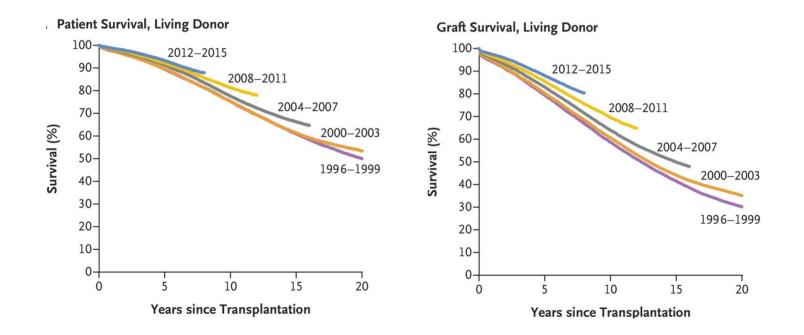
How the use of new *surrogate* outcomes may improve transplantation results?

Maarten Naesens

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

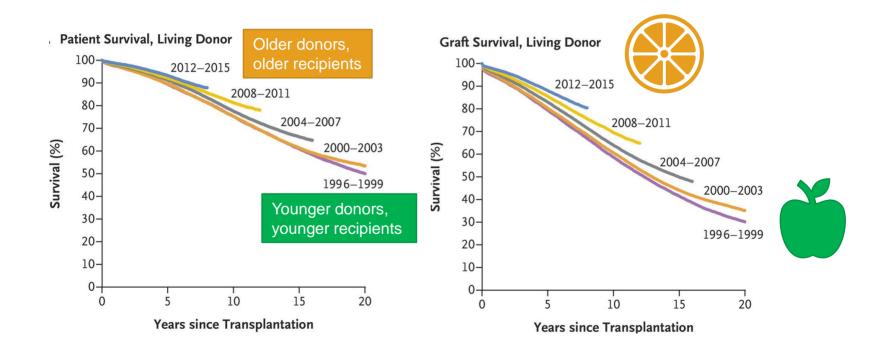
KU LEUVEN

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



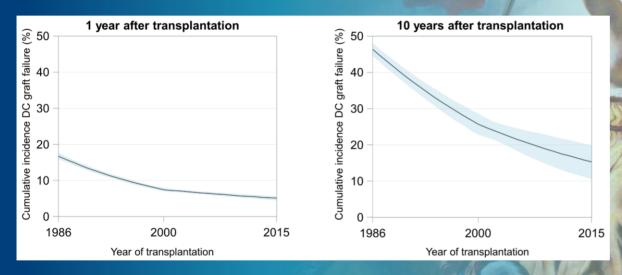
Hariharan et al. NEJM 2021

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



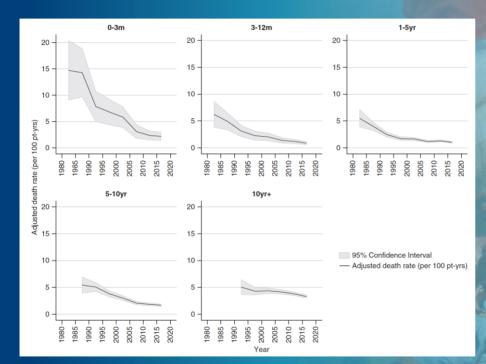
Hariharan et al. NEJM 2021

Kidney transplantation - a quiet revolution Graft failure



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

Kidney transplantation - a quiet revolution Patient death



Ying et al J Am Soc Nephrol 2020

The quiet revolution

Pretransplant work-up

Immunosuppressive agents

Cancer/infection management

Transplant outcome

Cardiovascular maintenance

Allocation rules (matching)

Immunologic

risk assessment

Post-transplant graft monitoring

Donor management

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)		
Ciclosporin	1983	Ciclosporin and low-dose CS	Randomized superiority trials	Graft loss or death		1	1	J	¢
MMF	1995	MMF, ciclosporin and CS±ATG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	(J	1
Daclizumab	1997	Daclizumab, ciclosporin and CS±AZA	Randomized superiority trials	BPAR by 6 months	=	=	=	J	1
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	=	=	=	J	=
Sirolimus	1999	Sirolimus, ciclosporin and steroids	Randomized superiority trials	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	J	Ţ
Everolimus	2003	Everolimus, ciclosporin and basiliximab±CS	Randomized equivalence trial	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	=	Ţ
Belatacept	2011	Belatacept, MMF, CS and basiliximab	Randomized noninferiority trials	Noninferiority for BPAR, graft loss and death; superiority for GFR	=	=	=	1	1



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

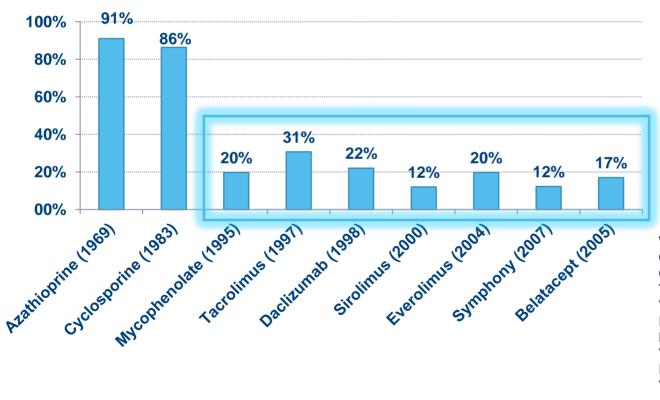
KEYWORDS Immunosuppressants, solid organ transplantation, CHMP, EMEA, guideline

"The primary efficacy endpoint for induction, initial and/or maintenance prophylaxis (primary prophylaxis) should be efficacy failure rate using a composite endpoint consisting of:

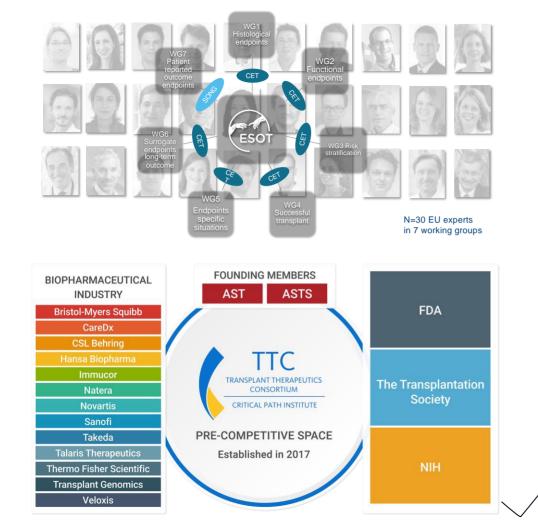
- a) patient death;
- b) graft failure;
- c) biopsy confirmed acute rejection;
- d) graft (dys)-function"

7 Westlerry Circus, Canary Wharf, London, E14 4HB, UK Tel, (44-20) 74 18 84 00 Far (44-20) 74 18 85 13 E-mait: <u>mait@emaa.europa.eu</u> 180//www.emea.europa.eu © European Medicines Agency.2008.Reproduction is authorised provided the source is acknowledged.

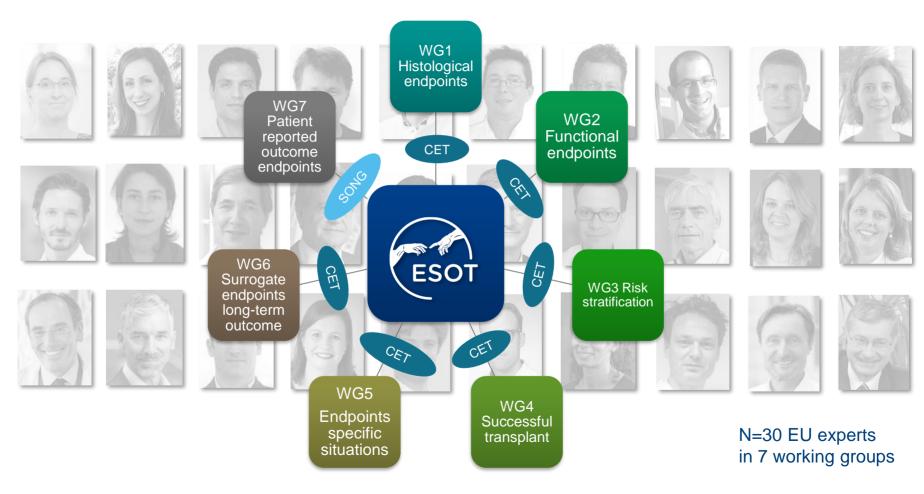
Reducing BPAR helped in the early decades but is less relevant nowadays



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













Special Issue



CONTENSUS REPORT publication 20 May 202 data 10.32889-2022 Total

publicited 33 May 2022 doi: 10.33898-2022.10740

Alloimmune Risk Stratific tion for Kidney Transplant Rejection

Orici Bastavi II. Obiar Travest it. Maria Jana Ballai J. Geren & Biltmin J. Bastava Burbis Pranz Cleas", Lionel Couzi', Lucrezia Furier", Uwe Heemann", Nizem Marrode ", Rainer Oberbauer⁴, Liset Pengel¹¹, Stefan Schneeberger¹² and Maarten Naezena¹⁰

Inclusion and Dates Description (10 Oblicity Internet Neutral Resolute Date)

rent types of kidney transplantations are performed worldwide, including biological dwarse dononheopient combinations, which entail datinct publicit/graft outcomes. Thus, propen/immunological and non-immunological risk stratific tion should be considered, especially for publicits included in interventional tandomized clinical trials. This paper was prepared by a working group within the European Society for Organ Transplantation which submitted a Broad Scientific Advice request to the European Medicines Agenci (EMA) relating to clinical trial endpoints in kidney transplantation. After collaborative interactions, the EMA sent its final response in December 2020, hishlighting the CVIntUOULIN: following: 1) transplantations performed between human leukocyte antigen (HLA) identical donars and recipients carry signific rity lower immunological risk than those Beneficial DOTE: and Annual An as before preserved and therefore less immunogenc tran grants warr owneed out any op-system to its exit and angle-antigen basid testing is the gold standard to establish the repetitive of serological single-simple basic sisting is the good standard to eace in the represence or sercogood sensitization and is used to define the presence of a recipient's circulating donor-specific antibodies (HLADSA); 4) molecular HLA mismatch analysis should help to further improve sales 2 May 2 and 2 May diffic It to integrate information into clinical practice/study design: 5) further clinical validation of other immune assays, such as those measuring articlenor cellular memory (7/8 cell ELISpot assays) and non-HLA-DSA, is needed; 6) routine clinical tests that reliably measure invote immune alloreactivity are lacking.

Reparate alternance mit, crassmatch, high-risk bangleriation, indeskaalierd immunoappression, mite

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contactnots trave also been made normous acute (or activa) and chronic phanetypics of 1.5Me a. AMP, as defined in the limit Choself-acuto (Q), and outpryper within these phenotypes. In additise evidence has emerged to indicate that non-specific acute mjection, or early TCME, is becoming its networks as the primary endocids in foldingsy transplantation (e) because it is no longer considence Tangation 20 10741 revenues or new pressury endpoint in loancy transportation (4) because it is no longer considered a communication to an endpoint in loancy transportation (4) because it is no longer considered a second sec

perspectives and issues, and provides a roundation this Special Issue of Transplant International build.

