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Calcineurin Inhibitor Minimization in the Symphony Study: Observational Results 3 Years after Transplantation

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The Symphony study showed that at 1 year posttransplant, a regimen based on daclizumab induction, 2 g mycophenolate mofetil (MMF), low-dose tacrolimus and steroids resulted in better renal function and lower acute rejection and graft loss rates compared with three other regimens: two with low-doses of cyclosporine or sirolimus instead of tacrolimus and one with no induction and standard cyclosporine dosage. This is an observational follow-up for 2 additional years with the same endpoints as the core study. Overall, 958 patients participated in the follow-up. During the study, many patients changed their immunosuppressive regimen (e.g. switched from sirolimus to tacrolimus), but the vast majority (95%) remained on MMF. During the follow-up, renal function remained stable (mean change: −0.6 ml/min), and rates of death, graft loss and acute rejection were low (all about 1% per year). The MMF and low-dose tacrolimus arm continued to have the highest GFR (68.6 ± 23.8 ml/min vs. 65.9 ± 26.2 ml/min in the standard-dose cyclosporine, 64.0 ± 23.1 ml/min in the low-dose cyclosporine and 65.3 ± 26.2 ml/min in the low-dose sirolimus arm), but the difference with the other arms was not significant (p = 0.17 in an overall test and 0.077, 0.039 and 0.11, respectively, in pair-wise tests). The MMF and low-dose tacrolimus arm also had the highest graft survival rate, but with reduced differences between groups over time, and the least acute rejection rate. In the Symphony study, the largest ever prospective study in *de novo* kidney transplantation, over 3 years, daclizumab induction, MMF, steroids and low-dose tacrolimus proved highly efficacious, without the negative effects on renal function commonly reported for standard CNI regimens.

Key words: Calcineurin inhibition, cyclosporine A, follow-up studies, kidney transplantation, mycophenolate mofetil, sirolimus, tacrolimus

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Introduction

In recent years, progress in immunosuppressive regimens has resulted in fewer acute rejection episodes and excellent short-term outcomes in renal transplantation (1,2), and current research is increasingly targeting factors influencing long-term graft and patient survival (3,4). In this context, there has been considerable interest in immunosuppressive regimens which permit reduction or elimination of calcineurin inhibitor (CNI)-associated and other chronic toxicities, while maintaining adequate immunosuppression (5–10).

The strategies of CNI avoidance, withdrawal and reduced dosing were tested in two large studies (8,11) that were designed at the time when the efficacy of mycophenolate mofetil (MMF) and daclizumab had been established. The use of reduced doses of CNIs was deemed necessary to maintain efficacy and this research line led to the Efficacy Limiting Toxicity Elimination (ELiTE)-Symphony study (9), which was designed to assess whether reduced doses of the adjunct immunosuppressants cyclosporine (CsA), tacrolimus or sirolimus added to the MMF-based regimen containing daclizumab could reduce toxicity (specifically, nephrotoxicity) while maintaining acceptable acute rejection rates. At 1 year posttransplant, the MMF- and daclizumab-based regimen with low-dose tacrolimus and corticosteroids gave superior renal function, graft survival and acute rejection rates compared with regimens containing low-dose CsA or low-dose sirolimus with induction, or standard-dose CsA without induction. Serious adverse events occurred more frequently with low-dose sirolimus than those with the other regimens.

Ekberg H *et al*.

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Dr Rupert Major
12/2/14

Background

- Balance between acute rejection post-transplant and chronic allograft nephropathy/rejection

Minimise acute reject and maximise (short-term) graft survival and function

Minimise nephrotoxic immunosuppressants

(and minimise opportunistic infections)

Background - Efficacy Limiting Toxicity Elimination (ELITE)–Symphony Study

The NEW ENGLAND JOURNAL of MEDICINE

Ekberg H *et al*. Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation. *N Engl J Med* 2007;357:2562-75.

