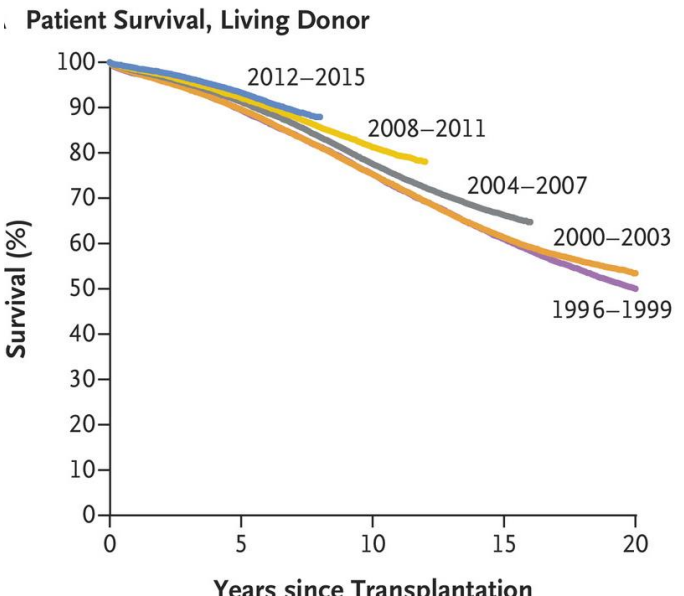
# How the use of new *surrogate* outcomes may improve transplantation results?

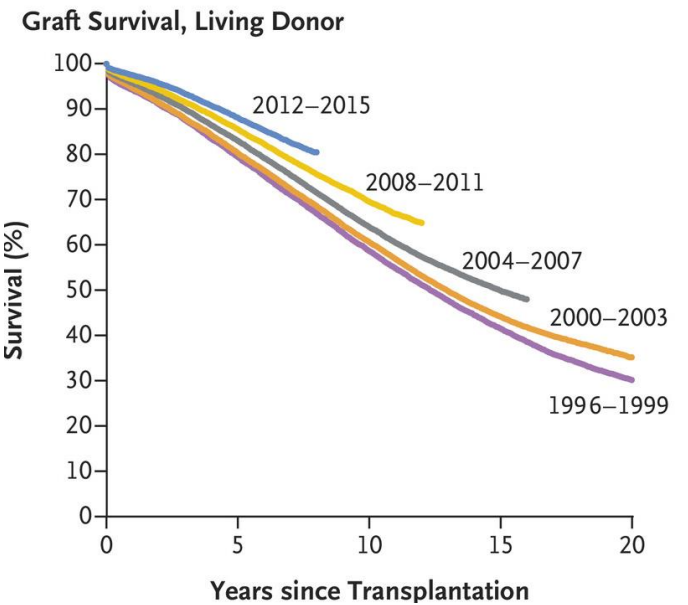
Maarten Naesens

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

KU LEUVEN

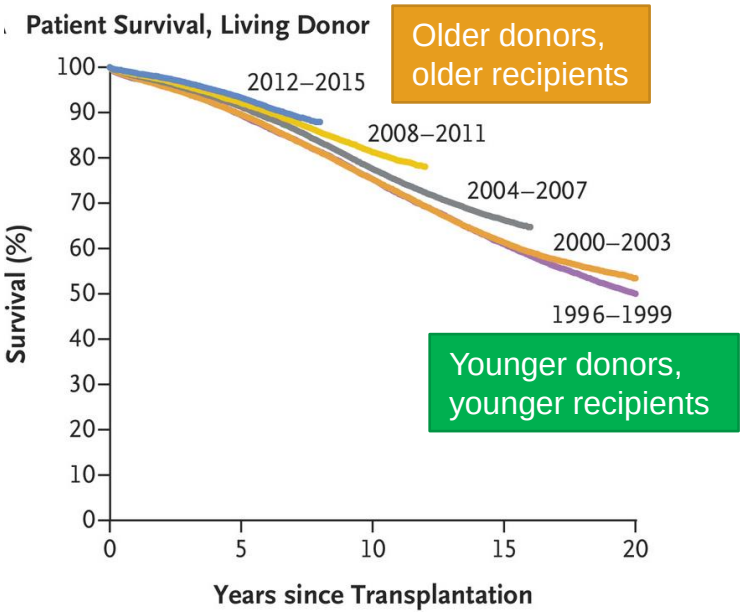
# The improvement in outcomes after kidney transplantation over the past 25 years seems to be rather modest

