

How the use of new *surrogate* outcomes may improve transplantation results?

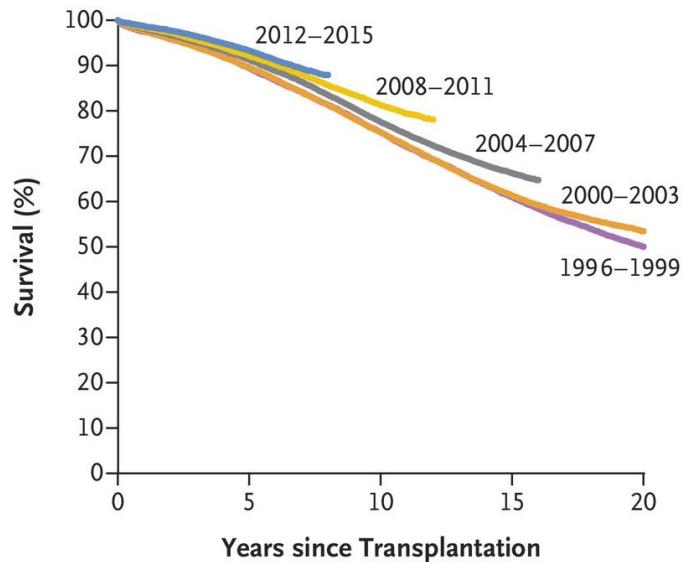
Maarten Naesens

Societat Catalana de Transplantament 17th Congress March 23rd 2023 - Barcelona

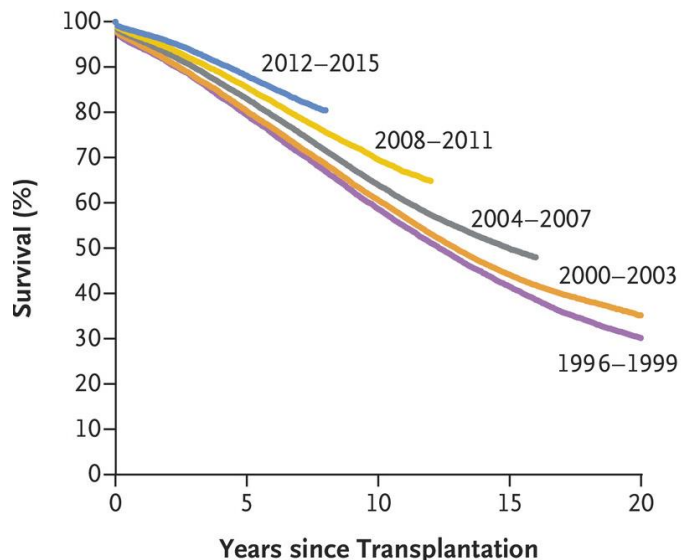
KU LEUVEN

The improvement in outcomes after kidney transplantation over the past 25 years seems to be rather modest

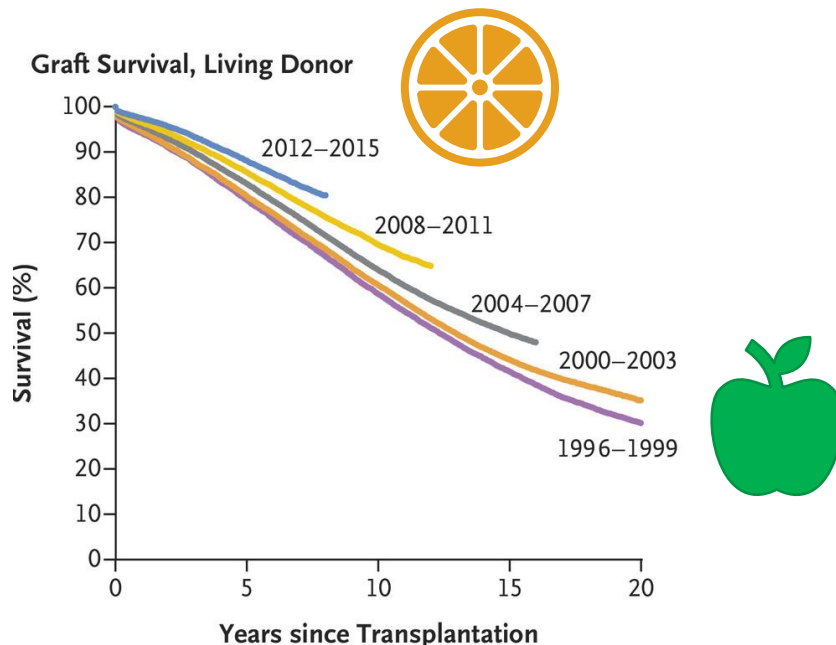
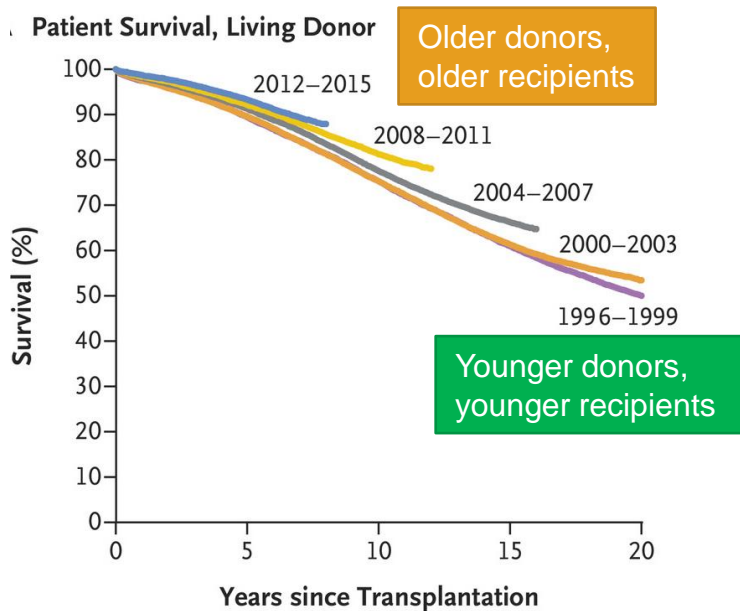
Patient Survival, Living Donor



Graft Survival, Living Donor

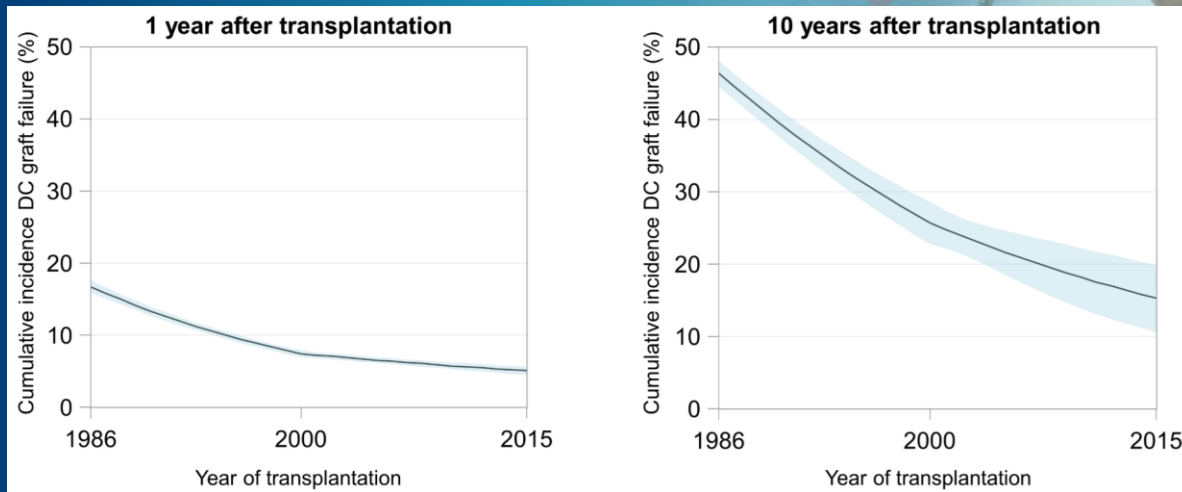


The improvement in outcomes after kidney transplantation over the past 25 years seems to be rather modest



Kidney transplantation - a quiet revolution

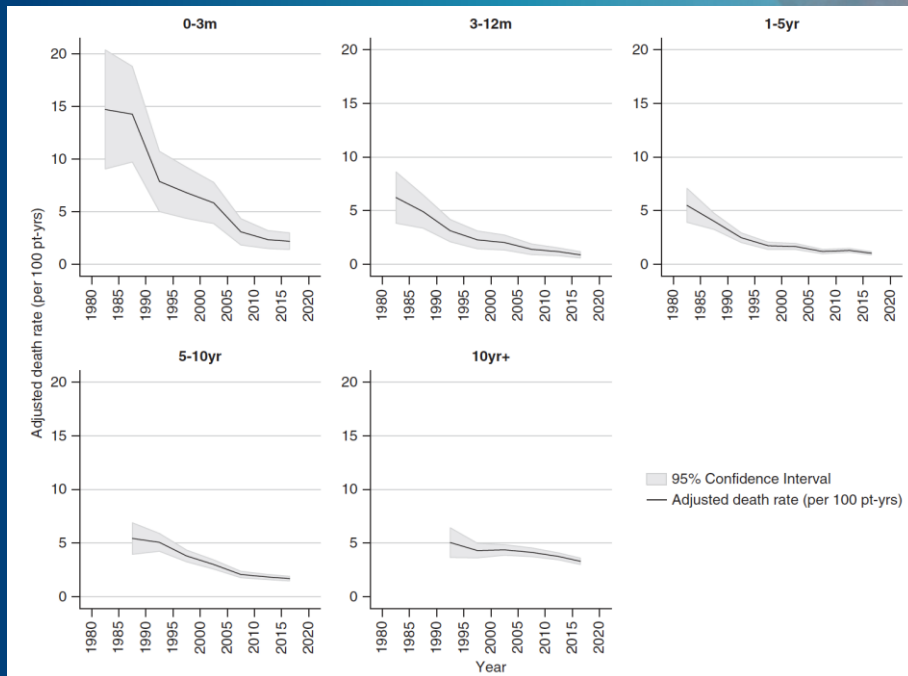
Graft failure



Coemans, Callemeyn, Naesens. N Engl J Med, 2022
Coemans et al Kidney Int 2018

Kidney transplantation - a quiet revolution

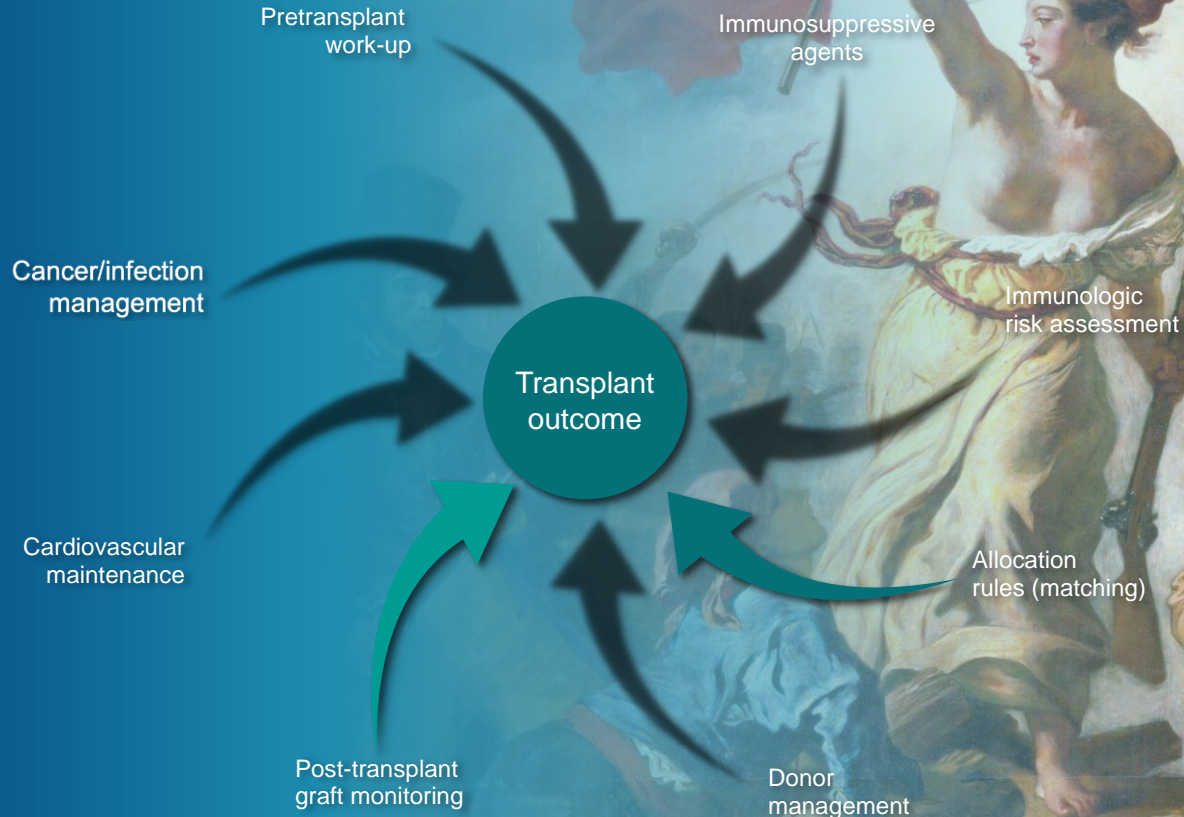
Patient death



Ying et al J Am Soc Nephrol 2020



The quiet revolution



Data used for the approval of immunosuppressive drugs in kidney transplantation: decreasing direct clinical benefit

