



KIDNEY TRANSPLANT CANDIDATE GUIDELINES

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DISCLOSURES

- None

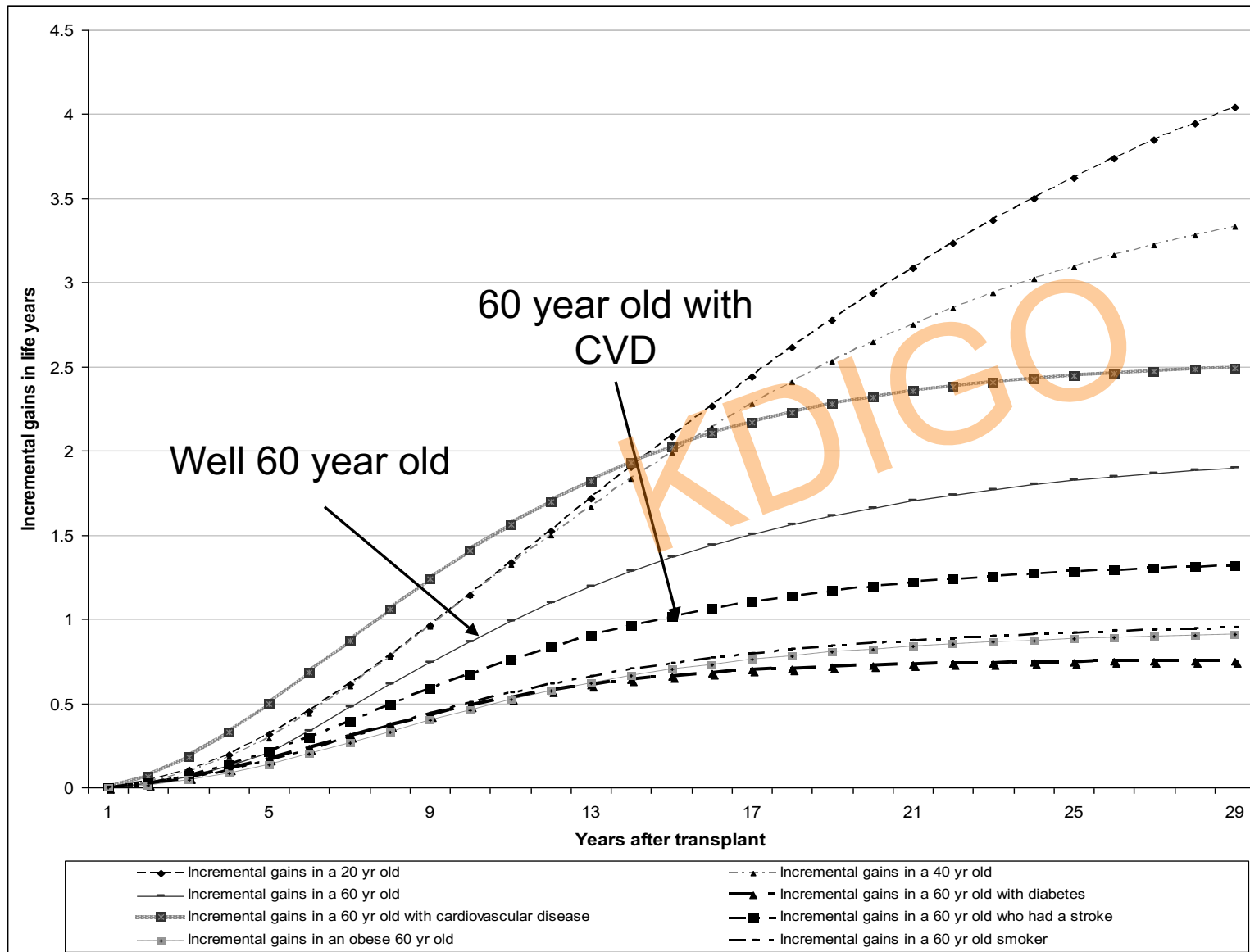
KDIGO

OUTLINE OF THE TALK

- Equitable access to transplantation
- Purpose of the guidelines
- Specific focus:
 1. Age criteria
 2. Co-morbidities – cardiovascular disease, diabetes and cancer,
 3. Adherence

KDIGO

Transplantation saves lives



Comparative Survival and Economic Benefits of Deceased Donor Kidney Transplantation and Dialysis in People with Varying Ages and Co-Morbidities

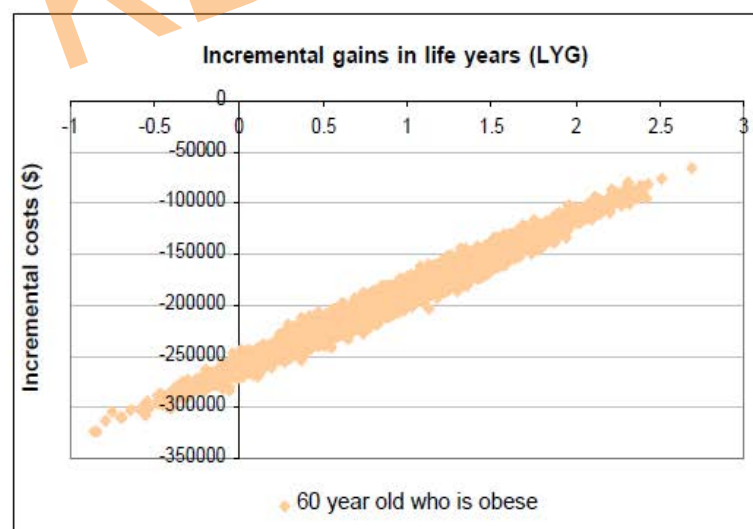
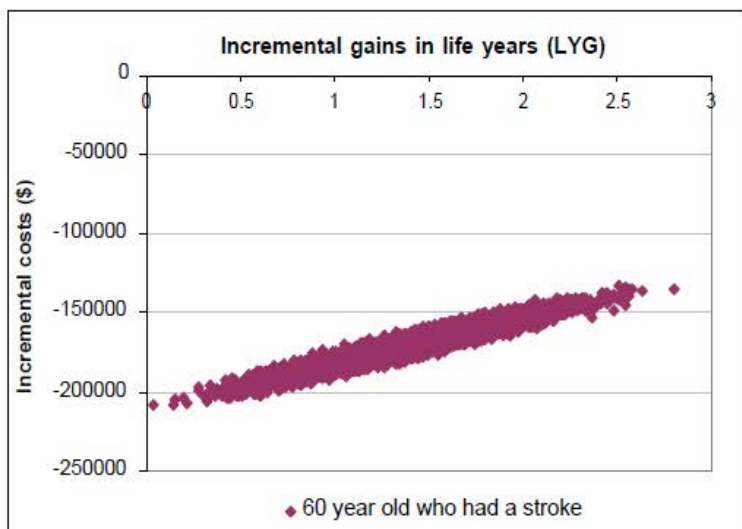
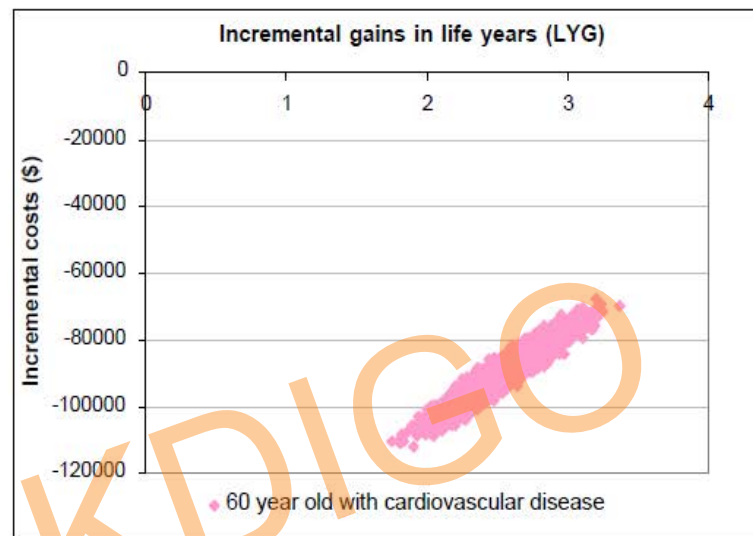
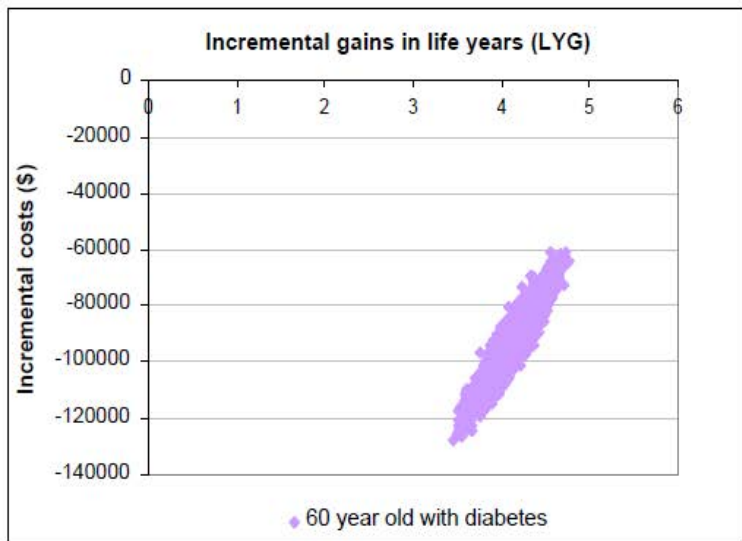
Germaine Wong^{1,2,3}, Kirsten Howard², Jeremy R. Chapman³, Steven Chadban⁴, Nicholas Cross⁵, Allison Tong¹, Angela C. Webster^{1,2,3}, Jonathan C. Craig^{1,2}



