NEPHROLOGY EDUCATION PORTAL

60TH ERA CONGRESS
MILAN & VIRTUAL
JUNE 15-18, 2023

NEP Special Edition
Summary Reports

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Late Breaking Clinical Trial I

Long-Term Renal Benefit Over 2 years With Nefecon Verified: The NeflgArd Phase III Full Trial Results

Richard Lafayette, USA

Introduction

The NeflgArd is a Phase III trial investigating the efficacy and long-term renal benefit of Nefecon, a targeted-release budesonide formulation designed to treat Immunoglobulin A nephropathy (IgAN). It was the first treatment approved by the FDA and EMA for adult patients with primary IgAN at risk of rapid disease progression. The initial results showed significant reduction in urine protein-to-creatinine ratio (UPCR) and a treatment benefit on estimated glomerular filtration rate (eGFR) compared to placebo after 9 months of treatment. This presentation presents the efficacy and safety data from the full long-term dataset of Nefecon in treating IgAN patients over a two-year period, including 9 months of treatment and 15 months of follow-up.

NeflgArd trial overview

The NeflgArd trial is a randomized, double-blind, two-part Phase III trial (figure 1). In the interim readout conducted in November 2020, the trial included 199 participants, with the primary endpoint being proteinuria and a key secondary endpoint being eGFR. The full Phase III trial, which included 364 patients, was designed to confirm the long-term renal benefit by observing reductions in proteinuria. Eligible participants were aged ≥18 years with biopsy-proven IgAN, proteinuria >1 g, eGFR >35–<90 mL/min/1.73 m², and well-controlled blood pressure. Patients with systemic diseases, kidney transplants, or other glomerulopathies were excluded from the study.

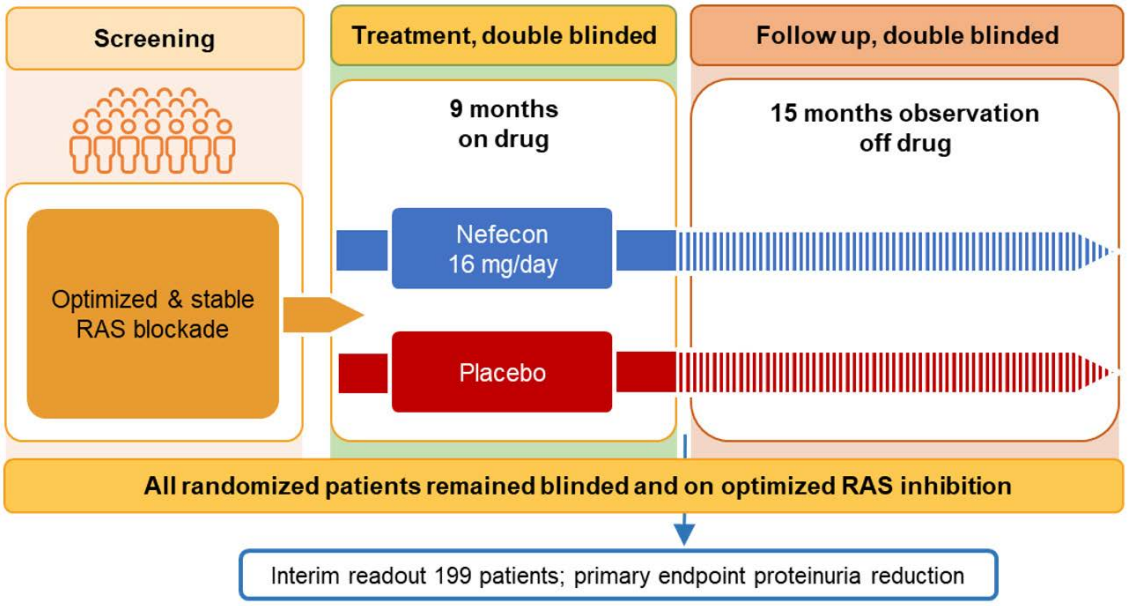


Figure 1.
NeflgArd trial design. RAS, renin–angiotensin system.

The trial included 364 patients with biopsy-proven IgAN and well-controlled blood pressure. Median age was 43 years, and the majority were male (64.3%) and white (75.8%). Baseline characteristics, including UPCR and eGFR, were well-matched between the Nefecon and placebo groups.