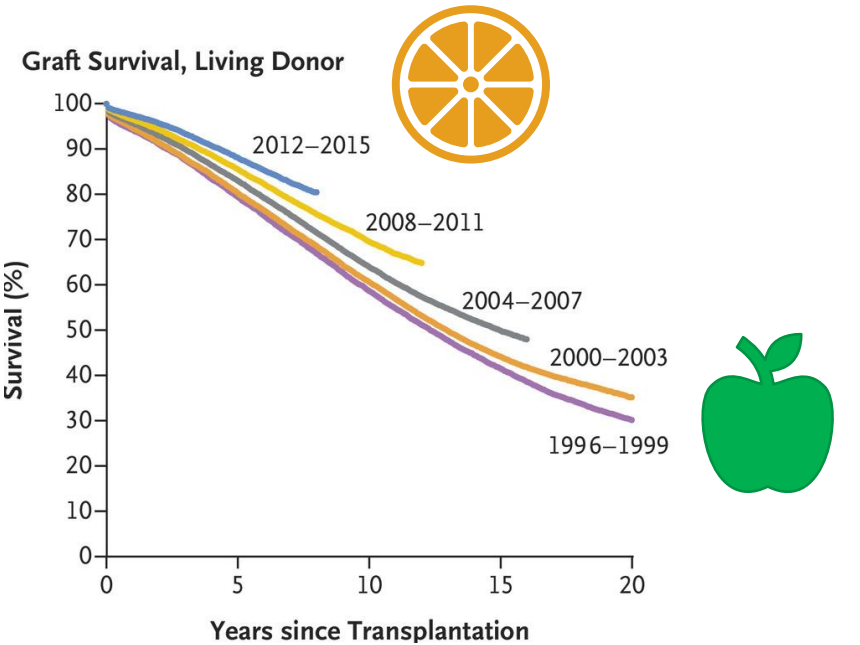



Hariharan et al. NEJM 2021

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

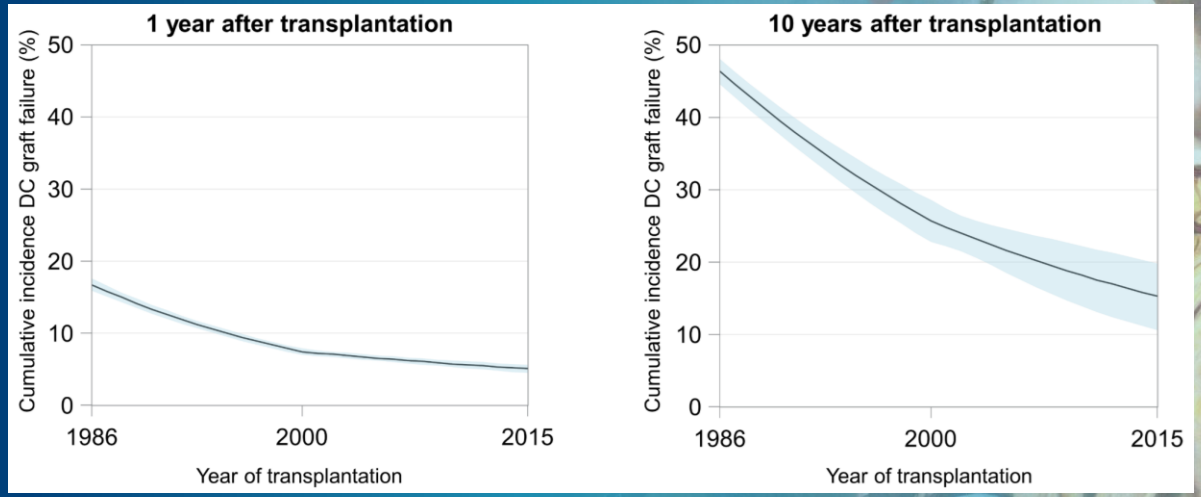



Hariharan et al. NEJM 2021

# Kidney transplantation - a quiet revolution

## Graft failure

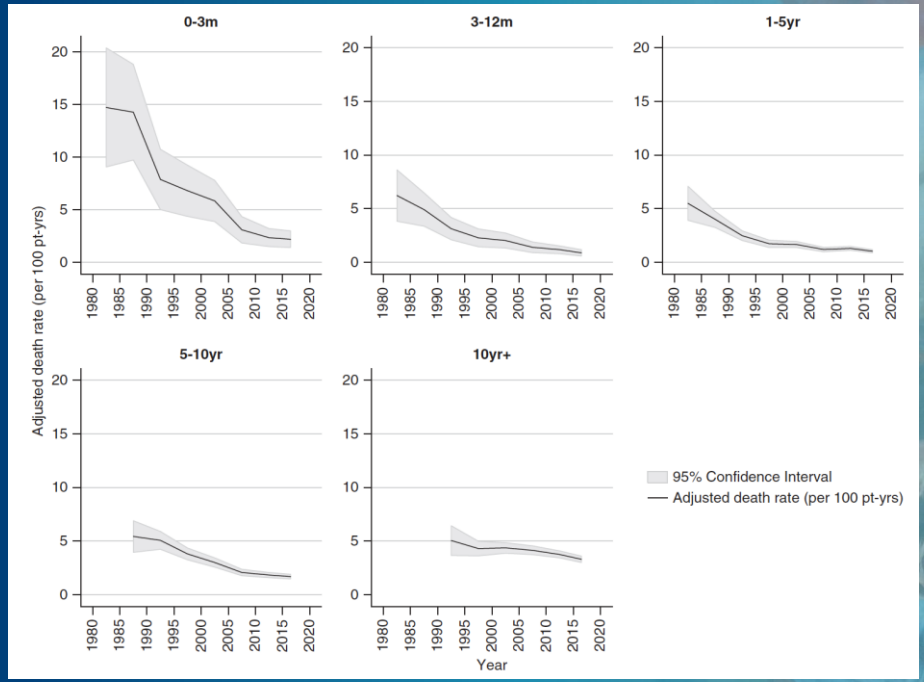



Coemans, Callemeyn, Naesens. N Engl J Med, 2022
Coemans et al Kidney Int 2018

E .Delacroix, 1830

# Kidney transplantation - a quiet revolution

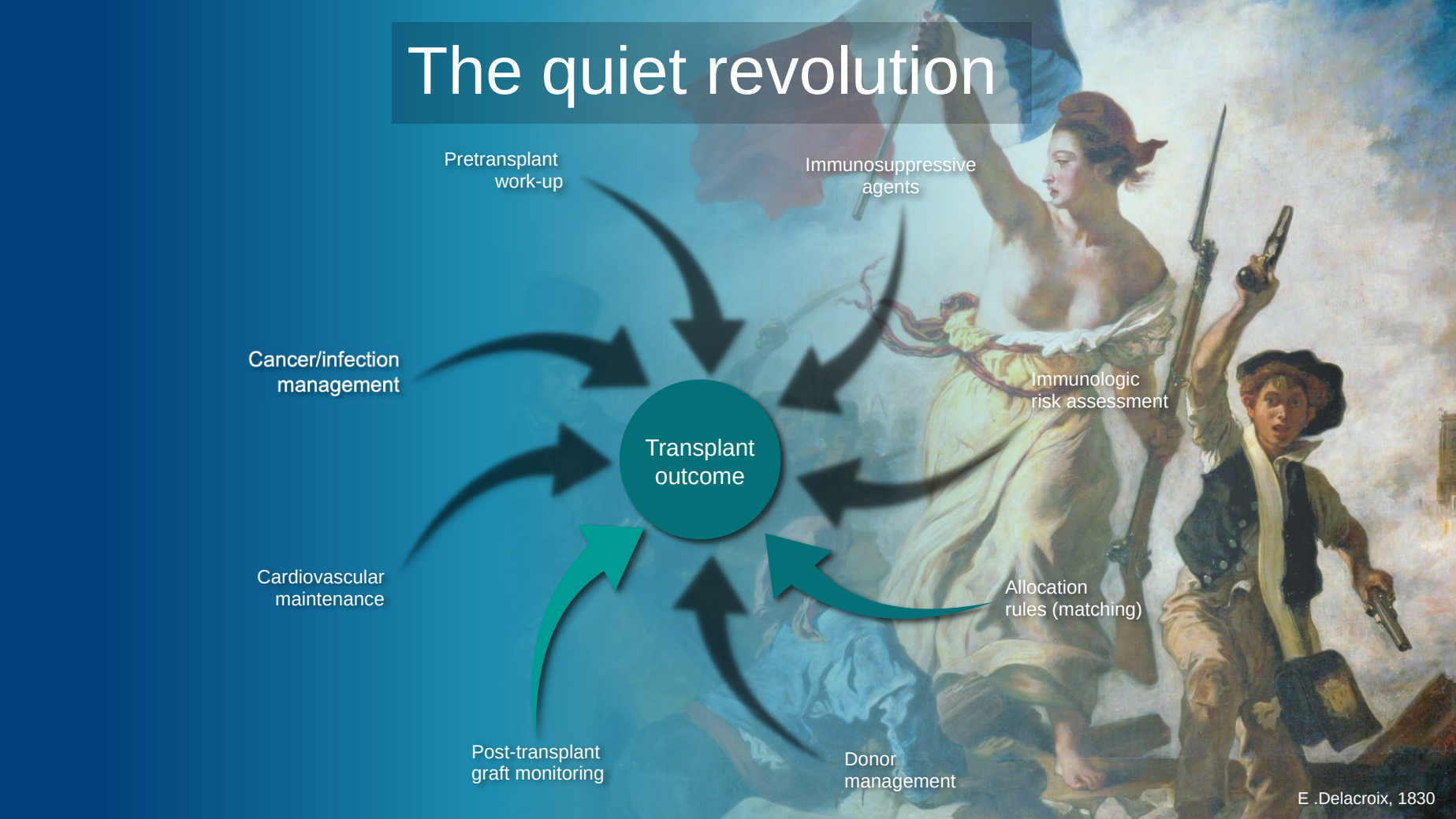
## **Patient death**




Ying et al J Am Soc Nephrol 2020

E .Delacroix, 1830

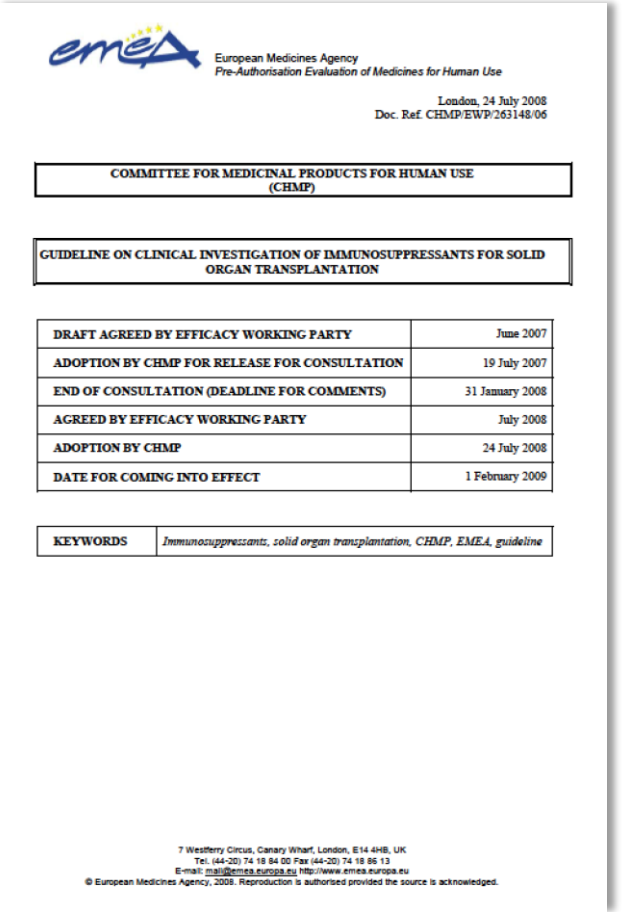
# The quiet revolution



# 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 | = | = | = | ↑ | ↑ |

Naesens & Thaunat Nat Rev Nephrol 2016



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 | *Immunosuppressants, solid organ transplantation, CHMP, EMEA, guideline* |

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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;*

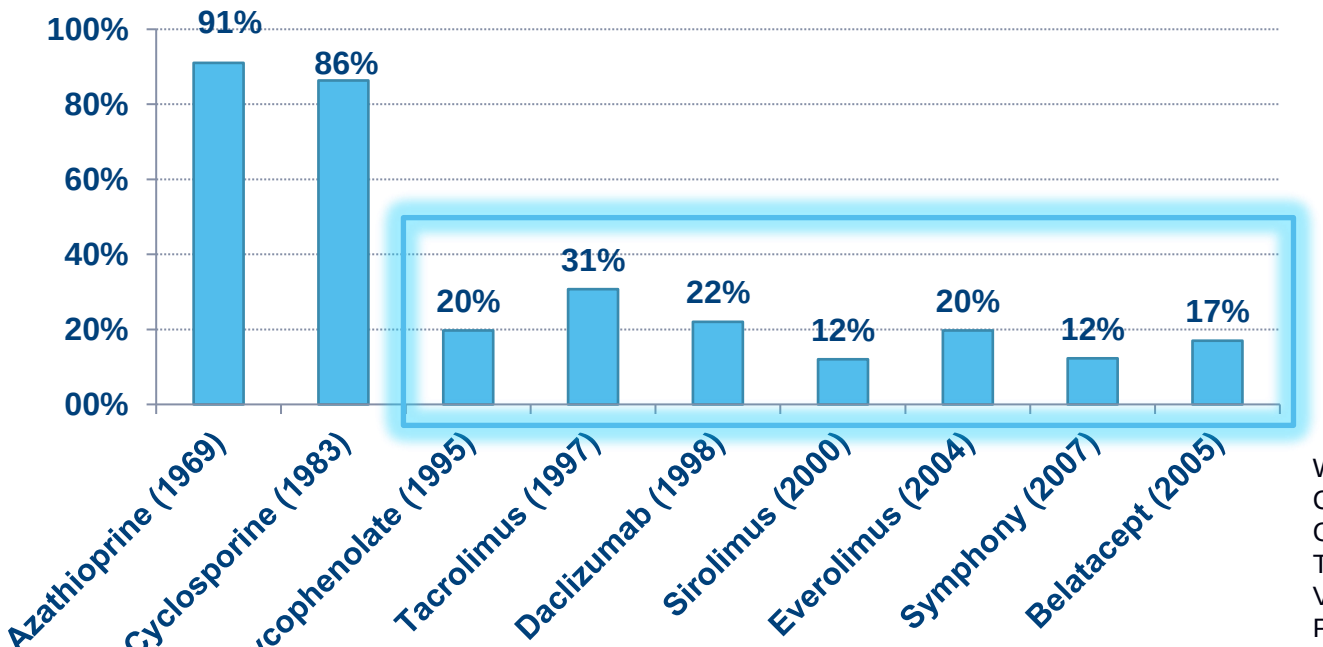
*b) graft failure;*

*c) biopsy confirmed acute rejection;*

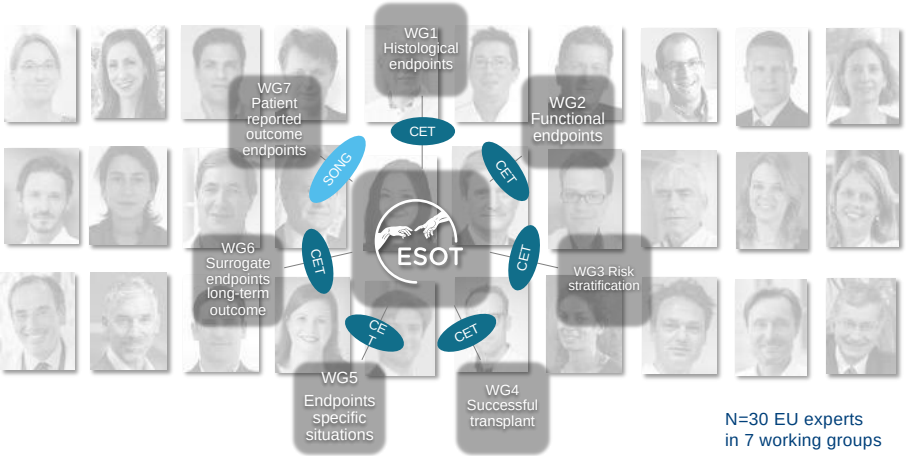
*d) graft (dys)-function"*

CHMP guideline for solid organ transplantation 2008

# 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




N=30 EU experts
in 7 working groups

AST

University of Manitoba

TCMR WG

Banff Foundation for Allograft Pathology

TTS
Transplantation Society

ESOT
Leading the way in transplantation

**BIOPHARMACEUTICAL INDUSTRY**

- Bristol-Myers Squibb
- CareDx
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- Natera
- Novartis
- Sanofi
- Takeda
- Talaris Therapeutics
- Thermo Fisher Scientific
- Transplant Genomics
- Veloxis