Drug	Year of approval*	Study regimen	Study design	Definition of efficacy failure	Graft survival	Patient survival	DC graft survival	Acute rejection	Graft function
AZA	1968	AZA and high-dose CS	Case series	Graft loss or death	NA	NA	NA	NA	NA
Ciclosporin	1983	Ciclosporin and low-dose CS	Randomized superiority trials	Graft loss or death	↑	↑	↑	↓	↓
MMF	1995	MMF, ciclosporin and CS±ATG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	↓	↑
Daclizumab	1997	Daclizumab, ciclosporin and CS±AZA	Randomized superiority trials	BPAR by 6 months	=	=	=	↓	↑
Tacrolimus	1997	Tacrolimus, azathioprine, CS and ALG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	↓	=
Basiliximab	1998	Basiliximab, ciclosporin and CS	Randomized superiority trials	BPAR by 6 months	=	=	=	↓	=
Sirolimus	1999	Sirolimus, ciclosporin and steroids	Randomized superiority trials	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	↓	↓
Everolimus	2003	Everolimus, ciclosporin and basiliximab±CS	Randomized equivalence trial	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	=	↓
Belatacept	2011	Belatacept, MMF, CS and basiliximab	Randomized noninferiority trials	Noninferiority for BPAR, graft loss and death; superiority for GFR	=	=	=	↑	↑



European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. CHMP/EWP/263148/06

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON CLINICAL INVESTIGATION OF IMMUNOSUPPRESSANTS FOR SOLID
ORGAN TRANSPLANTATION

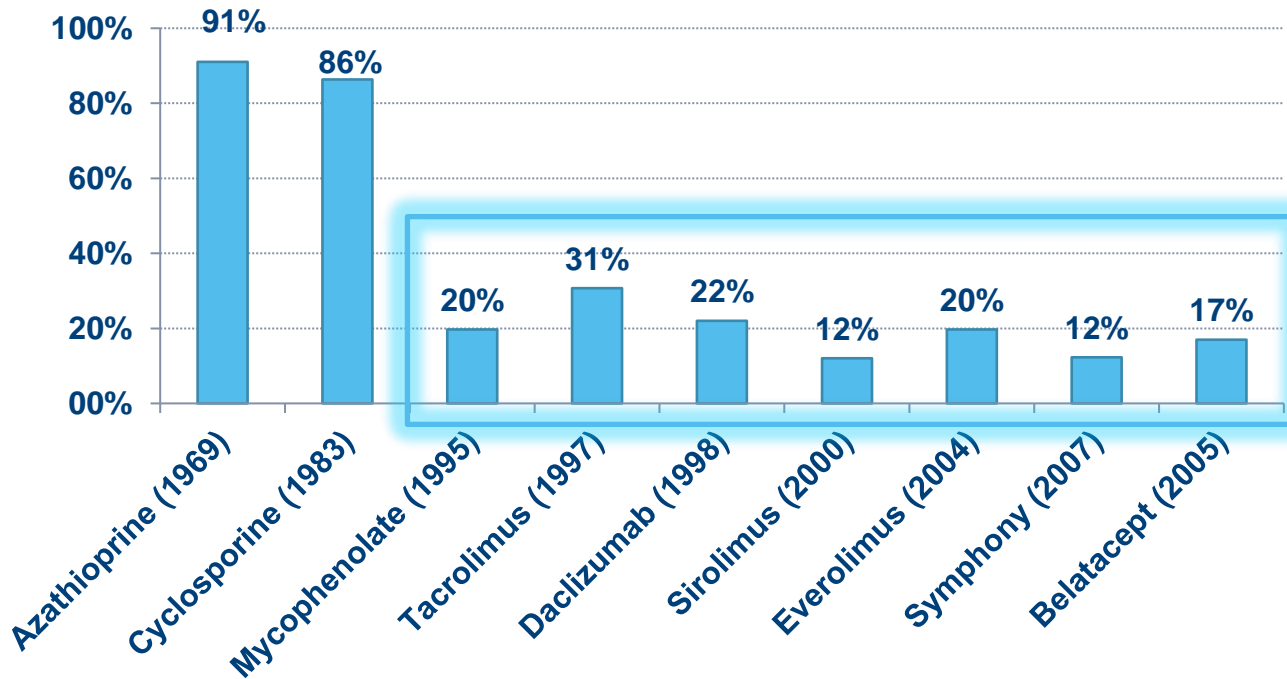
DRAFT AGREED BY EFFICACY WORKING PARTY	June 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 July 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2008
AGREED BY EFFICACY WORKING PARTY	July 2008
ADOPTION BY CHMP	24 July 2008
DATE FOR COMING INTO EFFECT	1 February 2009

KEYWORDS	<i>Immunosuppressants, solid organ transplantation, CHMP, EMA, guideline</i>
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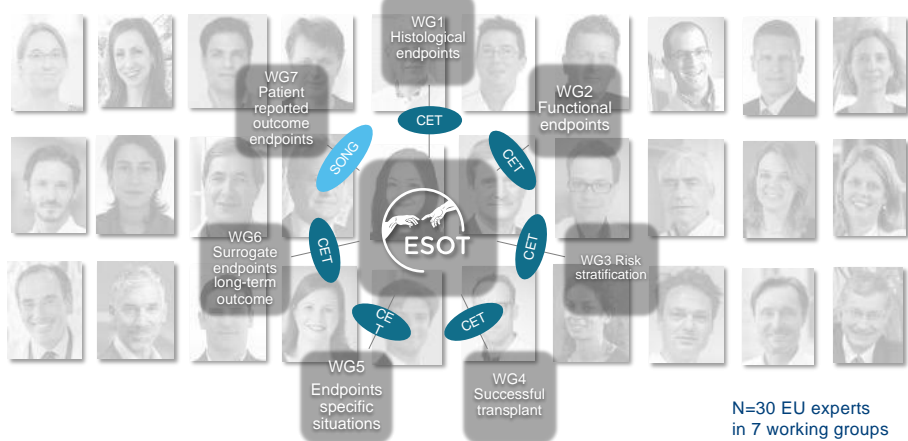
“The *primary efficacy endpoint* for induction, initial and/or maintenance prophylaxis (primary prophylaxis) should be efficacy failure rate using a *composite endpoint* consisting of:

- a) patient death;
- b) graft failure;
- c) biopsy confirmed acute rejection;
- d) graft (dys)-function”

Reducing BPAR helped in the early decades but is less relevant nowadays



Woodruff et al Lancet 1969
Canadian study NEJM 1983
Grinyo et al Lancet 1995
Tricontinent. study Transplant. 1996
Vincenti et al NEJM 1998
Pirsch et al Transplantation 1997
Kahan et al Lancet 2000
Vitko et al Transplantation 2004
Ekberg et al NEJM 2007
Vincenti et al NEJM 2005



AST



**UNIVERSITY
OF MANITOBA**

TCMR WG



BANFF FOUNDATION
FOR ALLOGRAFT PATHOLOGY

TTS
ransplantation Society



Leading the way
in transplantation

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Surrogate endpoints WG

**BIOPHARMACEUTICAL
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- Takeda
- Talaris Therapeutics
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- Transplant Genomics
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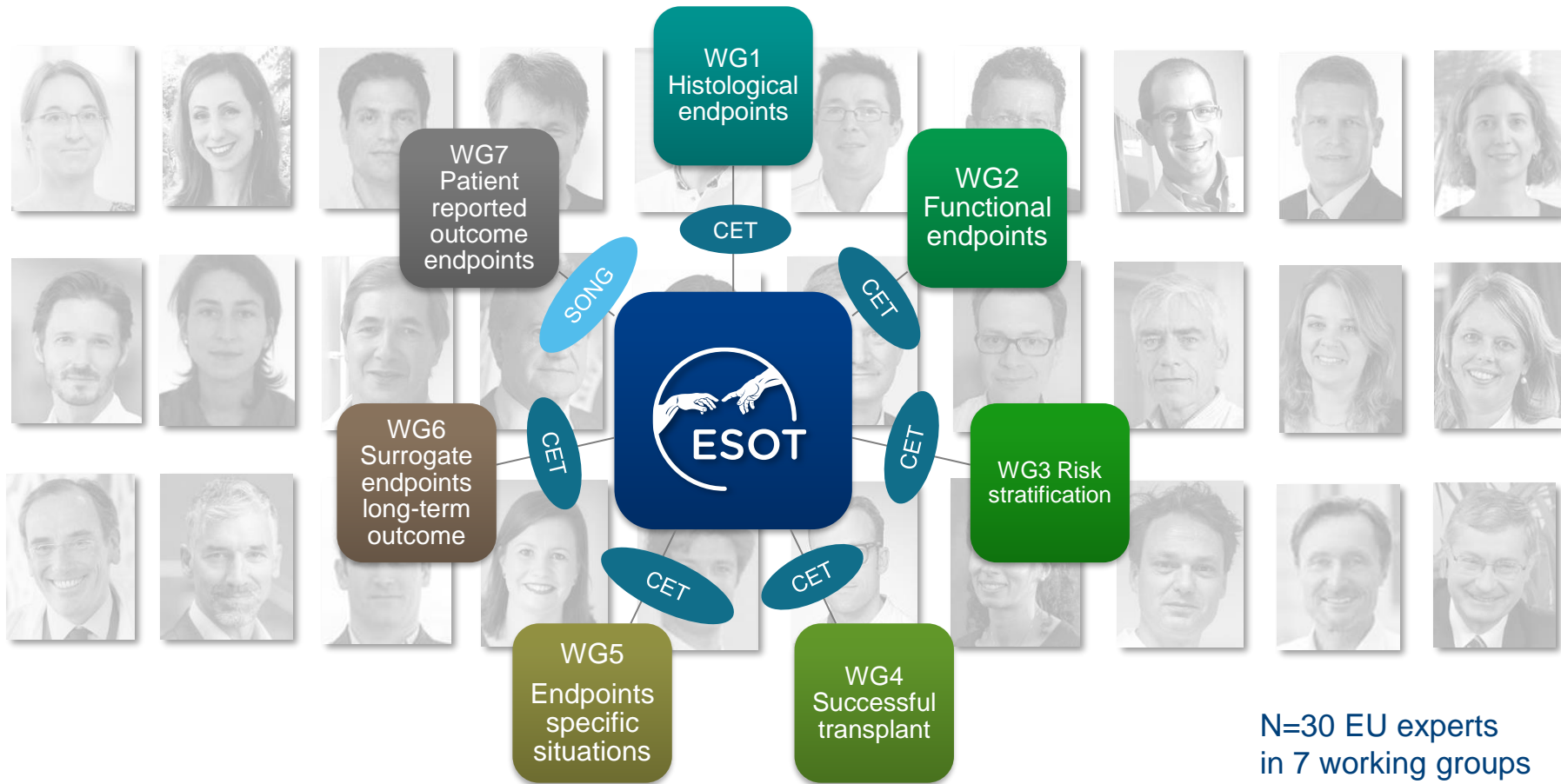


PRE-COMPETITIVE SPACE
Established in 2017

FDA

**The Transplantation
Society**

NIH



N=30 EU experts
in 7 working groups



ESOT meets EMA

Sept. 2017

1st ESOT workshop



May 2020

Submission to EMA



Dec. 2020

EMA responses



2nd ESOT workshop

Sept. 2019

ESOT—EMA
discussion meeting

Sept. 2020

EUROPEAN
MEDICINES
AGENCY



Special Issue

Transplant International



Clinical trial design and endpoints in kidney transplantation



Transplant International | | Publishing Partnerships



Alloimmune Risk Stratification for Kidney Transplant Rejection

Olaf Heeser¹, Oliver Theuerl¹, Maria Ines Balle², Georg A. Böhm³, Christian Rüdel⁴, Maria Budde⁵, Peter Christ⁶, Lutz Cordts⁷, Lutz Filler⁸, Uwe Heemann⁹, Stefan Himmels¹⁰, Rainer Jöhann¹¹, Jochen Knebel¹², Stefan Schönberger¹³ and Axel Heemann¹⁴*

Department of Nephrology and Dialysis, 1st Medical University Hospital, Saarland, Germany; 2, Department of Nephrology, University of Bonn, Germany; 3, Department of Nephrology, University of Cologne, Germany; 4, Department of Nephrology, University of Tübingen, Germany; 5, Department of Nephrology, University of Würzburg, Germany; 6, Department of Nephrology, University of Bonn, Germany; 7, Department of Nephrology, University of Bonn, Germany; 8, Department of Nephrology, University of Bonn, Germany; 9, Department of Nephrology, University of Bonn, Germany; 10, Department of Nephrology, University of Bonn, Germany; 11, Department of Nephrology, University of Bonn, Germany; 12, Department of Nephrology, University of Bonn, Germany; 13, Department of Nephrology, University of Bonn, Germany; 14, Department of Nephrology, University of Bonn, Germany

Different types of kidney transplantation were performed worldwide, including biologically diverse donor-specific combinations, which entail distinct pathogenic pathways. Thus, immunological and non-immunological risk profiles of recipient and donor combinations especially for patients included in interventional end-of-study trials. This paper was presented by a working group within the European Society for Organ Transplantation (ESOT) which submitted a Broad Scientific Advice request to the European Medicines Agency (EMA) last week in final response to December 2020, highlighting the following 12 key messages for clinical trial design: 1. Clinical trial design should be tailored to the specific donor and recipient combination. 2. Clinical trial design should be tailored to the specific donor and recipient combination. 3. Clinical trial design should be tailored to the specific donor and recipient combination.