Key Results

Efficacy Results

- Nefecon treatment resulted in a significant eGFR preservation of 5.05 mL/min/1.73 m² over 2 years compared to placebo (p<0.0001).
- The eGFR benefit observed at the end of the 9-month treatment period was sustained during the 15-month observational follow-up (figure 2).
- The eGFR benefit was consistent across different baseline UPCR subgroups, supporting the efficacy of Nefecon regardless of disease severity.
- UPCR reduction was significant with Nefecon, with a 30% reduction at 3 months, 50% at 6 months, and 30% at 9 months compared to baseline.

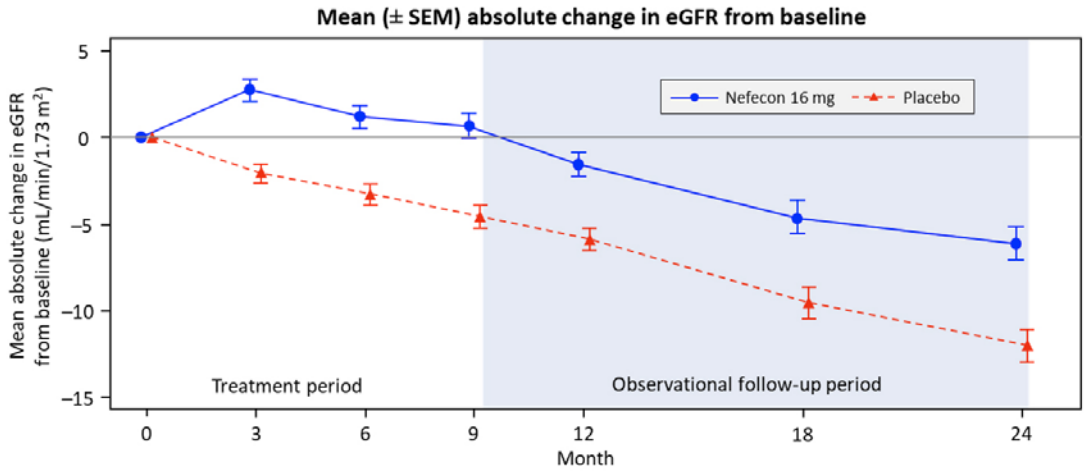


Figure 2. Primary endpoint – Mean (± SEM) absolute change in eGFR from baseline; eGFR, estimated glomerular filtration rate; SEM, standard error of the mean.

Safety Results

- Nefecon was generally well-tolerated, and the adverse events reported were consistent with those observed in the previous interim analysis.
- Common treatment-emergent adverse events included peripheral oedema, hypertension, and muscle spasms.

Conclusion

The NefIgArd Phase III trial met its two-year primary endpoint, demonstrating the long-term renal benefit of Nefecon in treating IgAN. Over a two-year period, nefecon treatment demonstrated significant eGFR preservation compared to placebo, with consistent benefits regardless of baseline UPCR levels. Nefecon was also generally well-tolerated. These data support nefecon and its potential as a disease-modifying treatment for IgAN.

Further reading

1. Barratt J, et al. Kidney Int Rep 2020;5:1620-1624.
2. Barratt J, et al. Kidney Int 2023;103:391-402.
3. Calliditas Therapeutics press release. Available from: https://www.calliditas.se/en/calliditas-announces-primary-endpoint-successfully-met-in-phase-3-nefigard-trial-evaluating-nefecon-in-iga-nephropathy/. Last accessed: July 2023.

Factor XIa Inhibition By Osocimab In Patients With End-Stage Kidney Disease Undergoing Haemodialysis

Wolfgang Winkelmayer, USA

Introduction

Patients with end-stage kidney disease (ESKD) undergoing haemodialysis face heightened risks of thromboembolic events and major bleeding. The benefits and net benefit of anticoagulation strategies remain uncertain in this population. Osocimab, an antibody targeting factor XIa to inhibit its activity, presents a potential treatment option for these patients. The CONVERT trial investigates osocimab's efficacy and safety in ESKD individuals on haemodialysis.