**FOUNDING MEMBERS**

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TRANSPLANT THERAPEUTICS CONSORTIUM
CRITICAL PATH INSTITUTE

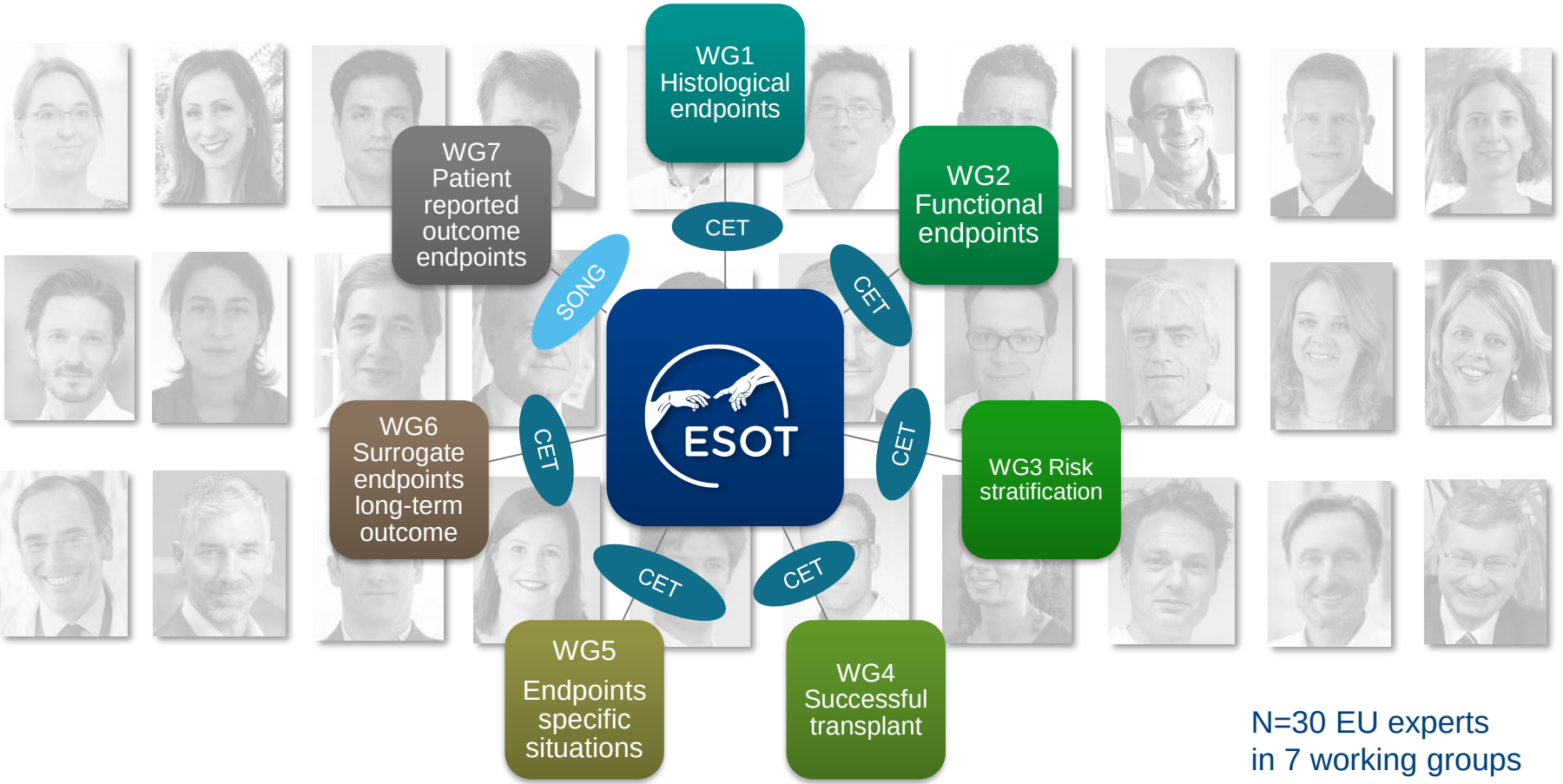
PRE-COMPETITIVE SPACE

Established in 2017

- FDA
- The Transplantation Society
- NIH

# BANFF FOUNDATION FOR ALLOGRAFT PATHOLOGY

## Surrogate endpoints WG




N=30 EU experts
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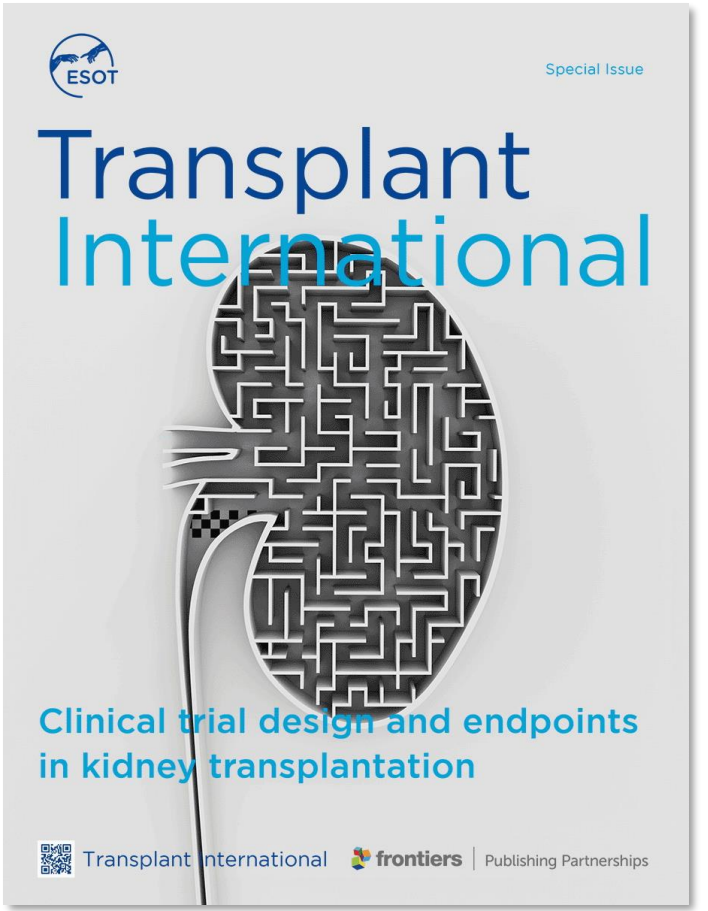
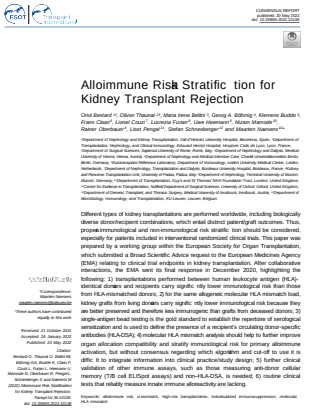
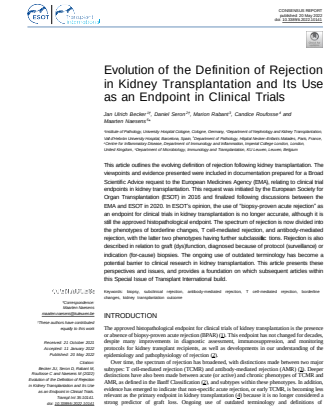
# ESOT meets EMA



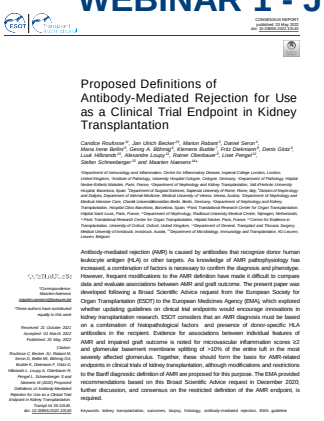


CONSENSUS REPORT

Alloimmune Risk Stratification for Kidney Transplant Rejection

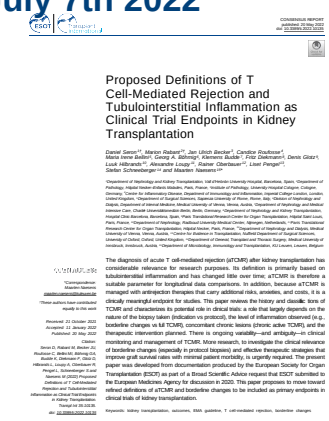

CONSENSUS REPORT

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

## WEBINAR 1 - July 7th 2022

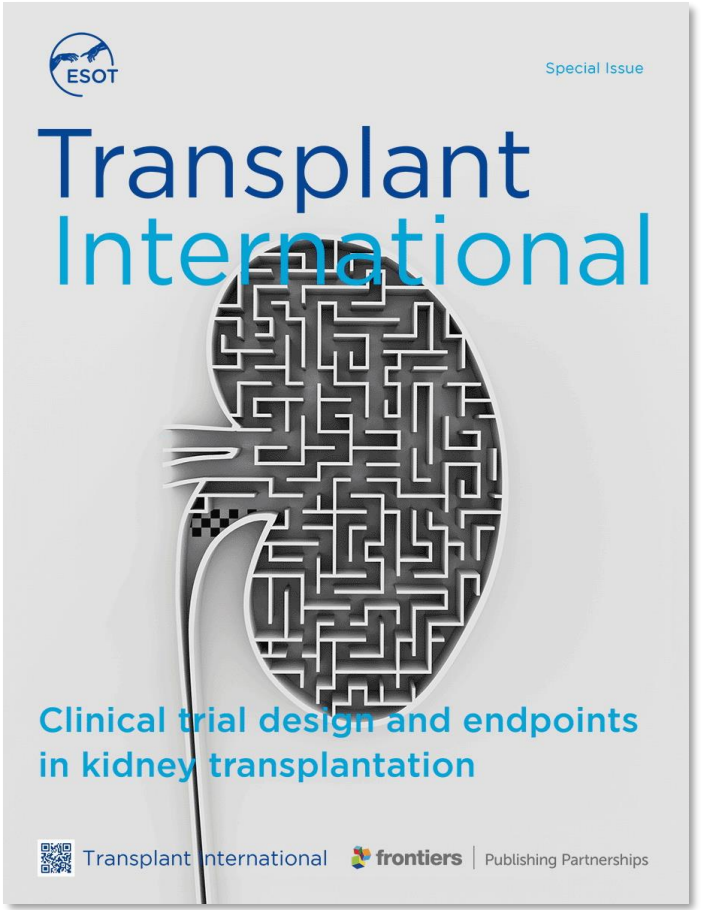

CONSENSUS REPORT

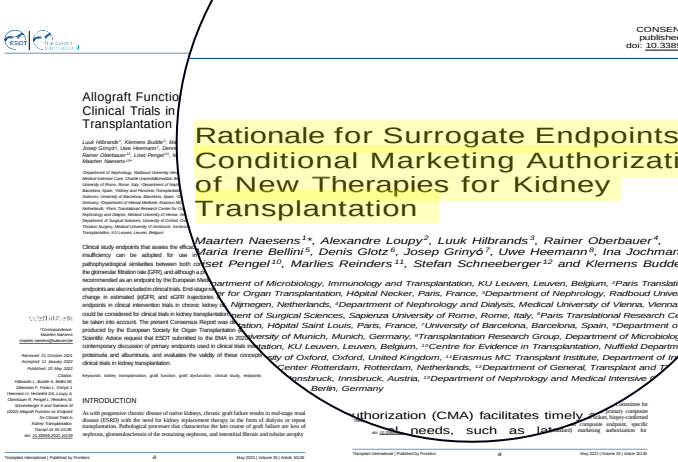
Proposed Definitions of Antibody-Mediated Rejection for Use as a Clinical Trial Endpoint in Kidney Transplantation


CONSENSUS REPORT

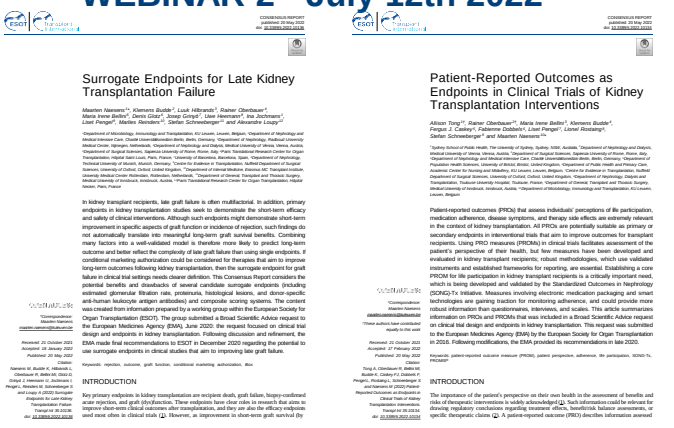
Proposed Definitions of T Cell-Mediated Rejection and Tubulointerstitial Inflammation as Clinical Trial Endpoints in Kidney Transplantation

go.esot.org/ti_ema01_txlive



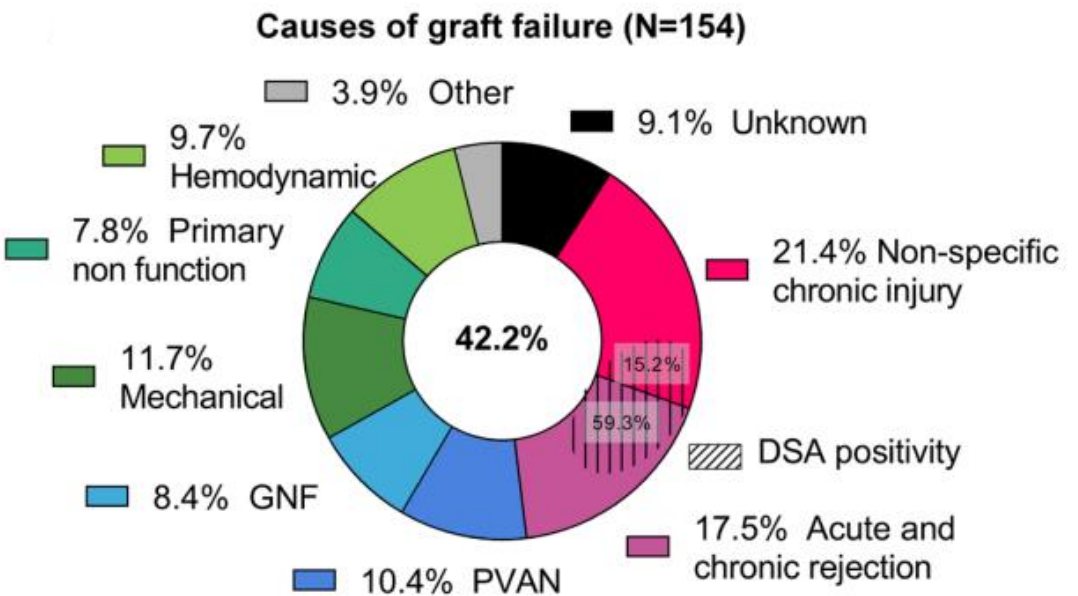




**WEBINAR 2 - July 12th 2022**



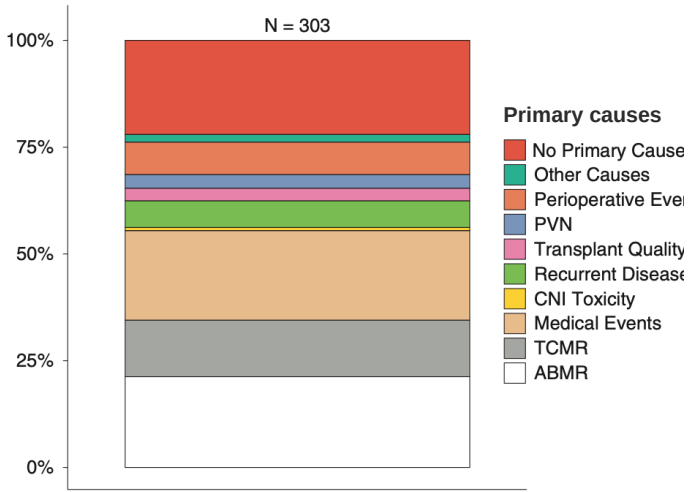

go.esot.org/ti_ema01_txlive

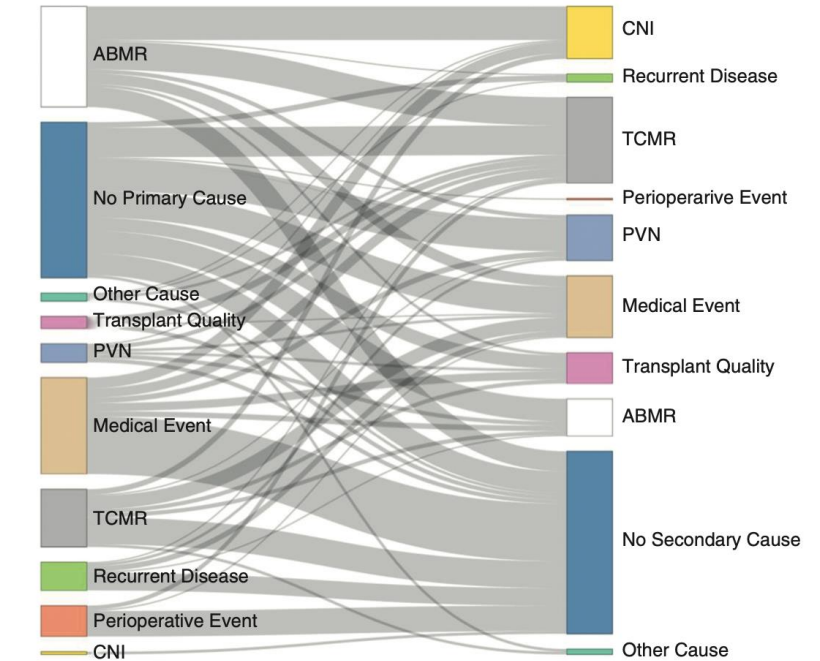
# Further improvement of outcomes can only when we target the actual causes of graft failure