The arrenoved historiathological endpoint for cli-

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Evolution of the Definition of Rejection

in Kidney Transplantation and Its Use as an Endpoint in Clinical Trials

24 Oblivies Disensity Magalial Barratives, Types, "Department of Pathology: Highla Uniter Extents Unlabes, Parts, Press, Particular to Information Disease Department of Internation and Enforcements, Content Online Lincoles, London.

an endpoint for clinical trials in kidney transplantation is no longer accurate, although it is

still the approved hatepathological endpoint. The spectrum of rejection is now divided into the phenotypes of borderline changes, T cell-mediated rejection, and antibody-enedlated rejection, with the latter two phenotypes having farther subcleasible tions. Rejection is also described in existin to certificate interneed because of protocol (surveillance) or

indication (for-cause) biopsies. The origing use of outdated terminology has become a

rotantial barrier to circical research in kirkey transplantation. This article measures there perspectives and issues, and provides a foundation on which subsequent articles within

The approxed hosephadogical analysis of reducid twin of laboy transpharations in the presence depairs many preparation of the start protocide for laboy transplate neglesis, as well as developments in our andersanding of the start and start of the start and start of the start of

Jan Ulrich Becker¹⁷, Daniel Seron²⁷, Marion Rabant³, Candice Routosse⁴ and

This satisfies realizes the earthies definition of rejection indication bidney transm viewpoints and avidence researched were included in documentation rearranged for a Record Verpoints and evidence presence where includes in documentation prepared for a broad Scientific Advice request to the European Medicines Agency (EMA), relating to chricial trial endpoints in kidney trainiplantation. This request was initiated by the European Society for Organ Transplantation (ESOT) in 2016 and finalized following discussions between the EMA and ESOT in 2020. In ESOT's opinion, the use of "biopsy-proven acute rejection" as

WEBINAR 1 - July 7th 2022

Correspondence Manager Manager

INTRODUCTION These authors have contributed equally to fits work

published 20 May 20 day 10.3389/s 2022 101

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

Daniel Seron ¹¹, Marion Rabart²⁷, Jan Ulrich Becker³, Candice Routsze⁴, Maria Imne Bellev¹¹, Georg A. Böhmio⁴, Nemenz Budde¹, Fritz Diekmann⁴, Denis Giotz⁴ ands¹⁰, Alexandre Loupy¹⁰, Rainer Oberbauer¹⁰, Litet Pengel meherner is and Manten Manner I¹⁰

The diagnosis of acute T cell-mediated rejection (aTCMR) after kidney transplantation ha considerable relevance for research purposes. Its definition is primarily based on subulcinterabilial inflammation and has changed little over time; aTCMR is therefore a CONTRACTORS. suitable parameter for longitudnal data comparisons. In addition, because aTCMR is managed with antirejection therapies that carry additional risks, anxieties, and costs, it is a clinically meaningful endpoint for studies. This paper reviews the history and classific tions of must with with and TOMR and characterizes its potential role in divical trials: a role that largely depends on the 21 Chailer 2021 Li dener 2021 Li dener 2021 regional 11 Journy 2022 Exception of an energy of the and energy of the and an energy of the an en

monitoring and management of TCMR. More research, to investigate the clinical relevan of borderine changes (especially in protocol biopsies) and effective therapeutic strategies that improve graft survival rates with minimal patient morbidity, is urgently required. The present #A paper was developed from documentation produced by the European Society for Orga Transplantation (ESOI) as part of a Broad Scientific Advice request that ESOI submitted to the European Medicines Agency for discussion in 2020. This paper proposes to move towar The Eulopean reactions vigency for declasion in Jului. It is paper proposes to move toward refined definitions of aTCMR and borderline changes to be included as primary endpoints in clinical bials of kidney transplantation.

Keywards kidney transplantation, subcomes, EMA guideline, T call-mediated regulars, landerine change dia 10 2000 0 2022 10:38

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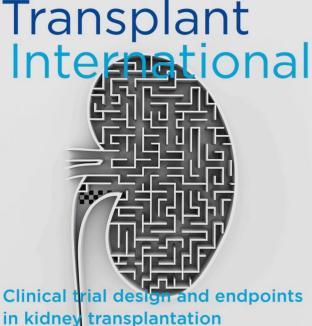
 \otimes Proposed Definitions of Antibody-Mediated Rejection for Use as a Clinical Trial Endpoint in Kidney Transplantation

Candice Routsze¹⁰, Jan Urich Backer¹⁰, Marion Rebart¹, Daniel Saron⁴, Maria Imen Ballio¹¹, Georg A. Böhnig¹, Klemens Budde¹, Pritz Diekssen⁴, Danie Glote⁴, Lauk Höhnundt¹¹, Alexandra Loopy¹⁷, Rainer Chertwar⁴, Linet Pengel¹⁰, Stafan Schneeberger¹¹ and Mariten Naszam¹⁰

leukocyte antigen (HLA) or other targets. As knowledge of AMR pathophysiology has increased a combination of factors is necessary to confirm the discretes and observing increased, a compression of factors is receasely to continn the diagnosis and prenotype However, frequent modifications to the AMR definition have made it difficult to compres data and evaluate associations between AMR and graft outcome. The present paper was Companies Units and evenues associated scientific Advice request from the European Society for Organ Transplantation (ESOT) to the European Medicines Agency (EMA), which explores whether updating guidelines on cinical trial endpoints would encourage innovations in which is a subject of the second seco AMR and impairs of participants of an another intervention and impairs of an another intervention and impairs of an another intervention and impairs of an another intervention and interventin and intervention and interventio endpoints in chrisel trials of kidwy transplantation, although modifications and nativities to the Banff diagnostic definition of AMR are proposed for this purpose. The EMA provide recommendations based on this Broad Scientific Achieve request in December 2021 further discussion, and consensus on the restricted definition of the AMR endpoint, is

rejection (AMR) is caused by antibodies that

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Special Issue

national

CONSENSUS REPOR published: 20 May 2022 doi: 10.3389/ti.2022.10137

Allograft Functio Clinical Trials i Transplantation

Lusk Hibrands¹, Klemens Budde¹ Rainer Oberbauer¹⁰, Liset Pengel Maarten Neezens¹⁰