The CONVERT Trial: Overview and Key Results

The CONVERT trial, a phase IIb, randomized, double-blind, placebo-controlled study, evaluated the safety and efficacy of osocimab in ESKD patients undergoing haemodialysis. Primary safety outcomes were clinically relevant bleeding (major and clinically relevant non-major bleeding), and assessment of moderate, severe, and serious adverse events. Exploratory efficacy outcomes included factor XIa inhibition and major adverse vascular events (vascular death, non-fatal myocardial infarction or stroke, major limb amputation, acute limb ischemia, and symptomatic venous thromboembolism). The trial included 704 participants randomized into three arms: lower-dose osocimab (N=235), higher-dose osocimab (N=234), and placebo (N=235) (figure 1).

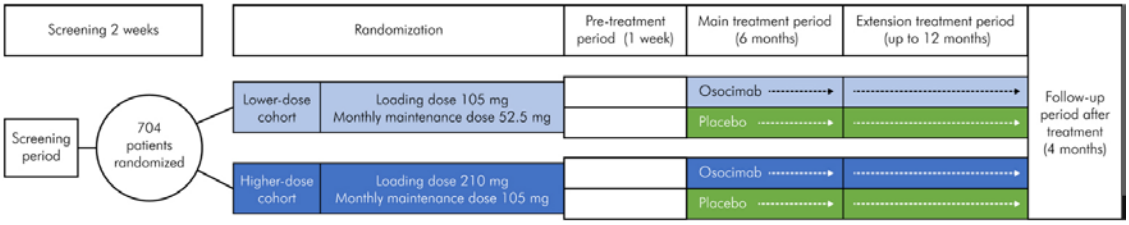


Figure 1. CONVERT: a Phase IIb, randomized, double-blind, placebo-controlled, parallel-group study in individuals with kidney failure undergoing haemodialysis.

Baseline Characteristics

- Participants across treatment arms had well-balanced baseline demographics and clinical characteristics.
- Median age was 61 years, 64% were male, and the mean BMI was 28 kg/m^2.
- Most participants (96%) were receiving heparin, and over 40% were receiving low-dose aspirin.

Safety and Efficacy Outcomes

Osocimab demonstrated a generally well-tolerated safety profile, with similar adverse events observed in both osocimab and placebo groups. Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity. The most common TEAEs included COVID-19, renal transplant, pneumonia, and COVID-19 pneumonia. No bleeding events were reported in the 26 participants treated with osocimab (N=13, each arm) who had major surgery or intervention, including the 13 participants who underwent kidney transplantation (figure 2).

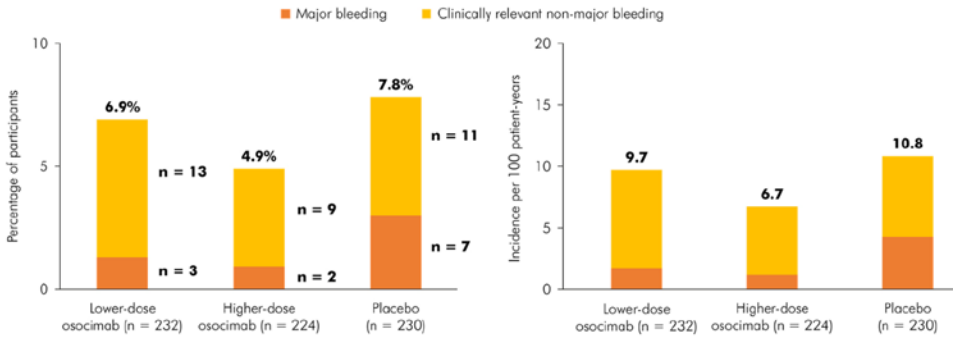


Figure 2. Clinically relevant bleeding. Bleeding was classified as major if it was overt and associated with a decrease in haemoglobin of 2 g/dL or more; necessitated transfusion of two or more units of blood; occurred in a critical area or organ; or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria of major bleeding, but that necessitated medical examination or intervention, or had clinical consequences.

Osocimab demonstrated rapid, dose-dependent, and sustained inhibition of factor XIa relative to baseline (figure 3).