Van Loon et al Transplantation 2020

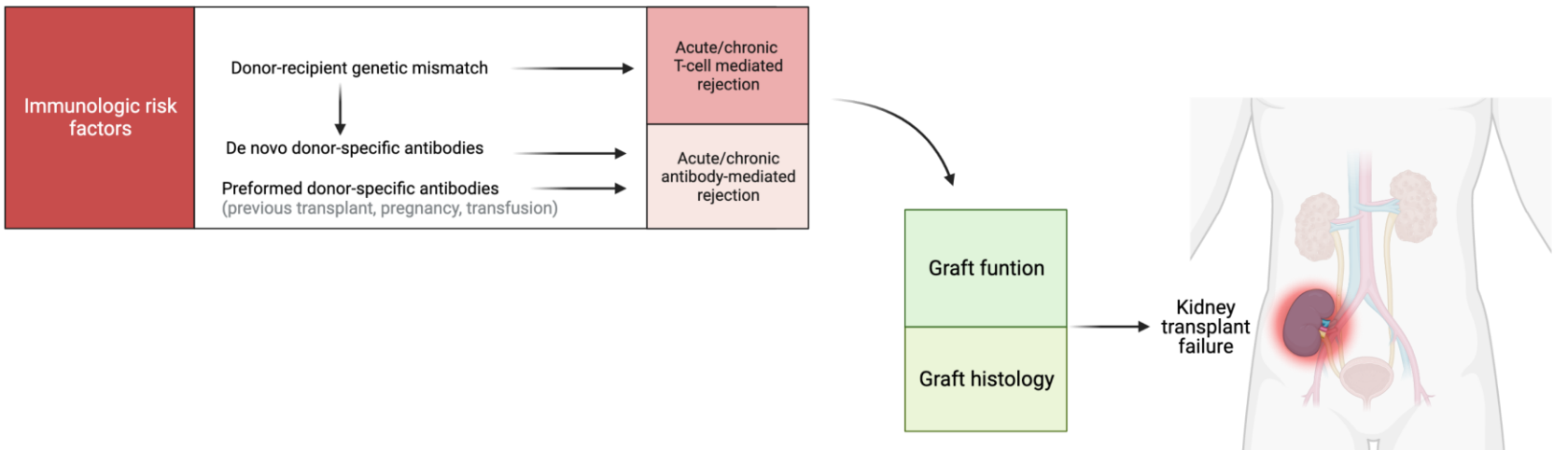
# Graft failure is a complex process with primary and secondary causes




Mayrdorfer et al. JASN 2021

# The multifactorial causes of graft failure




Adapted from Naesens M et al Transplant Int 2022

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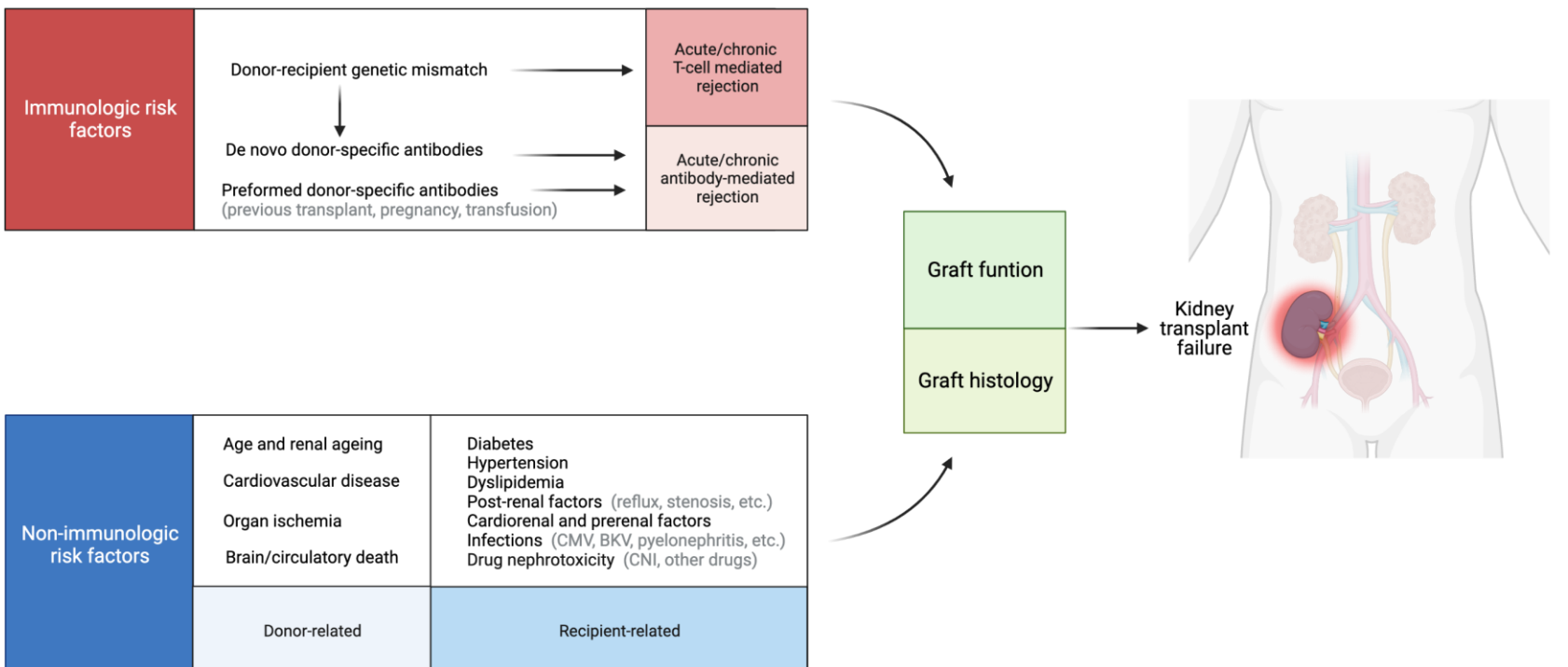


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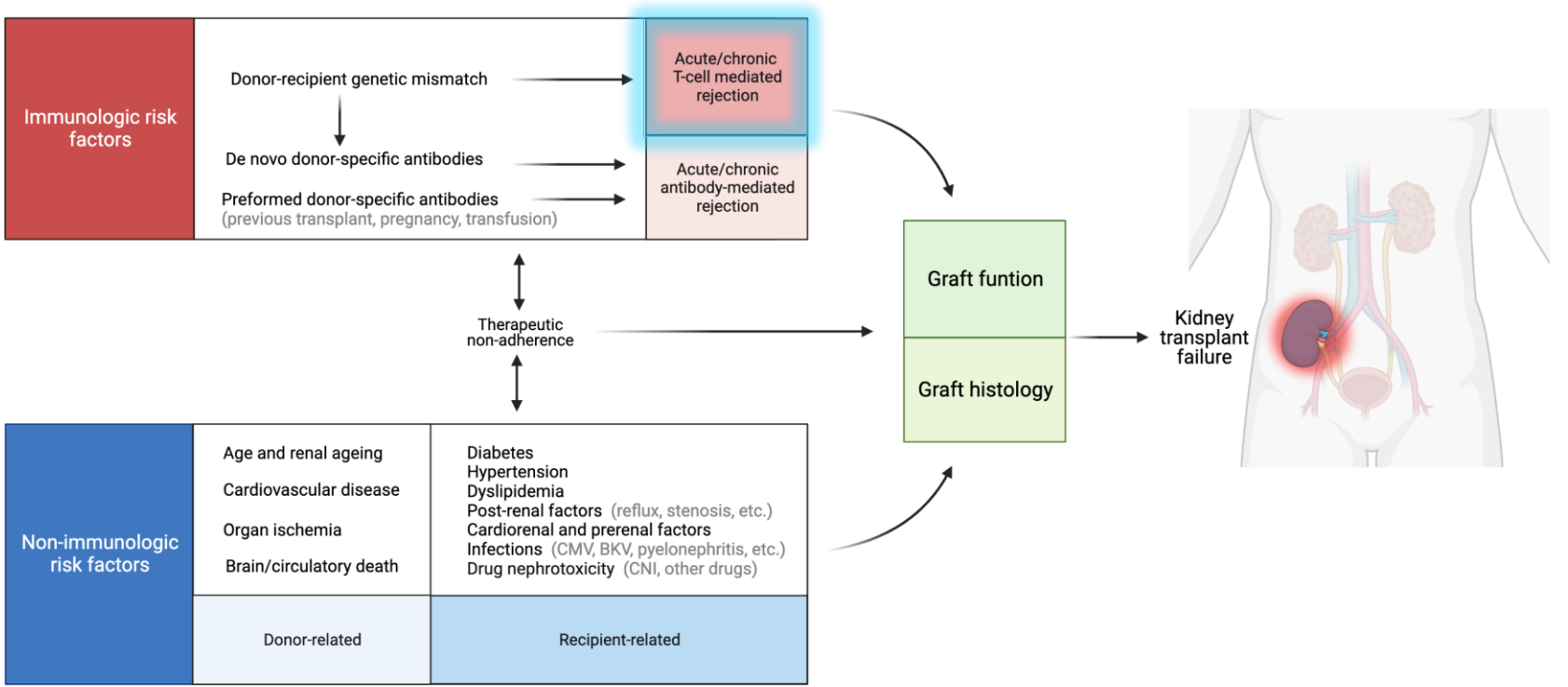
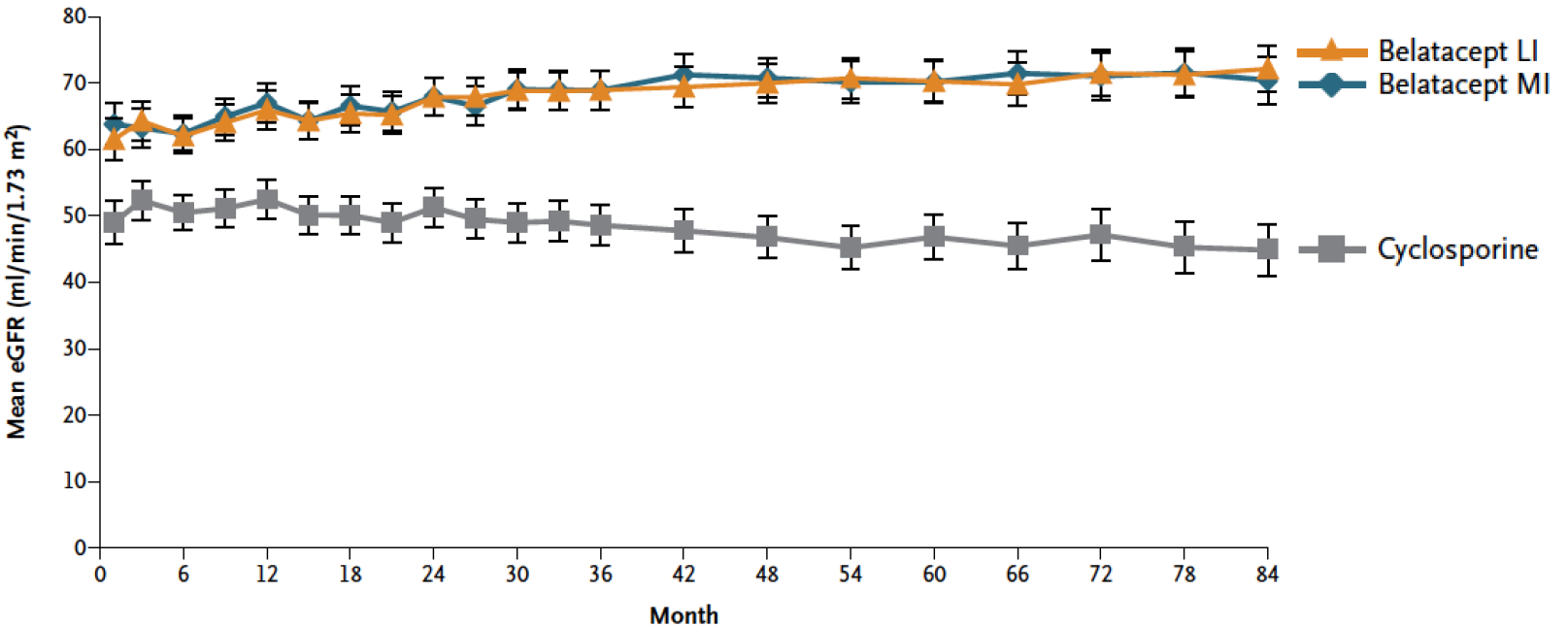
# The multifactorial causes of graft failure