PLoS ONE | www.plosone.org

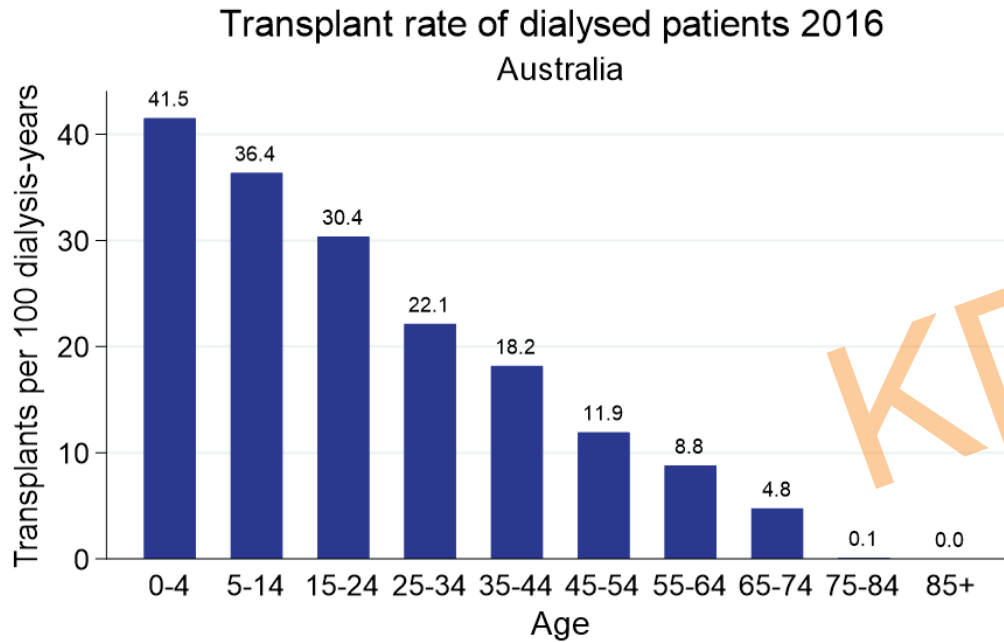


And cost savings – despite comorbidities



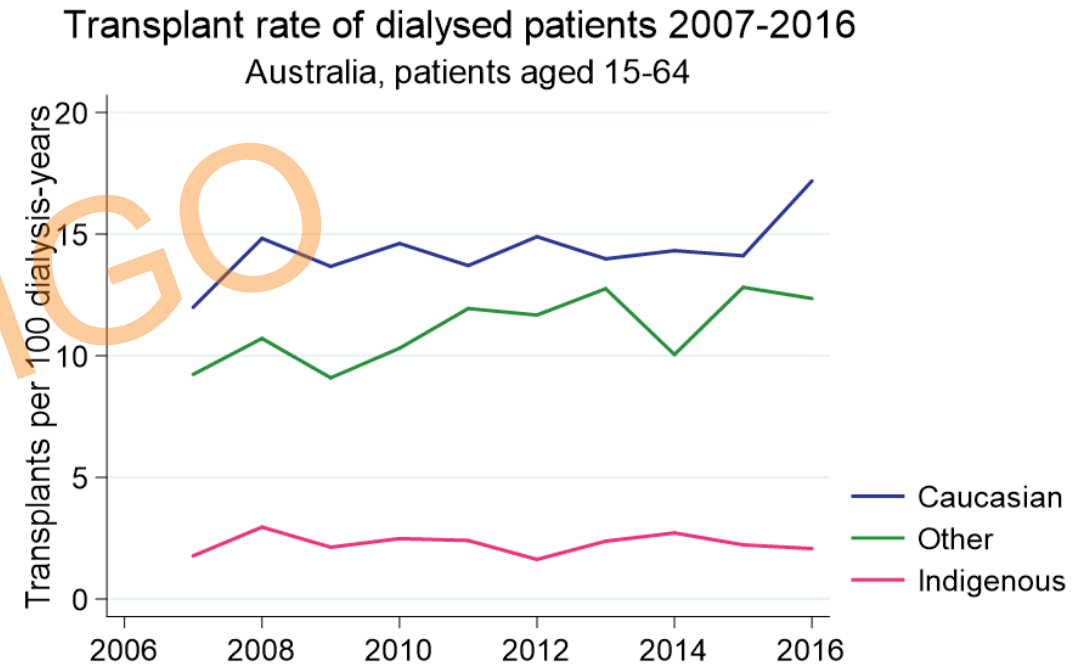
In highly selected group of patients!

Disparities in access to transplantation



2017 ANZDATA Annual Report, Figure 7.4.1

Age



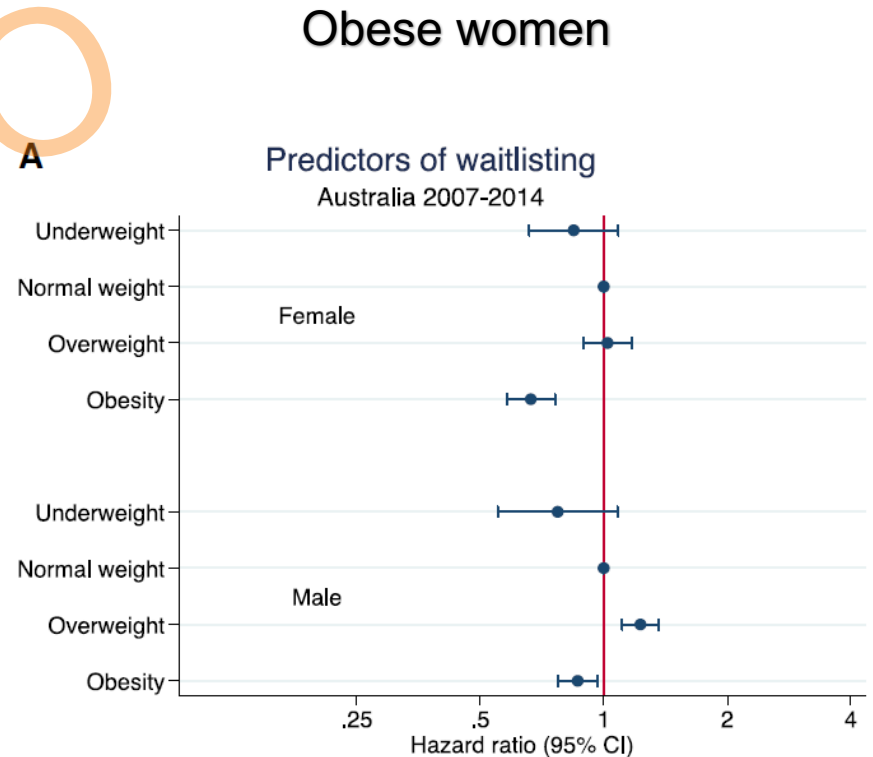
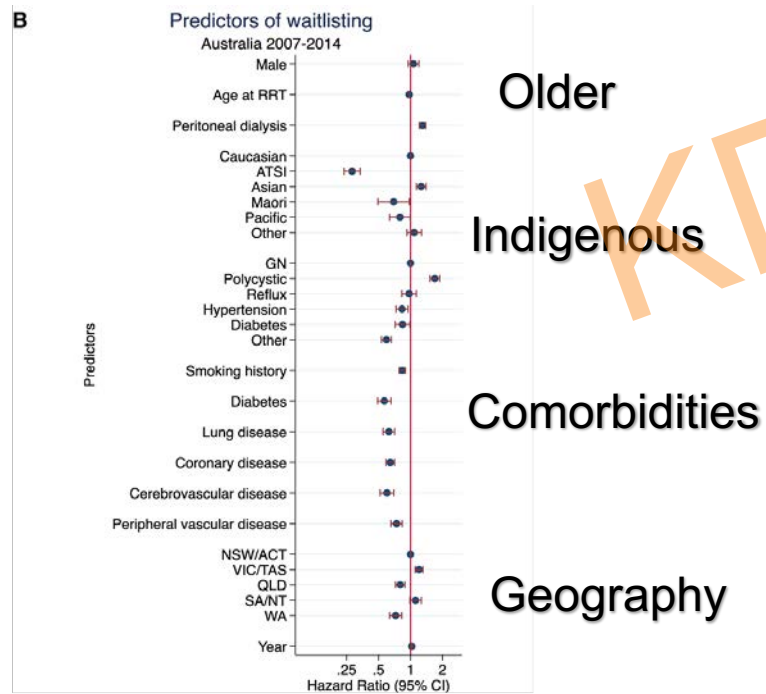
2017 ANZDATA Annual Report, Figure 7.5.1

Ethnicity

Disparities to listing

Obesity and gender-biased access to deceased donor kidney transplantation

Maleeka Ladhani^{1,2,3}, Jonathan C. Craig^{2,4} and Germaine Wong^{1,2,5}





Summary of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation

Steven J. Chadban, BMed, PhD,^{1*} Curie Ahn, MD, PhD,² David A. Axelrod, MD, MBA,³ Bethany J. Foster, MD, MSCE,⁴ Bertram L. Kasiske, MD,⁵ Vijah Kher, MD, DM,⁶ Deepali Kumar, MD, MSc,⁷ Rainer Oberbauer, MD, PhD,⁸ Julio Pascual, MD, PhD,⁹ Helen L. Pilmore, MD,¹⁰ James R. Rodrigue, PhD,¹¹ Dorry L. Segev, MD, PhD,¹² Neil S. Sheerin, BSc, PhD,¹³ Kathryn J. Tinckam, MD, MMSc,⁷ Germaine Wong, MD, PhD,¹⁴ Ethan M. Balk, MD, MPH,¹⁵ Craig E. Gordon, MD, MS,¹⁶ Amy Earley, BS,¹⁷ Valerie Rofeberg, ScM,¹⁵ and Gregory A. Knoll, MD, MSc^{18*}

Transplantation ■ April 2020 ■ Volume 104 ■ Number 4

Working Group
Co-Chairs: Steve Chadban and Greg Knoll
Evidence review team led by Ethan Balk

RATIONALE FOR CLINICAL PRACTICE GUIDELINES

- Systematically developed statements to assist practitioner and patient decisions about **appropriate health care for specific clinical circumstances**
- Potential to **improve the quality, delivery and process of care** with the ultimate objective of improving **overall patient outcomes**.
- Guidelines **summarize the current medical knowledge**, weigh the benefits and harms of diagnostic procedures and treatments, and give specific recommendations based on this information.
- At the same times, guidelines should provide relevant information about the **scientific evidence-base** supporting these recommendations..

KDIGO NOMENCLATURE AND DESCRIPTION FOR GRADING GUIDELINE RECOMMENDATIONS

- The strength of the recommendation is indicated as **Level 1 or 2 or not graded**
- The quality of the supporting evidence is shown as **A, B, C or D**

GRADE	Patients	Clinicians	Policy
Level 1			
We recommend	Most people would want the recommended course of action and only a few would not.	Most patients should receive the recommended course of action	The recommendation can be evaluated as a candidate for developing a policy or performance measure
Level 2			
We suggest	Majority of people would want the recommended course of action but many would also not	Different choices for different patients. Important to consider patient's values and preferences	The recommendation is likely to generate substantial debate and involvement of key stakeholders before policy can be determined.

