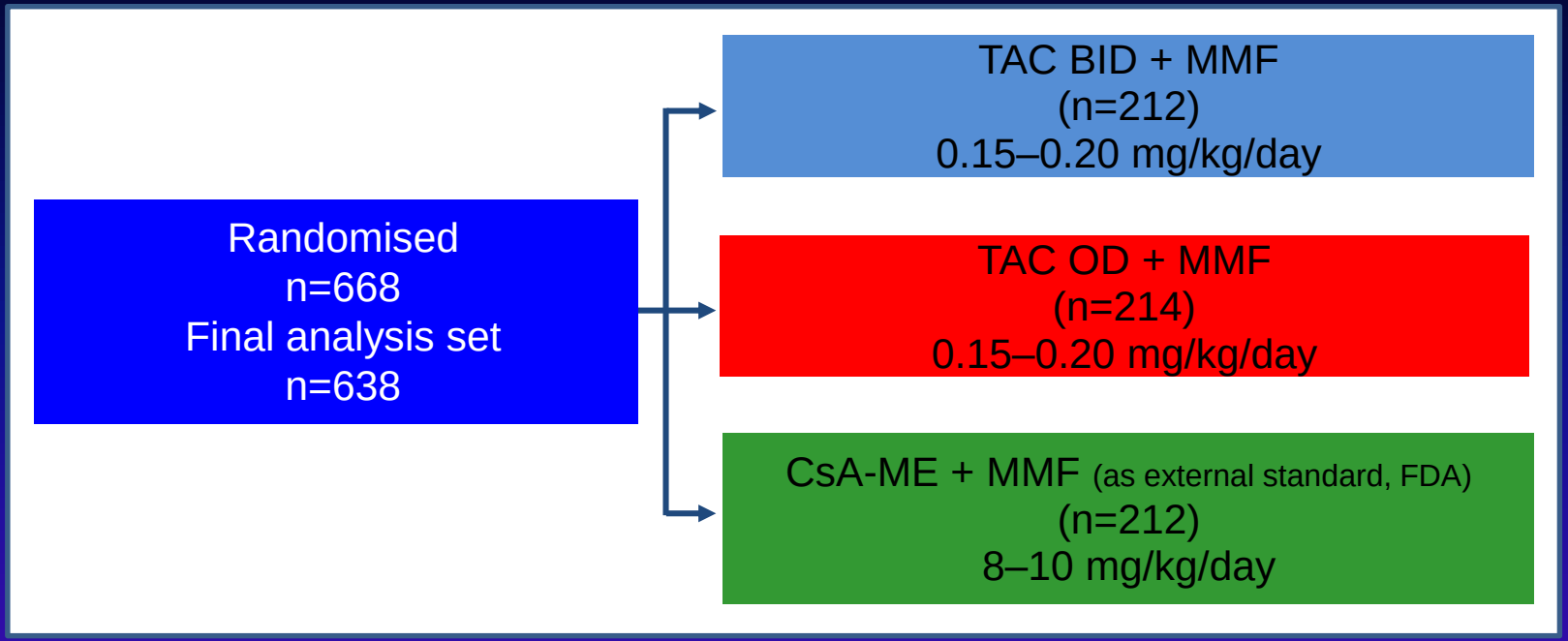
Conversion Prograf to ADVAGRAF Maastricht approach



Advagraf Clinical Data in *De Novo* Kidney Transplant Patients

US Phase III, Multicentre Open-Label, Kidney Tx Study

All patients received MMF, corticosteroids and basiliximab induction.