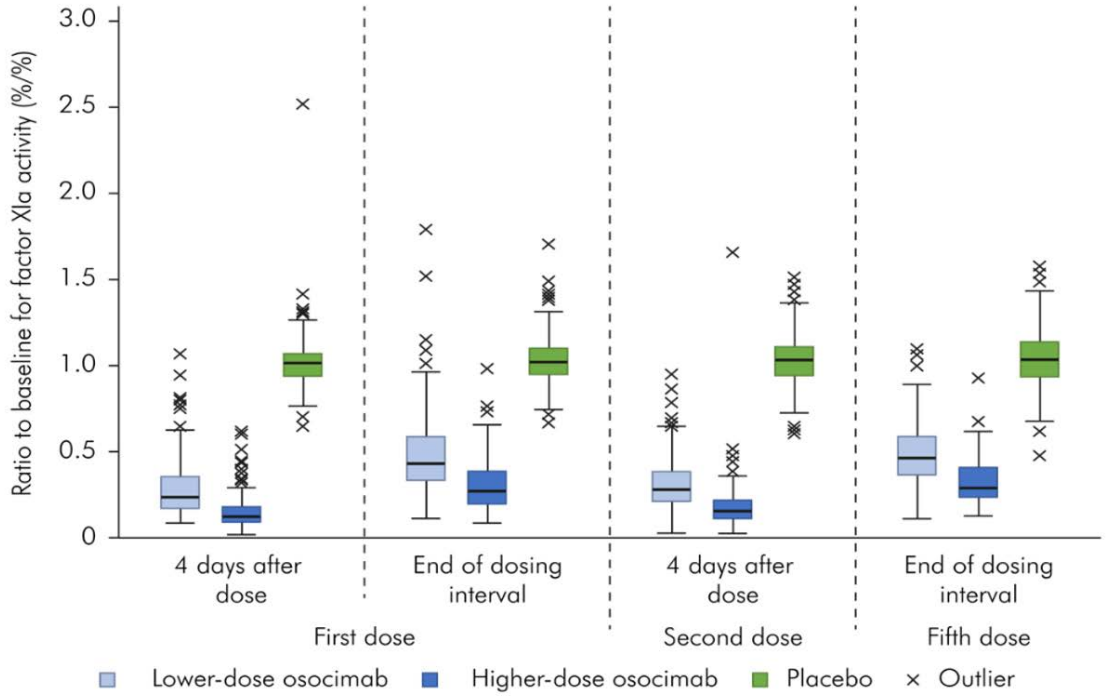


Figure 3. Factor XIa inhibition relative to baseline. The medians are indicated by the horizontal lines in the boxes; the boxes indicate the 25th and 75th percentiles; and the vertical lines extend to a maximum distance of 1.5 interquartile ranges – any value more extreme is plotted separately.

Exploratory assessment of antithrombotic efficacy revealed that osocimab-treated participants exhibited a significantly reduced relative risk of partial or complete clotting compared to those who received placebo.

Conclusion

The results of the CONVERT trial indicate that both doses of osocimab have safety profiles similar to placebo, which is consistent with past clinical experience. Furthermore, exploratory findings suggest osocimab has potential to provide antithrombotic effects beyond those of heparin. Phase III trials are needed to determine whether osocimab reduces the risk of thromboembolic events in participants with kidney failure undergoing haemodialysis. These findings underscore osocimab's potential as a therapeutic option for this patient population, potentially improving anticoagulation management and patient outcomes.

Further reading

1. Asselta R et al. Blood 2017;130(4):e1–6.
2. Beavers CJ et al. J Cardio Pharmacol 2020;76:645–9.
3. ClinicalTrials.gov (NCT04523220). Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04523220. Last accessed: July 2023.
4. Eikelboom J et al. Kidney Int 2021;100:1199–207.
5. Gailani D, Gruber A. Arterioscler Thromb Vasc Biol 2016;36(7):1316–22.
6. Meijers J et al. N Engl J Med 2000;9;342(10):696–701.
7. Nopp S et al. Front Cardiovasc Med 2022;9:903029.
8. Preis M et al. Blood 2017;129(9):1210–5.
9. Reinecke H et al. J Am Soc Nephrol 2009;20:705–11.
10. Webster AC et al. Lancet 2017;389:1238–52.

Intranasal Niclosamide For Pre-Exposure Prophylaxis Against SARS-CoV-2 In A Vulnerable, Largely Vaccinated Renal Patient Population

Rona Smith, United Kingdom

Introduction

Despite vaccination, some individuals remain at risk of Covid-19 infection, necessitating the exploration of antigen-independent pre-exposure prophylaxis options. Niclosamide, a salicylamide with in vitro activity against viruses, including SARS-CoV-2, was formulated as an intranasal spray (UNI911). This study evaluates the safety and efficacy of intranasal niclosamide in a vulnerable, largely vaccinated (~90%) renal patient population.