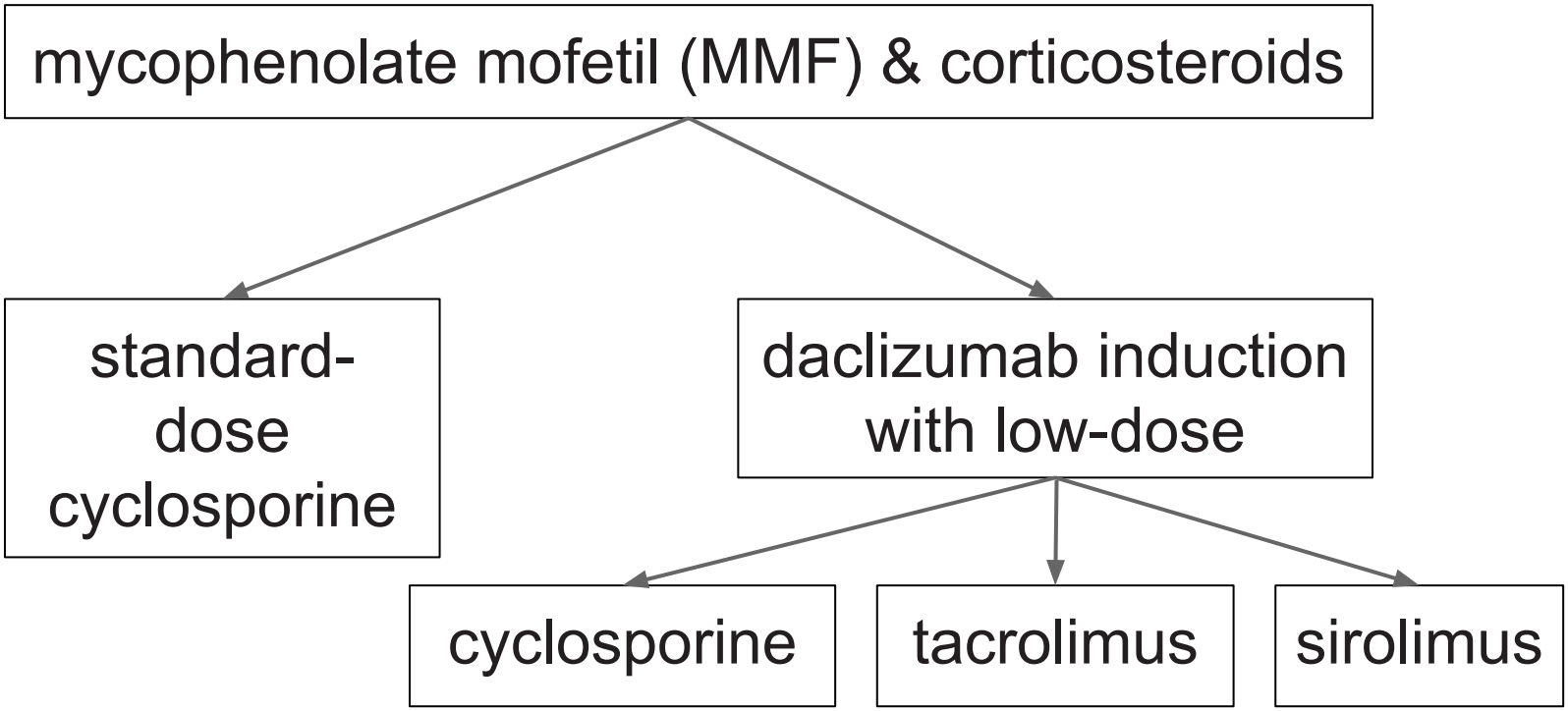
Aim: to evaluated the efficacy and relative toxic effects of four immunosuppressive regimens.

Methods: randomised trial of 1645 renal-transplant recipients

Primary end point: estimated glomerular filtration rate (CG-eGFR), as calculated by the Cockcroft–Gault formula, 12 months after transplantation

Secondary end points: included acute rejection and allograft survival.

Background - Efficacy Limiting Toxicity Elimination (ELITE)–Symphony Study



Background - Efficacy Limiting Toxicity Elimination (ELITE)–Symphony Study

Results: At 12 month follow-up, in low-dose tac group:

- mean calculated GFR higher
- biopsy-proven acute rejection was lower
- allograft survival significantly higher
- serious adverse event rate equal (higher in low-dose sirolimus group)

Conclusion: A regimen of daclizumab, mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus may be advantageous for renal function, allograft survival, and acute rejection rates….