KDIGO NOMENCLATURE AND DESCRIPTION FOR GRADING GUIDELINE RECOMMENDATIONS

Grade	Quality of evidence	Meaning
A	High	We are absolutely confident that the true effect lies close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

SCOPE of the guideline

- **Access**
- **Age**
- **Adherence**
- Psychosocial factors
- Paediatric issues
- Smoking
- Surgical issues including obesity
- **Diabetes**
- Infections
- **Cardiovascular disease**
- **Cancer**
- Causes of kidney failure
- Pulmonary disease
- Peripheral vascular disease
- Gastrointestinal and liver disease
- Haematological disorder
- Bone and mineral metabolism
- Immunological assessment

KDIGGO

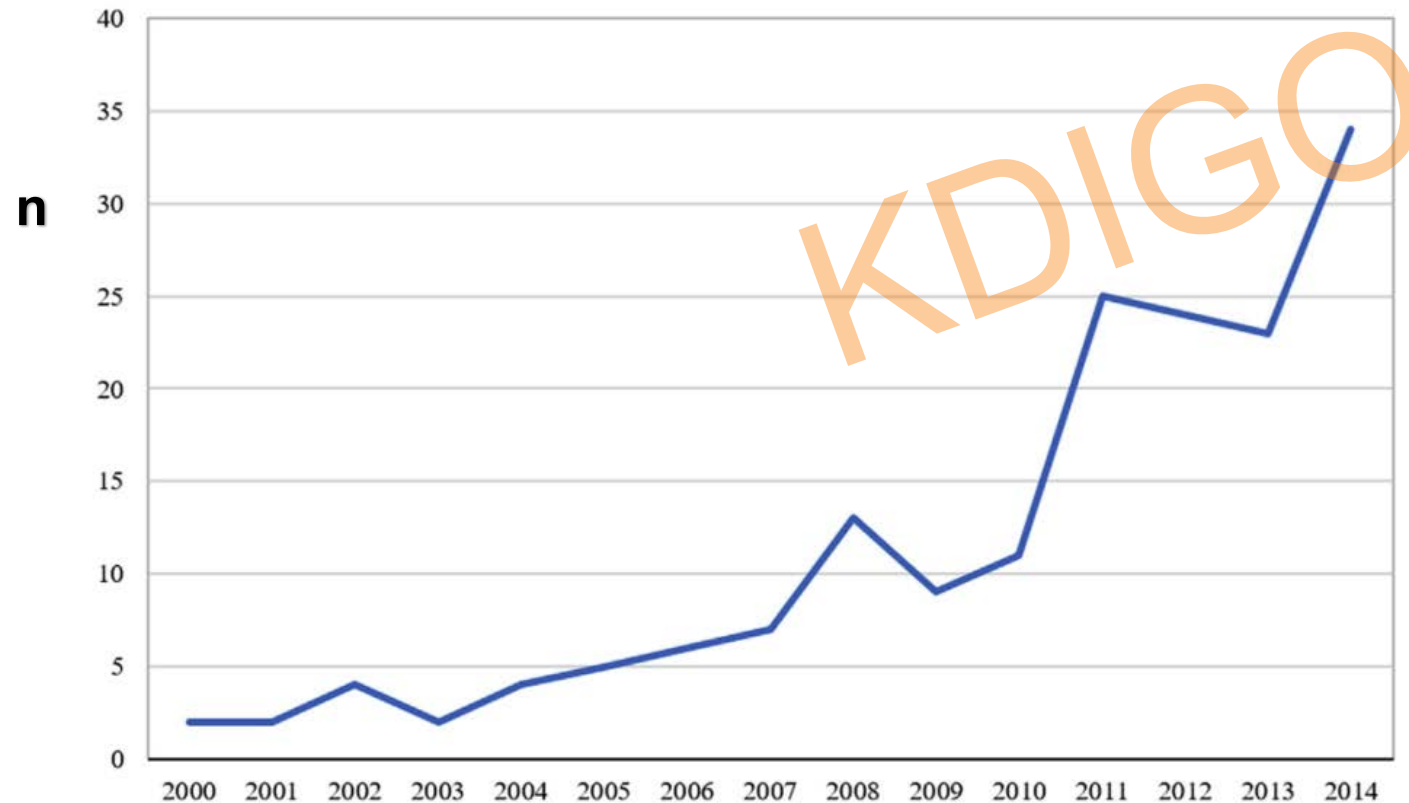
Age criteria

KDIGO

Age criteria

Risk Factors for Early Graft Failure and Death After Kidney Transplantation in Recipients Older Than 70 Years

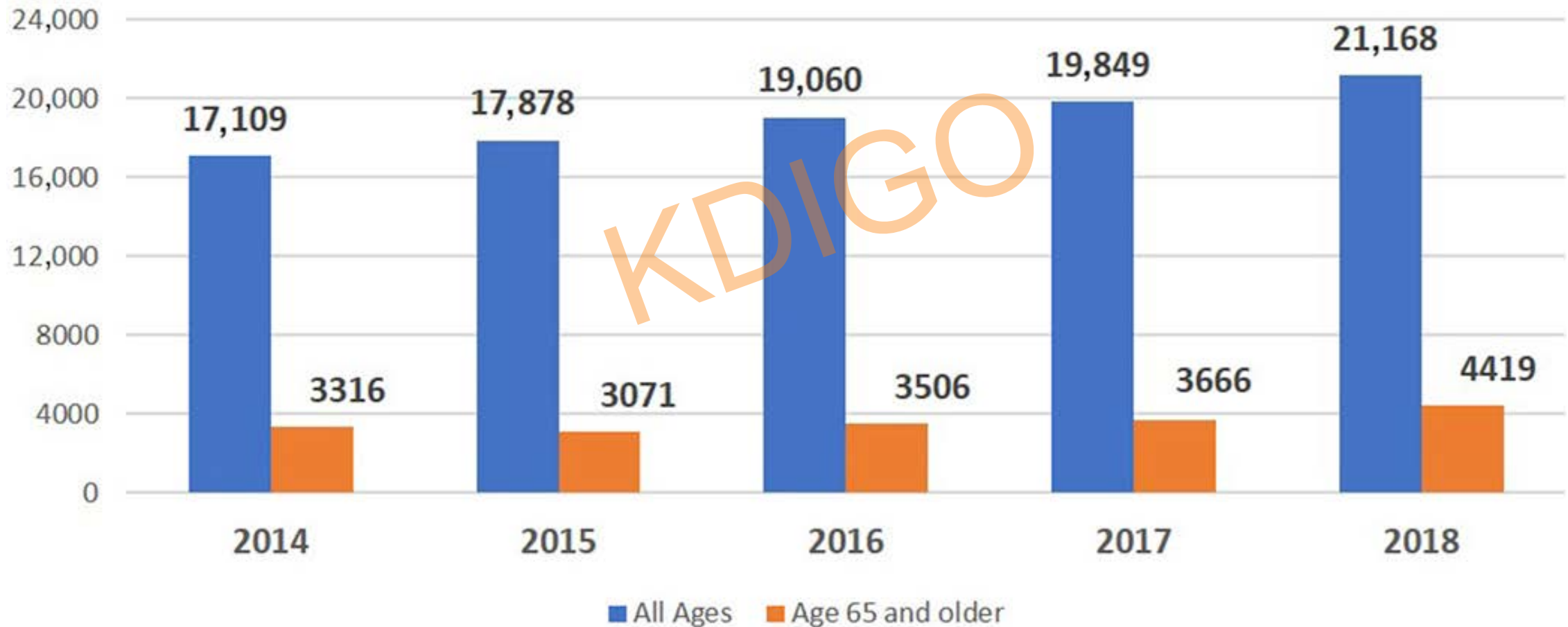
Increase in the transplantation rate of older patients in France



Kidney Int Rep (2019) 4, 656–666; <https://doi.org/10.1016/j.ekir.2019.01.014>

Similar patterns are observed in the US

Kidney Transplants



Risk factors for early graft failure and death after kidney transplantation in recipients older than 70 years