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

Maarten Naesens¹*, Alexandre Loupy², Luuk Hilbrands³, Rainer Oberbauer⁴, Ciriotatory reports the assess the effort. Inadiancy can be adopted for use a Maria Irene Bellini⁵, Denis Glotz⁶, Josep Grinyó⁷, Uwe Heemann⁸, Ina Jochmans⁹, artoryosizogi animika towa to conset Pengel¹⁰, Marlies Reinders¹¹, Stefan Schneeberger¹² and Klemens Budde¹³ the ofermentian Electron rate (CPEr) and although a it of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium, ≥Paris Translational Res endpoints are also included in clinical trials. End-stato r for Organ Transplantation, Höpital Necker, Paris, France, *Department of Nephrology, Radboud University Medi duringe in estimated (e)GFR, and eGFR trajectories exports in disal intervention total in drank biarry Nijmogen, Netherlands, "Department of Nephrology and Dialysis, Medical University of Vienna, Vienna, Austria

on of the considered for closed high in kidney transdanted pent of Surgical Sciences, Sapienza University of Rome, Rome, Italy, "Paris Translational Research Center for 0.000.00088 be taken into account. The present Conse tion, Hogital Saint Louis, Paris, France, University of Barcelona, Barcelona, Spain, "Department of Ne rendured by the European Society for Other Transplantation produced by the European Society for Organ Transpleration of Microbiology, and the State of Control of Microbiology, and the State of Control of Control of Microbiology, and the State of Control of Some load input the CUI scenes of the CUI is scenes of the CUI is an exact on the CUI is a constrained with the cuit of the CUI is a constrained with the cuit of the cuit is a constrained with the cuit of the c proteinuria and albuminuria, and evaluates the validity of these conce sity of Oxford, Oxford, United Kingdom, "Erasmus MC Transplant Institute, Department of In drical trials in kidney transplantatio nter Rotterdam, Rotterdam, Netherlands, 12 Department of General, Transplant and

Berlin, Germany

Keywords holew barralizations and headers and desheriters cloud study embored INTRODUCTION nosive chronic disease of native kidneys, chronic staft failure results in st

As was programmer cannot, and and it have a balance, the same through the same and a same through the same and the kidney replacement therapy in the form of dialysis or repeat transplantation. Publiclogical processes that characterize the late course of graft failure are loss of netherony elementary leaves of the memory and interactival threats and tabular strends 10.33899.2022.10139

sbruck. Innsbruck. Austria. 13 Department of Nephrology and Medical Intensiv horization (CMA) facilitates timely needs, such as

WEBINAR 2 - July 12th 2022 Call Channel CONSENSUS REPORT published 20 May 2022 dec 20 20 May 2022 10 136



Surrogate Endpoints for Late Kidney Transplantation Failure

Kiemens Budde², Luuk Hibrands³, Reiner G ne Bellin⁴, Denis Glotz⁴, Josep Grind⁷, Uwe Heamann⁴, Ins Jochman rgel⁴, Marles Reinders¹⁰, Stefan Schneeberger¹¹ and Alexandre Loupy

in kidney transplant recipients, late graft failure is often multifactorial. In addition, prim endpoints in kidney transplantation studies seek to demonstrate the short-term efficiency and safety of clinical interventions. Although such endpoints might demonstrate short-term rovement in specific aspects of graft function or incidence of rejection, such findings do not automatically translate into meaningful knowlearn graft survival herefits. Combining many factors into a well-validated model is therefore more likely to predict long-te outcome and better reflect the complexity of late graft failure than using single endpoints. It conditional marketing authorization could be considered for through any in the trademic long-term outcomes following kidney transplantation, then the surrogate endpoint for graft falura in chical bia sating needs clearer definition. This consistent Report considers the potential benefits and drawbacks of several candidate surrogate endpoints (including estimated glomerular filtration rate, proteinuria, histological lesions, and donor-specifi anti-human leukocyte antigen antibodies) and composite scoring systems. The content was created from information prepared by a working group within the European Society fo Organ Transplantation (ESOT). The group submitted a Broad Scientific Advice request to the European Medicines Agency (EMA), June 2022: the request focusion on chical this design and endpoints in kidney transplantation. Following discussion and refinement, the FMA marks final succementations to FSOT in December 2020 secretion the rotential to use surrogate endpoints in clinical studies that aim to improving late graft failure

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INTRODUCTION

mary endpoints in kidney transplantation are recipient death, graft failure, biopey (jection, and graft (dys)function. These endpoints have clear roles in research the schere-term clearied outcomes after transmissing and they are also the efficace

Patient-Reported Outcomes as Endpoints in Clinical Trials of Kidney Transplantation Interventions

n Tong¹⁴, Rainer Oberbauer²⁴, Maria Irene Beller², Klemens Budde a: J. Caskey¹⁴, Fablerne Dobbels¹⁴, Liset Pangel¹⁷, Lisnel Rosteing¹⁴, n Schneeberger²⁴ and Maarien Naezans¹⁰⁴