CONFLICT OF INTEREST

The authors declare that the research was conducted in accordance with the ethical standards of the responsible human research ethics committee and with the declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study. ***Correspondence:** Axel Heemann, axel.heemann@klinik.uni-bonn.de **RECEIVED:** 15 November 2021 **ACCEPTED:** 22 December 2021 **PUBLISHED:** 05 January 2022 **CITATION:** Heeser O, Theuerl O, Balle M, Böhm GA, Rüdel C, Budde M, Christ P, Cordts L, Filler U, Heemann U, Himmels S, Johann R, Knebel J, Schönberger S and Heemann A (2022) Alloimmune Risk Stratification for Kidney Transplant Rejection. *Front. Med.* 9:860439. doi: 10.3389/fmed.2021.860439



Evolution of the Definition of Rejection in Kidney Transplantation and Its Use as an Endpoint in Clinical Trials

Jan Ulrich Becker¹, Daniel Sauer², Marion Rabner³, Christian Rüdel⁴ and Stefan Himmels⁵*

Department of Nephrology, University of Bonn, Germany; 2, Department of Nephrology, University of Cologne, Germany; 3, Department of Nephrology, University of Tübingen, Germany; 4, Department of Nephrology, University of Würzburg, Germany; 5, Department of Nephrology, University of Bonn, Germany

This article defines the evolving definition of rejection following kidney transplantation. The respective and evidence presented were included in documentation prepared for a Broad Scientific Advice request to the European Medicines Agency (EMA) under its clinical trial design in kidney transplantation. The request was issued by the European Society for Organ Transplantation (ESOT) in 2019 and finalized following discussion amongst the EMA and ESOT in 2020. In ESOT's opinion, the use of 'biopsy proven acute rejection' as an endpoint in clinical trials in kidney transplantation is no longer adequate, although it was the approved nomenclature endpoint. The structure of rejection is now divided into the phenomenon of transplant rejection, 'T cell-mediated rejection' and antibody-mediated rejection, with the latter term phenotype having further subtypes. Thus, Rejection is also described in relation to graft dysfunction, diagnosed because of protocol surveillance or re-biopsy (re-coaxial biopsies). The ongoing state of continual knowledge has become a potential barrier to clinical research in kidney transplantation. This presents theoretical perspectives and issues, and provides a foundation on which subsequent evidence within the field should be based. © 2022 Becker, Sauer, Rabner, Rüdel and Himmels. **KEYWORDS:** kidney transplantation, rejection, antibody-mediated rejection, T cell-mediated rejection, histologic rejection, biopsy proven acute rejection

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WEBINAR 1 - July 7th 2022

Proposed Definitions of Antibody-Mediated Rejection for Use as a Clinical Trial Endpoint in Kidney Transplantation

Christian Rüdel¹, Jan Ulrich Becker², Marion Rabner³, Daniel Sauer⁴, Maria Ines Balle⁵, Georg A. Böhm⁶, Alexander Budde⁷, Jochen Schönberger⁸, Stefan Schönberger⁹ and Axel Heemann¹⁰*

Department of Nephrology and Dialysis, 1st Medical University Hospital, Saarland, Germany; 2, Department of Nephrology, University of Bonn, Germany; 3, Department of Nephrology, University of Cologne, Germany; 4, Department of Nephrology, University of Tübingen, Germany; 5, Department of Nephrology, University of Würzburg, Germany; 6, Department of Nephrology, University of Bonn, Germany; 7, Department of Nephrology, University of Bonn, Germany; 8, Department of Nephrology, University of Bonn, Germany; 9, Department of Nephrology, University of Bonn, Germany; 10, Department of Nephrology, University of Bonn, Germany

Antibody-mediated rejection (AMR) is caused by antibodies that recognize donor human leukocyte antigen (HLA) or other targets. As knowledge of AMR pathophysiology has increased, consideration is required to clarify the HLA definition used in clinical trials. However, frequent modifications to the AMR definition have made it difficult to compare data and submit applications to regulatory agencies. This project was presented by a working group within the European Society for Organ Transplantation (ESOT) which submitted a Broad Scientific Advice request from the European Medicines Agency (EMA) last week in final response to December 2020, highlighting the following 12 key messages for clinical trial design: 1. Clinical trial design should be tailored to the specific donor and recipient combination. 2. Clinical trial design should be tailored to the specific donor and recipient combination. 3. Clinical trial design should be tailored to the specific donor and recipient combination.

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Proposed Definitions of T Cell-Mediated Rejection and Tubulointerstitial Inflammation as Clinical Trial Endpoints in Kidney Transplantation

Daniel Sauer¹, Marion Rabner², Jan Ulrich Becker³, Christian Rüdel⁴ and Stefan Himmels⁵*

Department of Nephrology, University of Bonn, Germany; 2, Department of Nephrology, University of Cologne, Germany; 3, Department of Nephrology, University of Tübingen, Germany; 4, Department of Nephrology, University of Würzburg, Germany; 5, Department of Nephrology, University of Bonn, Germany

The diagnosis of acute T cell-mediated rejection (ATCMR) after kidney transplantation has considerable relevance for clinical trial design. It is currently defined based on tubulointerstitial inflammation and has changed little over time. ATCMR is however a suitable parameter for longitudinal trials. This paper reviews the history and details. Use of TCMR and characteristics is pointed out in detail with a view to the largely open issues in the field. The results are summarized in a table. The results are summarized in a table. The results are summarized in a table.

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Special Issue

Transplant International



Clinical trial design and endpoints in kidney transplantation



Transplant International | Publishing Partnerships



Allograft Function Clinical Trials in Transplantation

Luuk Hilbrands^{1*}, Alexander Loupy², Maarten Naesens^{1*}, Denis Glotz³, Josep Grinyó³, Ina Johansson⁹, Stefan Pongel¹⁰, Marlies Reinders¹¹, Stefan Schneeberger¹² and Clemens Budde¹³

Clinical study endpoints that assess the effect of immunosuppression on allograft function can be selected for use in the generalization of results to other populations. This review discusses the selection of endpoints for clinical trials in kidney transplantation. The review is organized into three sections: (1) endpoints that assess the effect of immunosuppression on allograft function, (2) endpoints that assess the effect of immunosuppression on patient survival, and (3) endpoints that assess the effect of immunosuppression on quality of life. The review concludes that the selection of endpoints for clinical trials in kidney transplantation should be based on the clinical question, the population, and the available data.

INTRODUCTION

As an allograft recipient, the donor of a kidney, chronic graft failure results in end-stage renal disease (ESRD) with the need for kidney replacement therapy in the form of dialysis or organ transplantation. Pathological processes that characterize the late course of graft failure are loss of nephrons, glomerulosclerosis of the remaining nephrons, and interstitial fibrosis with tubular atrophy.

ESOT 2022 | Volume 01 | Article 10137



Surrogate Endpoints for Late Kidney Transplantation Failure

Maarten Naesens^{1*}, Alexander Loupy², Luuk Hilbrands¹, Denis Glotz³, Josep Grinyó³, Ina Johansson⁹, Stefan Pongel¹⁰, Marlies Reinders¹¹, Stefan Schneeberger¹² and Clemens Budde¹³

In kidney transplant recipients, late graft failure is often multifactorial. In addition, primary endpoints in kidney transplantation studies seek to demonstrate the short-term efficacy and safety of clinical interventions. Although such endpoints might demonstrate short-term improvement in specific aspects of patient or recipient or recipient, such findings do not automatically translate into meaningful long-term graft survival benefits. Combining more factors into a multifactorial model is therefore more likely to predict long-term outcomes and better reflect the complexity of late graft failure than using single endpoints. If conditional monitoring approaches could be considered for therapies that aim to improve long-term outcomes following kidney transplantation, then the surrogate endpoint for graft failure in clinical trials settings needs careful selection. This review discusses the selection of potential surrogate endpoints of several candidate surrogate endpoints (including estimated glomerular filtration rate, proteinuria, histological features, and donor-specific and human leukocyte antigen antibodies) and composite scoring systems. The current review is organized into three sections: (1) endpoints that assess the effect of immunosuppression on allograft function, (2) endpoints that assess the effect of immunosuppression on patient survival, and (3) endpoints that assess the effect of immunosuppression on quality of life. The review concludes that the selection of endpoints for clinical trials in kidney transplantation should be based on the clinical question, the population, and the available data.

INTRODUCTION

Key primary objectives in kidney transplantation are recipient death, graft failure, biopsy-confirmed acute rejection, and graft loss (1). These objectives have clear value to recipients and are also important to clinicians. However, it is important to know their graft survival (2).

ESOT 2022 | Volume 01 | Article 10138

CONSENSUS REPORT published: 20 May 2022 doi: 10.3389/ftri.2022.10137



Rationale for Surrogate Endpoints and Conditional Marketing Authorization of New Therapies for Kidney Transplantation

Maarten Naesens^{1*}, Alexandre Loupy², Luuk Hilbrands³, Rainer Oberbauer⁴, Maria Irene Bellini⁵, Denis Glotz⁶, Josep Grinyó⁷, Ina Johansson⁹, Stefan Pongel¹⁰, Marlies Reinders¹¹, Stefan Schneeberger¹² and Clemens Budde¹³

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Conditional marketing authorization (CMA) facilitates timely access to new therapies for kidney transplantation. CMA is a regulatory pathway that allows for the marketing of new drugs for the treatment of kidney transplantation. CMA is based on the assumption that the benefits of the new drug outweigh the risks. CMA is a conditional approval, meaning that the drug is only approved for a limited period of time. During this period, the drug is monitored closely. If the drug is found to be safe and effective, it can be converted to a full marketing authorization. CMA is a valuable tool for the development of new therapies for kidney transplantation.

ESOT 2022 | Volume 01 | Article 10139

WEBINAR 2 - July 12th 2022

ESOT 2022 | Volume 01 | Article 10139

Surrogate Endpoints for Late Kidney Transplantation Failure

Maarten Naesens^{1*}, Alexander Loupy², Luuk Hilbrands¹, Denis Glotz³, Josep Grinyó³, Ina Johansson⁹, Stefan Pongel¹⁰, Marlies Reinders¹¹, Stefan Schneeberger¹² and Clemens Budde¹³

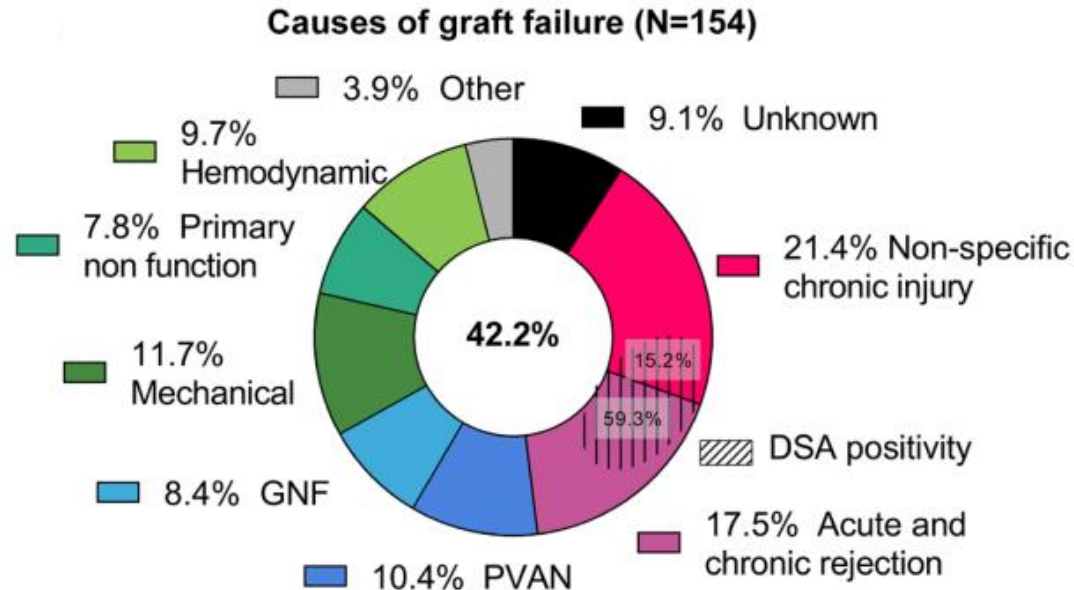
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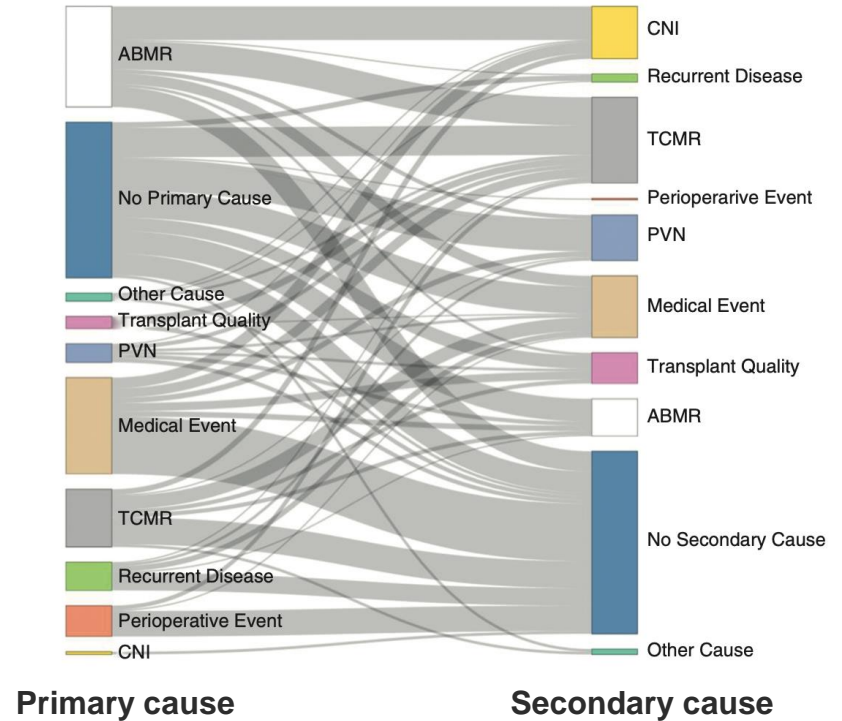
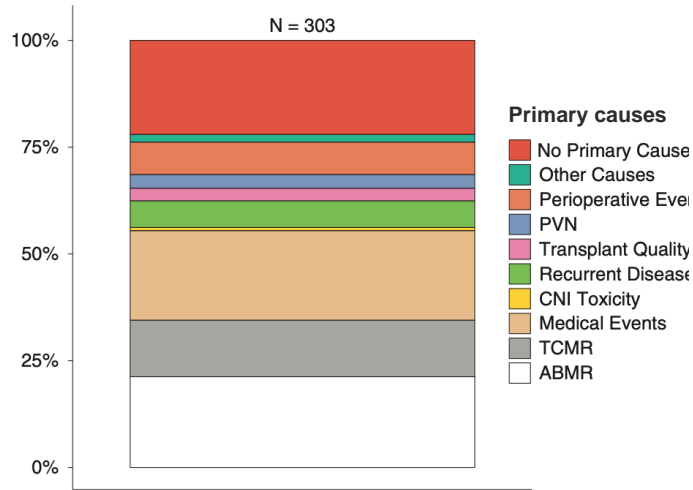
ESOT 2022 | Volume 01 | Article 10139