Study Population

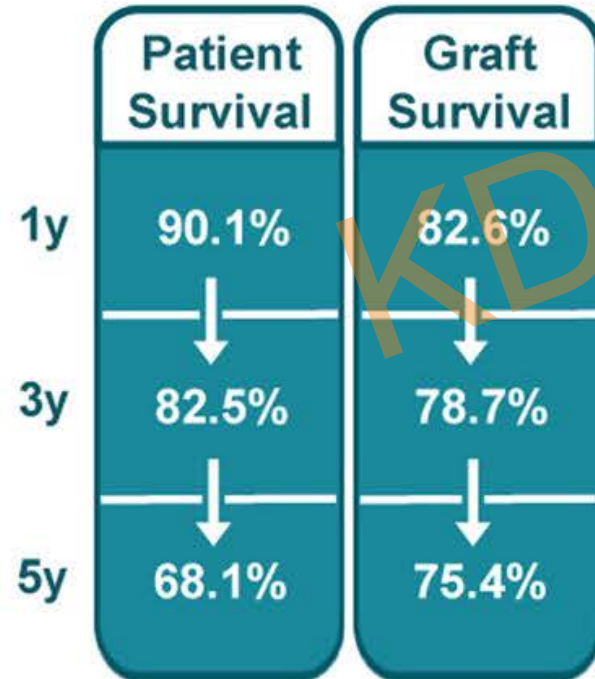


171 patients receiving a kidney transplant over 4y period





Mean age : 73.3 ± 2.5 years

Patient & Graft Survival



Risk factors for death or graft failure during the first year post-transplant

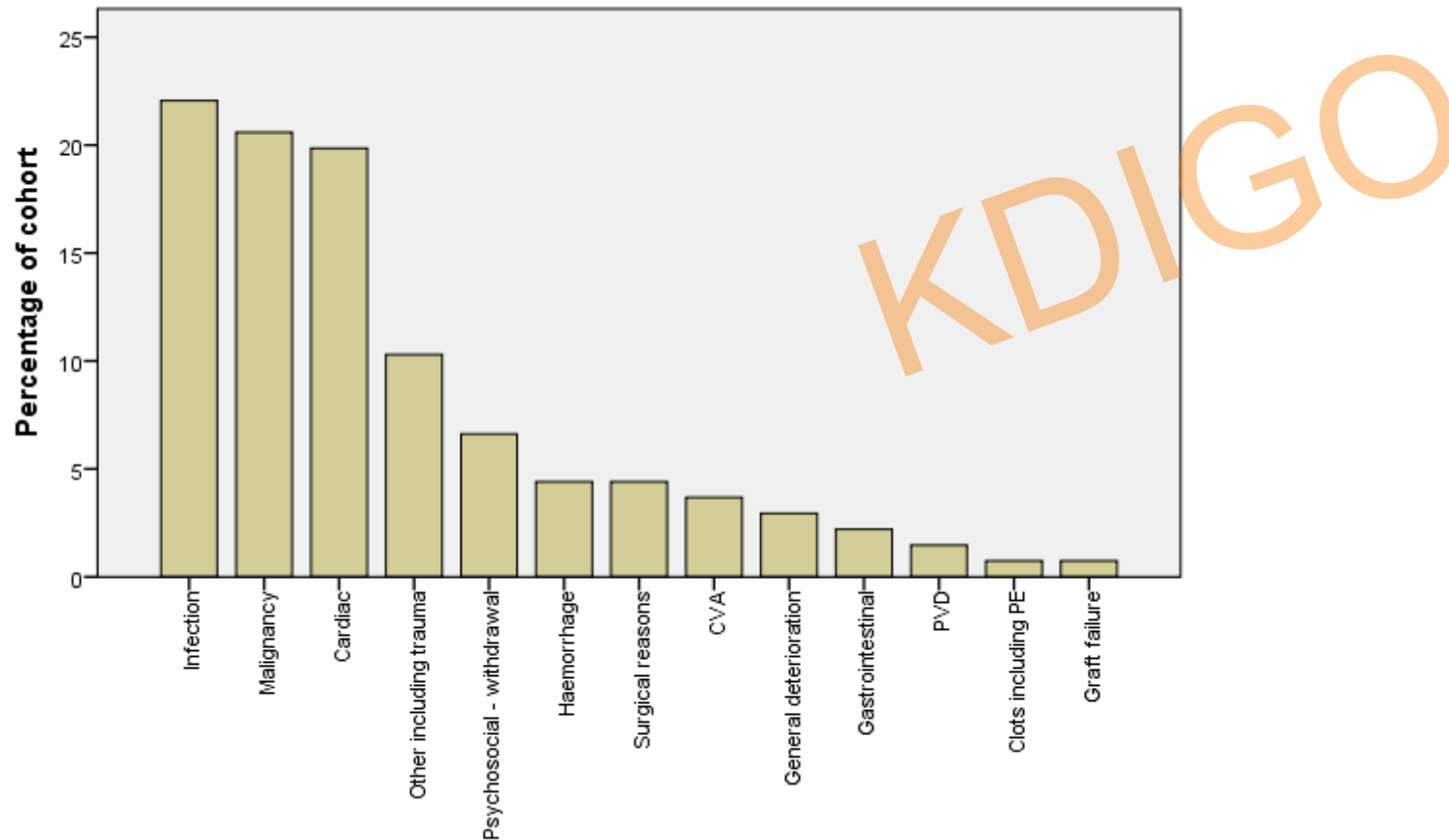
	Risk Factor	OR (95% CI)
Baseline	Arrhythmia	2.26 (1.08-4.80)
	 LVEF <56%	2.38 (1.18-4.83)
	 HLA Antibodies	2.10 (1.04-4.20)
Post-Transplant	Deceased CV Donor	5.18 (1.22-22.2)
	Acute Rejection	2.77 (1.20-6.30)

CONCLUSION:

In kidney transplant recipients older than 70, cardiac evaluation and immunosuppression optimization seem to be crucial to improve short-term patient and graft survival.

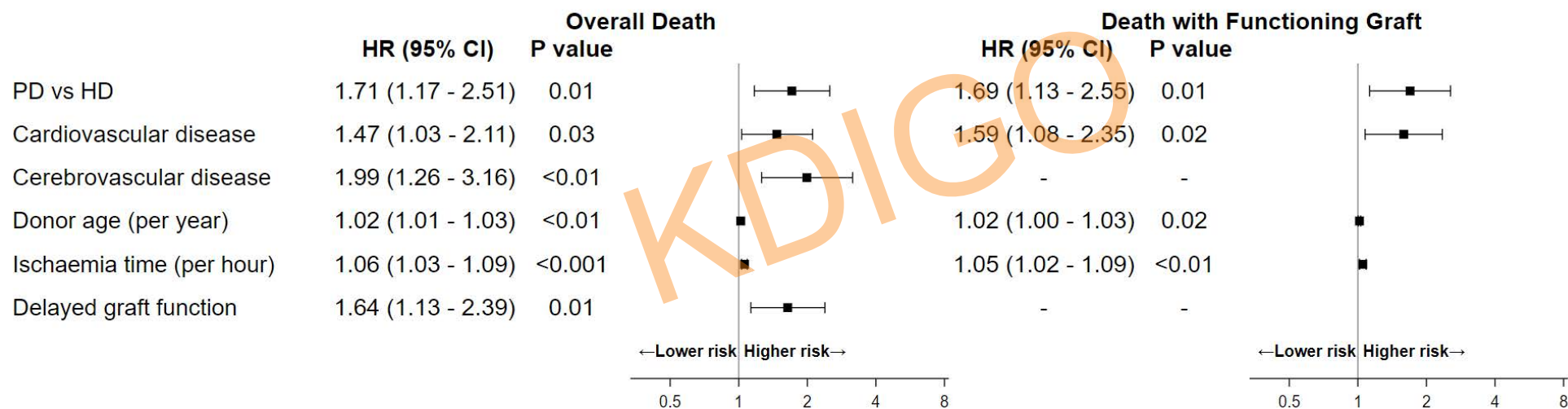
Australian Data

Causes of death in patients over age 65 years

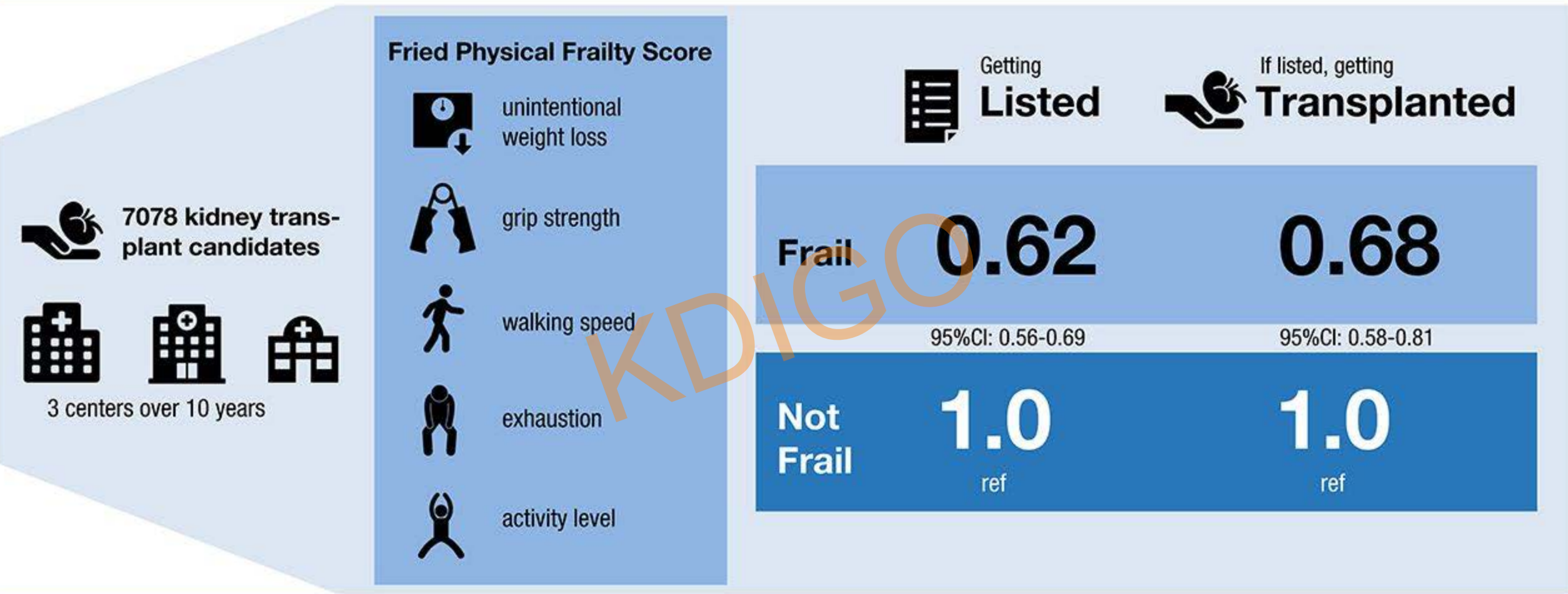


Australian data

Risk factors of death in older transplant recipients



How do frail people do with a kidney transplant evaluation?



Conclusions Frailty is associated with lower chance of getting listed for a kidney transplant and subsequently a lower chance of actually getting a kidney transplant.

Christine Haugen, Nadia Chu, Hao Ying, Fatima Warsame, et al. **Frailty and Access to Kidney Transplantation.** CJASN doi: 10.2215/CJN.12921118. **Visual Abstract** by Joel Topf, MD, FACP

Age criteria

- Do not exclude patients from kidney transplantation because of age alone, but rather consider the context of other comorbidities, including frailty, that may impact on outcomes about the suitability of kidney transplantation (ungraded)

KDIGO

Shared-decision making process for older transplant candidates

- Expected survival on dialysis
- Expected quality of life on dialysis
- Expected survival with a functioning graft
- Post-transplant expectations
- Balancing the risk of over vs. under immunosuppression