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Patient-reported outcomes (PROs) that assess individuals' perceptions of its participation medication adherence, dasase symptoma, and herapy side efforts are other perception in the context of kidney transplantation. All PRCs are potentially suitable as primary or secondary environments in intersectional trials that aim to improve redormers for transmise secondary enclorers in merversorer trais trait are to improve curcorres for transport recipients. Using PRO measures (PROMs) in clinical trials facilitates assessment of the patient's perspective of their health, but few measures have been developed and evaluated in kidney transdant terinients; travat methodologies, which use validated struments and established frameworks for reporting, are essential. Establishing a con-PROM for life participation in kidney transplant recipients is a critically important new which is being developed and validated by the Standardized Outcomes in Nephrolog CUSTANULUS: (SONG)-Tx Initiative. Measures involving electronic medication packaging and aman Companies International Intern recruicing an experiment of the second secon strated on chrical bial design and endpoints in kidney transplantation. This request was submitted to an to the European Medicines Agency (BMA) by the European Society for Organ Transplantatio et 21 Owner 2021 in 2016. Following modifications, the EMA provided its recommendations in late 2020.

Published 23 May 2022 Keywords

- INTRODUCTION

The importance of the patient's perspective on their own health in the assessment of benefits at risks of therapeutic interventions is videly acknowledged (1). Such information could be nelvoard for denoting requestions recording transment of these. benefitivide balance assessments : specific thermostic chima (7). A material antennation (2001) dow they information success 10.3389/0.2022.10134

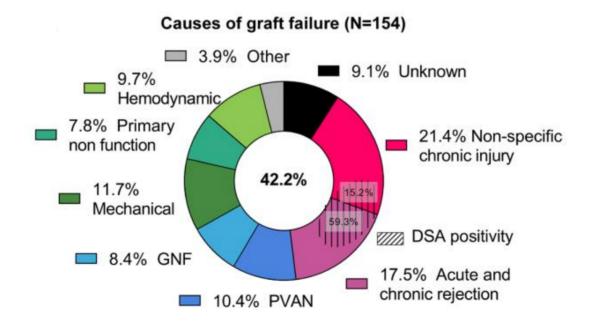


Clinical trial design and endpoints in kidney transplantation

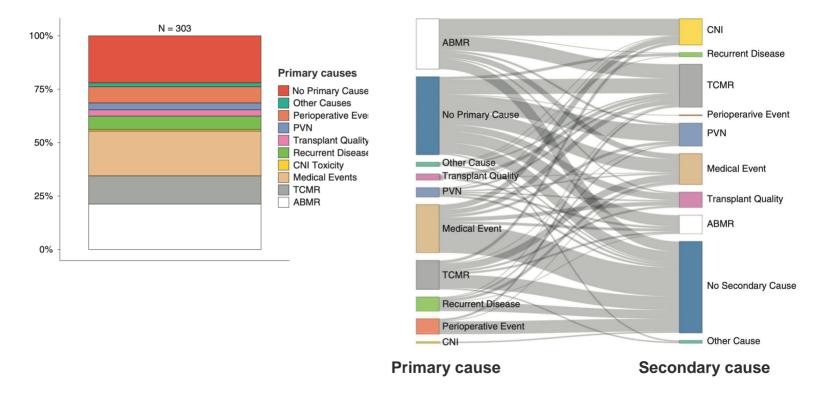
Transplant

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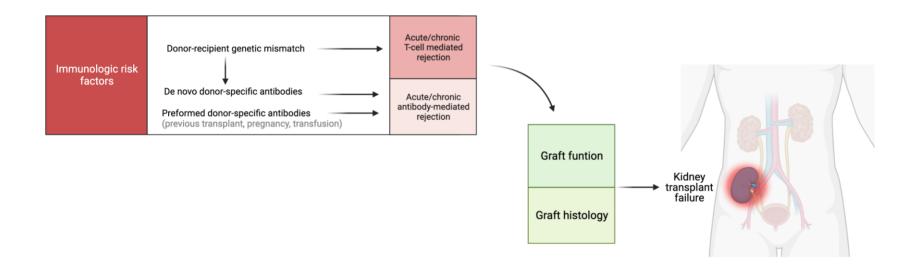
Further improvement of outcomes can only when we target the actual causes of graft failure



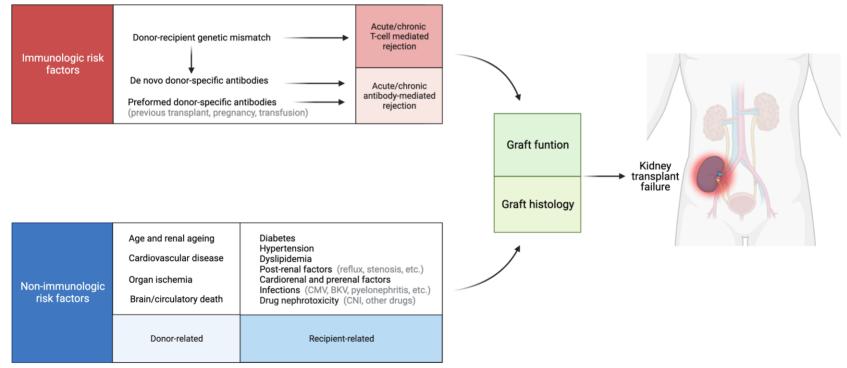
Graft failure is a complex process with primary and secondary causes