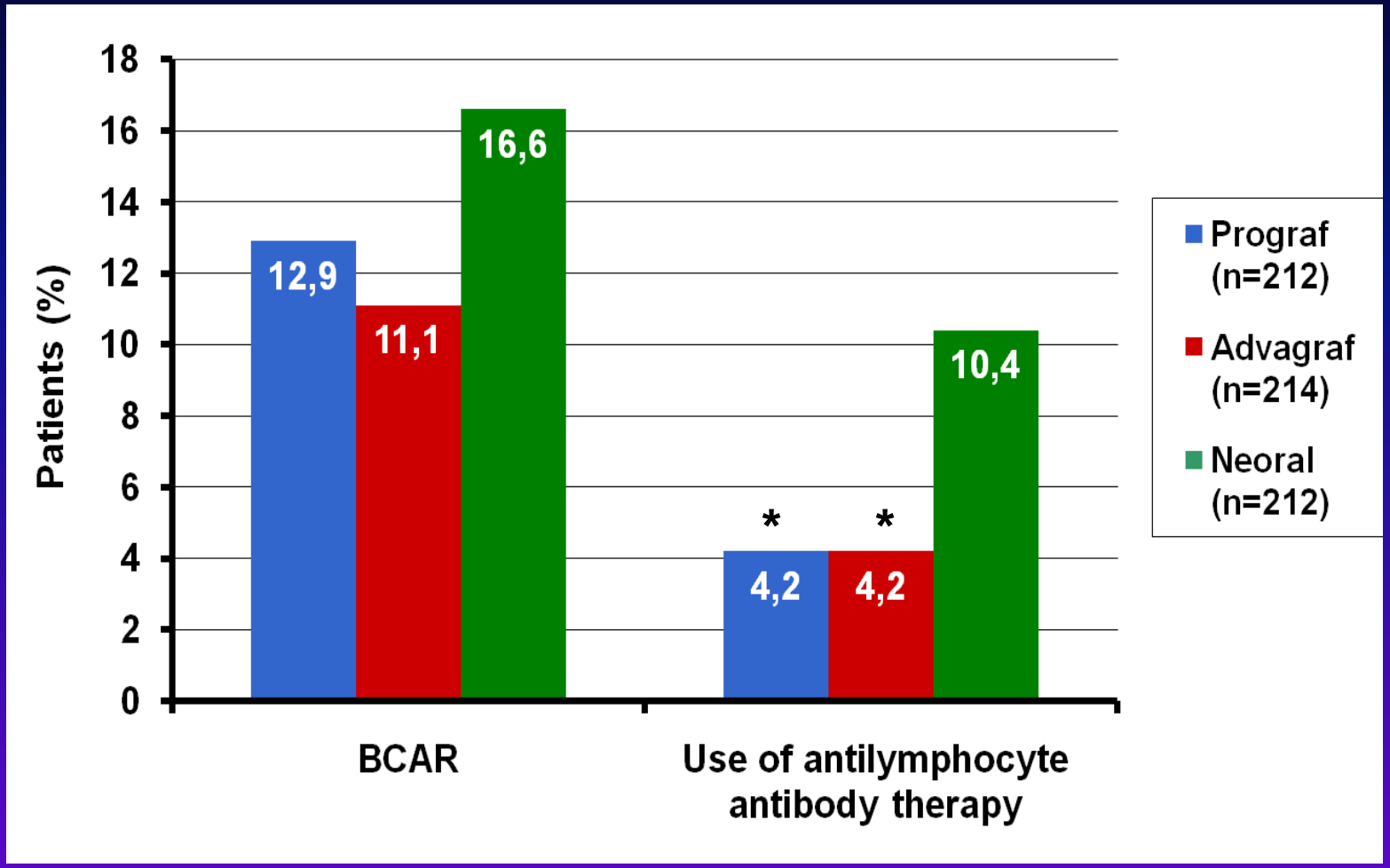


Target trough levels (ng/mL)	Tacrolimus	CsA-ME
Days 0–90	7–16	125–400
>Day 90	5–15	100–300

CsA-ME = ciclosporin A microemulsion

Silva HT Jr, et al. Am J Transplant 2007;7(3):595–608

Comparable Acute Rejection and Antibody Use With Advagraf and Prograf at 2 Years



*p≤0.015 versus Neoral

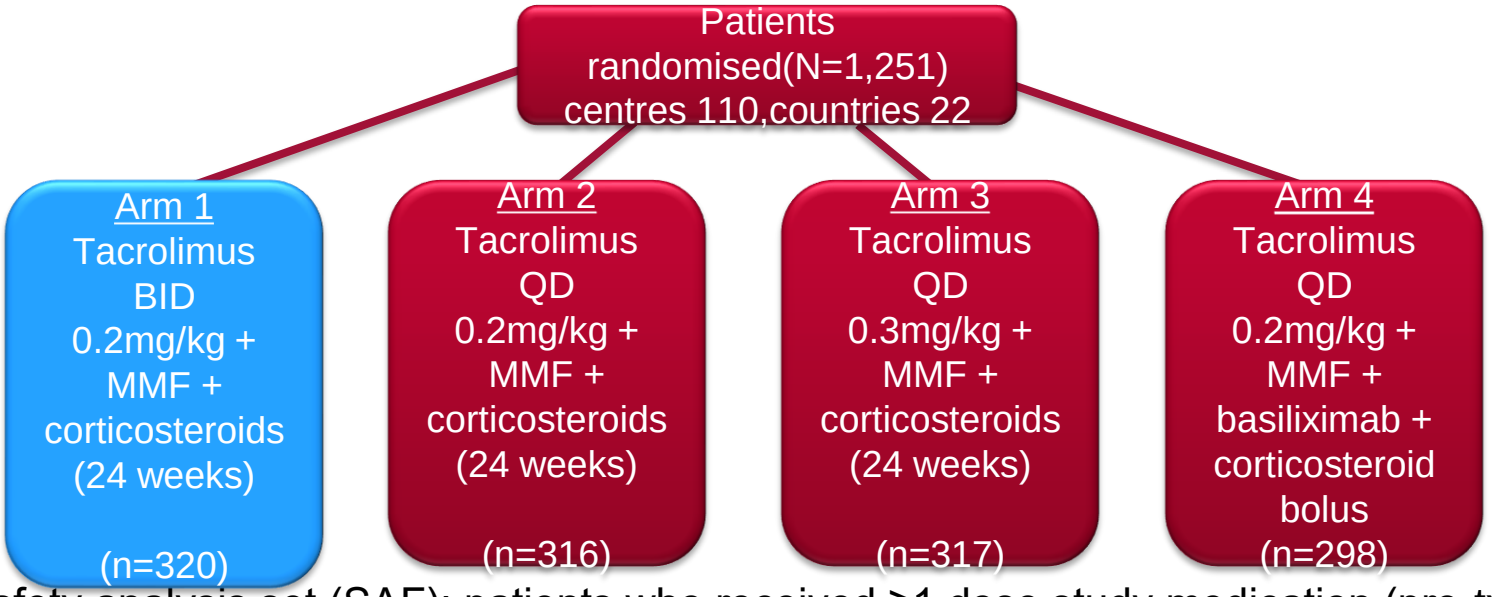
Yang H, et al. Am J Transplant 2007;7(Suppl 2):183 Abs 144