go.esot.org/ti_ema01_txlive

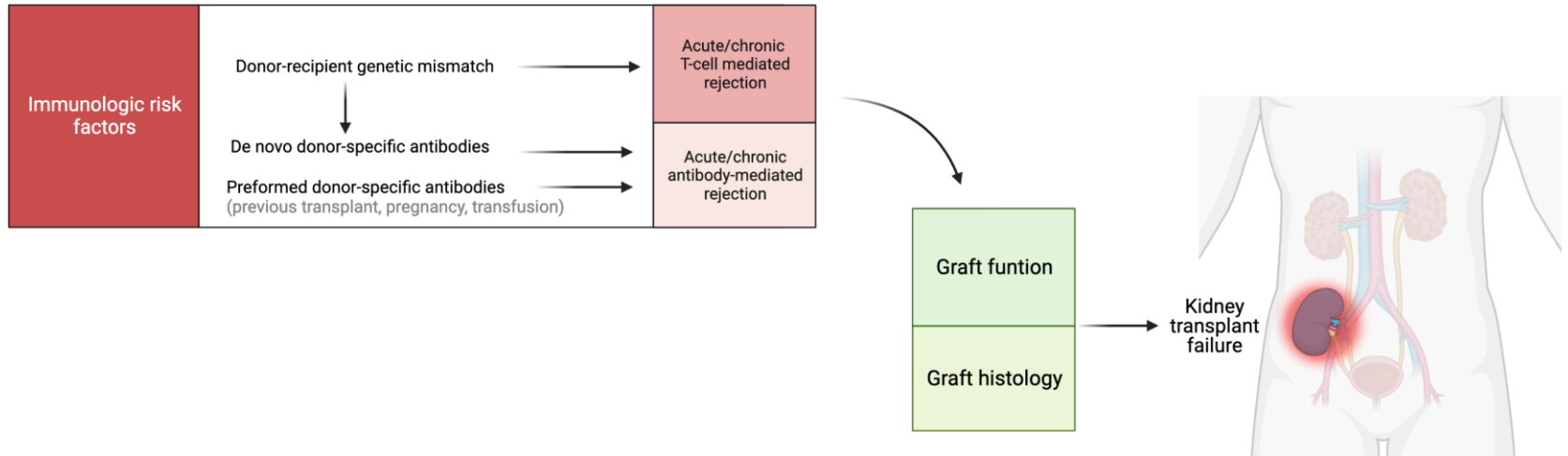
Further improvement of outcomes can only when we target the actual causes of graft failure



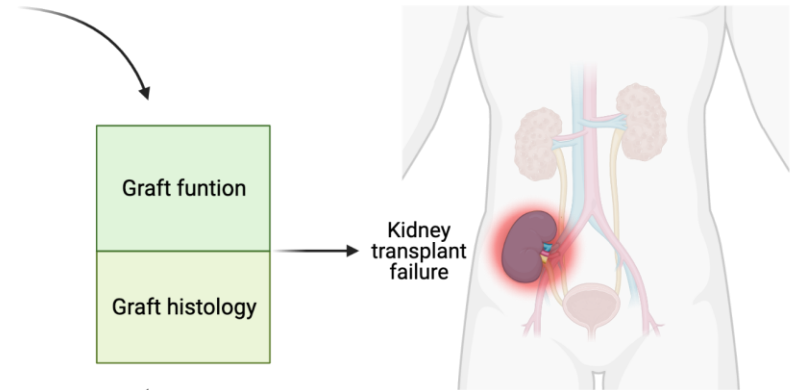
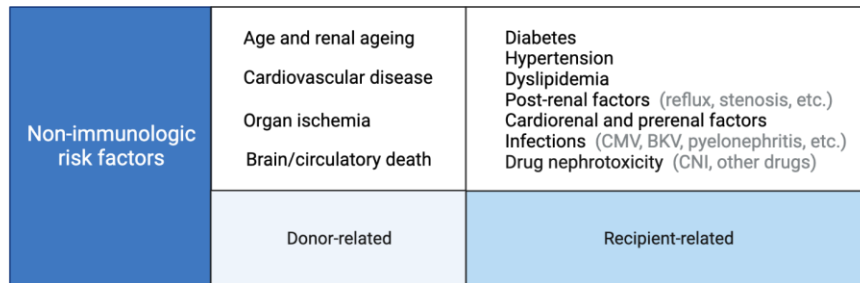
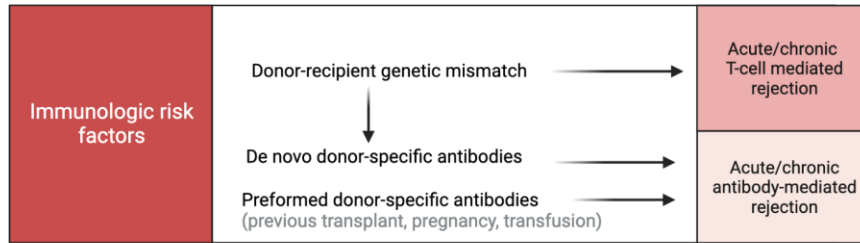
Graft failure is a complex process with primary and secondary causes



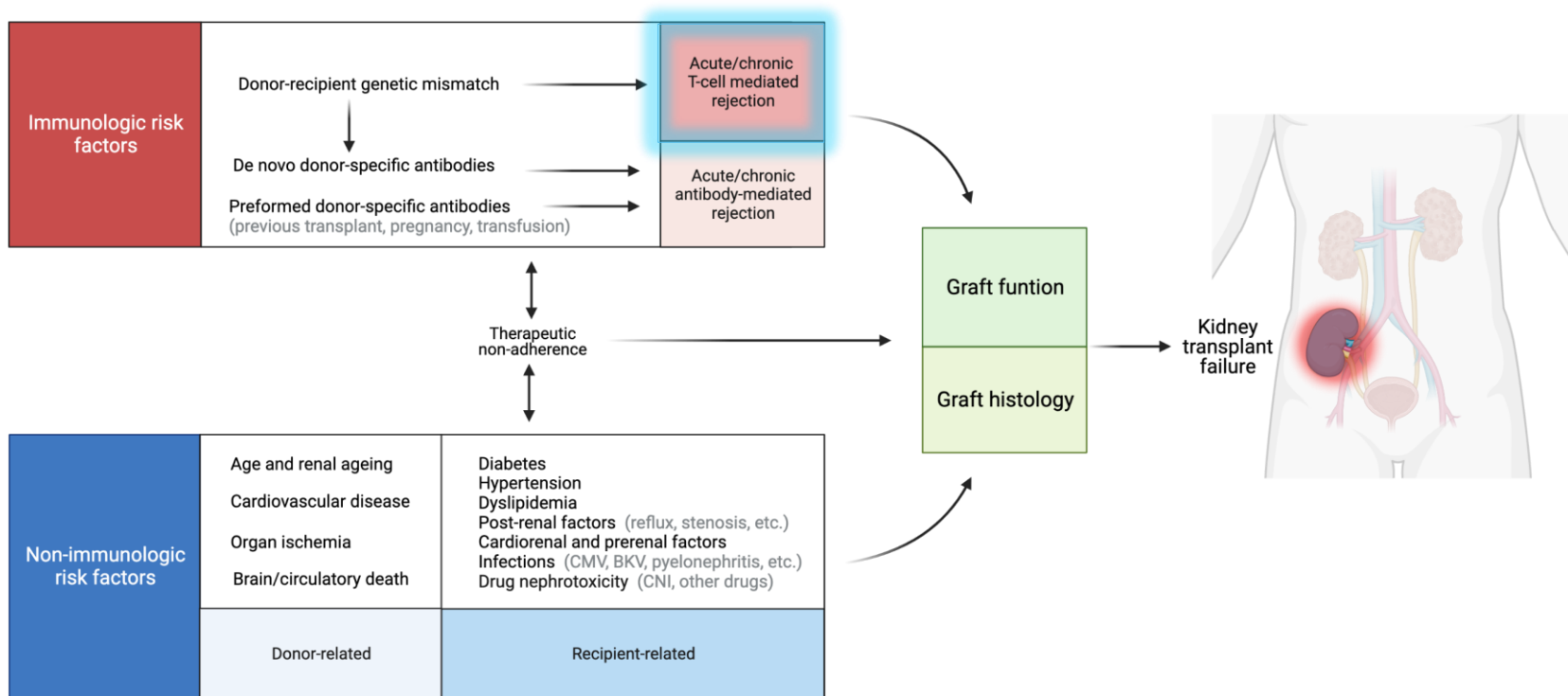
The multifactorial causes of graft failure



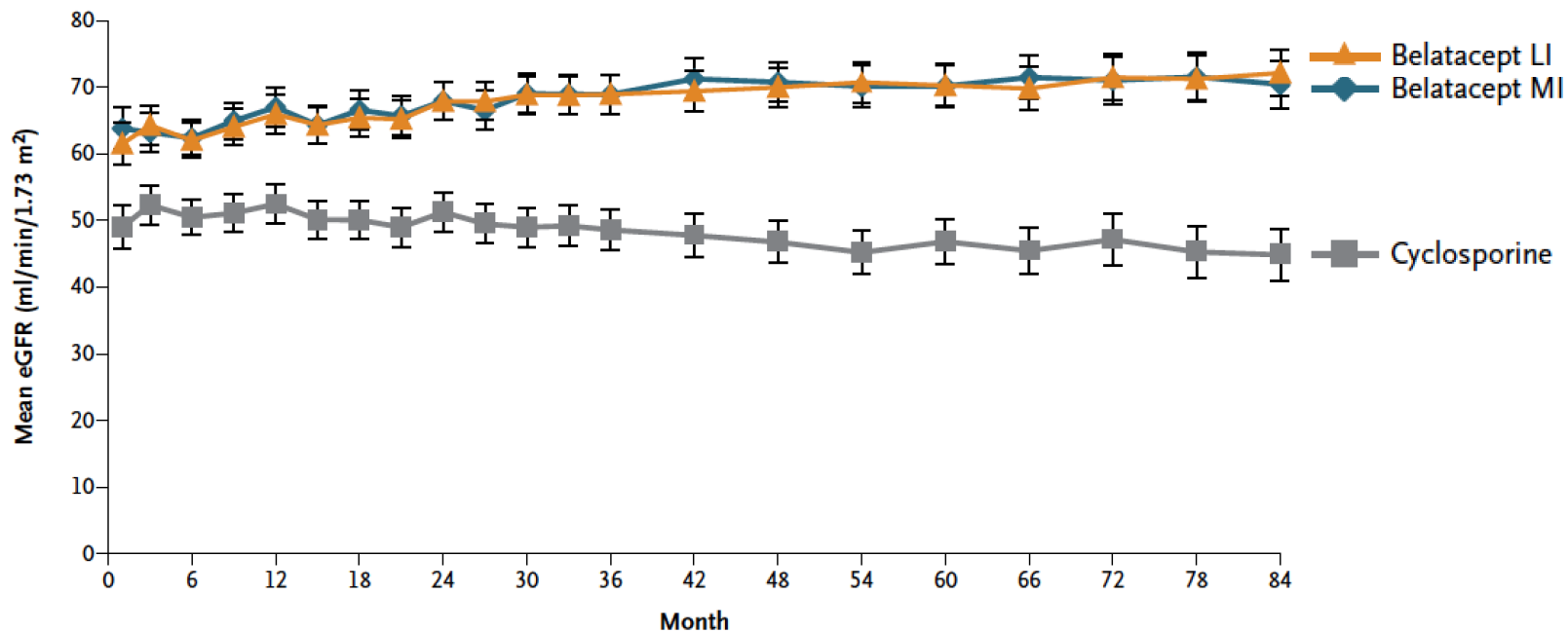
The multifactorial causes of graft failure



The multifactorial causes of graft failure

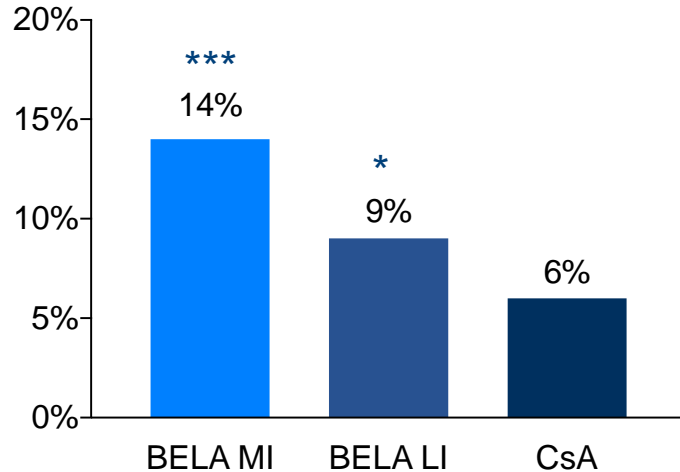


The BENEFIT study confirms the beneficial effect of belatacept in terms of eGFR

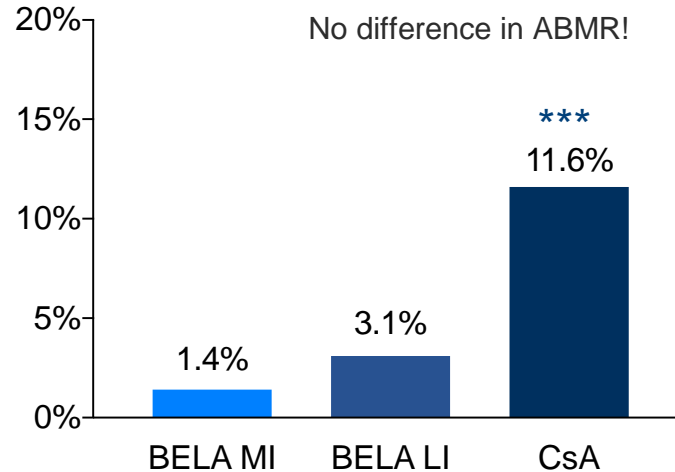


The rejections in the BENEFIT study were T-cell mediated with low risk of DSA formation

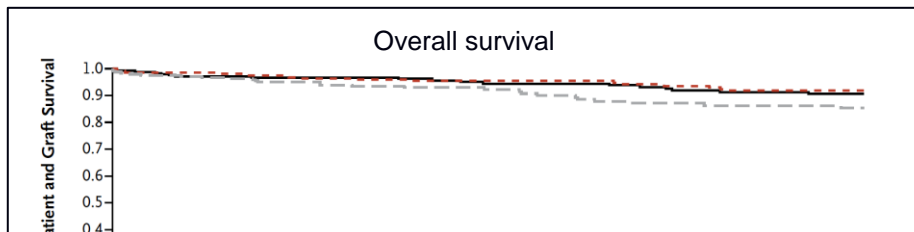
Acute rejection occurrence



De novo DSA occurrence

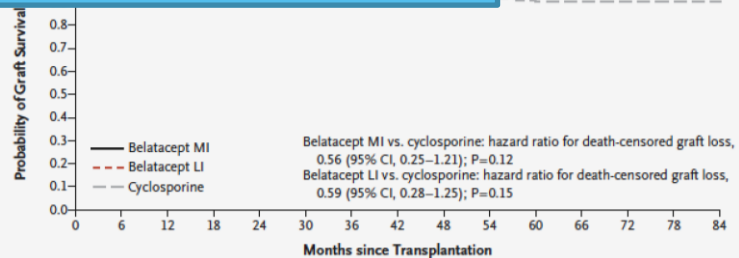
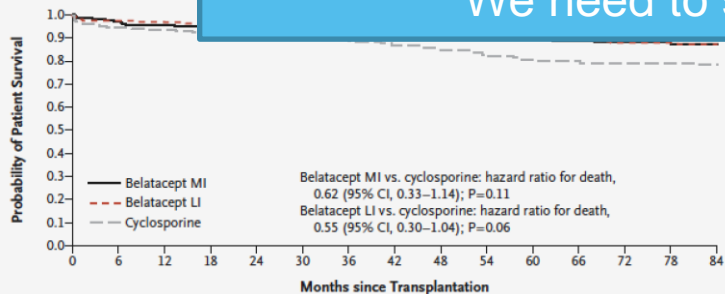


Belatacept is the first IS agent to show improved overall survival since CsA



Not all that happens in the first year post-transplantation is directly predictive of outcome (BPAR wasn't!)