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Methods - Study Design

After conclusion of 1 year core study:

- core study participants offered opportunity to enroll in 2 year follow-up
- included regardless of protocol violations or discontinuation of treatment in core study
- no specific mandatory treatment
- immunosuppressant regime could be changed from randomised treatment
- ‘centers were recommended to follow a consistent strategy’

Methods - Study Design

- 3 monthly serum creatinine
- 6 monthly other bloods and clinical assessment (including adverse events)
- ‘main efficacy parameter’ (i.e. not pre-set specific primary and secondary outcomes)
  - eGFR (C-G formula)
  - acute rejection
  - graft loss
  - death
- ‘safety parameters included’
  - CV events
  - malignancies
  - opportunistic infections

Methods - Statistical Analysis

‘The analysis of this follow-up study was exploratory and employed descriptive statistics and inferential methods without correction for multiplicity’

No pre-set way of analysing data - i.e. analysis by original group, analysis by cross-over, exclude those who violated protocol, include……..

Methods - Statistical Analysis

‘On-treatment’ definition:

- tough level of assigned drug at randomisation during last 6 months of 2 year follow-up
- received MMF
- SCr at 2 years (i.e. month 36 post-randomisation)

Methods - Statistical Analysis

‘Analysis of renal function with imputation of missing values’

- graft loss imputated as eGFR 10mL/min
- month 18 value used for month 24
- month 30 value used for month 36

Results - CORE STUDY

1645 patients randomised

over 83 sites

in 15 countries

Intention to treat population (ITT pop) - base on original randomised group

- 1589 patients (96.6%)
- 65% male, 93% Caucasian, median age 47 (range 18.1 to 75.8)
- 64% deceased donors (22% expanded criteria)
- ‘Treatment groups well balanced’ - demographics, ESRF cause, donor characteristics, Tx risk profile