Trial Overview

This trial is part of a platform studies protocol which enable the efficient evaluation of multiple agents under a single master protocol. For the niclosamide trial, participants were recruited between February 2021 and November 2022, with 826 receiving niclosamide and 825 receiving a placebo. The primary efficacy endpoint was the reduction of symptomatic Covid-19 infections, and the safety profile was closely monitored. The trial involved 2-weekly symptom checks, in-person visits, and telephone consultations over 6-9 months (figure 1).

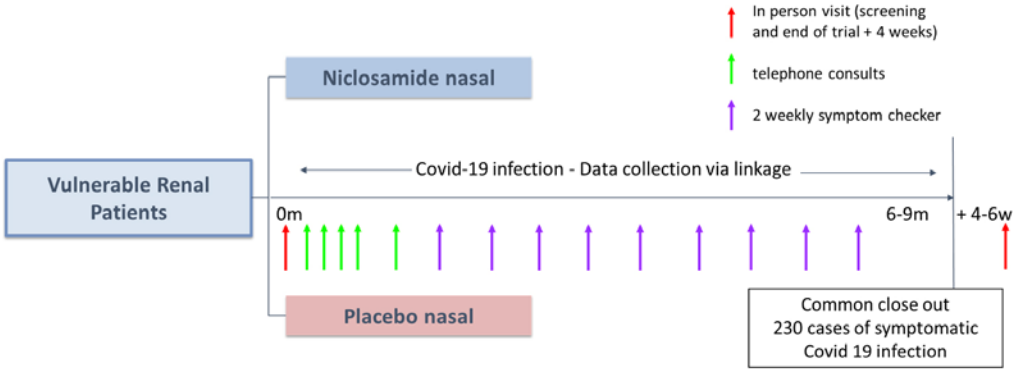


Figure 1. Niclosamide Arm Trial Design. m, months; w, weeks.

Key Results

The primary efficacy analysis did not demonstrate a significant benefit of intranasal niclosamide over placebo in reducing symptomatic Covid-19 infections. The incidence of symptomatic Covid-19 infections was similar between the niclosamide (13.0%) and placebo (16.8%) groups (figure 2). Additionally, the stratified Cox model with covariates showed no significant difference for symptomatic Covid-19 infection between treatment groups (HR=1.020, 95% CI 0.788-1.320).