We need to see the whole picture



We need more realistic and feasible endpoints for future trials

Currently Approved Endpoints	Limitations
Patient/graft survival at 5 or 10 years	<ul style="list-style-type: none">• Cost prohibitive
Patient/graft survival at 1 year	<ul style="list-style-type: none">• Now irrelevant for superiority trials• Good survival is already achieved (~ 95%), making it difficult to show further improvement
Acute rejection	<ul style="list-style-type: none">• T-cell and antibody-mediated rejection do not have the same impact on graft outcome

More realistic (surrogate) endpoints should better reflect the multidimensional causes of graft failure, and not solely focus on graft function or rejection.

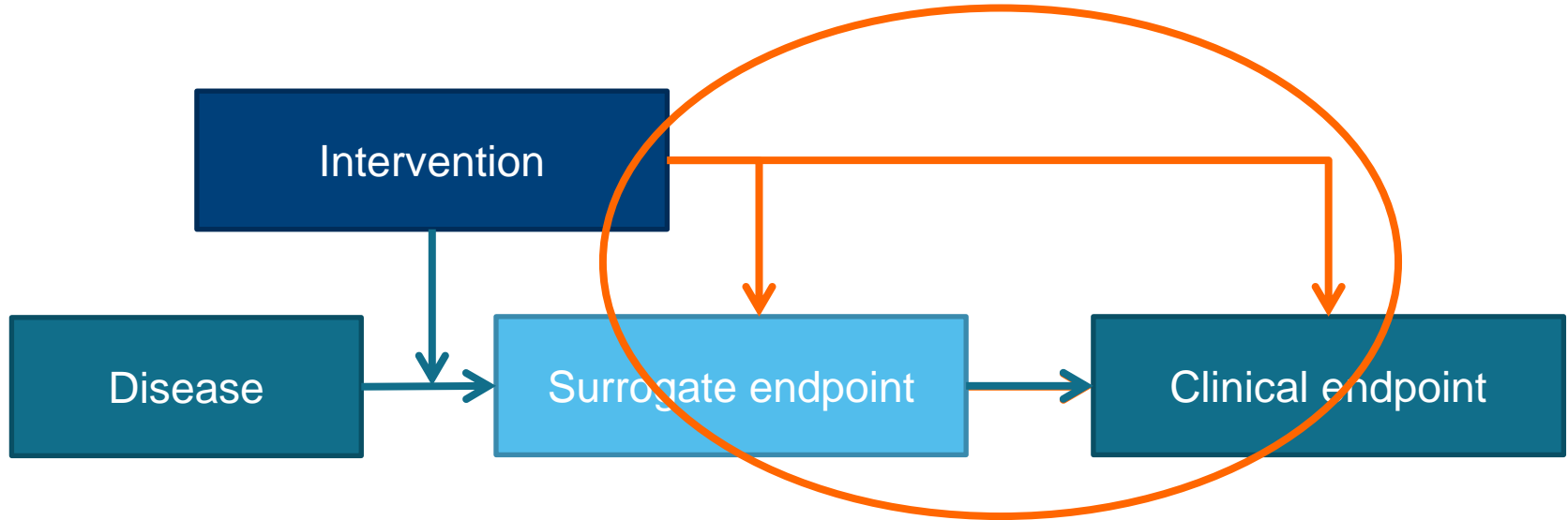
Towards surrogate endpoints for long-term graft failure



Towards surrogate endpoints for long-term graft failure



Towards surrogate endpoints for long-term graft failure



Needs to be validated!

Surrogate endpoints for clinical trials need to be well validated

Disease process



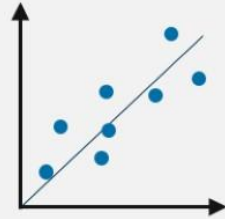
Sufficiently understood

Biology of surrogate



Plausible

Relationship



Strong

Treatment



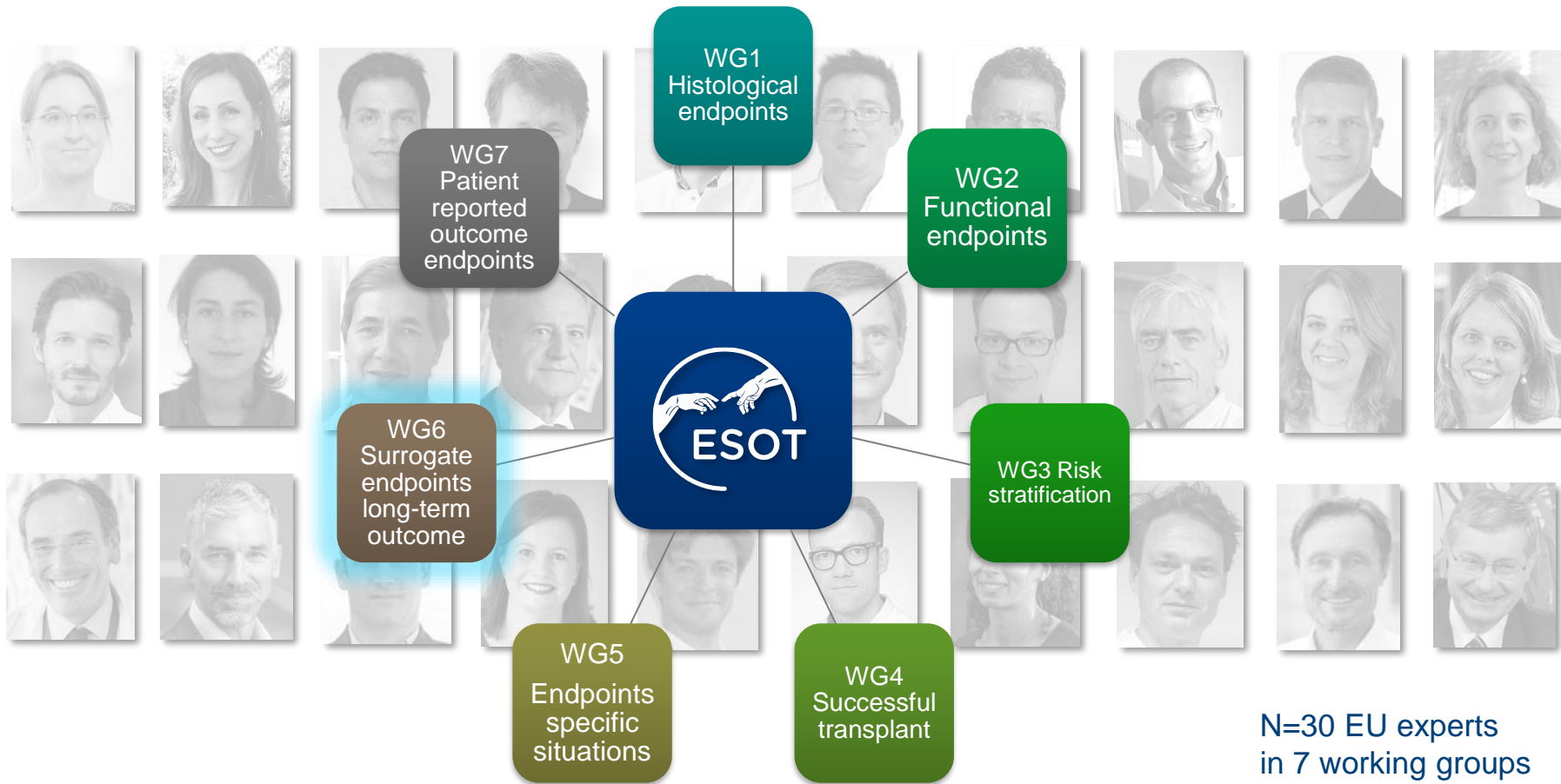
Effect on both clinically meaningful endpoint and surrogate endpoint of choice

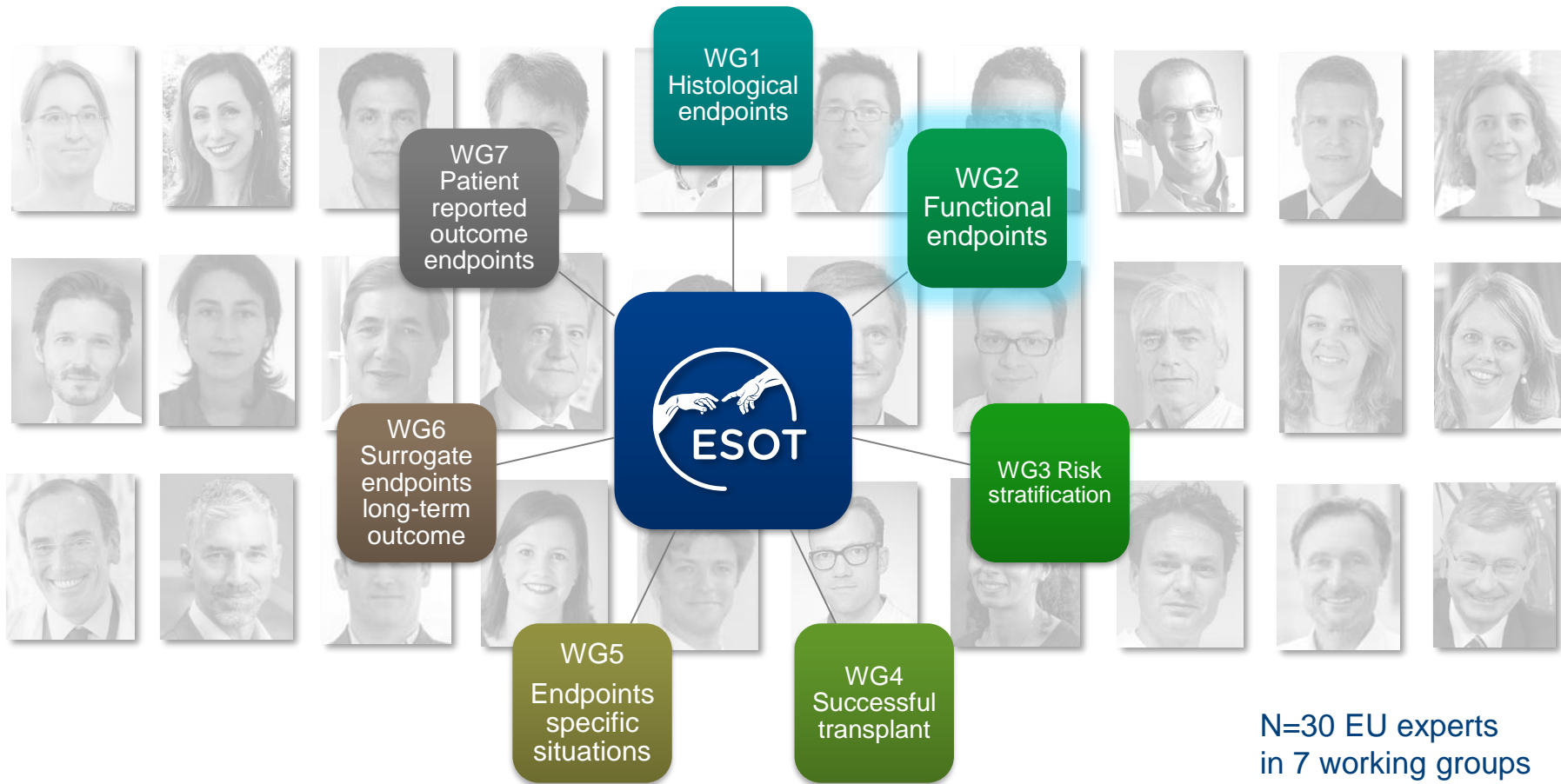


	Kasiske et al 2010 USRDS Risk-Prediction Tool	Foucher et al. 2010 Kidney Transplant Failure Score (KTFS)	Moore et al. 2011 LOTESS Composite Risk Score	Schnitzler et al. 2012 USRDS Predictive Model	Shabir et al. 2014) Birmingham Risk Score	Prémaud et al. 2017 Adjustable score for prediction of graft failure (AdGFS)
Development set	USRDS registry data (N=59,091)	Multicentre French registry (DIVAT; N=2169)	Multicentre national cohort study (N=2763)	USRDS registry data (N=87,575)	Single-centre UK data (N=651)	Single-centre French data (N=664)
External validation	No	Yes (N=317)	Yes (single UK centre; N=731)	No	Yes (2 European centres and 1 Canadian centre; N=1998)	Yes (2 other French centres; N=896)
Prediction time point	12 months post-transplant	12 months post-transplant	Variable time after 12 months post-transplant	12 months post-transplant	12 months post-transplant	Time adjusted (only for 'rejection')
Outcome parameter	Overall graft failure at 5 years after transplantation	Death-censored graft failure at 8 years	Overall graft failure and death-censored graft failure over time; follow-up time not specified	Overall graft failure beyond 1 year post-transplant, up to 9 years	Overall graft failure and death-censored graft failure at 5 years post-transplant	Death-censored graft failure beyond 2 years post-transplant, up to 10 years
		Recipient gender; recipient				