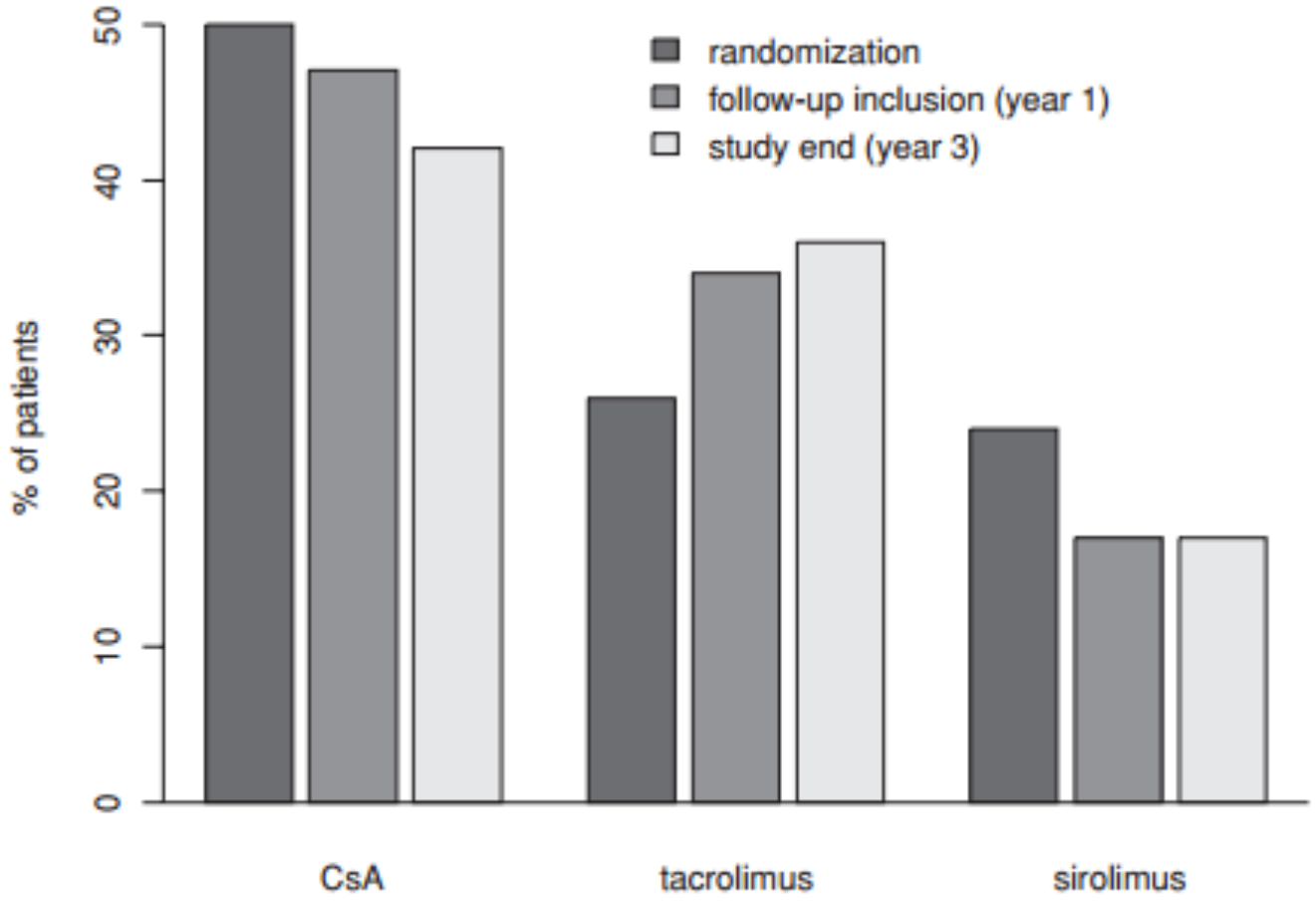
Results - Follow-up Study

958 patients (60% of ITT pop)

67 (79%) of original centres

56% of follow-up ITT patients were part of the on-treatment analysis

‘no noteworthy imbalance between treatment groups’



CsA
50%
47%
42%

Tac
25%
34%
36%

Sir
25%
17%
17%

None
0%
2%
5%

Figure 1: Percentage of patients receiving CsA, tacrolimus and sirolimus at randomization (considering only patient participating in the follow-up), at inclusion in the follow-up (year 1) and at the end of the study (year 3). At randomization, 50% of the core ITT patient population received CsA (either standard or low dose), 25% received tacrolimus and 25% received sirolimus.

However,

- potential selection bias as pts with better eGFR more likely to be enrolled in follow-up
  - 66ml/min for included versus 60ml/min for those not participating
- 230 withdrew (24%) from study
  - 8% graft loss
  - 5% death
  - 19% ‘failure to return’
  - 7% ‘consent withdrawal’
  - 61% ‘other’

At year 3

- 62% to 69% on triple therapy
- 28% steroid free
- 95% on MMF
- Average trough levels….
  - Standard CsA 114+-56ng/ml
  - Low dose CsA 103+-71ng/ml
  - Tac 6.5+-2.3ng/ml
  - Siro 7.0+-3.2ng/ml

Efficacy

- In the four arms ‘renal function was stable’ between months 12 and 36 (ITT)
  - overall -0.6ml/min +-14.8
  - Standard dose CyS +1.2, low dose siro +1.1
    - ?difference statistically significant
  - Low dose CyS -2.5, low dose tac -1.9
- On-treatment analysis - eGFR at 12 and 36 months only
  - ?low-dose sirolimus best?

Endpoint	Standard-dose cyclosporine	Low-dose cyclosporine	Low-dose tacrolimus	Low-dose sirolimus	All groups[a]
Month 12: Mean CG-GFR (±SD) [mL/min], on-treatment population[c]	65.7 ± 19.2	67.9 ± 19.9	71.1 ± 22.7	69.8 ± 22.4	68.7 ± 21.1
Month 36: Mean CG-GFR (±SD) (mL/min), on-treatment population	67.1 ± 26.5	65.6 ± 22.7	69.6 ± 23.7	71.1 ± 25.4	68.1 ± 24.5