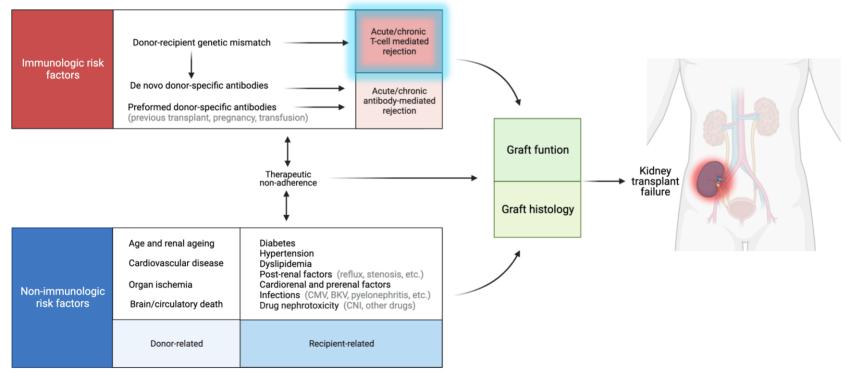
The multifactorial causes of graft failure



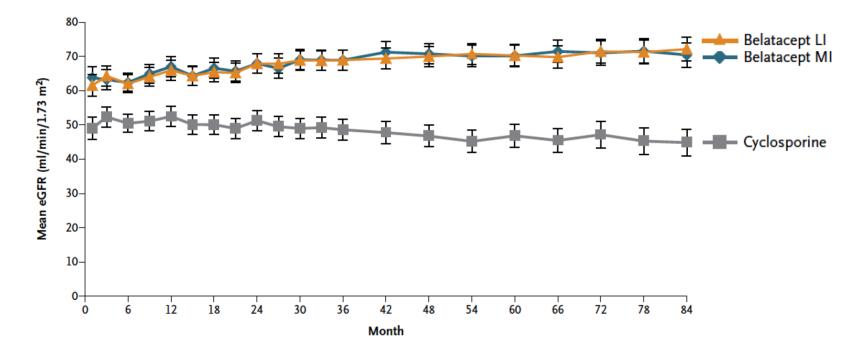
The multifactorial causes of graft failure



The multifactorial causes of graft failure

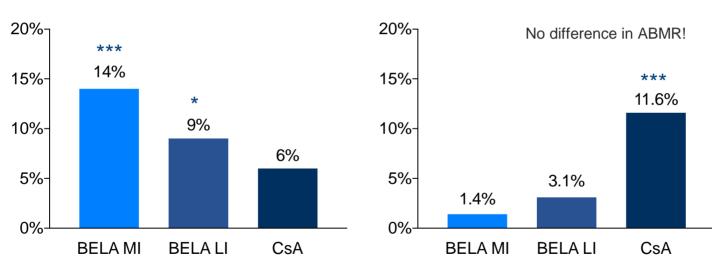


The BENEFIT study confirms the beneficial effect of belatacept in terms of eGFR



Vincenti F et al. N Eng J Med 2016

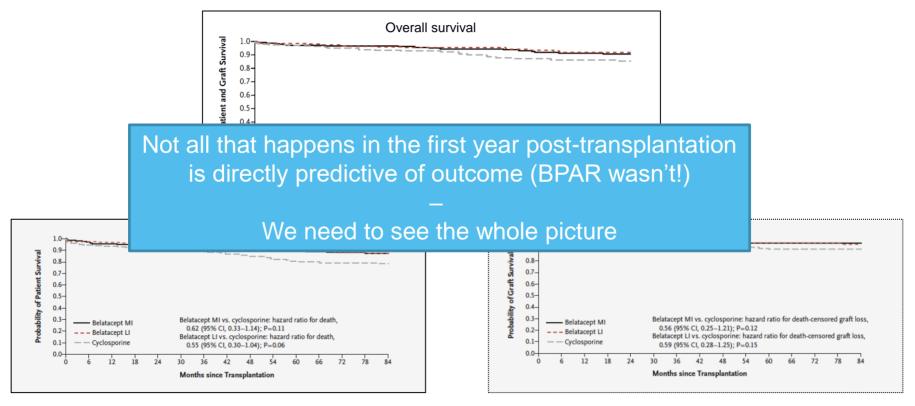
The rejections in the BENEFIT study were T-cell mediated with low risk of DSA formation



Acute rejection occurence

De novo DSA occurence

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



We need more realistic and feasible endpoints for future trials

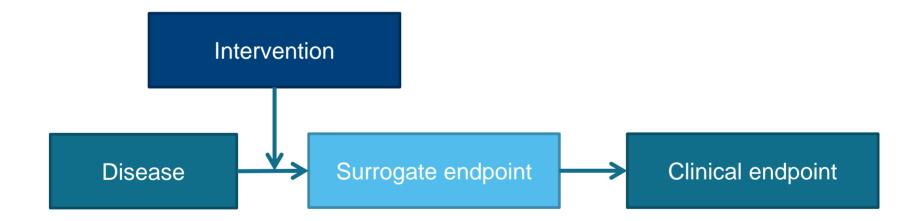
Currently Approved Endpoints	Limitations
Patient/graft survival at 5 or 10 years	Cost prohibitive
Patient/graft survival at ${f 1}$ year	 Now irrelevant for superiority trials Good survival is already achieved (~ 95%), making it difficult to show further improvement
Acute rejection	 T-cell and antibody-mediated rejection do not have the same impact on graft outcome