Optimizing ImmunoSuppression After Kidney Transplantation with ADVAGRAF™ (the OSAKA study)

A multicentre, four-arm, randomised, open-label clinical study investigating optimised dosing in a PROGRAF™-/ADVAGRAF-based immunosuppressive regimen in kidney transplant patients

ADV/11/0011/EU December 2011

Study design and analysis populations



Safety analysis set (SAF): patients who received ≥1 dose study medication (pre-tx!)

n=311 n=309 n=307 n=287

Full analysis set (FAS): all patients from the SAF who were transplanted

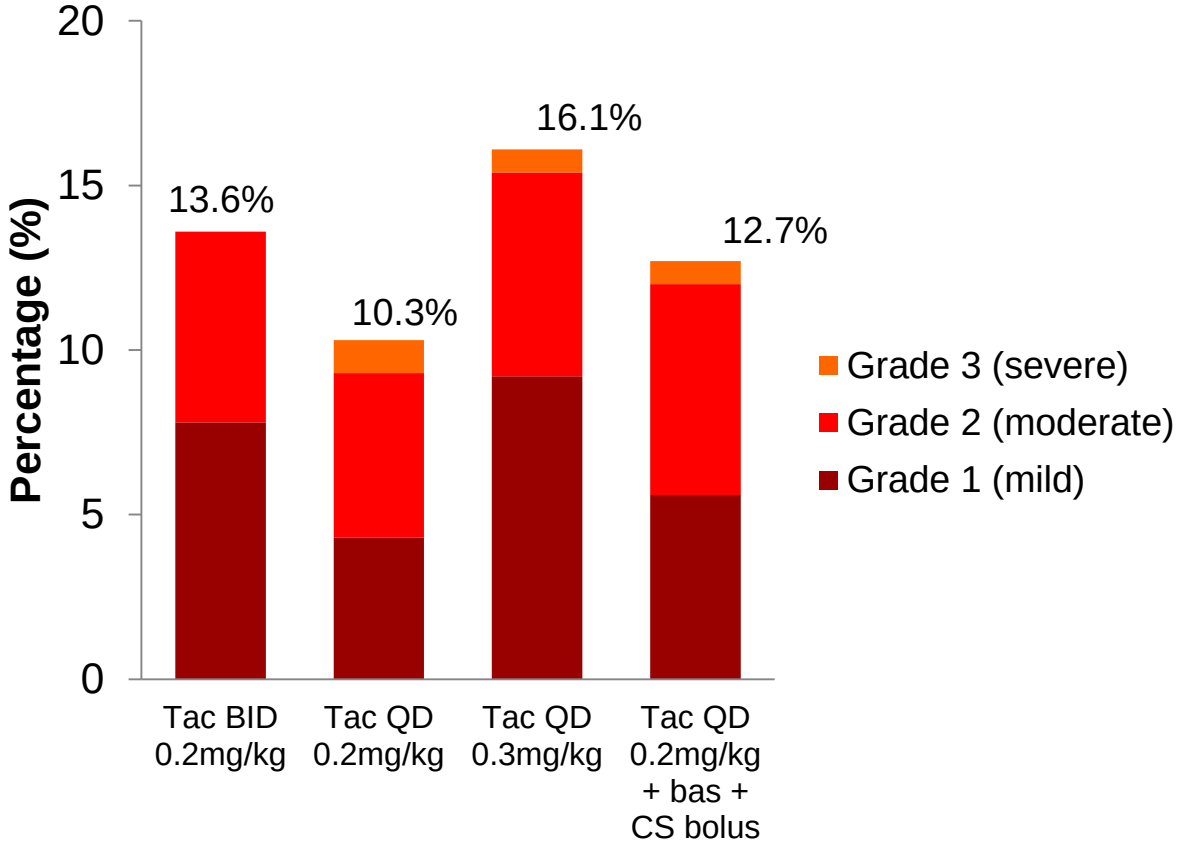
n=309 n=302 n=304 n=283

Per protocol set (PPS): all patients from the FAS who did not have major protocol deviations

n=237 n=263 n=246 n=230

Clinical results OSAKA

- Overall *similar renal function* was on tacrolimus QD- and BID-based therapy
- BCAR: *Low incidence*, *Comparable Time to first incidence* and *Severity*



(FAS)

Conclusion *De Novo* Advagraf vs. Prograf

- AUC lower at day 1 (30%) [1]
- Trough level (C_{24}) equal from day 3 onwards [2]
- Advagraf + MMF as effective as Prograft + MMF [3]

- When used with induction, dose as for Prograf. *
- Try to give pretransplant dose. *
- Living donor transplant: Start predosing for 2 days*