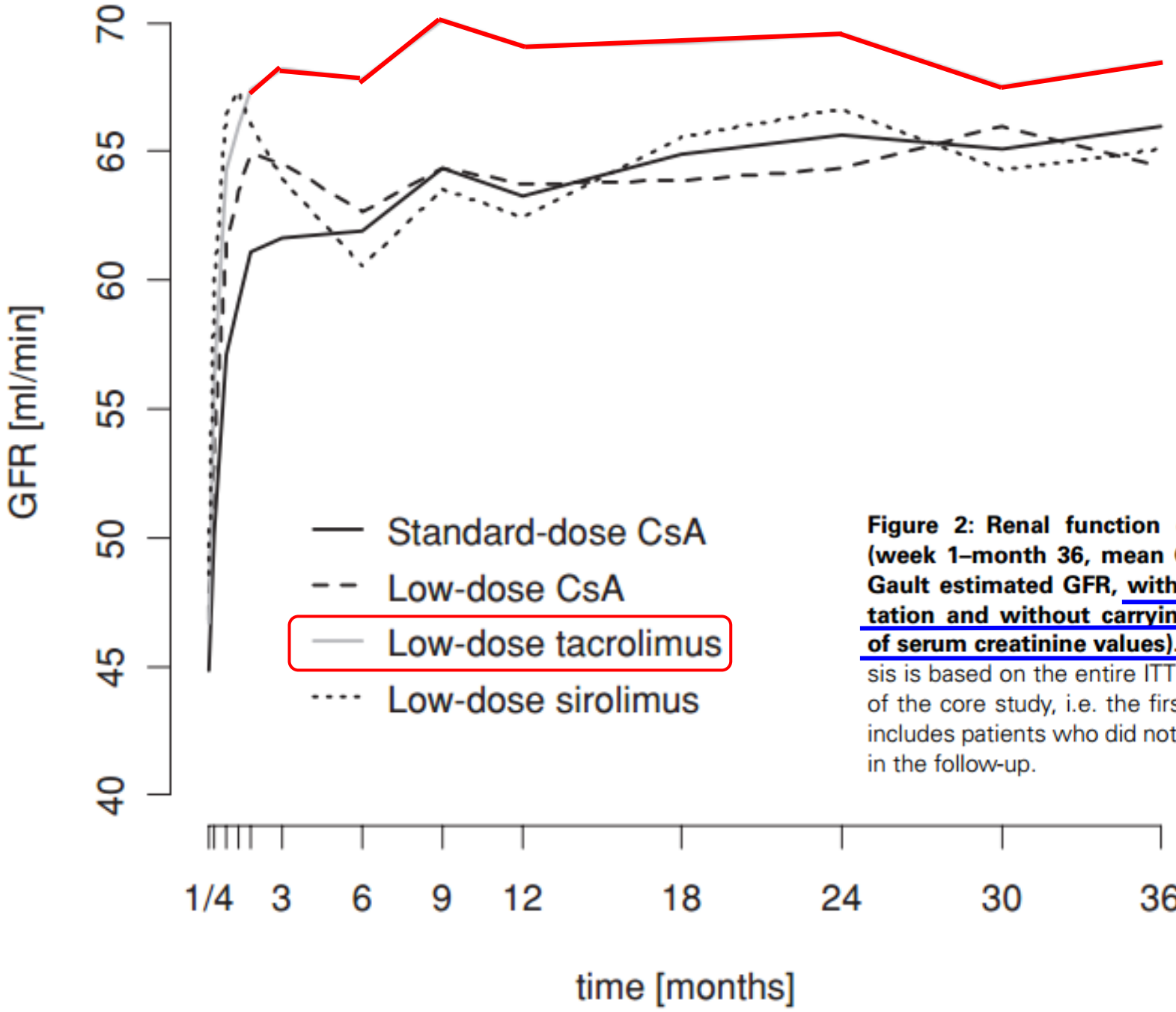


Figure 2: Renal function over time (week 1–month 36, mean Cockcroft–Gault estimated GFR, without imputation and without carrying forward of serum creatinine values). The analysis is based on the entire ITT population of the core study, i.e. the first year also includes patients who did not participate in the follow-up.