None of these prediction models has been validated as a surrogate endpoint

Post-transplant factors included in the model	eGFR at 12 months; hospitalization	Serum creatinine; acute rejection; creatinine at 3 months; 24-h proteinuria	eGFR at 12 months; eGFR evolution; acute rejection; serum urea at 12 months; serum albumin	eGFR at 12 months; acute rejection within the first year	acute rejection; eGFR; serum albumin; UACR	Serum creatinine; proteinuria; dnDSA; serum creatinine trajectory; acute rejection
Prognostic accuracy	C-statistic 0.65–0.78	ROC AUC 0.78 (0.73–0.80)	C-statistic 0.83 for death-censored graft failure; 0.70 for overall graft failure	Not reported	C-statistic 0.78–0.90 for death-censored failure; 0.75–0.81 for overall graft failure	ROC AUC at 10 years post-transplant 0.83 (0.76–0.89)
Calibration	Good	Not assessed	Good	Good	Good	Good
Limitations	No external validation set; No data on DSA; No data on proteinuria; Prognostic accuracy moderate	Small validation set; validity not tested in other countries; No data on DSA; No data on rejection phenotype	Small validation set; validity not tested in other countries; No data on DSA; No data on rejection phenotype; Prediction time point variable	No external validation set; No data on DSA; No data on proteinuria; No data on rejection phenotype	No data on rejection phenotype; No data on DSA;	Small validation sets and validity in other countries not tested; not tested in living donors or patients with pre-transplant DSA
Tested in randomized trial data	No	No	No	Yes, but calibration and validity as surrogacy for improved outcome by the intervention was not tested	No	No





Graft function as endpoint

✓ Endpoints that assess the efficacy of interventions in patients with CKD could be used in kidney transplantation trials

✓ A composite endpoint consisting of a 30–40% decline in eGFR or kidney failure occurrence could be used as endpoint for trials in kidney transplantation, like it is in CKD

✓ eGFR time course, expressed as slope, can be an acceptable surrogate endpoint in kidney transplantation

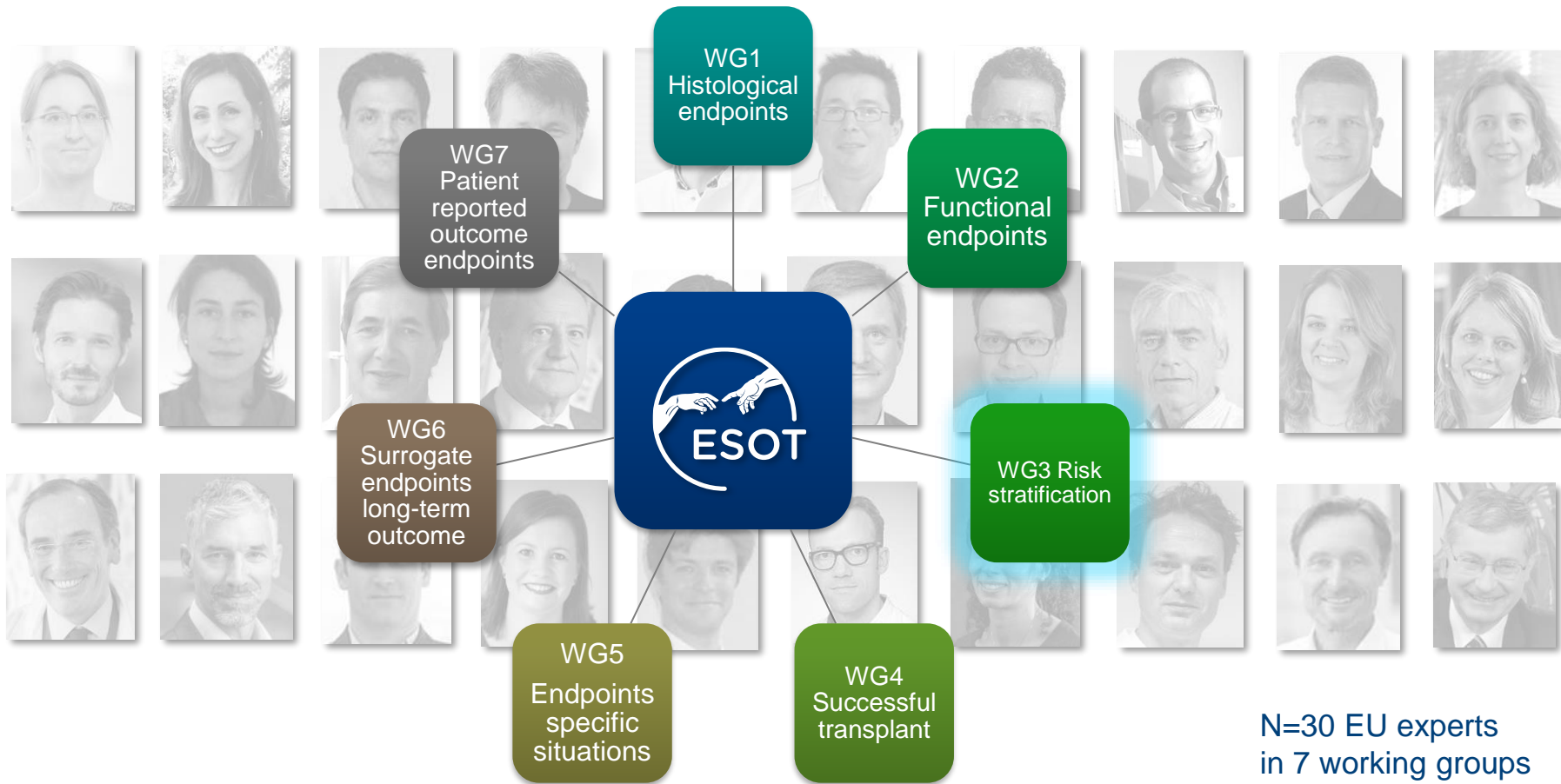
✓ Proteinuria or combinations of proteinuria and eGFR are not advocated as endpoint for clinical trials in kidney transplantation



Data used for the approval of immunosuppressive drugs in kidney transplantation: decreasing direct clinical benefit

Drug	Year of approval*	Study regimen	Study design	Definition of efficacy failure	Graft survival	Patient survival	DC graft survival	Acute rejection	Graft function
AZA	1968	AZA and high-dose CS	Case series	Graft loss or death	NA	NA	NA	NA	NA
Ciclosporin	1983	Ciclosporin and low-dose CS	Randomized superiority trials	Graft loss or death	↑	↑	↑	↓	↓
MMF	1995	MMF, ciclosporin and CS±ATG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	↓	↑
Daclizumab	1997	Daclizumab, ciclosporin and CS±AZA	Randomized superiority trials	BPAR by 6 months	=	=	=	↓	↑
Tacrolimus	1997	Tacrolimus, azathioprine, CS and ALG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	↓	=
Basiliximab	1998	Basiliximab, ciclosporin and CS	Randomized superiority trials	BPAR by 6 months	=	=	=	↓	=
Sirolimus	1999	Sirolimus, ciclosporin and steroids	Randomized superiority trials	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	↓	↓
Everolimus	2003	Everolimus, ciclosporin and basiliximab±CS	Randomized equivalence trial	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	=	↓
Belatacept	2011	Belatacept, MMF, CS and basiliximab	Randomized noninferiority trials	Noninferiority for BPAR, graft loss and death; superiority for GFR	↗+	↗+	=	↑	↑

In retrospect, the choice of the primary endpoints for belatacept was well chosen!





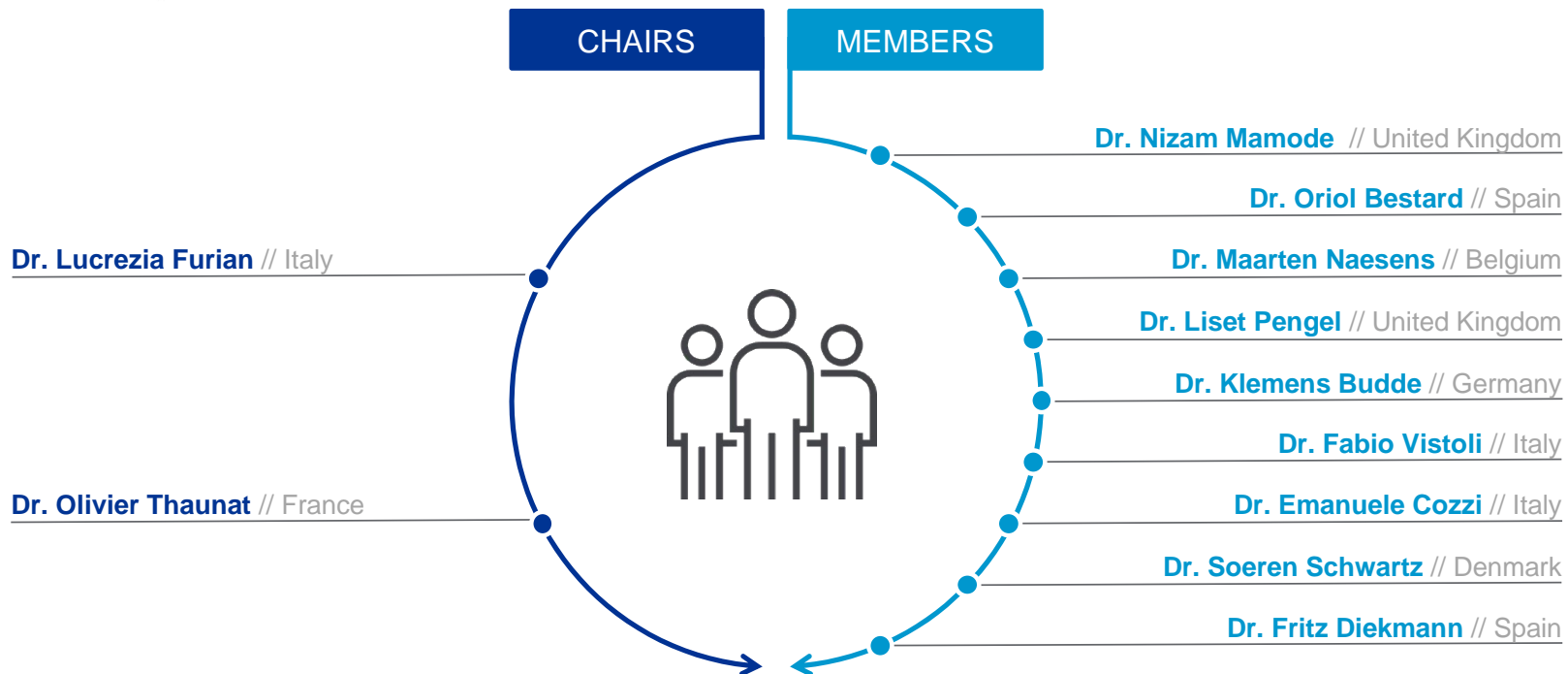
ESOT

Leading the way
in transplantation



ENGAGE
CONSENSUS

A PROJECT BY THE EUROPEAN SOCIETY FOR ORGAN TRANSPLANTATION (ESOT)



HUMORAL RISK

RISK CATEGORIES & MANAGEMENT

HUMORAL MEMORY



1. Day-zero DSA with positive CDC

=> Tx impossible. Require desensitization before Tx

2. Day-zero DSA with positive flow and negative CDC

=> Tx possible but very high risk for acute AMR and accelerated chronic AMR. Require adaptation of follow up and maintenance IS

3. Day-zero DSA with negative flow

=> Tx possible with risk for acute AMR, and acceptable medium-term graft survival. Require adaptation of follow up and maintenance IS

4. Absence of day-zero DSA but potential cellular memory against donor HLA

=> Tx possible with risk for AMR increased.