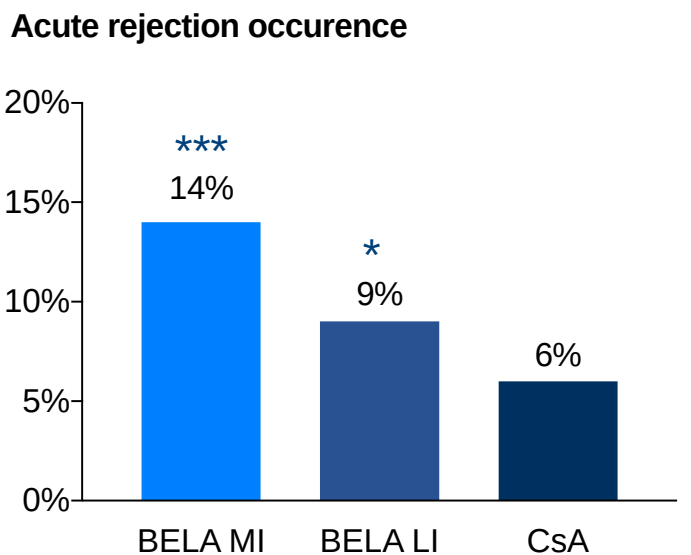

Adapted from Naesens M et al Transplant Int 2022

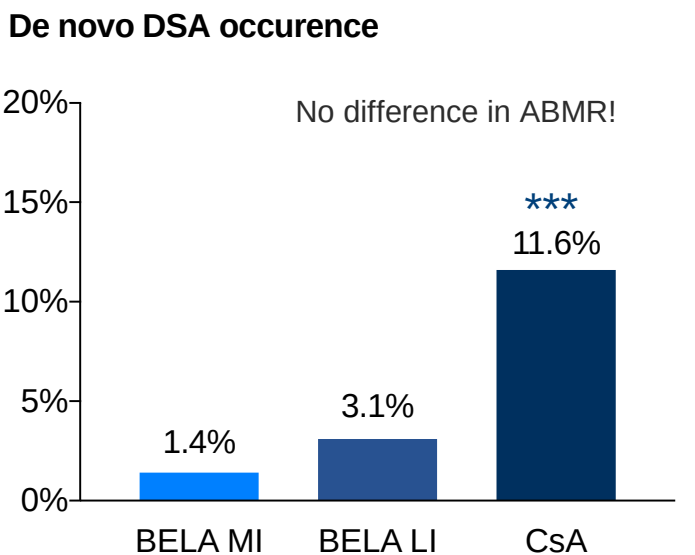
# The BENEFIT study confirms the beneficial effect of belatacept in terms of eGFR




Vincenti F et al. N Eng J Med 2016

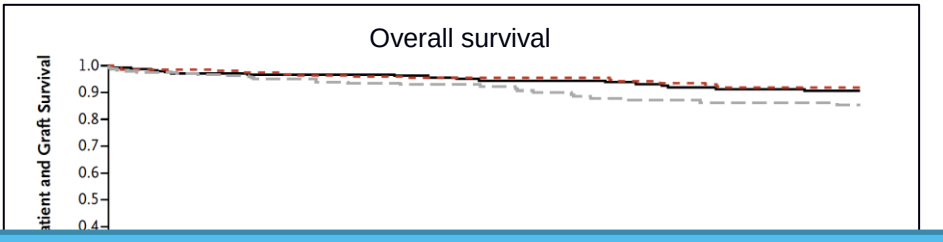
# The rejections in the BENEFIT study were T-cell mediated with low risk of DSA formation




Vincenti F et al. N Eng J Med 2016

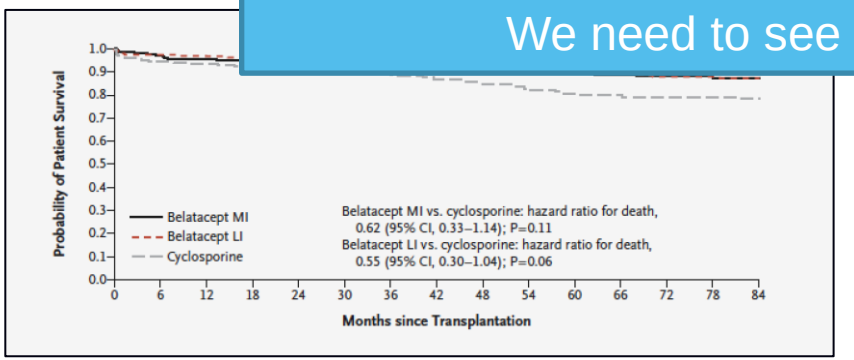
# Belatacept is the first IS agent to show improved **overall** survival since CsA

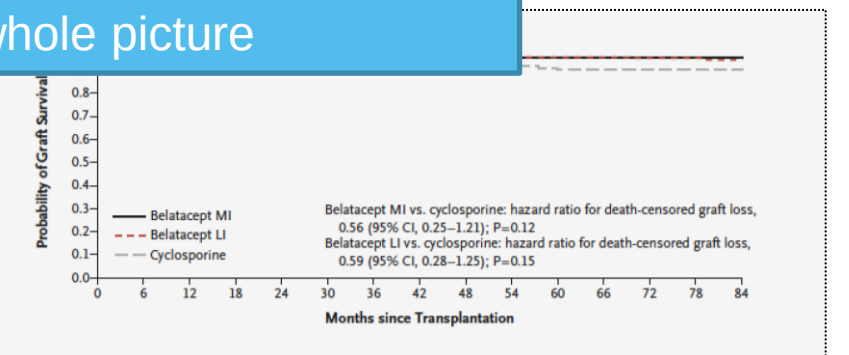



Not all that happens in the first year post-transplantation is directly predictive of outcome (BPAR wasn't!)

–

We need to see the whole picture




Vincenti F et al. N Eng J Med 2016

# We need more realistic and feasible endpoints for future trials

| Currently Approved Endpoints | Limitations |
|---|---|
| Patient/graft survival at **5** or **10** years | • Cost prohibitive |
| Patient/graft survival at **1** year | • Now irrelevant for superiority trials<br>• Good survival is already achieved (~ 95%), making it difficult to show further improvement |
| Acute rejection | • 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

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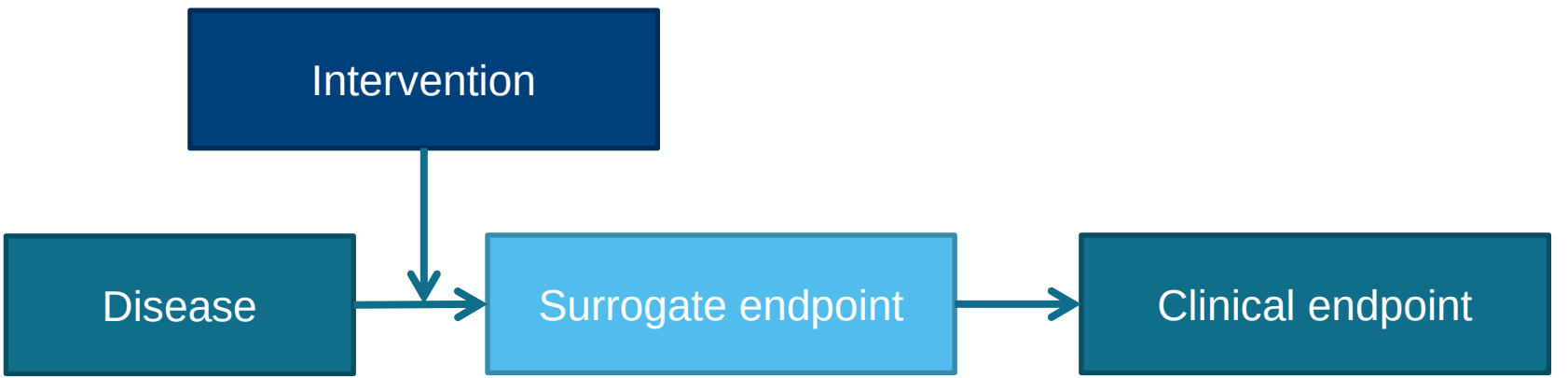
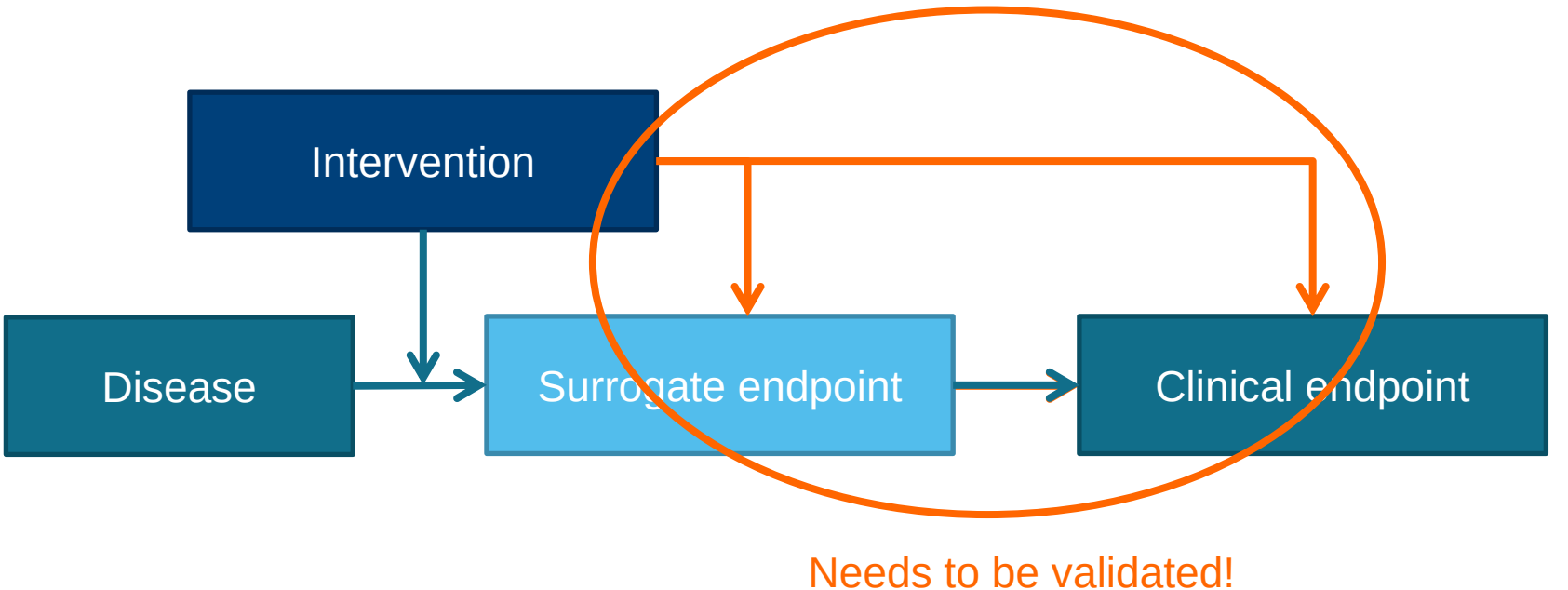
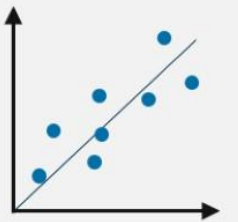