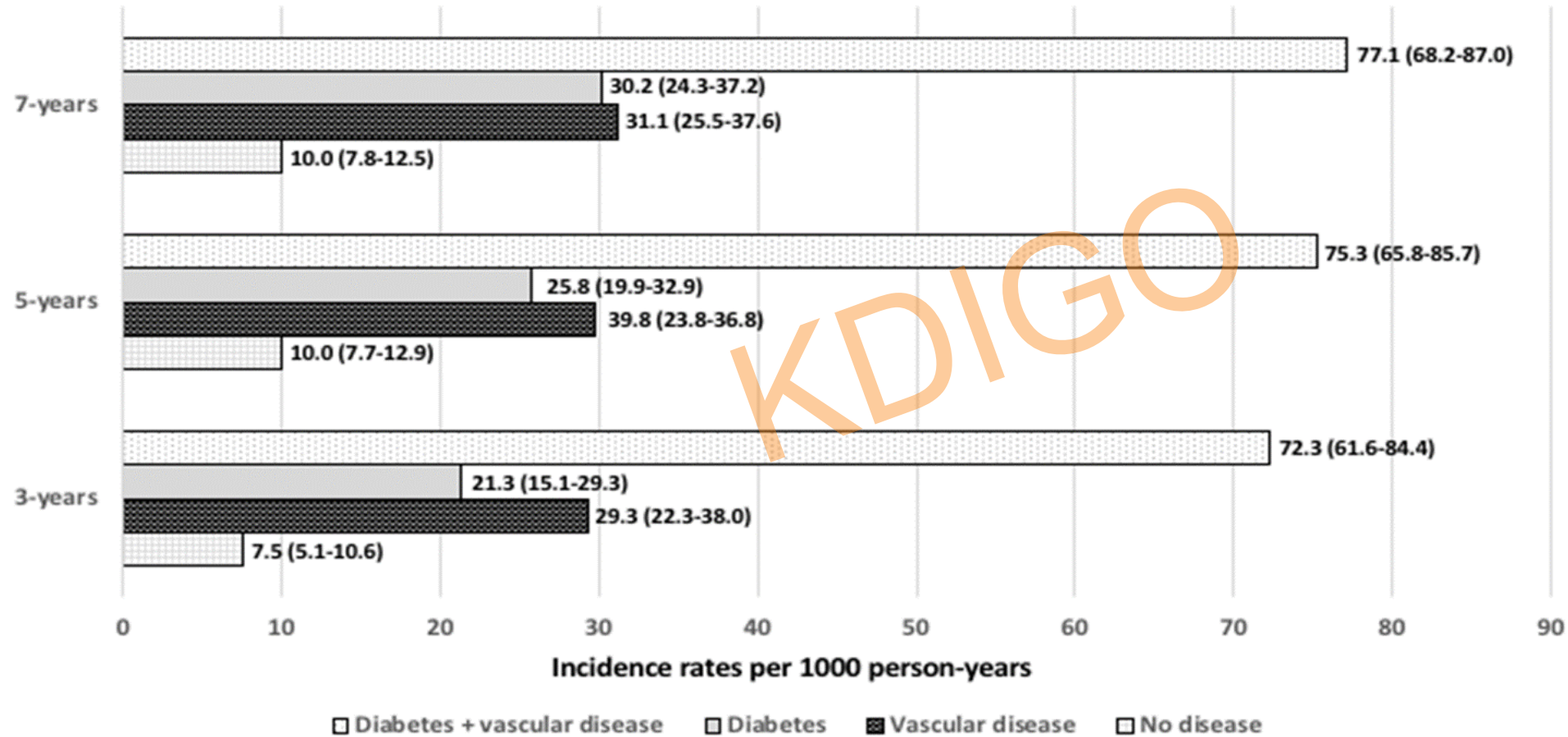
Diabetes and Cardiovascular disease

KDIGO

Diabetes and CVD

Figure 3

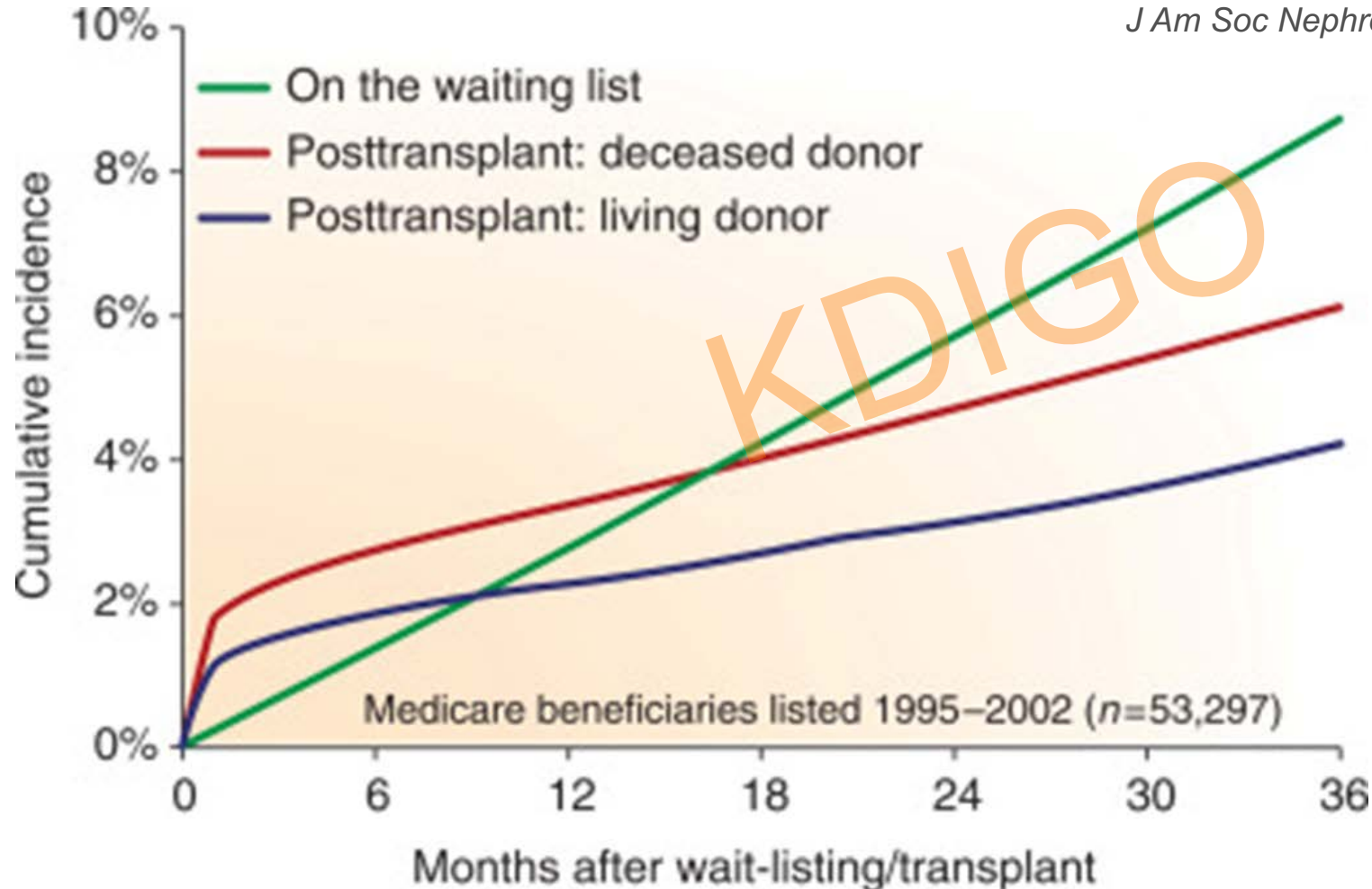
Kidney transplant recipients: first MACE or cardiac mortality



Lim WH et al manuscript submitted. Incidence rates of major adverse cardiovascular events (MACE) and cardiac mortality of kidney transplant recipients using data from linked administrative healthcare databases from Ontario, Canada (2005-2014, follow-up until 2018).

Risk of MACE on the waiting list and after transplantation

Acute myocardial infarction and kidney transplantation.
J Am Soc Nephrol. 2006; **17**: 900-907



Issues to consider during work-up for diabetic patients

- We recommend that candidates with type 1 or type 2 DM be considered for kidney transplantation (1B)
- We suggest that asymptomatic candidates at high risk for coronary artery disease (e.g. diabetes, previous CAD or with poor functional capacity) undergo **non-invasive CAD screening (2C)**
- We recommend that asymptomatic candidates with known CAD **not be revascularized exclusively to reduce perioperative cardiac events (1B)**
- Diabetes associated with higher risk of wound complications (not graded)

Screening for CVD in high-risk transplant candidates

- **WHO criteria**
- Condition must be **an important health problem**
- Condition should be a **recognizable latent or early symptomatic stage**
- **Natural history of the condition**, including development from latent to declared disease, should be adequately understood
- An **accepted treatment for patients** with recognized disease
- **Suitable test or examination** that has a high level of accuracy
- **Acceptable** to the population
- **Cost-effectiveness of the screening program**
- Screening should be a **continuing process**

Screening for CVD in high-risk transplant candidates

- **WHO criteria**
- Condition must be an **important health problem** **Yes**
- Condition should be a **recognizable latent or early symptomatic stage**
- **Natural history of the condition** should be adequately understood
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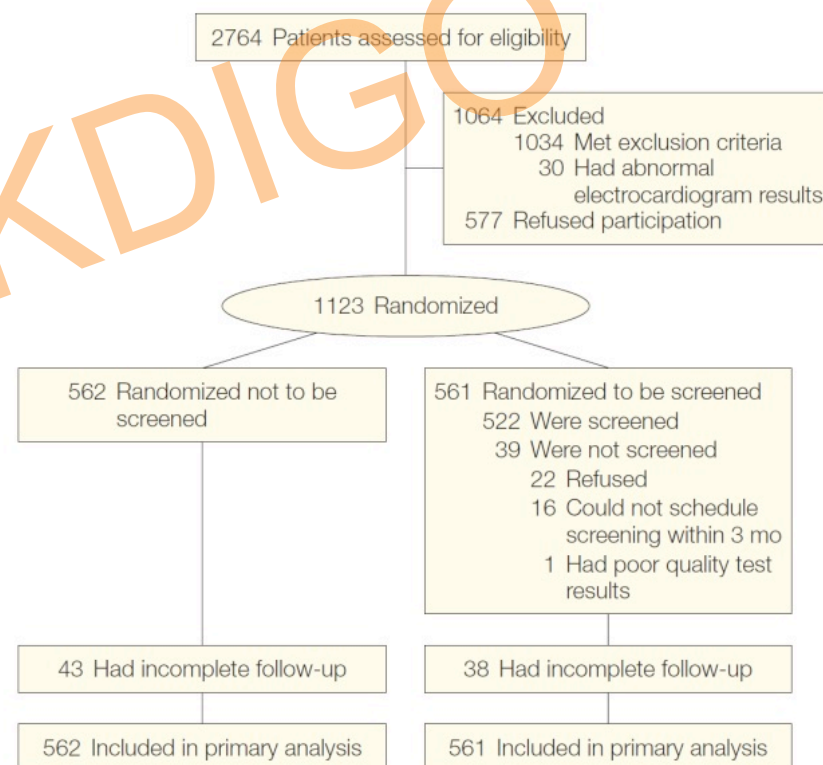
Uncertain

Evidence Cardiac Outcomes After Screening for Asymptomatic Coronary Artery Disease in Patients With Type 2 Diabetes

The DIAD Study: A Randomized Controlled Trial

JAMA, April 15, 2009—Vol 301, No. 15

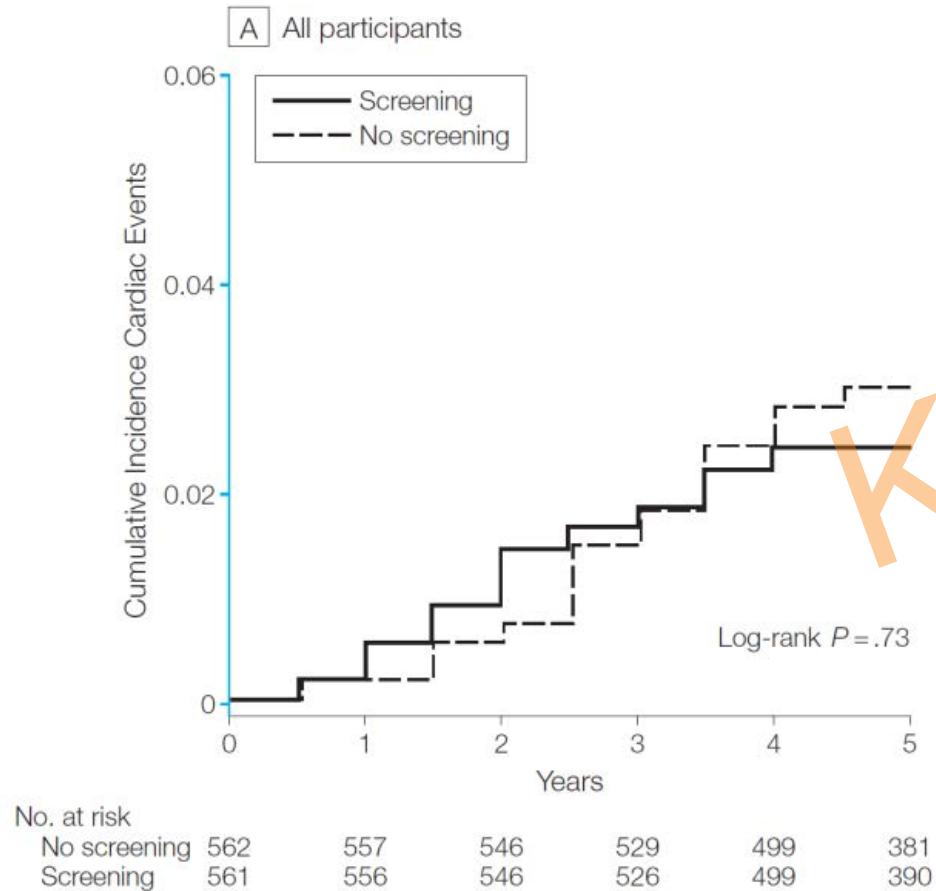
Figure 1. Flow of Study Participants



Evidence

Does not appear to have any benefits from routine screening in asymptomatic diabetic patients

But this trial exclude patients with kidney disease !!!