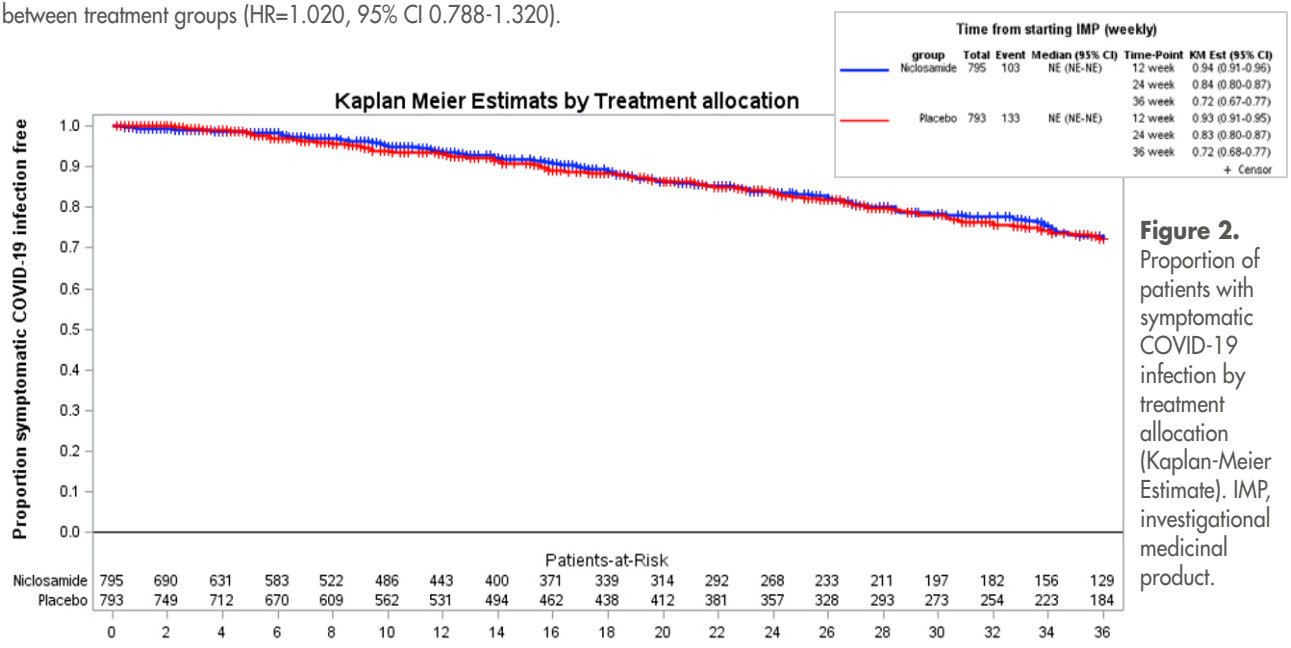


Figure 2. Proportion of patients with symptomatic COVID-19 infection by treatment allocation (Kaplan-Meier Estimate). IMP, investigational medicinal product.

The withdrawal rate was high in the niclosamide group, with 11.4% of participants reporting moderate/severe pain in the nose, 12.4% experiencing severe itch/burning sensation in the nose, and 15.8% reporting sneezing as reasons for discontinuation. Early dropouts were observed, and the niclosamide/placebo curves diverged within the first 4 weeks of the trial (figure 3). Most withdrawals were driven by patient choice, with 60.7% citing intolerance (versus 37.7% in the placebo group) as the reason for stopping intranasal niclosamide.

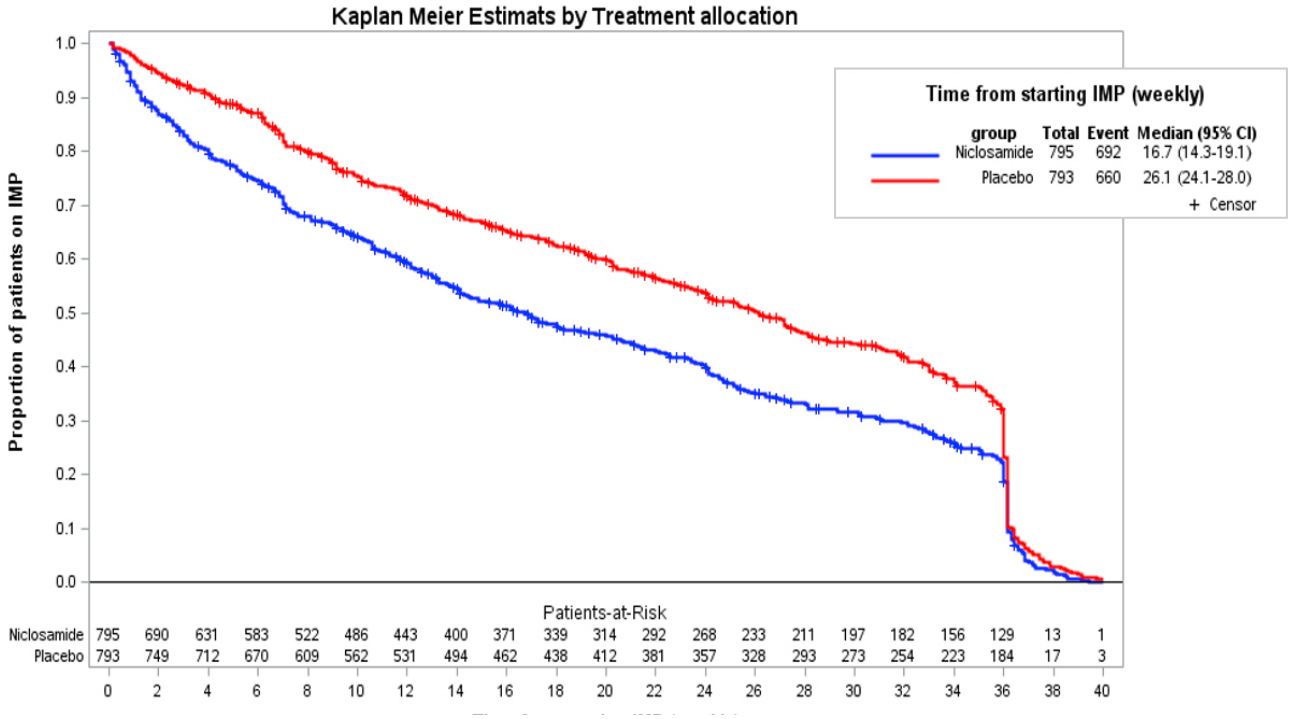


Figure 3. Proportion of patients on niclosamide (IMP) over time (Kaplan-Meier Estimate). IMP, investigational medicinal product.