# Towards surrogate endpoints for long-term graft failure

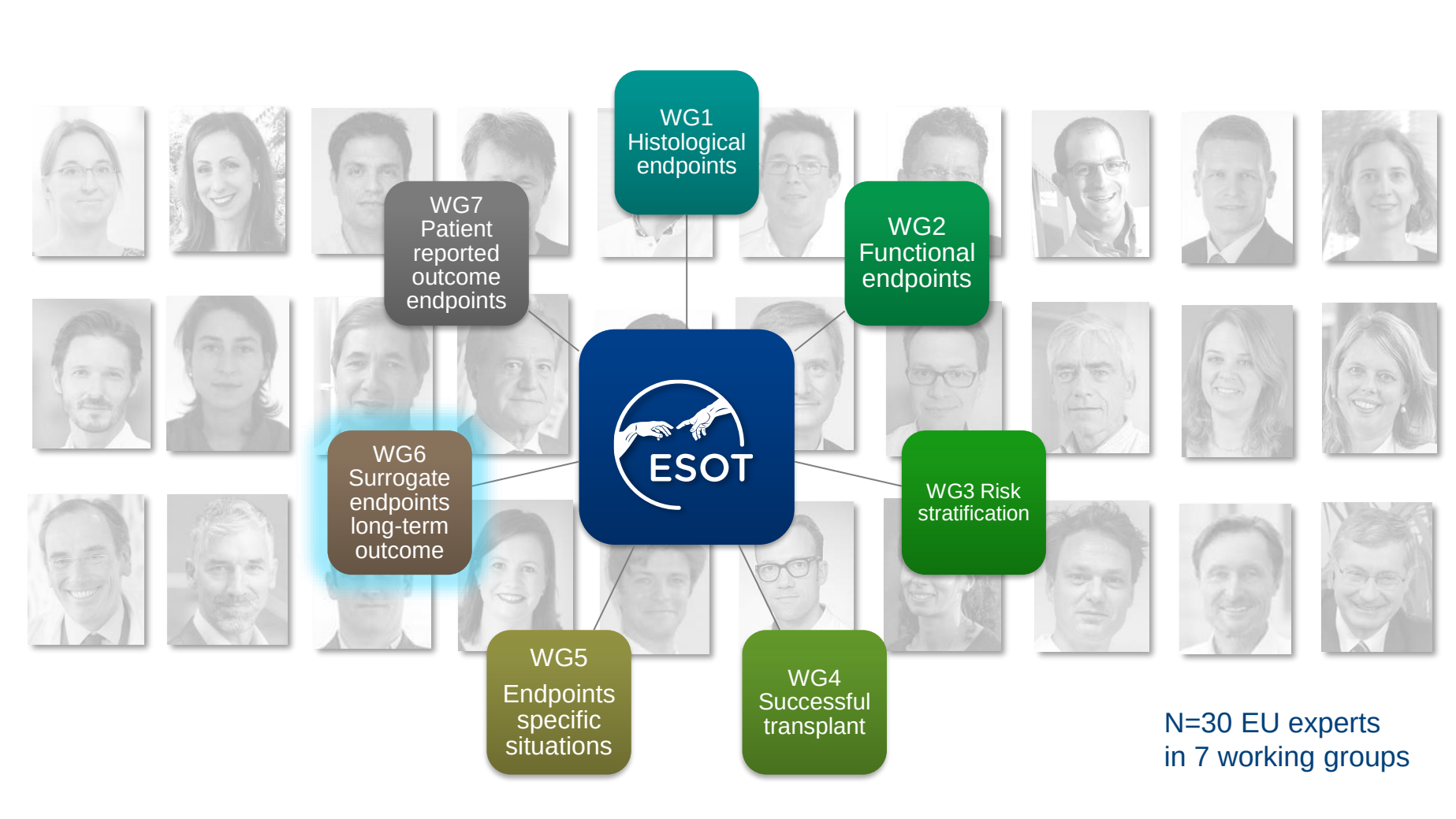


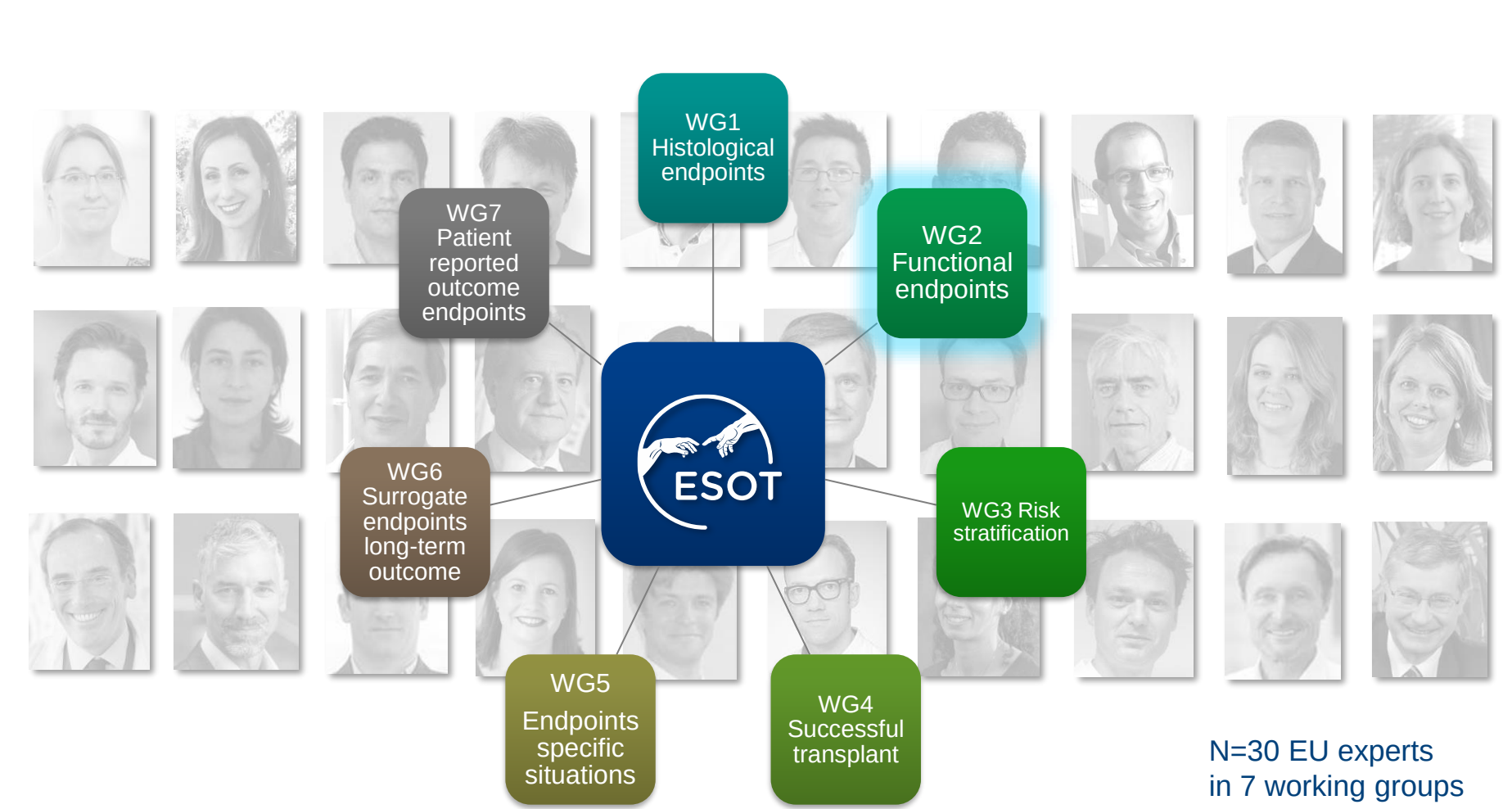
# Surrogate endpoints for clinical trials need to be well validated

| Disease process | Biology of surrogate | Relationship | Treatment |
| --- | --- | --- | --- |
|  |  |  |  |
| **Sufficiently understood** | **Plausible** | **Strong** | **Effect on both clinically meaningful endpoint and surrogate endpoint of choice** |

| | Kasiske et al 2010<br>URDS Risk-Prediction Tool | Foucher et al. 2010<br>Kidney Transplant Failure Score (KTFS) | Moore et al. 2011<br>LOTESS Composite Risk Score | Schnitzler et al. 2012<br>USRDS Predictive Model | Shabir et al. 2014)<br>Birmingham Risk Score | Prémaud et al. 2017<br>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 |
| **Post-transplant factors included in the model** | eGFR at 12 months; hospitalization | Recipient gender; recipient 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 |

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


WG1
Histological endpoints
WG2
Functional endpoints
WG3 Risk stratification
WG4
Successful transplant
WG5
Endpoints specific situations
WG6
Surrogate endpoints long-term outcome
WG7
Patient reported outcome endpoints
ESOT
N=30 EU experts
in 7 working groups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# 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

Hilbrands et al Transplant Int 2022

EMA

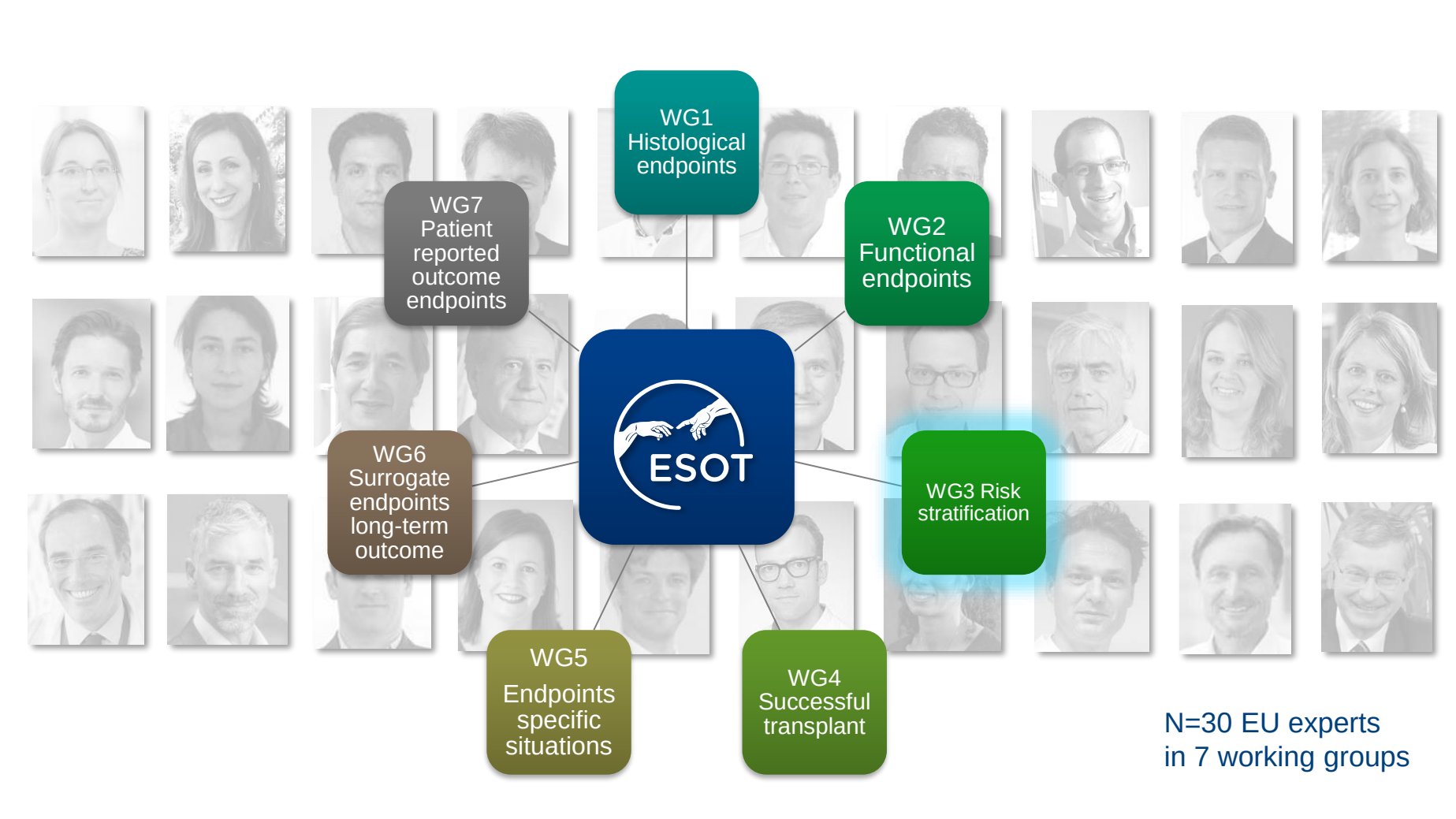
ESOT
Leading the way in transplantation

# 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!

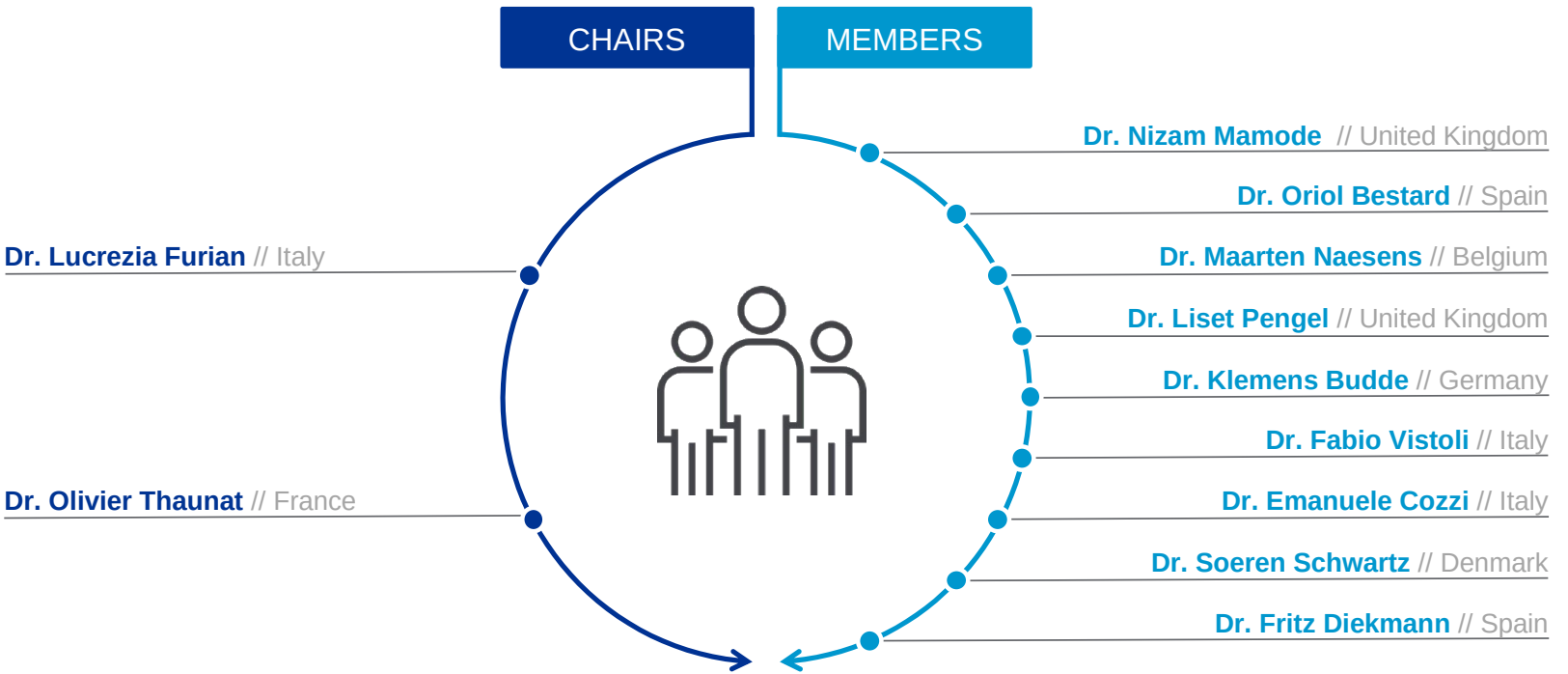
Naesens & Thaunat Nat Rev Nephrol 2016


WG1
Histological endpoints
WG2
Functional endpoints
WG3 Risk stratification
WG4
Successful transplant
WG5
Endpoints specific situations
WG6
Surrogate endpoints long-term outcome
WG7
Patient reported outcome endpoints
ESOT
N=30 EU experts
in 7 working groups