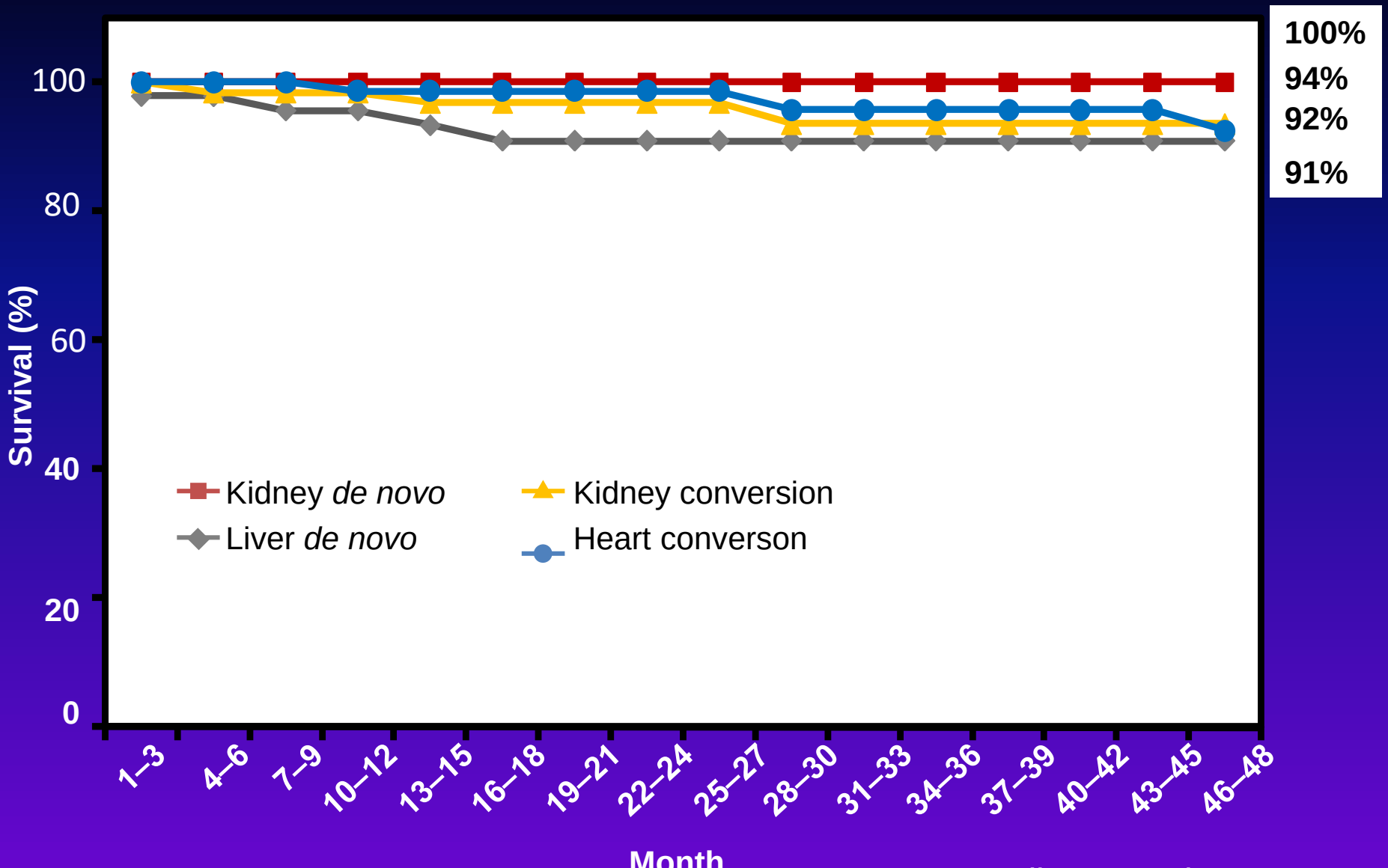
* Personal view Christiaans

1. ADVAGRAF Summary of Product Characteristics. Astellas Pharma Ltd
2. Undre NA. *Am J Transplant*. 2005;5(suppl 11):190. Abstract 132
3. Silva HT Jr, et al. *Am J Transplant*. 2007;7(3):595–608