Eagerly await for the results of the CARSK trial

CARSK stands for the "**C**anadian-**A**ustralasian **R**andomised Trial for **S**creening **K**idney Transplant Recipients for Coronary Artery Disease."



Accuracy of the screening tests

Cardiac Testing for Coronary Artery Disease in Potential Kidney Transplant Recipients: A Systematic Review of Test Accuracy Studies

Louis W. Wang, MM(ClinEpi)(Hons),¹ Magid A. Fahim, MD,² Andrew Hayen, PhD,¹
 Ruth L. Mitchell, MA(Inf),³ Stephen W. Lord, DM,⁴ Laura A. Baines, MD,⁵
 Jonathan C. Craig, PhD,^{1,3} and Angela C. Webster, PhD^{1,3,6}

Test	No. of Studies	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC	Variance of Random Effects of log(DOR)	P for Difference in Accuracy ^a
Overall Results (all studies)							
MPS	7	0.69 (0.48-0.85)	0.77 (0.59-0.89)	7.68 (1.99-29.67)	0.80	0.2763	}0.07
DSE	11	0.80 (0.64-0.90)	0.89 (0.79-0.94)	30.98 (10.66-90.03)	0.92	0.2224	
Only Studies With Reference Standard Threshold \geq70% Coronary Artery Stenosis							
MPS	6	0.68 (0.43-0.85)	0.80 (0.60-0.91)	8.15 (1.58-42.00)	0.81	0.3487	}0.2
DSE	8	0.78 (0.59-0.90)	0.87 (0.75-0.94)	24.40 (7.19-82.78)	0.90	0.2492	
Only Studies in Which Partial Verification Was Avoided							
MPS	7	0.68 (0.43-0.85)	0.80 (0.60-0.91)	8.15 (2.56-25.93)	0.81	0.3487	}0.1
DSE	9	0.74 (0.52-0.88)	0.88 (0.74-0.95)	20.41 (6.46-64.50)	0.89	0.2571	
Only Studies That Avoided Partial Verification and Had Reference Standard Threshold \geq70% Coronary Artery Stenosis							
MPS	6	0.68 (0.43-0.85)	0.80 (0.60-0.91)	8.15 (2.56-25.93)	0.81	0.3487	}0.2
DSE	8	0.78 (0.59-0.90)	0.87 (0.75-0.94)	24.40 (7.19-82.78)	0.90	0.2492	

Reasonable test overall test accuracies

ISCHEMIA CKD study

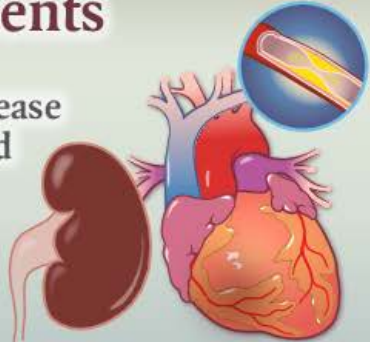
The NEW ENGLAND JOURNAL of MEDICINE

Managing Coronary Disease in Advanced Kidney Disease

OPEN-LABEL RANDOMIZED, CONTROLLED TRIAL

777 Patients

with stable
coronary disease
and advanced
CKD



Invasive Strategy

+ Medical
therapy

(N=388)



Conservative Care

Medical
therapy

(N=389)



Death or nonfatal MI

123

129

Adjusted HR 1.01; 95% CI, 0.79–1.29; P=0.95

Angina-related
health status

No difference in Seattle Angina
Questionnaire summary score

Invasive treatment did not reduce the rate of death or nonfatal MI
or improve angina-related health status

Limitations and applicability in transplant candidates

- Not really applicable to our candidates
- Early deaths from CVD occur in the peri-operative periods
- Transplantation surgery is complex
- Hemodynamic changes
- Blood loss and other factors may potentially influence the outcomes

Cancer

KDIGO

POTENTIAL CANDIDATE WITH A PRIOR CANCER

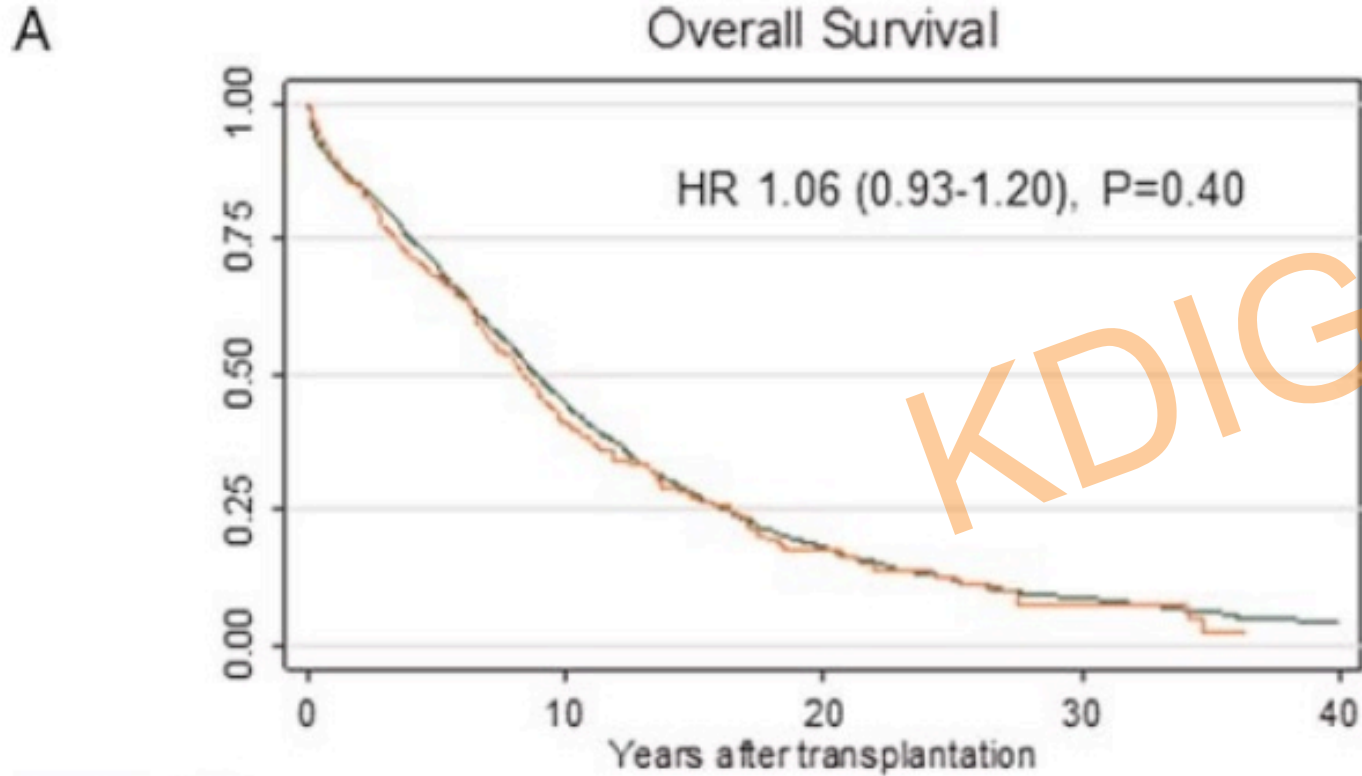
TYPE	STAGE	GUIDELINE					
		AST	CARI	B&D	CST	EBPG	MMOH
Renal cell carcinoma	Small or discovered incidentally	●	●	●			●
	Symptomatic	○	●	○		○	
	Large or Invasive	●		○			●
Bladder cancer	In-situ or non-invasive papilloma	●	●	●	●	○	●
	Invasive	○	○	○	○	●	○
Breast Cancer (a,b)	Stage 0-2 (including early stage)	○	○	○	○	●	○
	Stage 3-4 (advanced/invasive)	●	●	○	●	●	○
Colorectal Cancer (c)	Duke A or B1	○	○	○	○	○	○
	Duke C		●			○	○
	Duke D		●			○	○
	Patients with a history of colorectal cancer	●			●		
Uterine Cancer	Cancer of the uterine body	○	○			○	○
	Cervical cancer in-situ	○	●	●	○	○	●
	Invasive cervical cancer		●	○		●	●
Prostate Cancer	Localised	●	●				
	Invasive	○	○			○	○
Melanoma	In-situ	○	○	●	○		●
	Invasive	●	●	●	●	○	●
Non-melanoma skin cancers	Basal Cell Carcinoma					○	
	Squamous Cell Carcinoma						○
Leukemia		○			○		
Lung Cancer		○			○		
Lymphoma		○	○	○	○		○
Multiple Myeloma			●		●		
Testicular Cancer		○	○				○
Thyroid Cancer		○	○				○
Wilms Tumour		○	○	○			○

- Recommendations/suggested waiting times from various clinical practice guidelines

- Based on largely observational data on cancer recurrence rates

	Recommendation
●	0 years
○	Minimum 2 years
○	2-5 years
●	Minimum 5 years
●	Contraindicated
	No recommendation (or insufficient evidence)

PRIOR CANCER AND OVERALL SURVIVAL POST-TRANSPLANT



Number at risk

Years after transplantation	0	10	20	30	40
No cancer	5293	1640	266	37	4
Any cancer	377	106	18	3	0