Biopsy-proven Acute Rejection (BPAR)

1-3% for all groups over both the 2nd and 3rd years

Tac remained clearly superior ($p<0.0001$), because there was a large between group difference at year 1

Endpoint	Standard-dose cyclosporine	Low-dose cyclosporine	Low-dose tacrolimus	Low-dose sirolimus	All groups[a]
BPAR (excluding borderline) at 12 months (% of pts)	26	24	12	37	25
BPAR (excluding borderline) at 24 months (% of pts)	26	26	13	38	26
BPAR (excluding borderline) at 36 months (% of pts)	27	27	14	39	27
P value versus low-dose tacrolimus[d]	<0.0001	<0.0001	Reference	<0.0001	<0.0001
BPAR: increase between Month 12 and Month 36	1%	3%	2%	2%	2%

Graft and Patient Survival

Graft

- Again, because Tac was superior at end of main trial (year 1) it remained superior through study duration
- However, gap narrowed

Endpoint	Standard-dose cyclosporine	Low-dose cyclosporine	Low-dose tacrolimus	Low-dose sirolimus	All groups[a]
Death-censored graft survival at Month 12 (%)	92	94	96	92	94
Death-censored graft survival at Month 24 (%)	91	91	95	91	92
Death-censored graft survival at Month 36 (%)	91	91	93	89	91
P value versus low-dose tacrolimus[d]	0.051	0.20	Reference	0.019	0.11

- 95% survival at end of year 3, except standard dose CyS (94%)