Longterm Follow-up
De Novo and Conversion patients

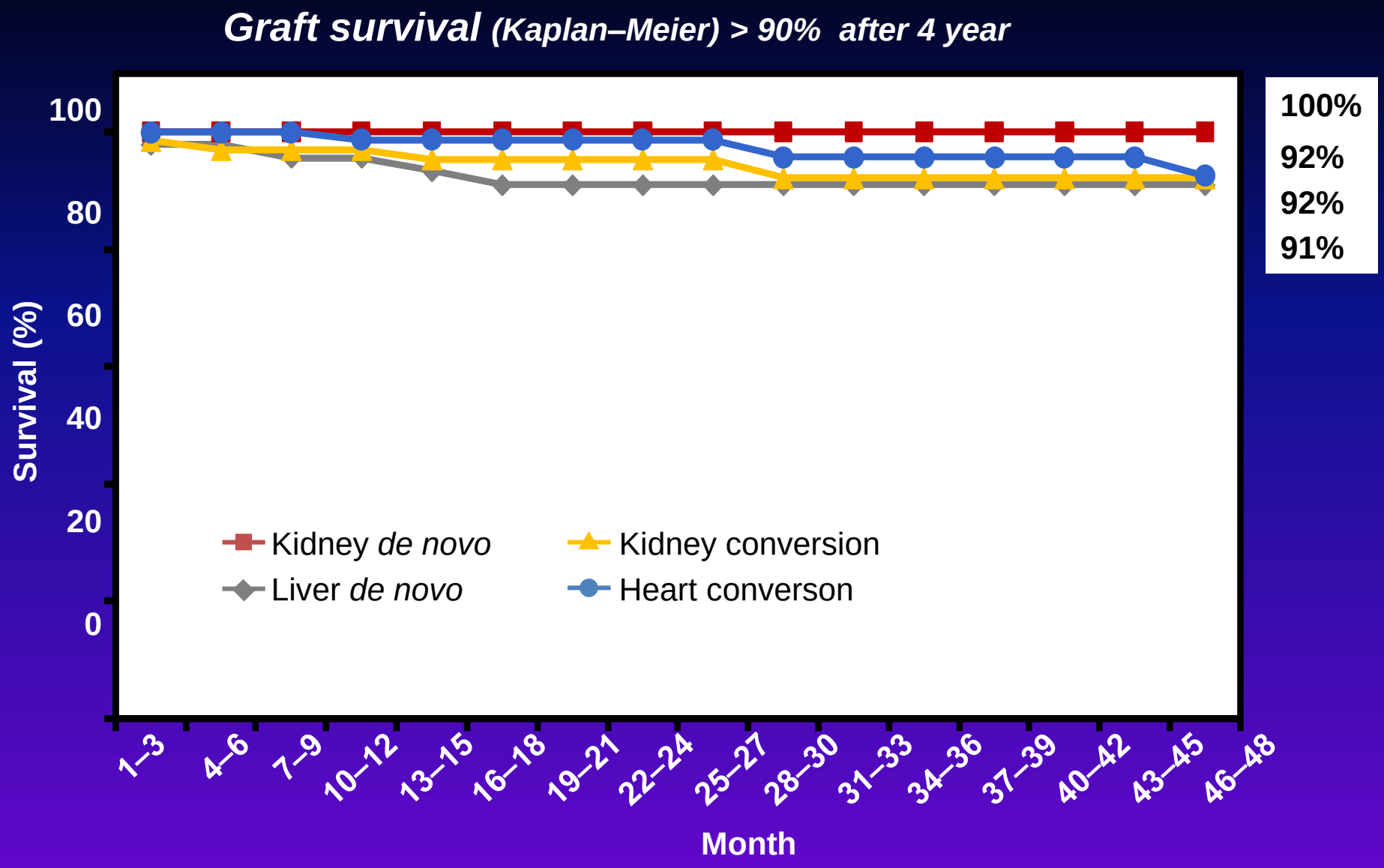
Advagraf phase II studies: 4 yr FU (conversion and de novo; kidney, liver, heart)

Patient survival (Kaplan–Meier) > 90% after 4 year



van Hooff et al, Clin Transpl 2011

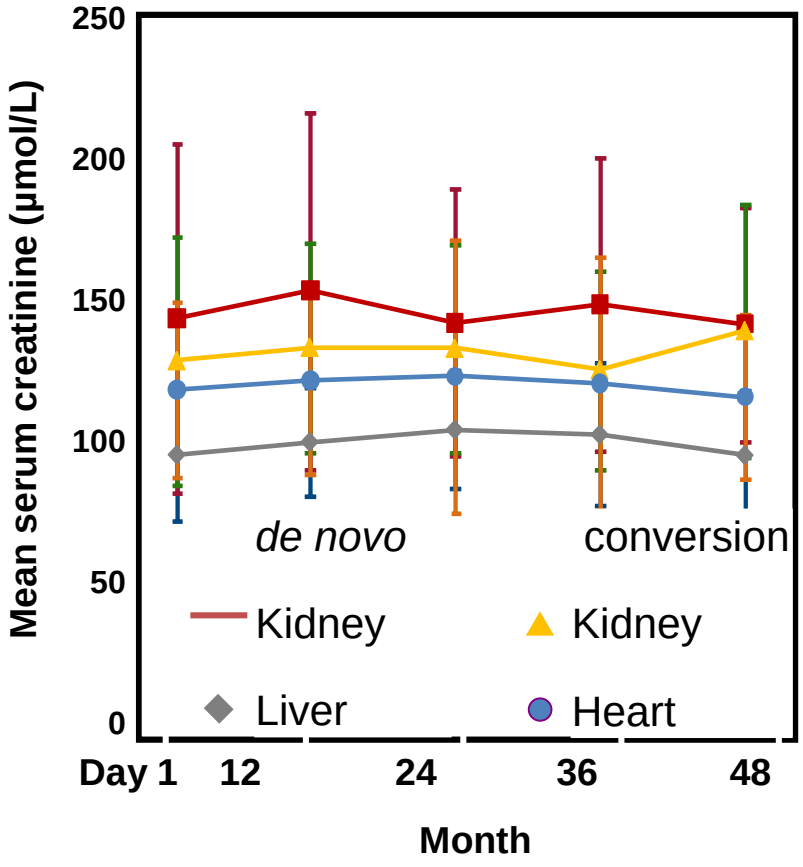
Advagraf phase II studies: 4 yr FU (conversion and de novo; kidney, liver, heart)