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

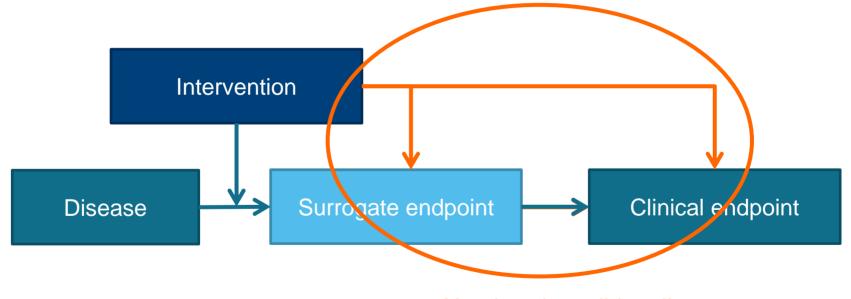
Towards surrogate endpoints for long-term graft failure



Towards surrogate endpoints for long-term graft failure

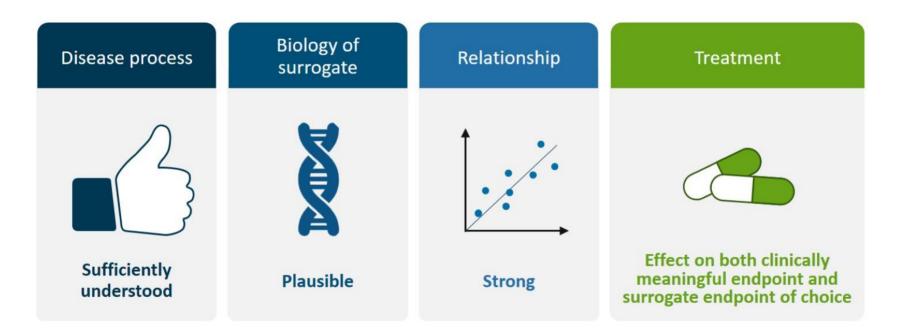


Towards surrogate endpoints for long-term graft failure



Needs to be validated!

Surrogate endpoints for clinical trials need to be well validated





	Kasiske et al 2010 URDS 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)	1 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	⁵ 12 months post-transplant	12 months post-transplant	Time adjusted (only for 'rejection')
Outcome parameter	Overall graft failure at 5 years after transplantation	s 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	U	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	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)	
Ciclosporin	1983	Ciclosporin and low-dose CS	Randomized superiority trials	Graft loss or death	1	1	1	J	(\downarrow)
MMF	1995	MMF, ciclosporin and CS±ATG	Randomized superiority trials	Composite of BPAR, graft loss, death or discontinuation	=	=	=	(J	1
Daclizumab	1997	Daclizumab, ciclosporin and CS±AZA	Randomized superiority trials	BPAR by 6 months	=	=	=	J	1
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	=	=	=	J	Ţ
Everolimus	2003	Everolimus, ciclosporin and basiliximab±CS	Randomized equivalence trial	Composite of BPAR, graft loss, death or loss to follow-up	=	=	=	=	(\downarrow)
Belatacept	2011	Belatacept, MMF, CS and basiliximab	Randomized noninferiority trials	Noninferiority for BPAR, graft loss and death; superiority for GFR	/ *	7 *	=	1	1

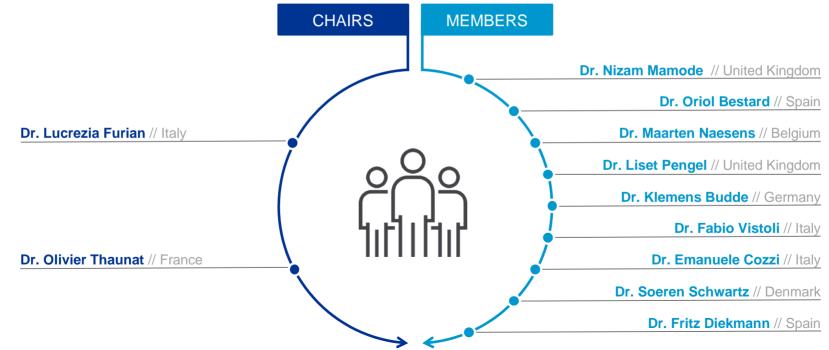
In retrospect, the choice of the primary endpoints for belatacept was well chosen!







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



	HU	MO	RAL	RISK
--	----	----	-----	------

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

NAIVE

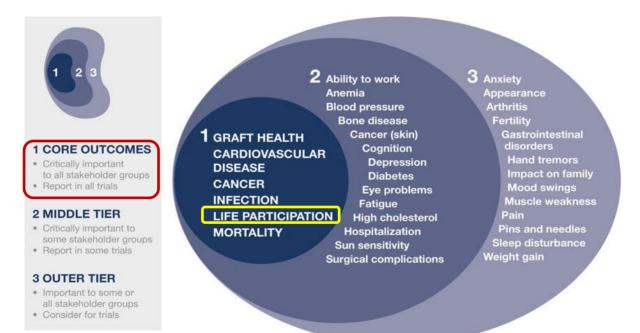
Bestard, Thaunat et al Transplant Int 2021 Bestard, Thaunat et al Transplant Int 2022





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

enjoyment, control and hope in their lives' 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
l could do my leisure activities e.g. exercise, hobbies, travel	0 1	□ 2	□ 3	□ 4	П 5	
l could do my family activities	0 1	□ 2	□ 3	□ 4	□ 5	
l could do my work e.g. job, housework, study	0 1	□ 2	□ 3	□ 4	□ 5	D
l could do my social activities with friends/others	П 1	□ 2	□ 3	□ 4	□ 5	D

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



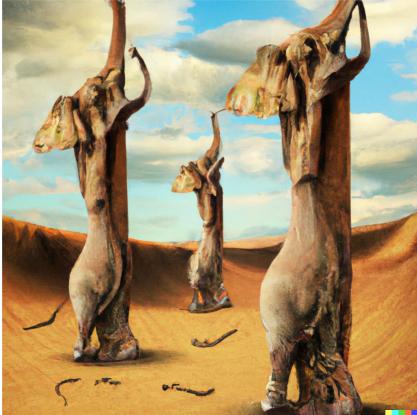
Patient-reported Outcomes as Endpoints in Clinical Trials of Kidney Tx Interventions