ESOT
Leading the way in transplantation

ENGAGE CONSENSUS

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



HUMORAL RISK

RISK CATEGORIES & MANAGEMENT

**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*

HUMORAL MEMORY

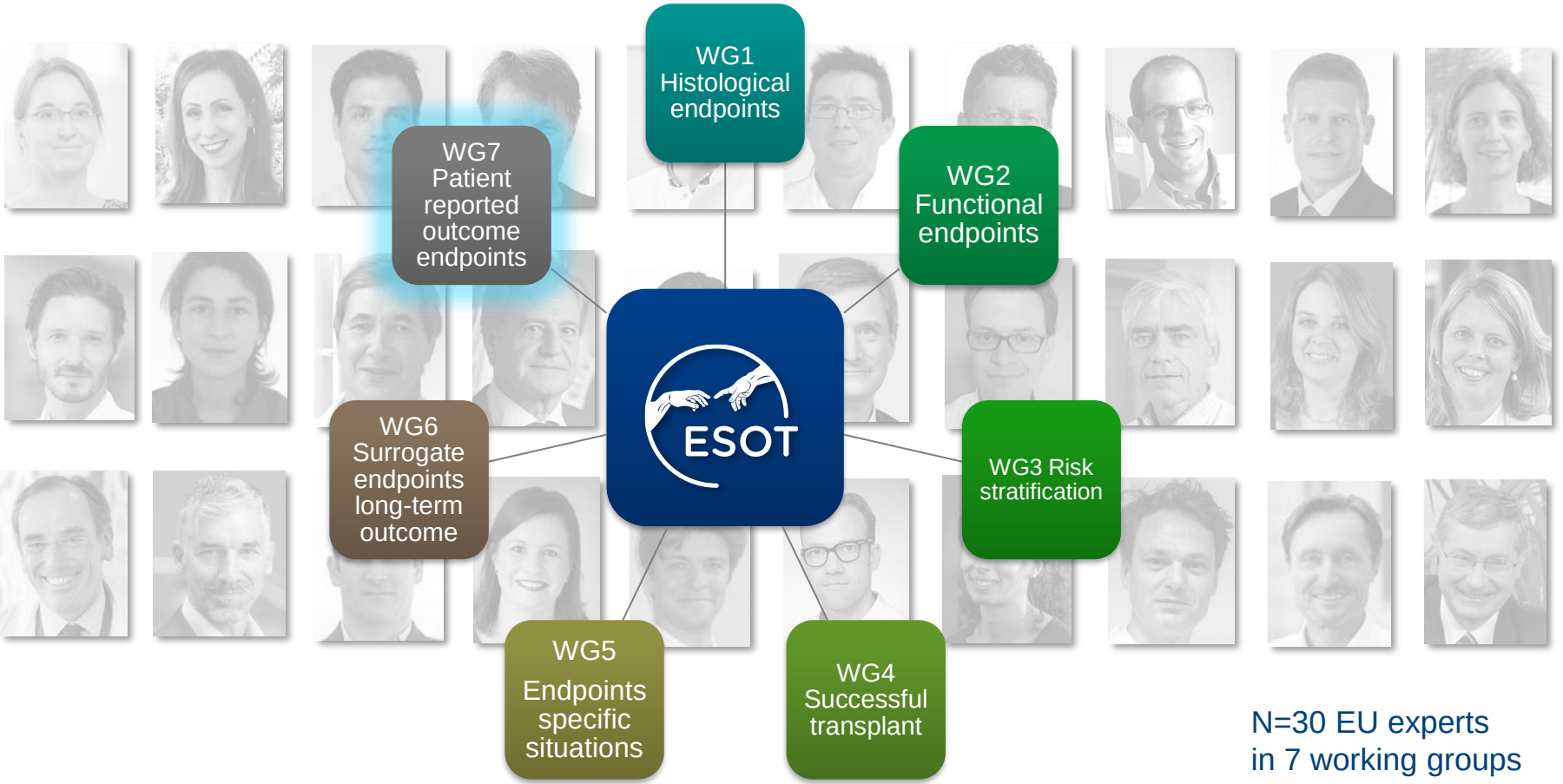
**SEROLOGICAL MEMORY**

**CELLULAR MEMORY**

**NAIVE**

Bestard, Thaunat et al Transplant Int 2021
Bestard, Thaunat et al Transplant Int 2022

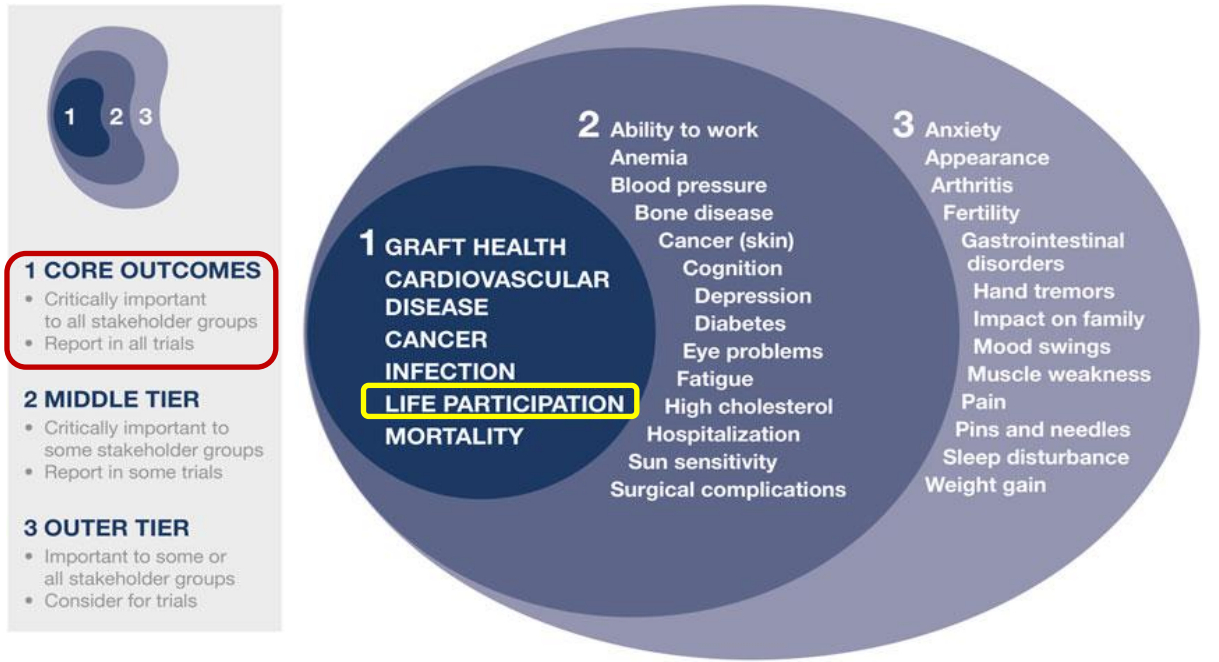
N=30 EU experts
in 7 working groups




N=30 EU experts
in 7 working groups

# 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)




SONG-Tx core outcomes. Reprinted from Tong et al. Kidney Int 2018

# 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 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| I could do my family activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| I could do my work e.g. job, housework, study | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| I could do my social activities with friends/others | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |