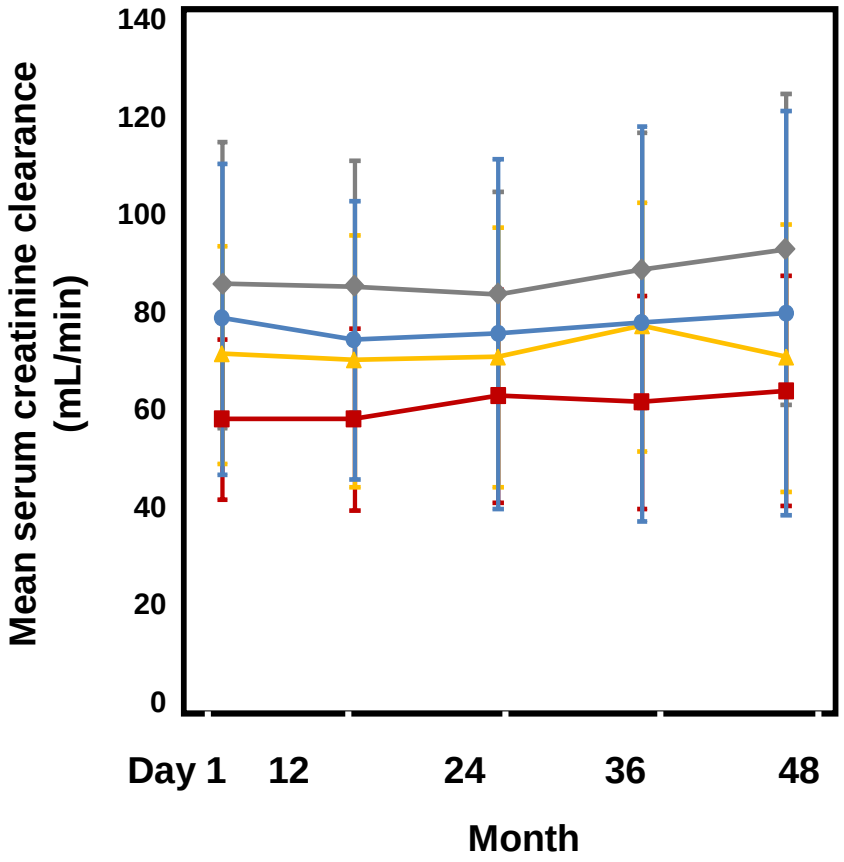


van Hooff et al, Clin Transpl 2011

Advagraf phase II studies: 4 yr FU (conversion and de novo; kidney, liver, heart)

Stable renal function over 4 year





van Hooff et al, Clin Transpl 2011

Ten-year data of the first European clinical experience with once-daily tacrolimus extended release formulation in renal transplant recipients.

Marielle Gelens, Johannes van Hooff, Monique Mullens, Maarten Christiaans

Background

Randomized clinical trials of Tac QD and Tac BID:

- Similar efficacy and safety in kidney transplant recipients
- Both *de novo* and *after conversion* from Tac BID to Tac QD.

However no long term follow-up data

- Follow-up (FU) in studies max 2 years
- Clinical outcome data up to max 5 years (van Hooff et al, Clin Transpl 2011:25:E1-E2).