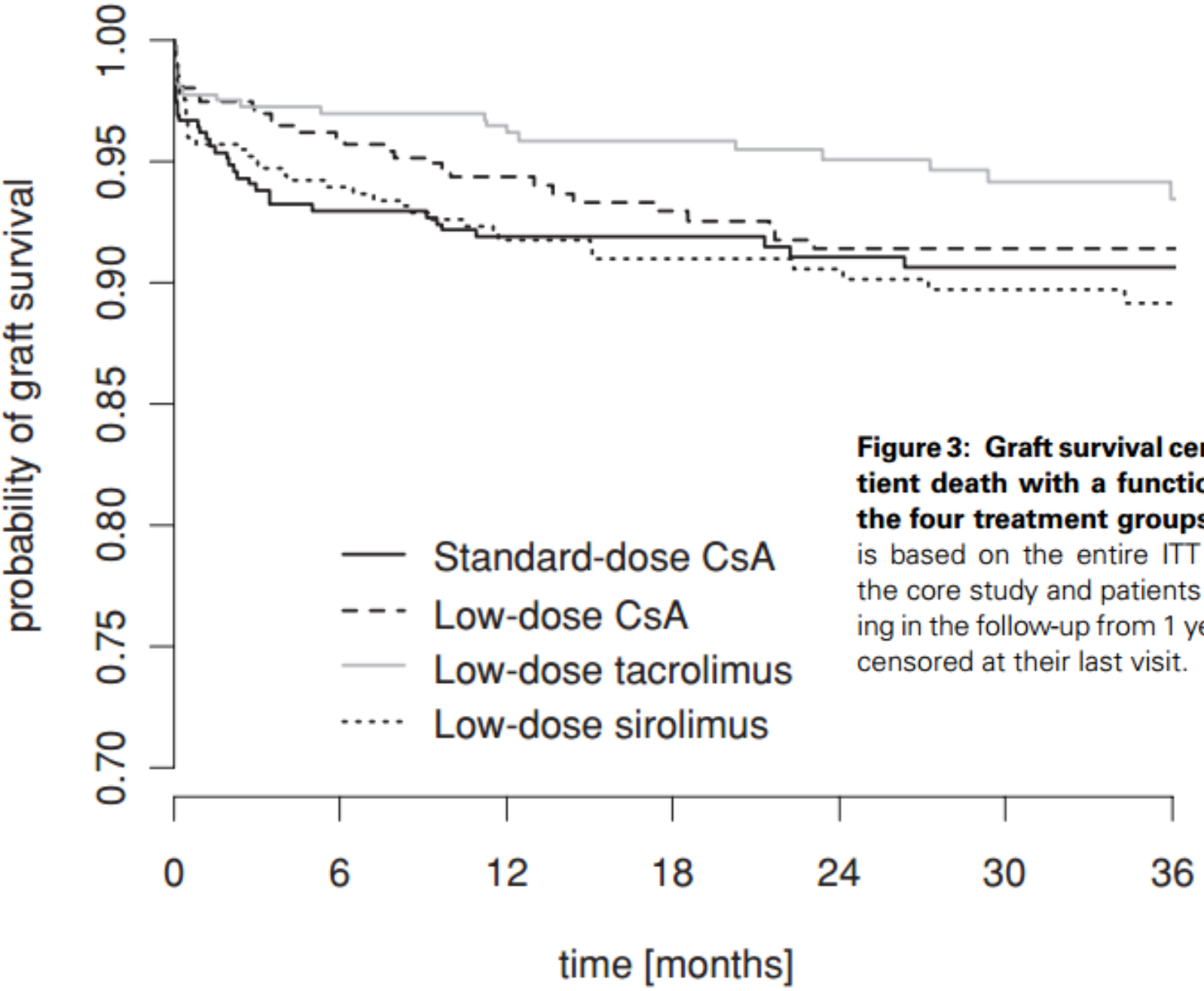


Figure 3: Graft survival censored for patient death with a functioning graft in the four treatment groups. The analysis is based on the entire ITT population of the core study and patients not participating in the follow-up from 1 year onward are censored at their last visit.

What factors were associated with graft loss (excluding death) between month 12 and 36?

Logistical regression used with co-variables of:

- renal function at month 12 → odds ratio: 2.1 for a 10ml/min eGFR decrease ($p<0.0001$)
- treatment group
- age ('patient and recipient')
- gender
- baseline diabetes
- acute rejection in 1st year

Safety

Table 4: Main safety endpoints

	Standard-dose cyclosporine	Low-dose cyclosporine	Low-dose tacrolimus	Low-dose sirolimus	All groups[a]
Number of patients experiencing at least one event during the follow-up (years 2 and 3, crude incidence rates)	n (%)	n (%)	n (%)	n (%)	n (%)
AEs	167 (73%)	180 (71%)	186 (74%)	168 (76%)	702 (73%)
SAEs	58 (25%)	66 (26%)	67 (27%)	71 (32%)	263 (28%)
Malignancies	8 (4%)	7 (3%)	8 (3%)	7 (3%)	31 (3%)
New-onset proteinuria	36 (16%)	39 (15%)	37 (15%)	37 (17%)	149 (16%)
Cardiovascular events[b]	12 (5%)	14 (6%)	6 (2%)	11 (5%)	43 (5%)
Cardiac events	9 (4%)	10 (4%)	4 (2%)	6 (3%)	29 (3%)
Cerebrovascular events	0 (0%)	2 (1%)	1 (0.4%)	1 (0.5%)	4 (0.4%)
Peripheral vascular events	3 (1%)	3 (1%)	1 (0.4%)	4 (2%)	11 (1%)

Proteinuria	24%	19%	19%	28%

Conclusions

Main study

- low dose tacrolimus arm best
  - better graft function
  - less acute rejection
  - less graft loss
- CNI-free had worst outcomes

Conclusions

- Observation Study Part (month 12 to 36)
  - mean eGFR, graft loss, BPAR and death all ~1% per annum
  - low dose Tac best outcomes
    - due to initial better outcomes in months 3-6 post-transplant
    - BUT - on as treated basis ?low-dose sirolimus better (eGFR only result given)
  - overall no difference from months 12 to 36
  - eGFR at month 12 the only tested factor that changed outcome at month 36
    - OR 2.1 for graft failure for every 10ml/min lower eGFR

Conclusions

- Observation Study Part (month 12 to 36)
  - ‘impact of the various and unsystematic treatment modifications….difficult to tackle’
  - ‘preferential inclusion of better-performing patients’
  - ‘the differences among the original ITT treatment …….were smaller than those at 1 year and did not reach statistical significance’

Conclusions

- Observation Study Part (month 12 to 36)
  - methodological limitations
    - only 50% of randomised patients concluded observational follow-up
    - observational in nature with ‘uncontrolled treatment modifications’
    - main study only included ‘low-to-normal’ risk patients
    - >90% Caucasians
    - COMPLEX, NON-PREDEFINED STATS
    - ITT basis - lots of crossover

‘The results of the Symphony study at 3 years after transplantation support the use of this immunosuppressive regimen in de novo kidney transplantation.’

Any questions?