- Guidelines for inclusion of PROs in clinical trial protocols:
- Reporting of PROs in randomized trials:

SPIRIT-PRO CONSORT-PRO

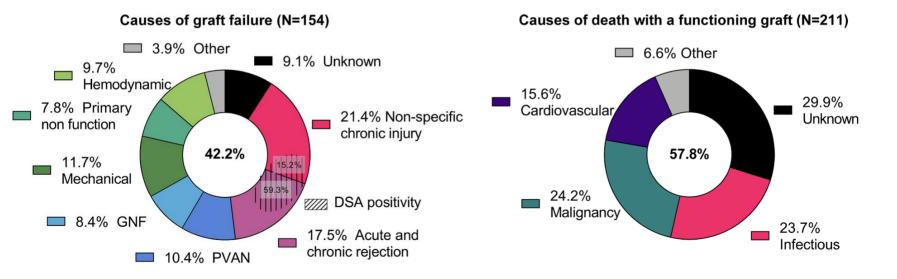
Tong et al. Transpl Int 2022; 35:10134

The elephant in the room



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

N=1000 pts transplanted 2004-2013

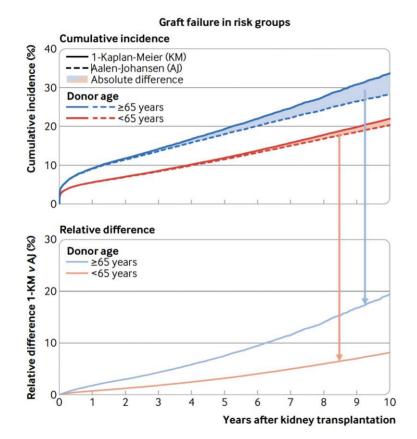


Van Loon et al Transplantation 2020

Patient survival is ill studied in transplantation

Countries		Number of KTR/ year	Populatio n in millions	KTR/ Millio n	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					
	dialysis for ESKD				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



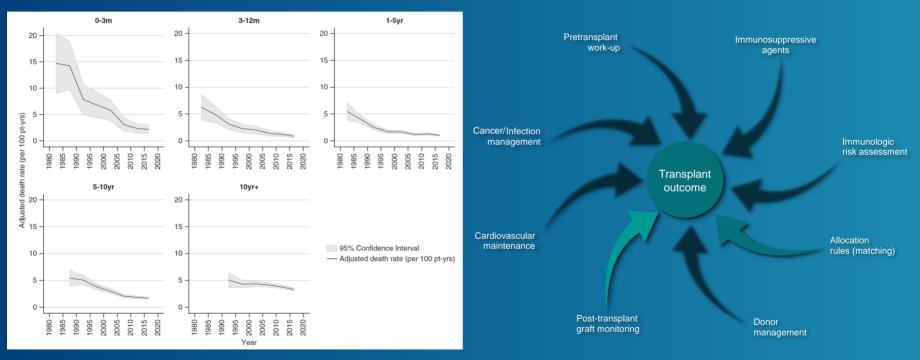
Cumulative incidence Relative difference 10 2 3 8 9

Death with functioning graft in risk groups

Years after kidney transplantation

Coemans et al BMJ 2022

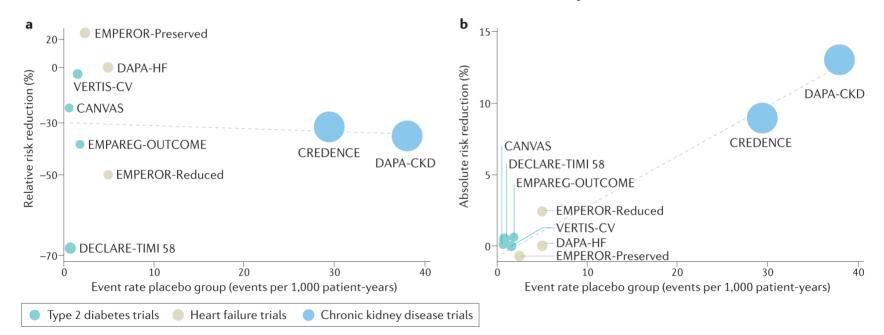
Kidney transplantation - a quiet revolution **Patient death**



Ying et al J Am Soc Nephrol 2020

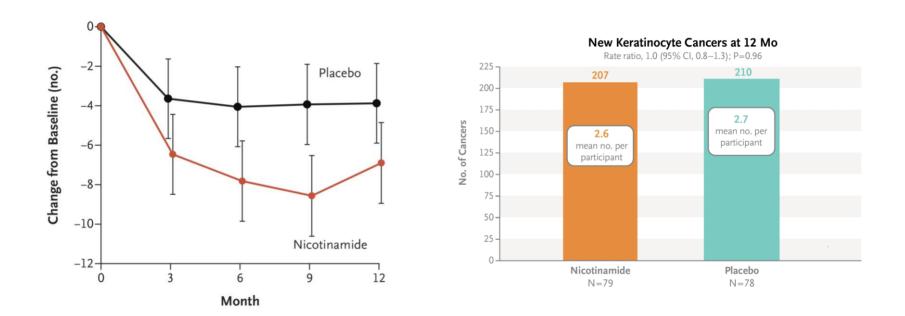
SLGT2 inhibitors in transplantation

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



Conclusion



Thank you!



NEPHROLOGY LEUVEN