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Patient and Graft survival

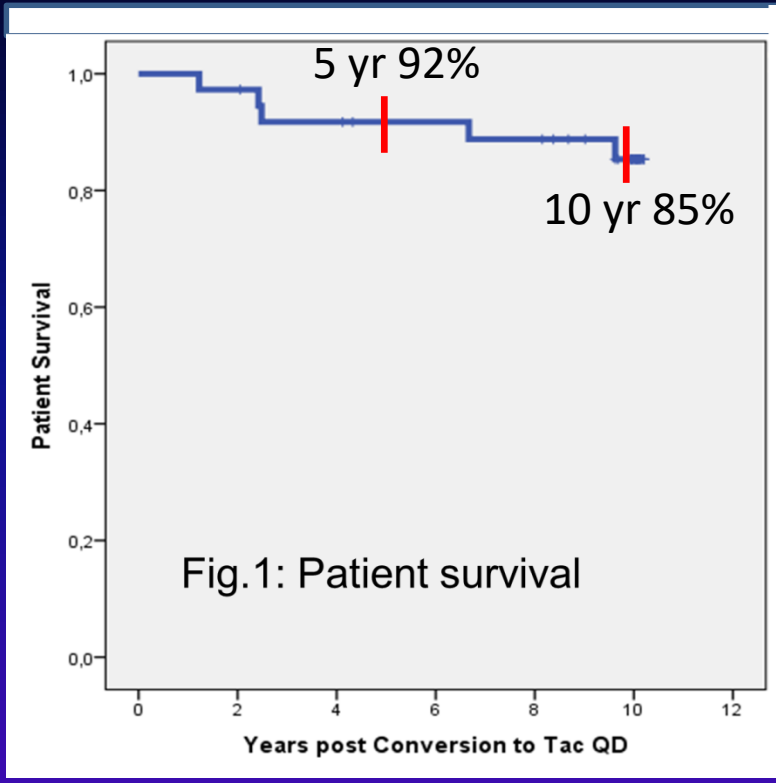


Fig.1: Patient survival

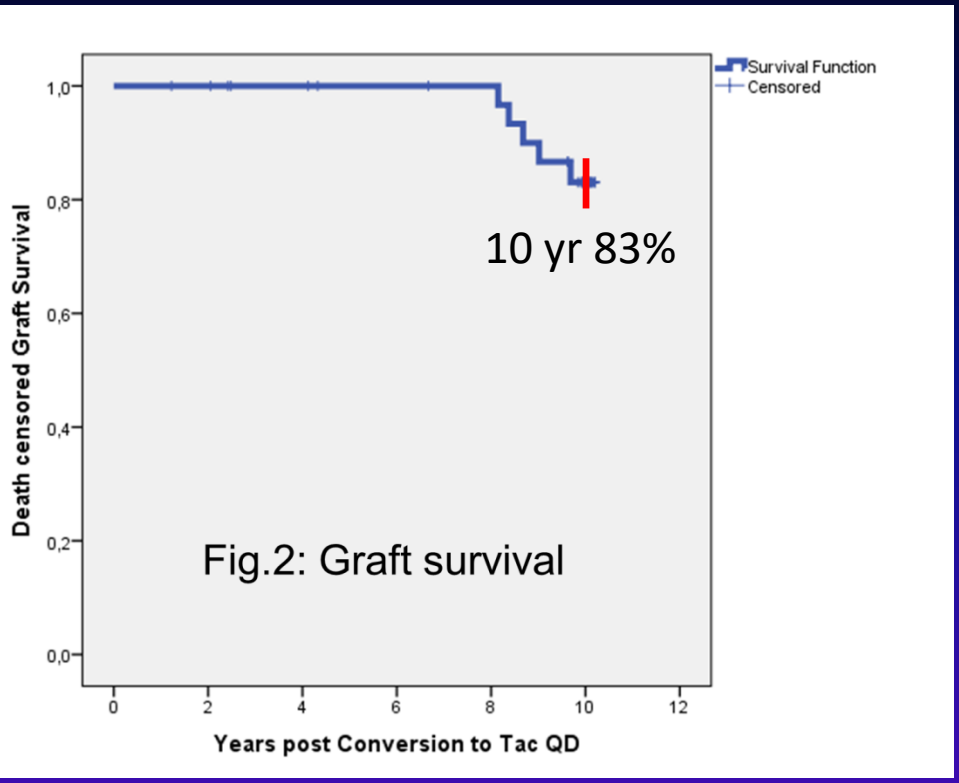


Fig.2: Graft survival

5 deaths with a functioning graft (1,2-9,2 year postconv):

- Pulmonary carcinoma,
- Pulmonary embolism,
- Cardiovascular disease (2x),
- Creutzfeldt-Jakob disease

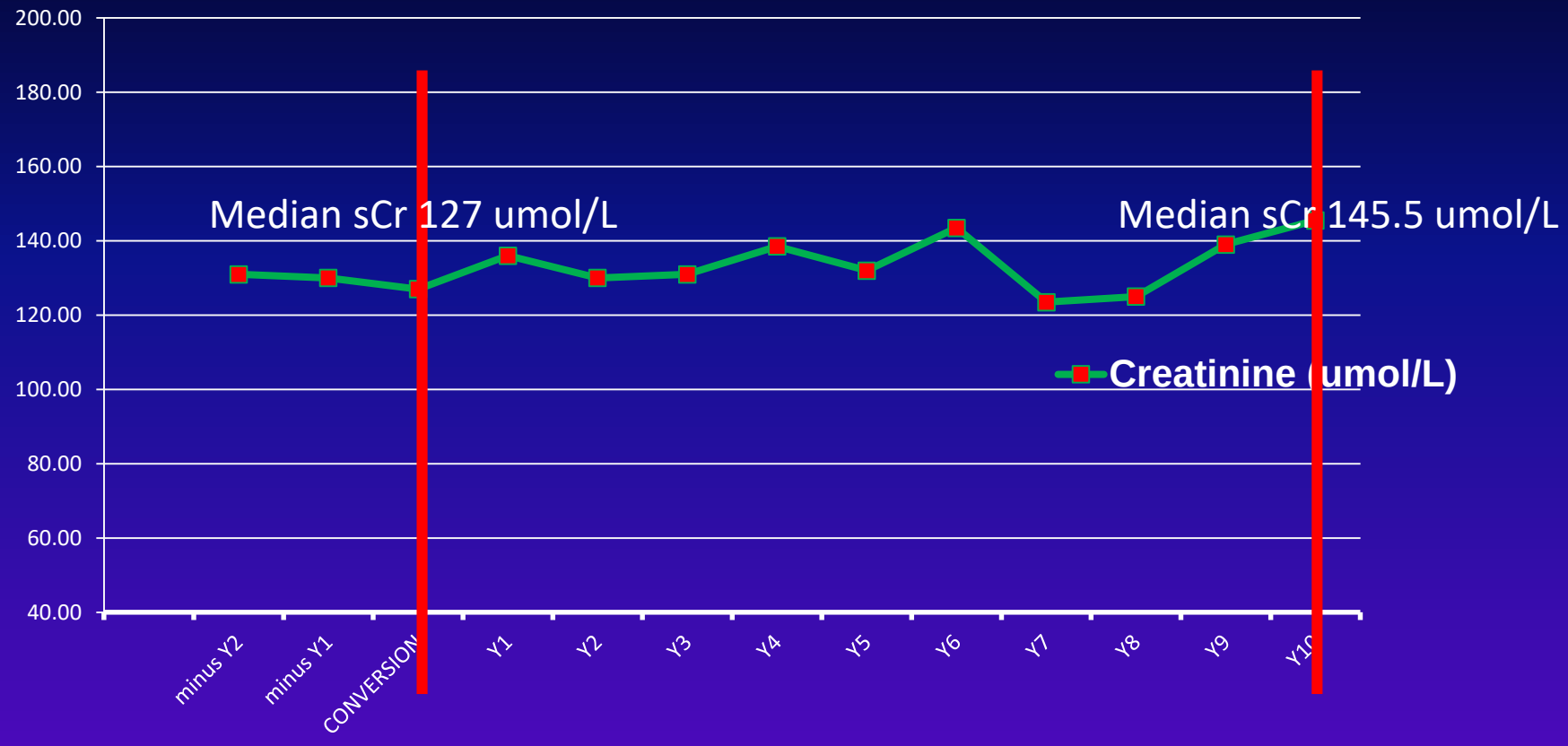
5 graft losses due to:

- 'chronic rejection' (no Bx),
- irreversible Acute Kidney Injury after cardiac surgery.
- Bx proven recurrence IgA-NP (3x),

No acute rejections during FU; 2x acute on chronic

Serum Creatinine during follow-up

10 yr data Maastricht conversion Prograf - Advagraf



27 patients: 24 patients with GS at year 10 and 3 patients censored at date of stop Tac QD.

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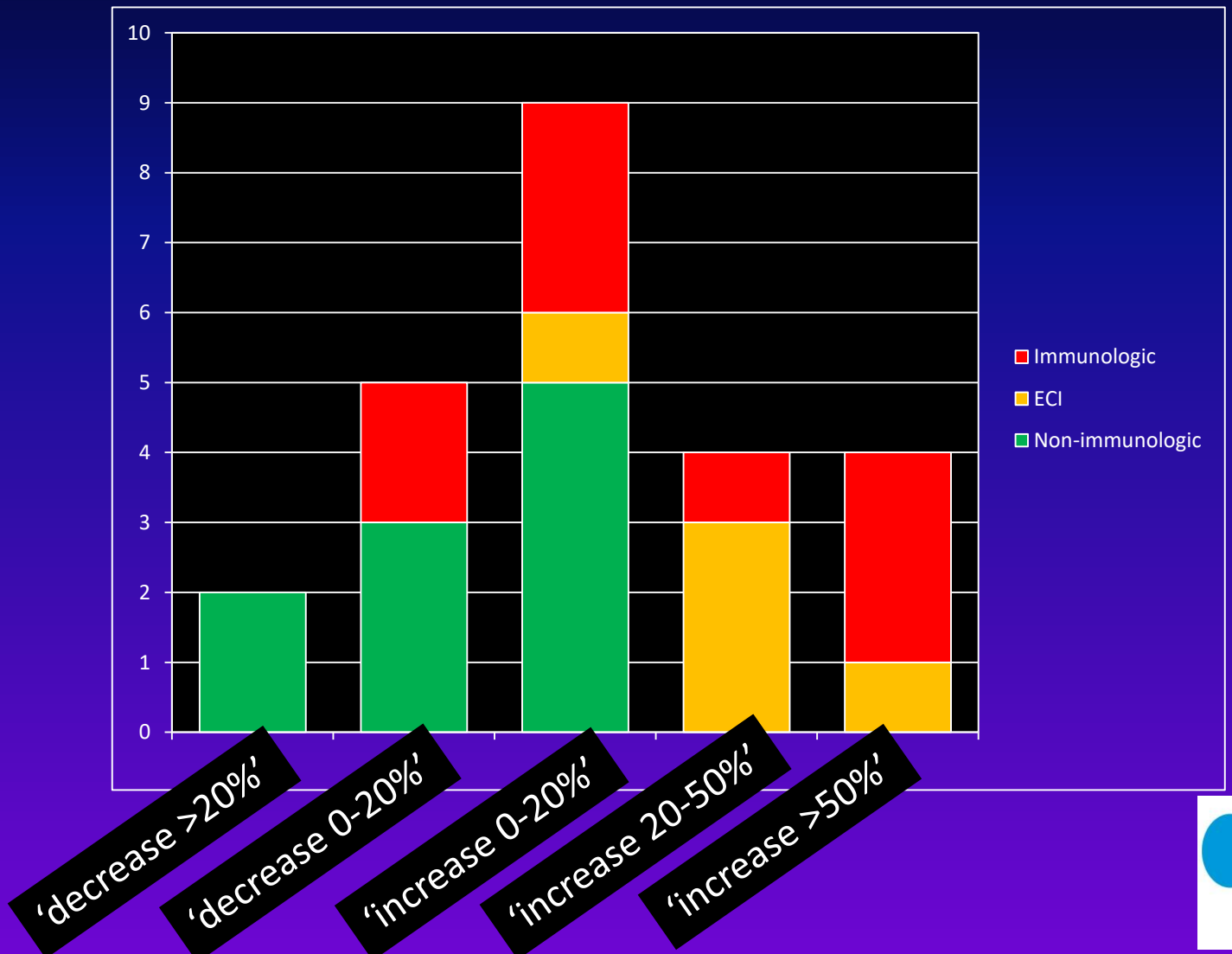
Change in serum creatinine over 10 years in relation to original renal disease category.



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Maastricht 10 yr data conversion from Prograf to Advagraf

- Very good 10 yr patient- and graft survival.
- Good preservation of renal function.
- Graft loss and decrease in eGFR mainly in patients with an immunological cause of renal failure
- ? Adaptation of IS-protocol for patient with immunological cause of renal failure; e.g. IgA

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Thank you for your attention

Questions?