4.a. Probable cellular memory if :

- historical DSA
- pregnancy and/or previous transplant with repeat Ag

4.b. Possible cellular memory if :

- transfusion(s) with no information on blood donors

5 no DSA and no cellular memory

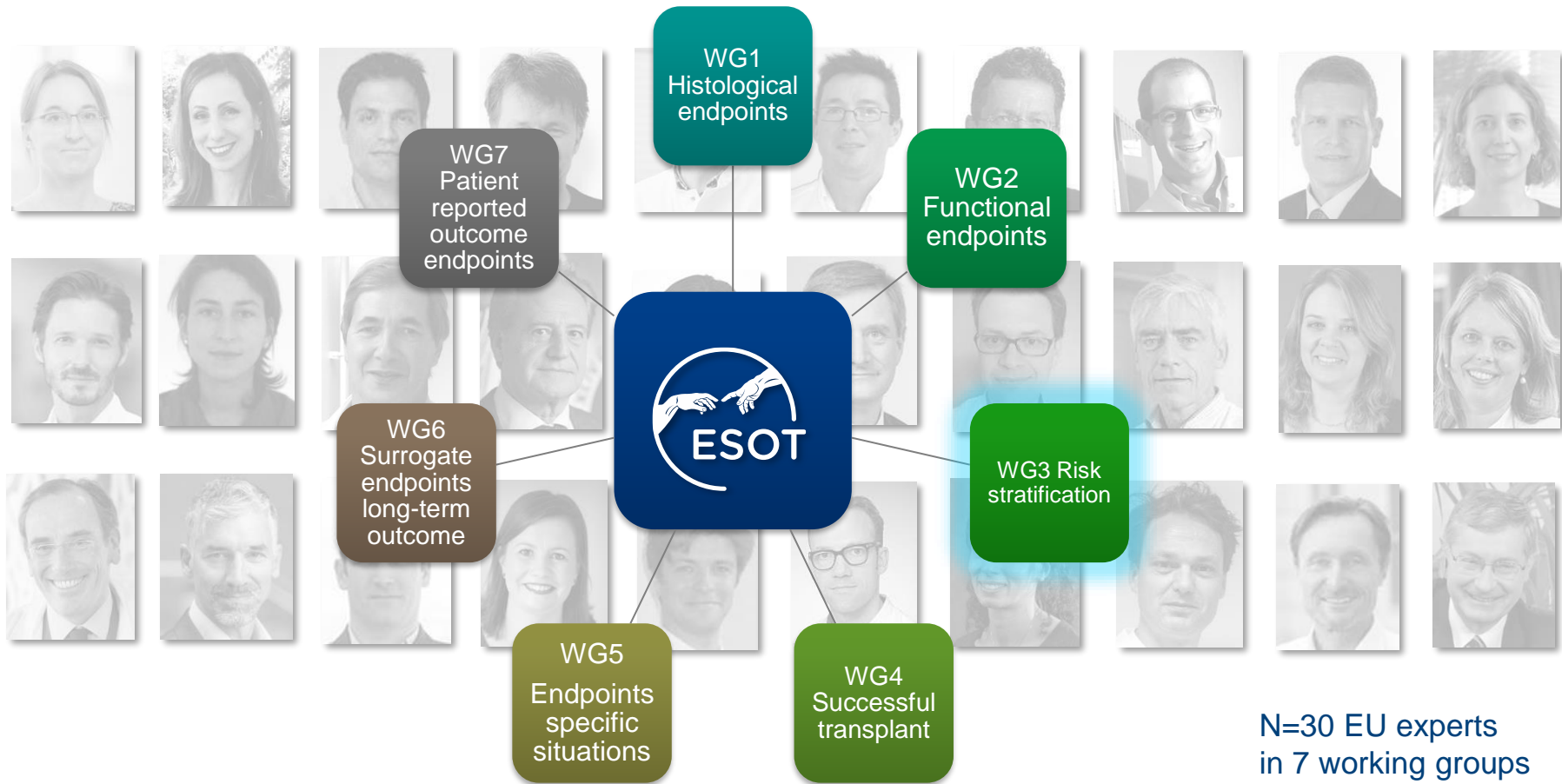
=> Tx possible lower risk for AMR but de novo DSA still possible

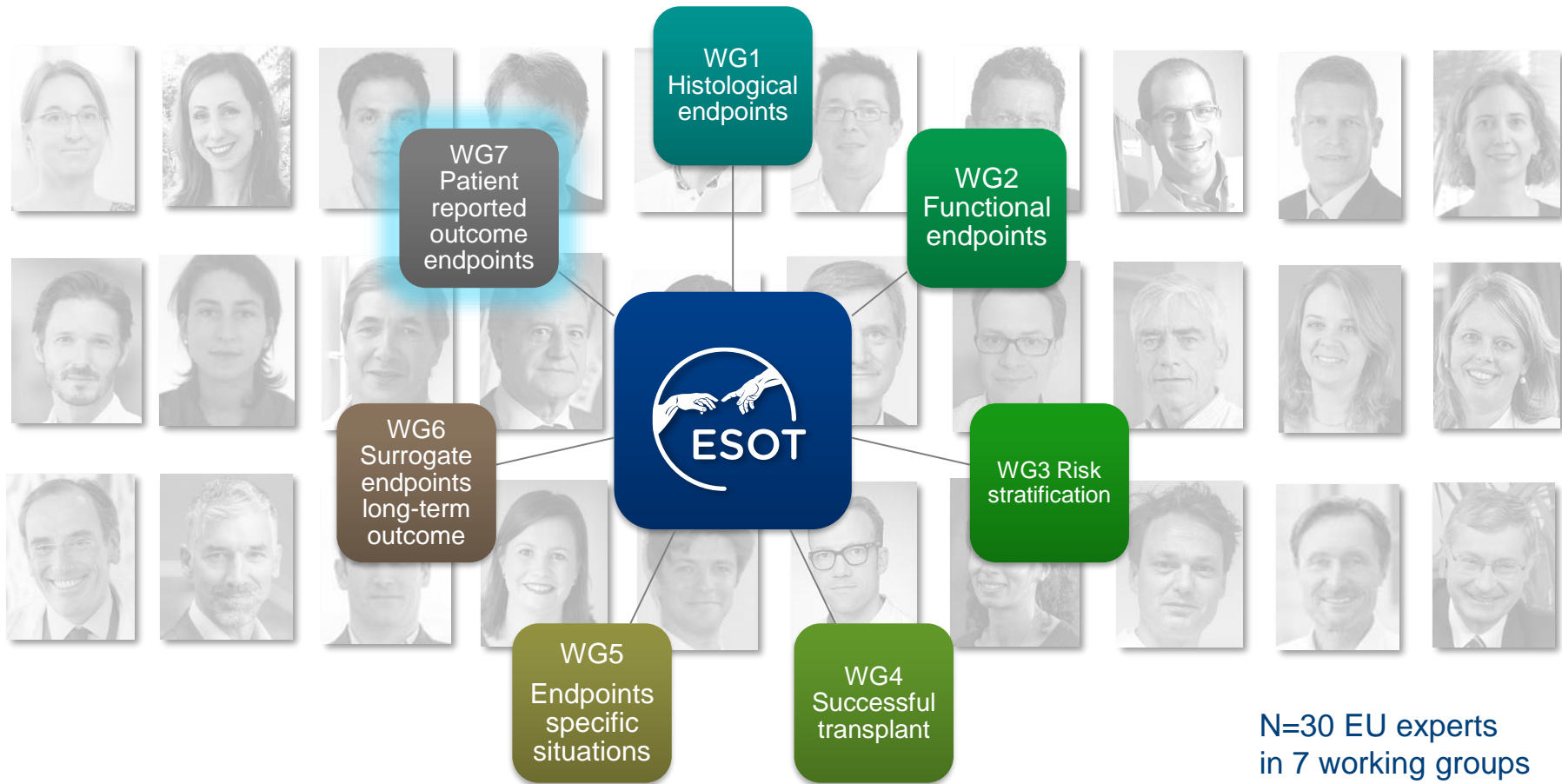
NB: patient with day-zero non DSA HLA antibodies are "good humoral responders" with possible increased risk for subsequent de novo DSA generation

SEROLOGICAL
MEMORY

CELLULAR
MEMORY

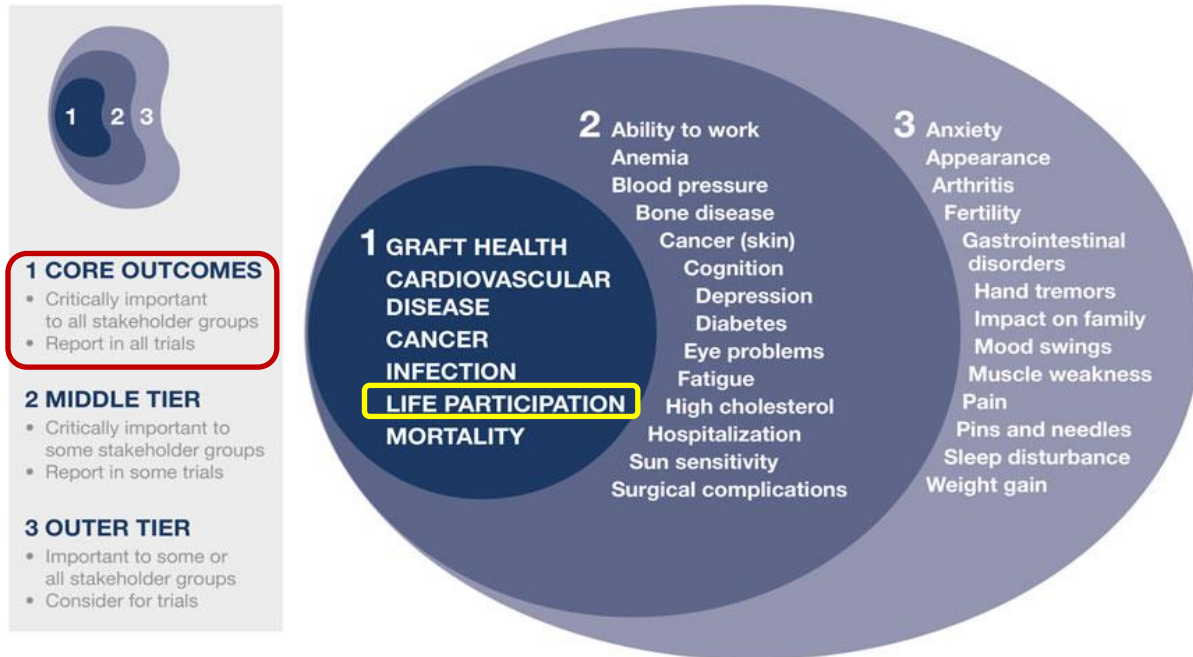
NAIVE





Life participation as a core outcome

Song-Tx initiative: consensus process involving over 1100 patients, caregivers and HCPs from 79 countries (participating in nominal group technique, an international Delphi survey and consensus workshops)



Definition and measurement of life participation

= *‘the ability to participate in activities that give patients a sense of fulfilment, enjoyment, control and hope in their lives’*

SONG-Tx Life Participation Core Outcome Measure

Please respond to each item by marking one box per row.
During the past month...

	Never	Rarely	Sometimes	Usually	Always	N/A
I could do my leisure activities e.g. exercise, hobbies, travel	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/>
I could do my family activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/>
I could do my work e.g. job, housework, study	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/>
I could do my social activities with friends/others	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/>

- Prefer not to specify different activities, so that they can interpret life participation based on their own context, priorities and values
- PROM derived from the PROMIS SF V2.0 item set, which has robust psychometric properties
- Items rephrased based on input from patients & caregivers
- Currently undergoing validation in kidney Tx

Does EMA (CHMP) agree with the proposed PROs as endpoints for use in clinical trials of kidney transplantation interventions?

EMA/CHMP's response

- CHMP agrees that these PROs are important to capture the patient's perception
- CHMP agrees that other PROMs might be needed than those typically being used (e.g. SF-36, SIP, etc)
- Need for validated instruments to measure life participation + determination of minimally important difference



Patient-reported Outcomes as Endpoints in Clinical Trials of Kidney Tx Interventions

- Guidelines for inclusion of PROs in clinical trial protocols: **SPIRIT-PRO**
- Reporting of PROs in randomized trials: **CONSORT-PRO**

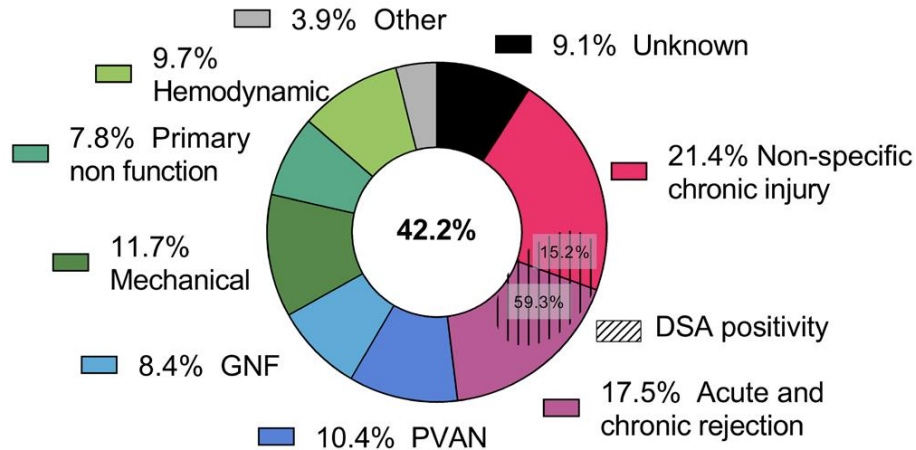
The elephant in the room



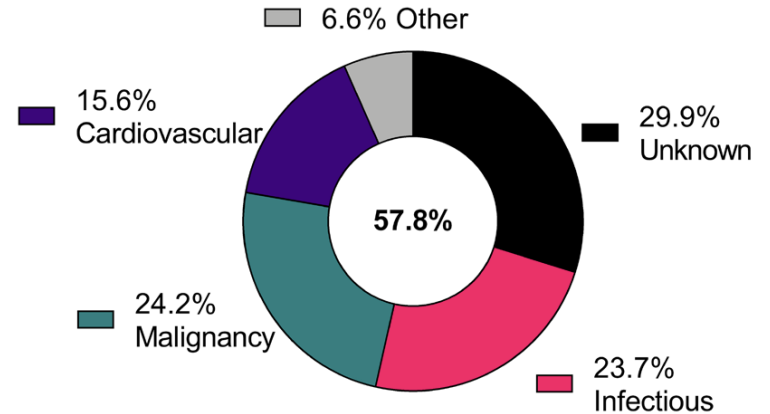
In higher risk populations, patient mortality is more frequent than graft failure

N=1000 pts transplanted 2004-2013

Causes of graft failure (N=154)