Norwegian Study

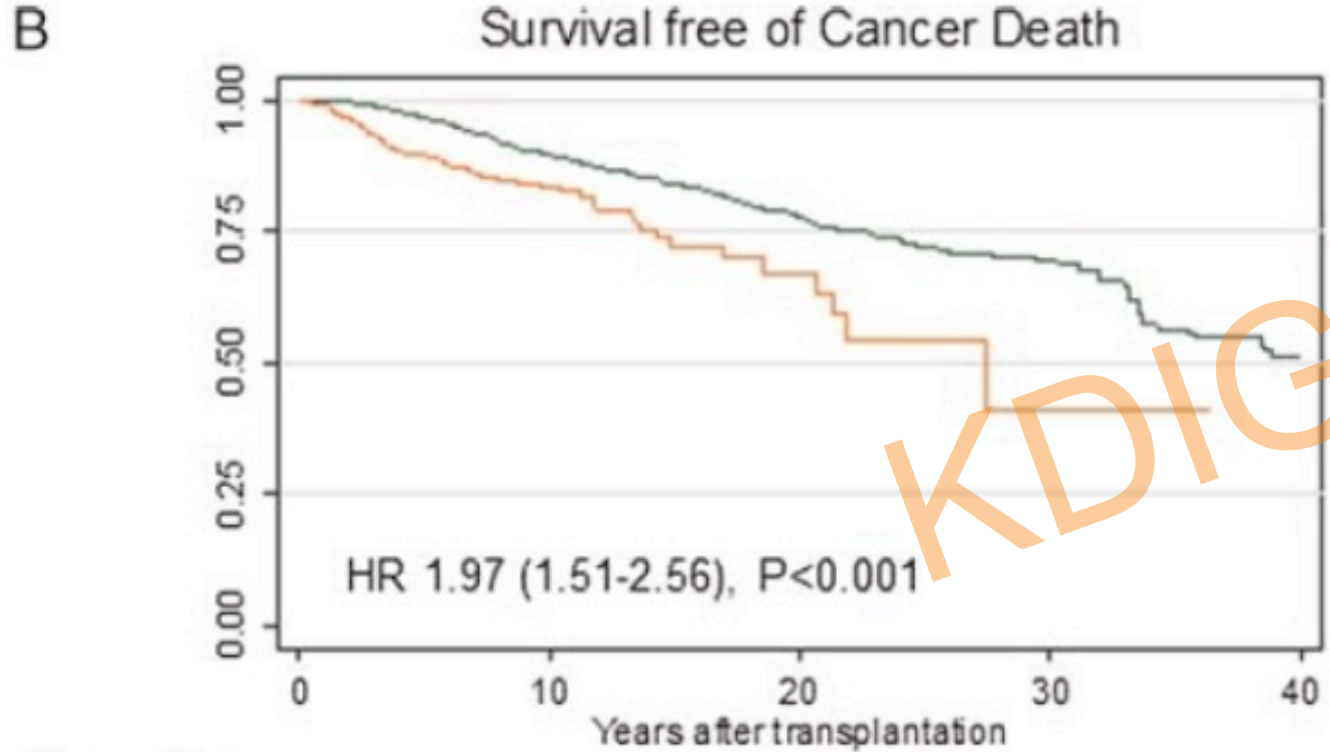
Policy of 1 year waiting period
(except NMSC and prostate cancer)

Matched analysis comparing with and
without Hx of cancer

No difference in overall and graft survival

Dahle et al., 2017 Transplantation

PRIOR CANCER AND CANCER SPECIFIC DEATH



Number at risk					
No cancer	5293	1640	266	37	4
Any cancer	377	106	18	3	0

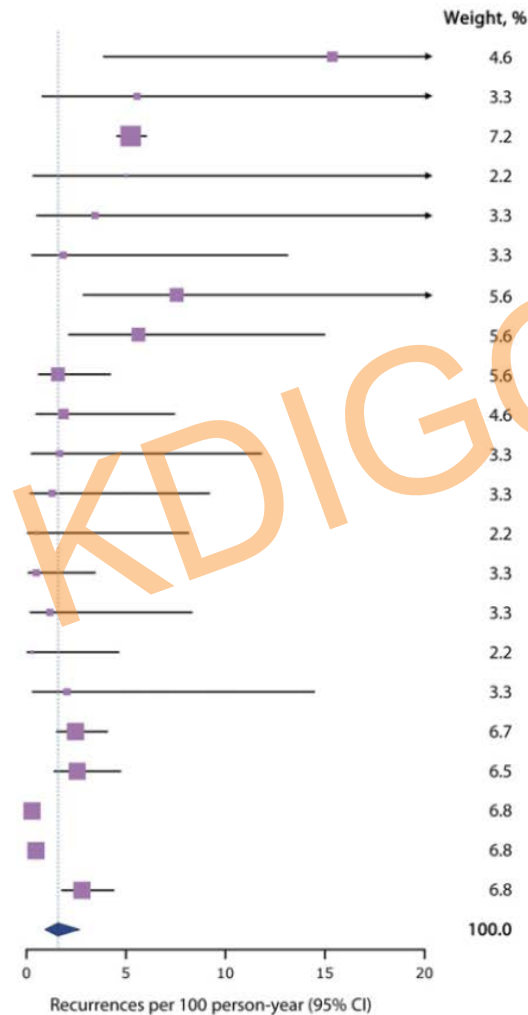
- Higher risk of cancer-related death among those with a prior cancer

Dahle et al., 2017 Transplantation

CANCER RECURRENCE AFTER KIDNEY TRANSPLANTATION

Study	Year	Recurrences	Total Person-years	Estimate (95% CI)	Weight, %
Alamartine et al ⁵³	1991	2	13	15.4 (3.9 to 61.5)	4.6
Dillon et al ⁵²	1991	1	18	5.6 (0.8 to 39.4)	3.3
Penn et al ³⁸	1993	185	3,533	5.2 (4.5 to 6.1)	7.2
Dousset et al ⁵¹	1995	0	10	5.0 (0.3 to 79.9)	2.2
Goldstein et al ⁵⁰	1996	1	29	3.5 (0.5 to 24.5)	3.3
Levitt et al ³⁵	1996	1	54	1.9 (0.3 to 13.2)	3.3
Koerner et al ⁴⁹	1997	4	53	7.6 (2.8 to 20.1)	5.6
Kelly et al ⁴⁸	1998	4	71	5.6 (2.1 to 15.0)	5.6
Danpanich al ⁴⁷	1999	4	251	1.6 (0.6 to 4.3)	5.6
Saigal et al ⁴⁶	2001	2	107	1.9 (0.5 to 7.5)	4.6
Grande et al ⁴⁵	2003	1	60	1.7 (0.2 to 11.8)	3.3
Ward et al ⁴⁴	2004	1	77	1.3 (0.2 to 9.2)	3.3
Ladowski et al ⁴³	2006	0	98	0.5 (0.0 to 8.2)	2.2
Benten et al ⁴²	2008	1	204	0.5 (0.1 to 3.5)	3.3
Jain et al ⁴¹	2009	1	85	1.2 (0.2 to 8.4)	3.3
Fernandez al ³⁹	2010	0	171	0.3 (0.0 to 4.7)	2.2
Metcalfe al ⁴⁰	2010	1	49	2.0 (0.3 to 14.5)	3.3
Sigurdardottir et al ³²	2012	15	607	2.5 (1.5 to 4.5)	6.7
Chung et al ²⁸	2014	10	390	2.6 (1.4 to 4.8)	6.5
Viecelli et al ²⁷	2014	19	6,770	0.3 (0.2 to 0.4)	6.8
Singh et al ²⁶	2015	18	3,718	0.5 (0.3 to 0.8)	6.8
Hellstrom et al ²³	2016	18	646	2.8 (1.8 to 4.4)	6.8
Overall		289	17,014	1.6 (1.0 to 2.6)	100.0

$I^2 = 87.3\%$, $P < 0.001$

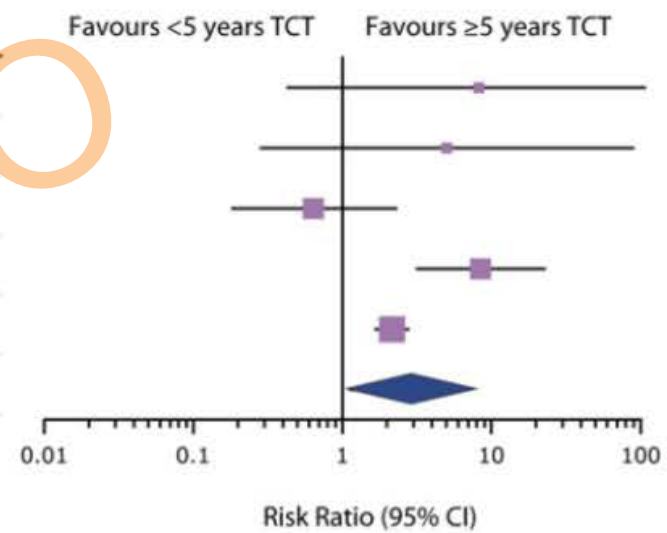


- Systematic review of 57 studies
Meta-analysis of 39 studies
- Overall estimated recurrence rate: **1.6 per 100 person-years**
- Substantial heterogeneity between studies

Acuna et al., 2017 Transplantation Reviews

WAITING TIME AND CANCER RECURRENCE AFTER KIDNEY TRANSPLANTATION

Study	TCT < 5 years		TCT ≥ 5 years		Risk Ratio IV, Random, 95% CI		Weight, %
	Recurrences	Total	Recurrences	Total	Favours < 5 years TCT	Favours ≥ 5 years TCT	
Desai et al ³⁰	2	13	0	22	8.21	(0.42 to 158.96)	7.6
Desai et al ²⁹	2	8	0	8	5.00	(0.28 to 90.18)	7.9
Hellstrom et al ²³	5	38	7	57	0.64	(0.18 to 2.33)	21.7
Sigurdardottir et al ³²	20	42	4	71	8.45	(3.10 to 23.05)	26.1
Hanaway et al ³⁶	165	466	56	340	2.15	(1.64 to 2.81)	36.7
Overall	192	567	67	498	2.80	(1.12 to 7.01)	100.0



$I^2=65\%$, $p=0.03$

Note – high heterogeneity

A higher risk of cancer recurrence in patients who have waited shorter than 5 years after cancer remission