- 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

Ju A, et al. Transplantation 2018

# 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**

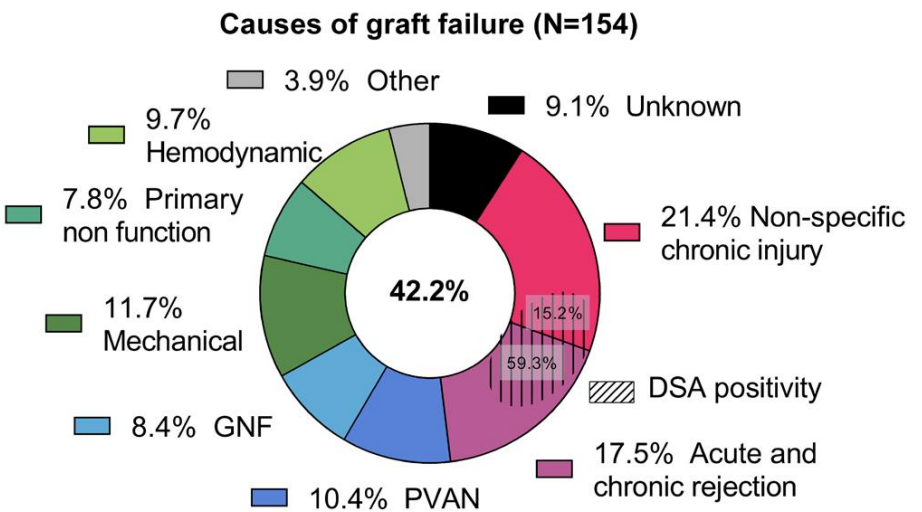
Tong et al. Transpl Int 2022; 35:10134

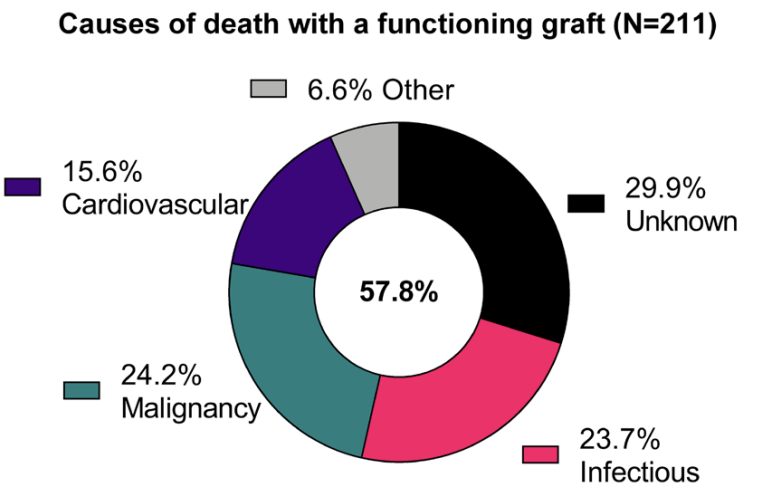
# The elephant in the room

Generated with DALL-E in the style of Dalí

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

**N=1000 pts transplanted 2004-2013**



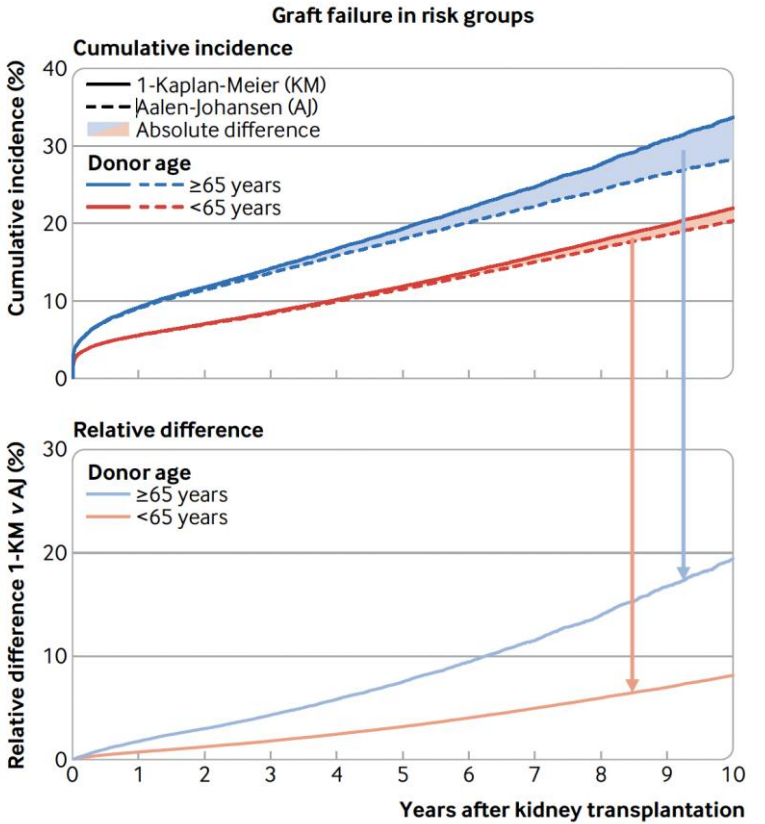

Van Loon et al Transplantation 2020

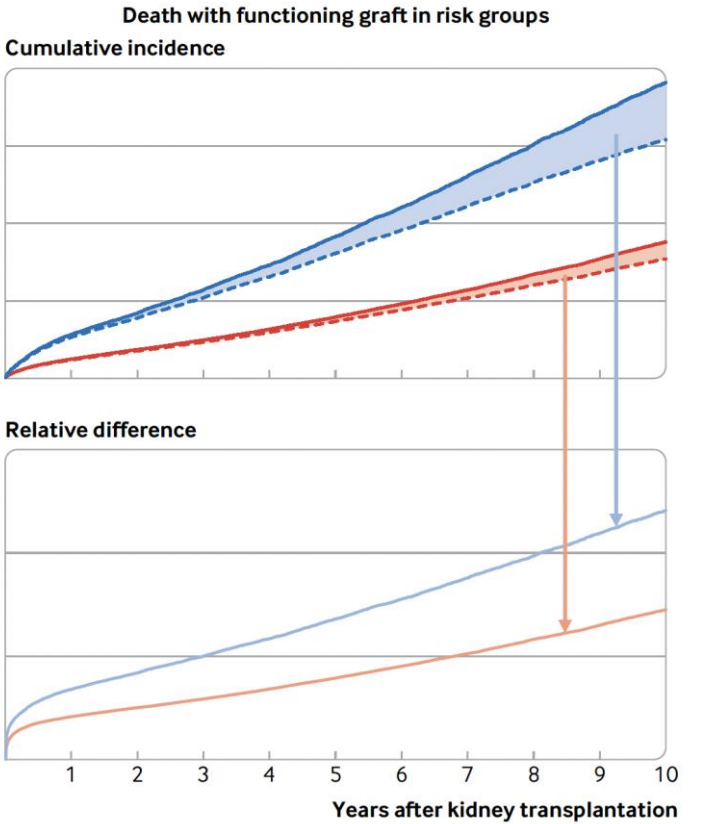
# Patient survival is ill studied in transplantation

| 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% |

Hariharan et al In preparation

# Censoring for death in endpoint predictions is not accurate

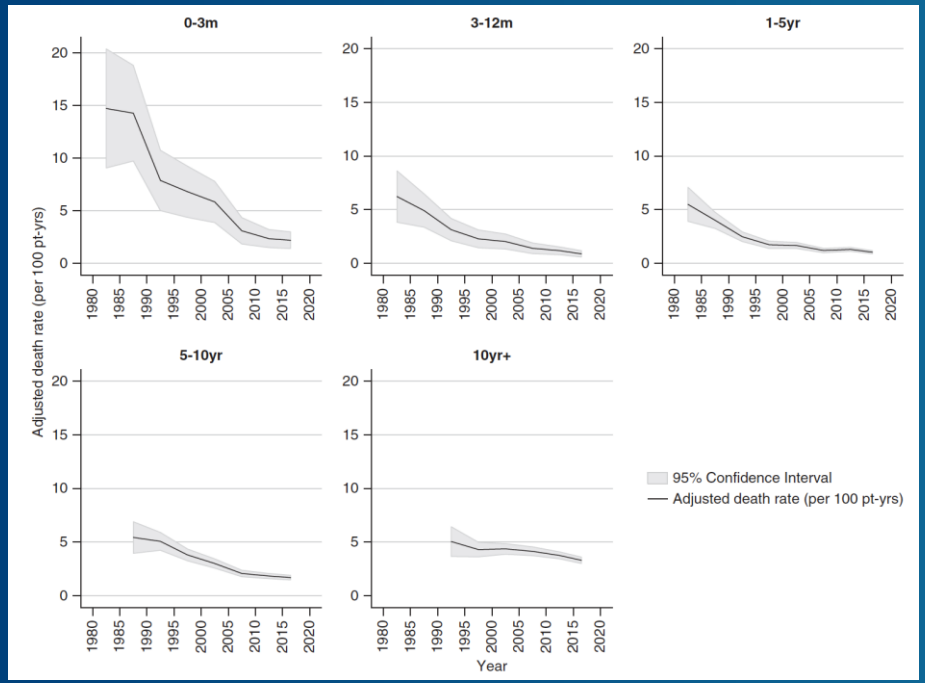


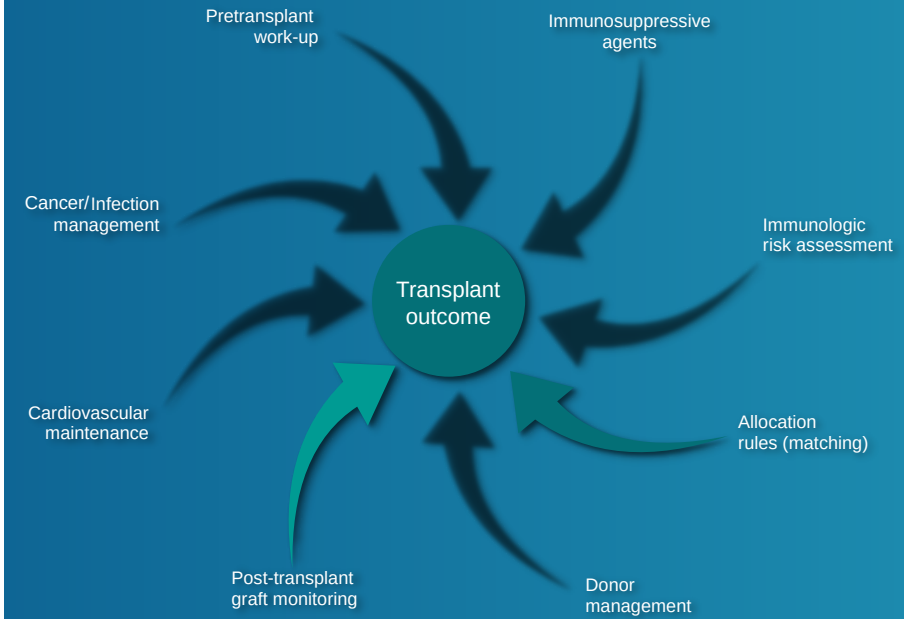




Coemans et al BMJ 2022

# Kidney transplantation - a quiet revolution

## **Patient death**

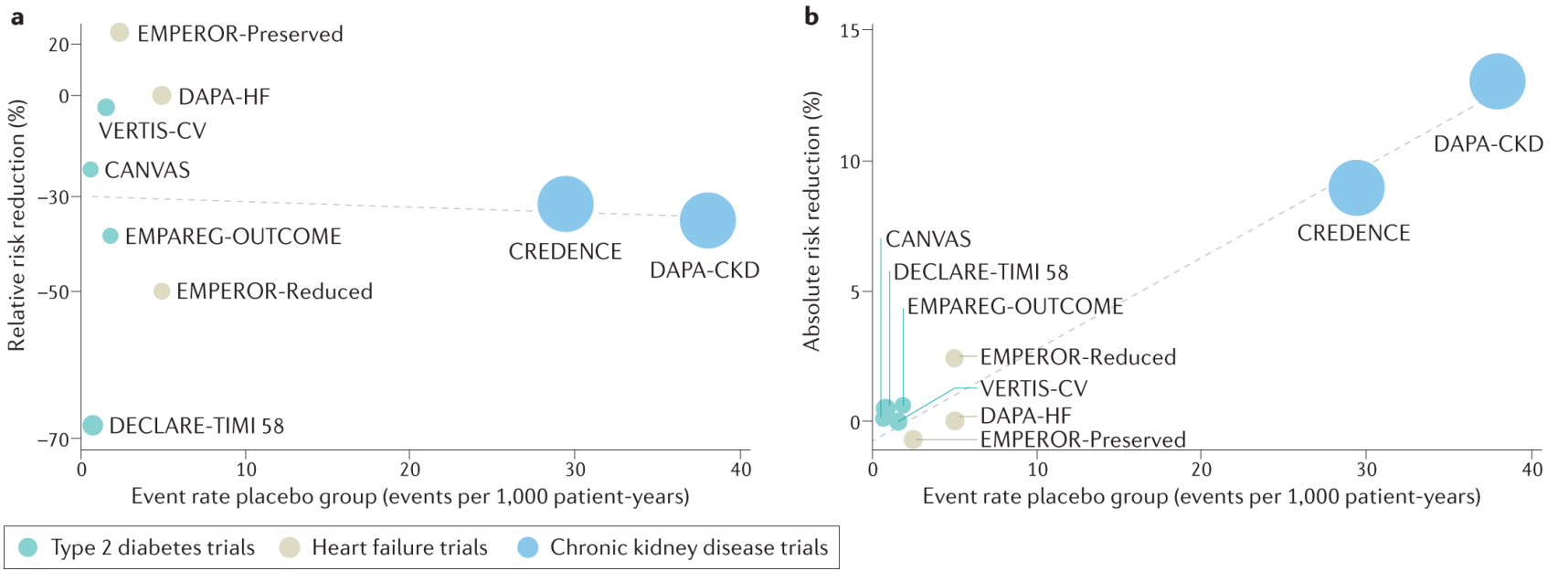



Ying et al J Am Soc Nephrol 2020

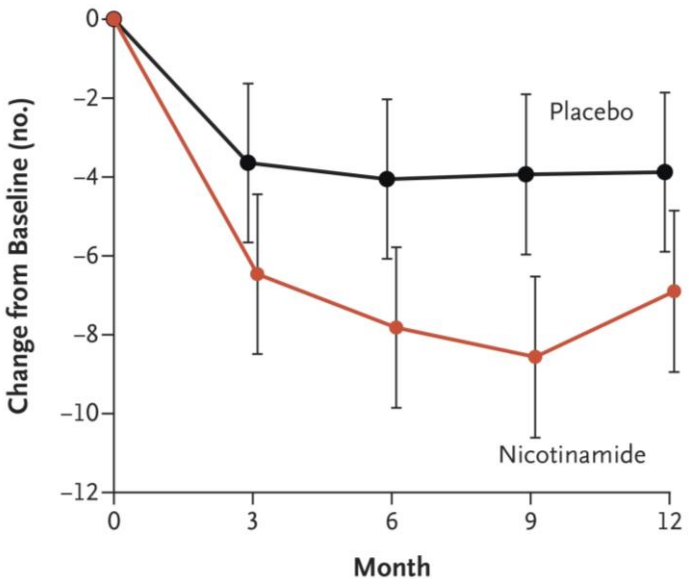
# SLGT2 inhibitors in transplantation

**Effect of SGLT2 inhibitors on kidney failure.**

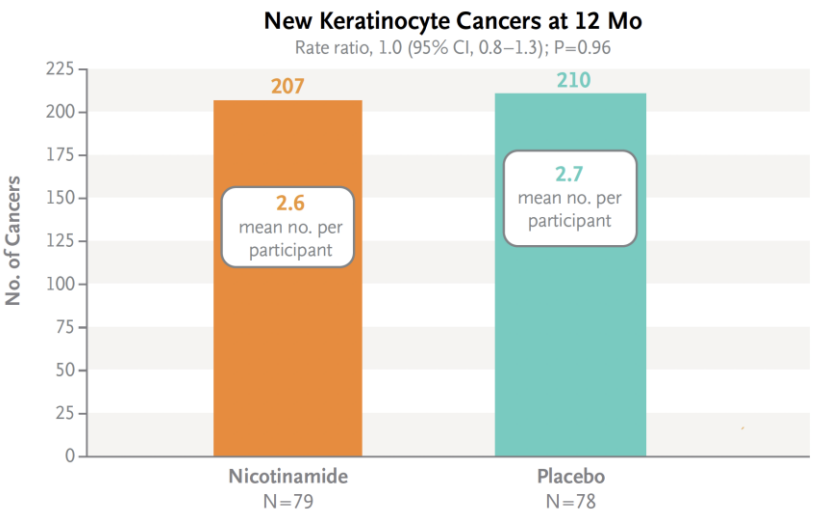



Van der Aart - van der Beek et al Nature Reviews Nephrology 2022

# Studies specific for other outcomes after transplantation




Chen et al NEJM 2015




Allen et al NEJM 2023

# Conclusion

Surrogate endpoints

eGFR evolution

Risk stratification

Patient-reported outdomes

Mortality

# Thank you!

NEPHROLOGY
LEUVEN

KU LEUVEN