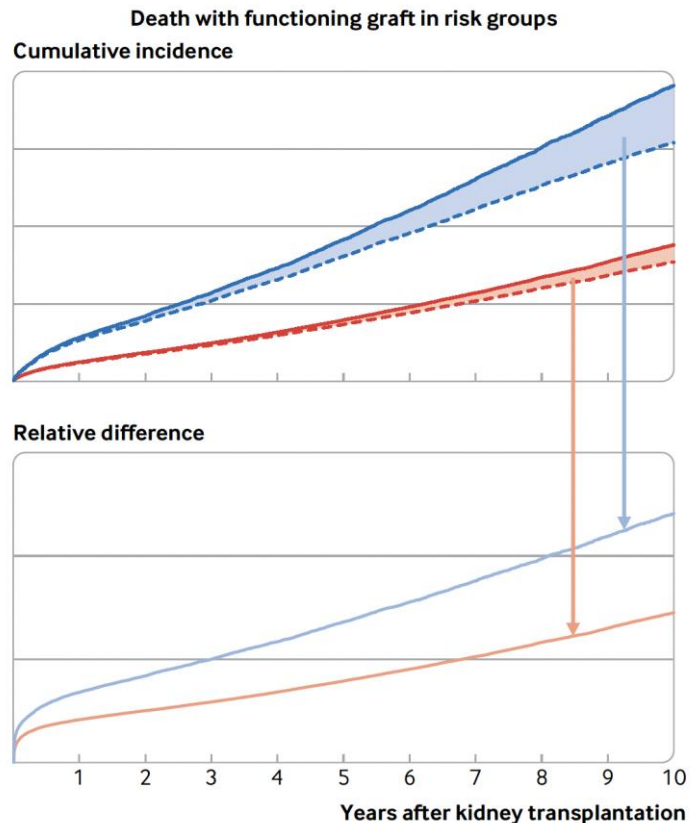
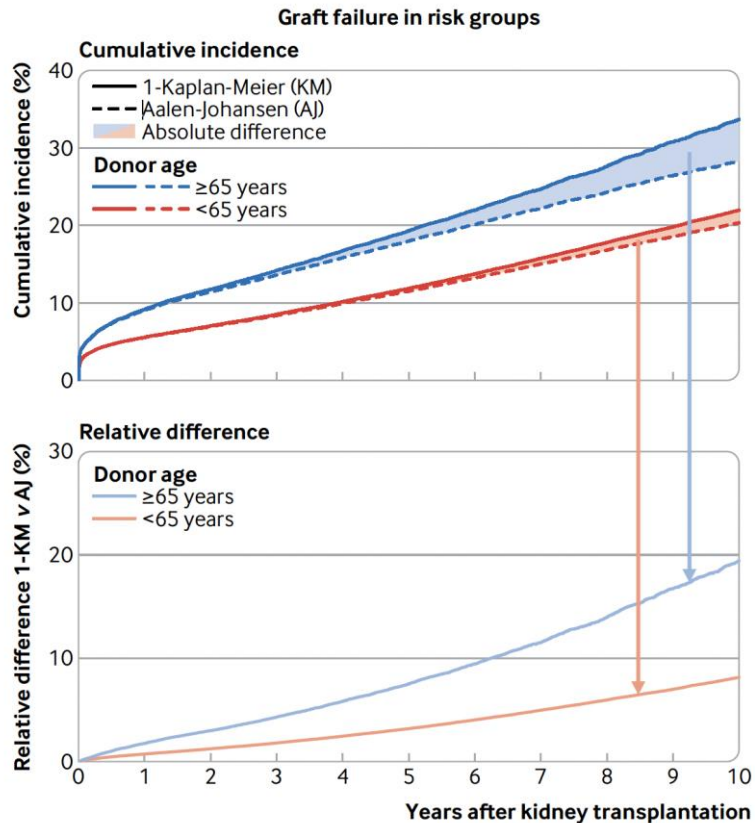
Causes of death with a functioning graft (N=211)



Patient survival is ill studied in transplantation

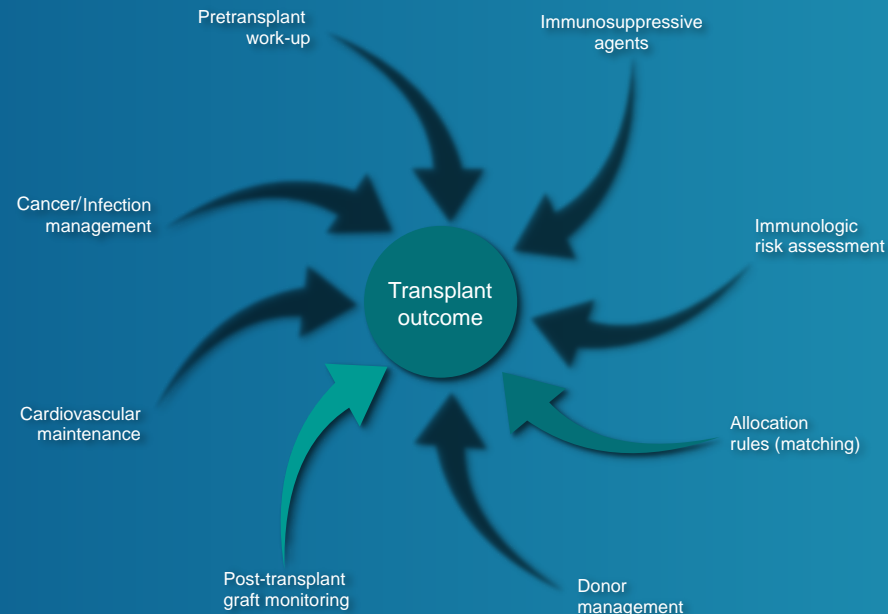
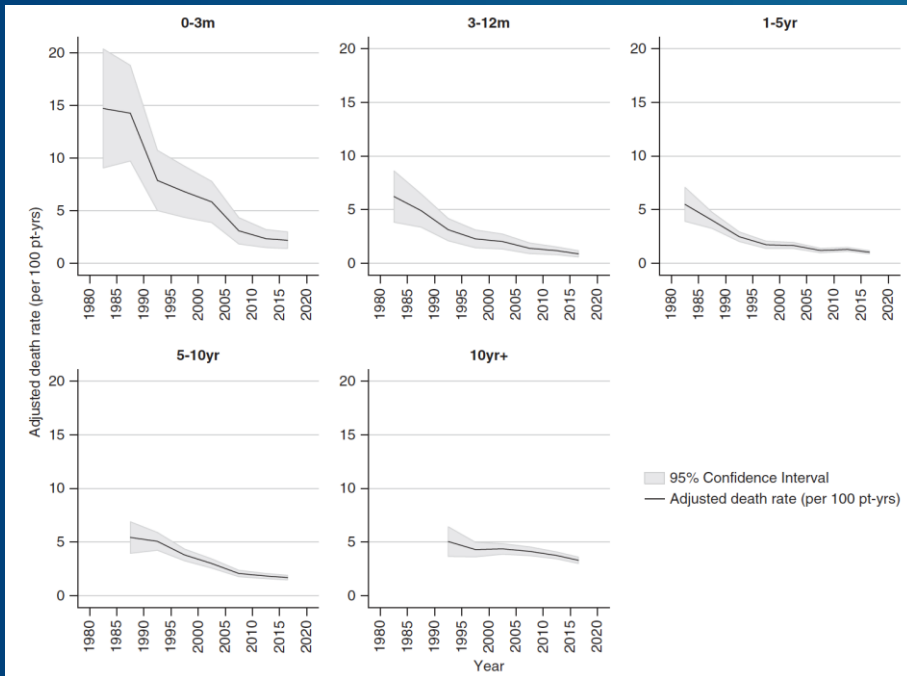
Countries	# of patients on dialysis for ESKD	Number of KTR/ year	Population in millions	KTR/ Million	Patient Survival (%) after LD transplant at years			Patient Survival (%) after DD transplant at years			Graft Survival (%) after LD transplant at years			Graft Survival (%) after DD transplant at years		
					3	5	10	3	5	10	3	5	10	3	5	10
Belgium	8,333	360	11.7	31	100	98	95	93	89	73	96	94	85	94	92	84
Brazil	150,000	6200	212	29	96	94	84	88	84	74	90	85	73	79	71	55
Canada	29,835	1,281	38.2	34	97	95	89	93	89	74	94	90	77	88	80	56
Finland	1,903	275	5.5	50	98	97	90	93	87	70	96	93	83	89	82	63
France	50,501	3,252	67.8	48	98	95	88	92	86	70	94	89	76	83	76	56
India*	175,000	9,500	1,417	7	na	73	67	na	na	na	90	83	75	85	83	70
Italy	46,500	2,000	59	34	98	99	92	95	93	86	96	93	86	91	88	78
Japan	347,671	1,700	125	14	98	97	92	94	91	82	96	93	83	90	86	72
Norway	1,700	250	5.3	47	96	94	83	90	82	60	94	88	73	87	78	52
S Korea	123,122	2,200	51.4	43	98	96	91	93	90	83	na	na	na	na	na	na
Spain**	65,740	3,400	48	71	97	96	90	91	86	72	91	86	72	76	65	55
Singapore	8,268	72	4.1	18	98	96	89	95	92	81	96	94	77	96	86	68
UK	29,500	3,500	67	52	96	94	86	93	90	76	95	84	71	90	77	51
USA	786,000	25,499	332	76	96	93	81	93	86	67	95	88	70	89	78	54
					86%			74%			77%			62%		

Censoring for death in endpoint predictions is not accurate



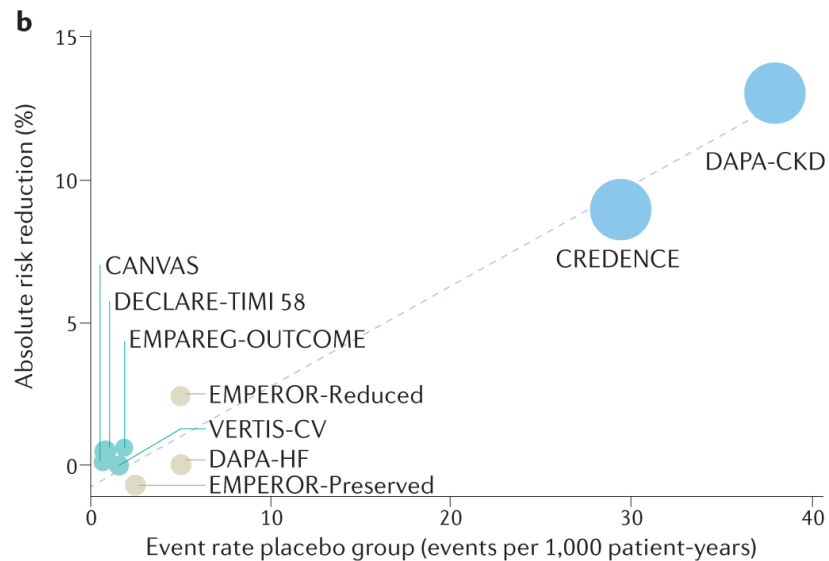
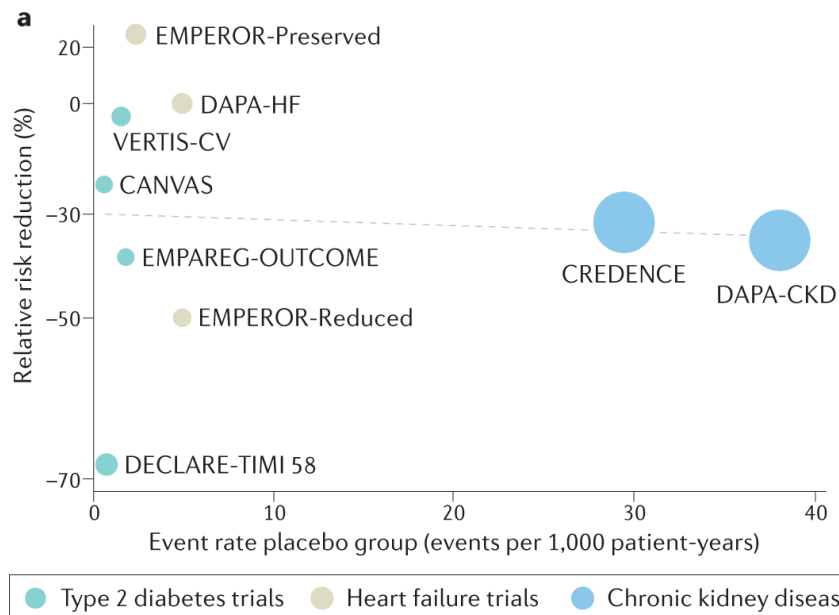
Kidney transplantation - a quiet revolution

Patient death

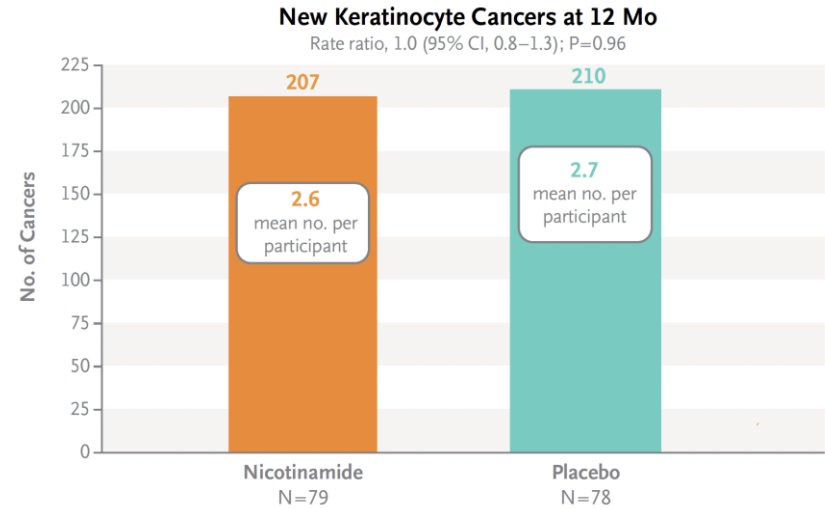
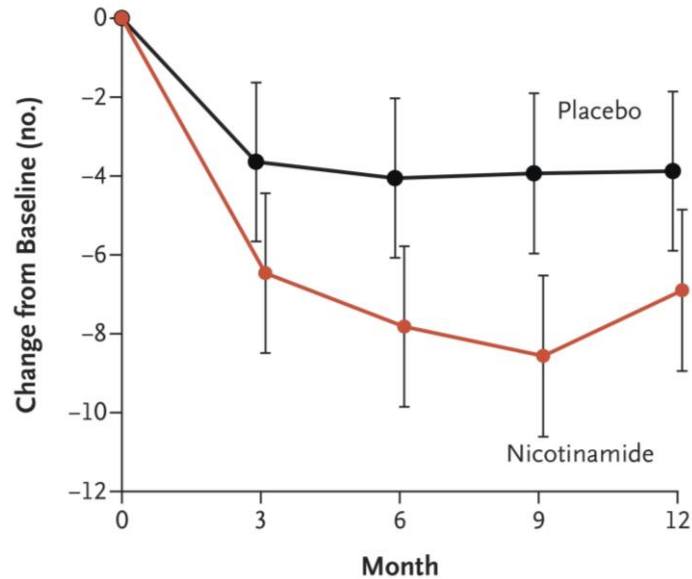


SGLT2 inhibitors in transplantation

Effect of SGLT2 inhibitors on kidney failure.



Studies specific for other outcomes after transplantation



Conclusion



Surrogate
endpoints



eGFR
evolution



Risk
stratification



Patient-reported
outcomes



Mortality

Thank you!



**NEPHROLOGY
LEUVEN**