Acuna et al., 2017 Transplantation Reviews

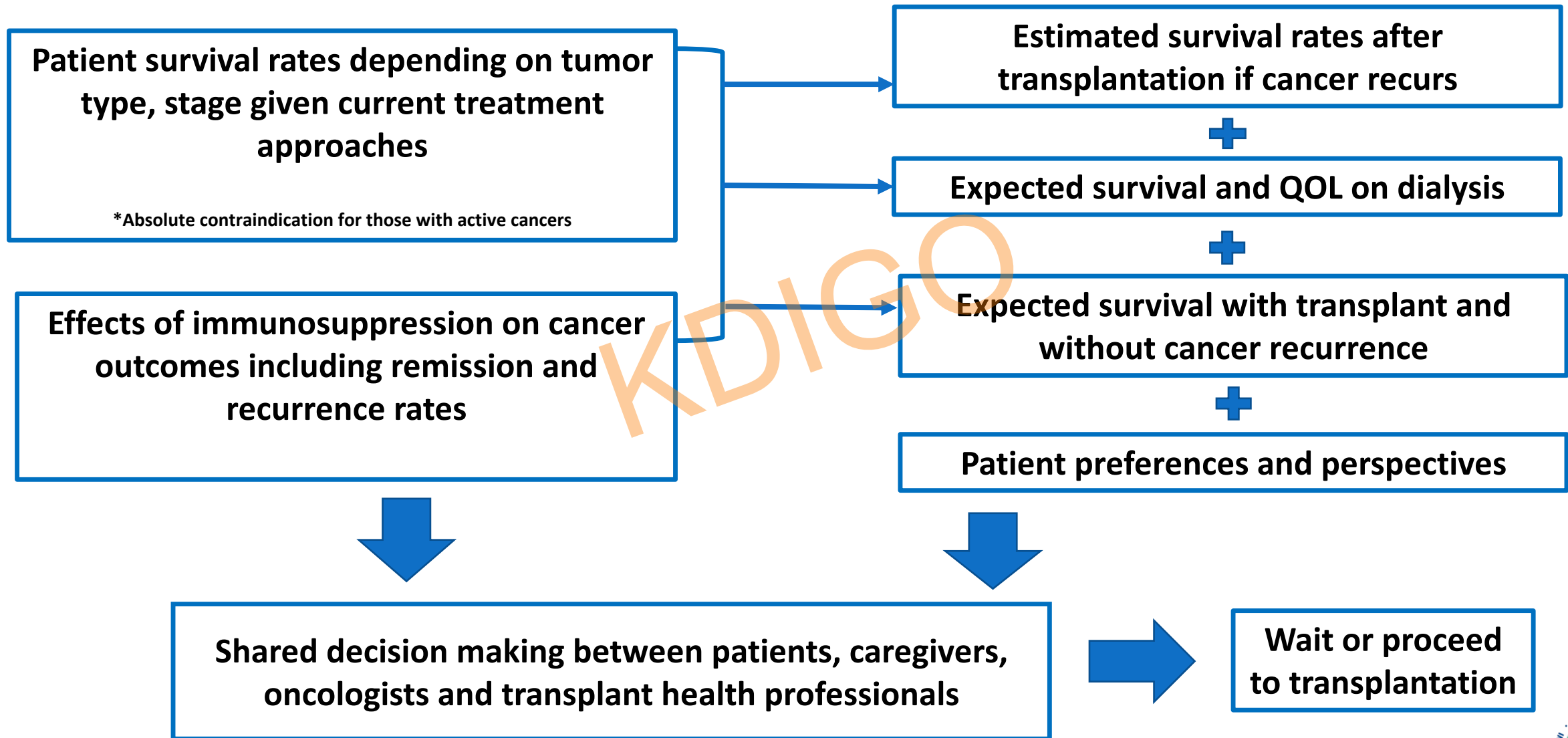
KDIGO RECOMMENDATIONS

- 11.2.1: We recommend that candidates with **acute malignancy be excluded** from kidney transplantation except for those with indolent and low-grade cancers such as prostate cancer (Gleason score ≤ 6), superficial non-melanoma skin cancer, and incidentally detected renal tumors (≤ 1 cm in maximum diameter) (1B)
- 11.2.2: **Timing of kidney transplantation** after potentially curative treatment for cancer **is dependent on the cancer type and stage at initial diagnosis** (not graded) (**Table 14**)
- 11.2.3: We recommend no waiting time for candidates with curatively treated (surgically or otherwise) non-metastatic basal cell and squamous cell carcinoma of the skin; melanoma in-situ; small renal cell carcinoma (< 3 cm); prostate cancer (Gleason score ≤ 6), carcinoma-in-situ; thyroid cancer (follicular/papillary < 2 cm of low grade histology) and superficial bladder cancer (1C).
- 11.2.4: Decisions about transplantation for candidates in remission from cancer should be made collaboratively with oncologists, transplant nephrologists, patients and their caregivers (not graded)

TABLE 14.**Recommended waiting times between cancer remission and kidney transplantation⁹¹**

Breast	Early	At least 2 years
	Advanced	At least 5 years
Colorectal	Dukes A/B	At least 2 years
	Duke C	2-5 years
	Duke D	At least 5 years
Bladder	Invasive	At least 2 years
Kidney	Incidentaloma (< 3 cm)	No waiting time
Uterine	Early	At least 2 years
	Large and invasive	At least 5 years
	Localized	At least 2 years
Cervical	Invasive	At least 5 years
	Localized	At least 2 years
Lung	Invasive	At least 5 years
	Localized	2-5 years
Testicular	Localized	At least 2 years
Melanoma	Invasive	2-5 years
	Localized	At least 5 years
Prostate	Invasive	Contraindicated
	Gleason ≤ 6	No waiting time
	Gleason 7	At least 2 years
Thyroid	Gleason 8-10	At least 5 years
	Papillary/Follicular/ Medullary	
	Stage 1	No waiting time
Hodgkin Lymphoma	Stage 2	At least 2 years
	Stage 3	At least 5 years
	Stage 4	Contraindicated
	Anaplastic	Contraindicated
	Localized	At least 2 years
Non-Hodgkin Lymphoma	Regional	3-5 years
	Distant	At least 5 years
	Localized	At least 2 years
Post-transplant lymphoproliferative disease	Regional	3-5 years
	Distant	At least 5 years
	Nodal	At least 2 years
	Extranodal and cerebral	At least 5 years

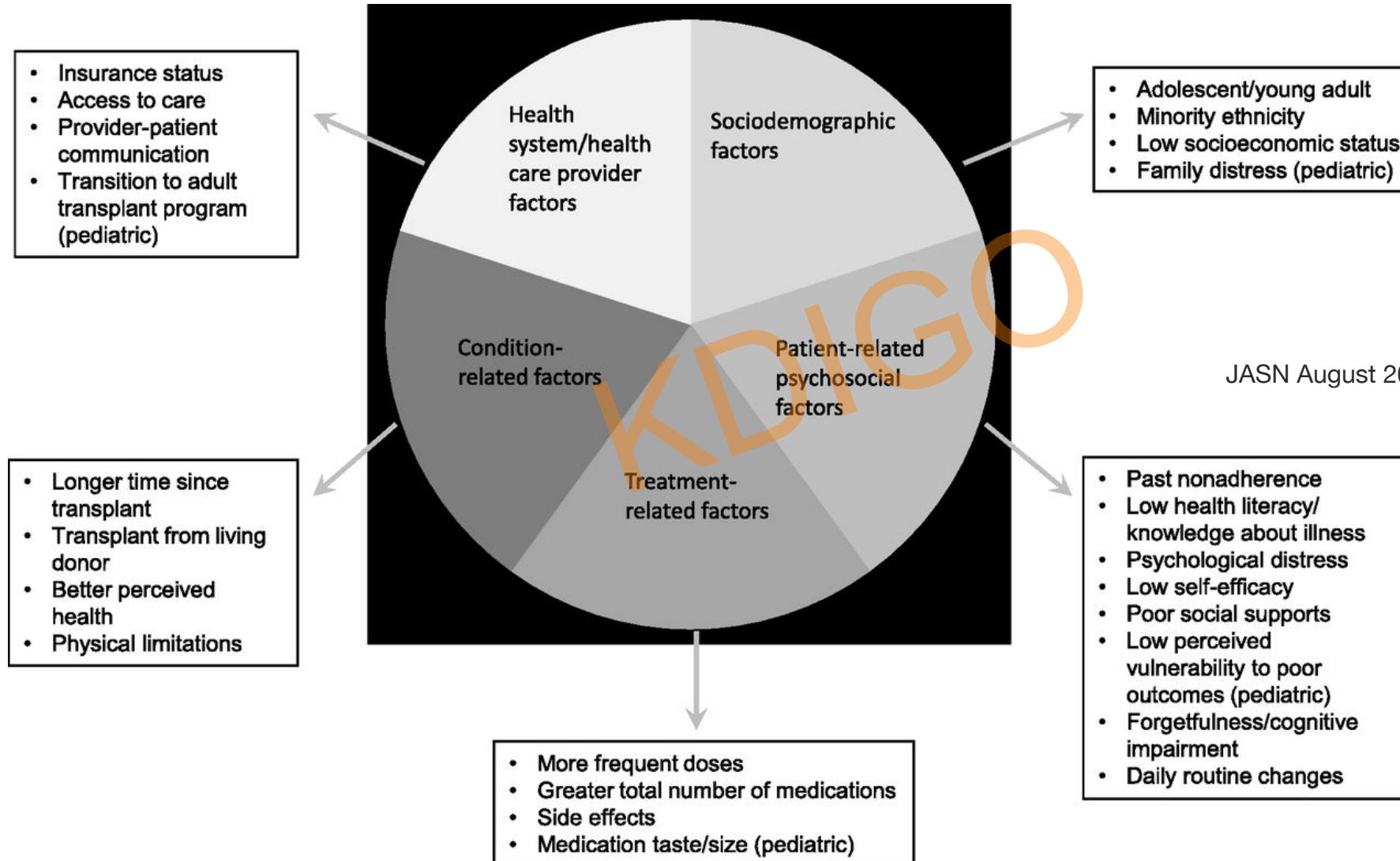
CONSIDERATION FOR TRANSPLANTATION IN CANDIDATES WITH PRIOR CANCERS AND IN COMPLETE REMISSION



Adherence

KDIGO

Adherence after transplantation



JASN August 2017, 28 (8) 2290-2301

KDIGO recommendations

- Assess adherence and adherence barriers pre-transplantation. Appropriate adherence-based education, counselling pre-transplant and post-transplant surveillance should be provided
- Candidates with a history of nonadherence from kidney transplantation should not be excluded except for those with on-going, health-compromising nonadherent behaviour despite education and counselling

Summary

- Transplant assessment is complex.
- This guideline provides **recommendations for evaluation** of individual aspects of a **candidate's profile** such that each risk factor and comorbidity are considered.
- This guideline is intended to be **global**.
- The goal is to assist transplant professionals to assimilate all data relevant to an individual, consider this within their **local health context**, and make an overall judgment on candidacy for transplantation.



KDIGO Transplant Candidate Guideline Work Group Meeting

Thank you very much