No major safety signals were observed during the trial. The number of patients experiencing at least one serious adverse event (SAE) was comparable between the niclosamide (N=93) and placebo (N=97) groups. Additionally, a pre-planned competing risks model showed a 3% absolute difference in infections (12.7% niclosamide vs. 15.7% placebo) at week 24.

Conclusion

The trial did not establish the efficacy of intranasal niclosamide as pre-exposure prophylaxis against Covid-19 in the renal patient population. While no major safety signals were observed, intranasal niclosamide was poorly tolerated primarily due to local nasal symptoms. Despite the negative outcome, the study showcased various positives, including being the largest pre-exposure prophylaxis trial of a repurposed agent globally and its successful implementation in a challenging patient population. The platform design demonstrated the efficiency of evaluating multiple agents under a single master protocol.

Further reading

1. Braga et al. Nature 2021;594(7861):88-93.
2. Humphrey et al. Trials 2023;24:185.

CONVINCE: Comparison Of High-Dose HDF And High-Flux HD

Peter J Blankestijn, The Netherlands

Introduction

The CONVINCE (Comparison of high-dose HDF and high-flux HD) study aimed to evaluate the clinical benefit of high-dose haemodiafiltration (HDF) in post-dilution mode compared to high-flux haemodialysis (HD) in terms of all-cause mortality. The study was designed to address the uncertainty surrounding the efficacy of high-dose HDF and to provide evidence for the use of this treatment modality in patients with kidney failure.

Study Overview

The CONVINCE study is a prospective randomized international multicentre clinical trial that enrolled 1360 patients from 61 clinics across 8 countries. Patients were included based on their likelihood to achieve a convection volume of at least 23L per treatment session and their ability to complete patient-reported outcome assessments. The primary objective was to compare HDF when delivered consistently in high-dose, with high-flux HD treatment in terms of all-cause mortality. Secondary objectives included cause-specific mortality, composite of fatal and non-fatal cardiovascular (CV) events, all-cause and infection related hospitalisations and patient-reported outcomes (figure 1).

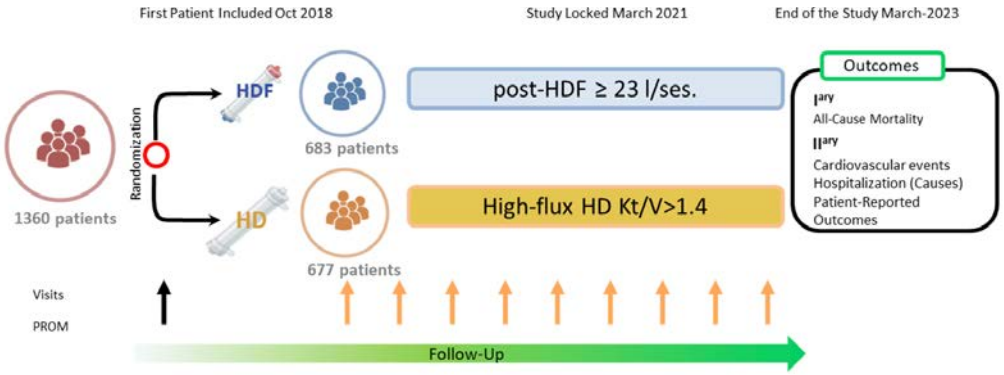


Figure 1. CONVINCE trial design. PROM, Patient Reported Outcome Measure; HDF, haemodiafiltration; HD, haemodialysis.

Key Results

The study found that high-dose HDF in a dose of >23L convection volume per session in post-dilution mode resulted in a lower risk of death compared to high-flux HD. Specifically, the hazard ratio for all-cause mortality was 0.77 (95% CI: 0.65-0.93), indicating a reduction in all-cause mortality risk for patients receiving high-dose HDF (figure 2). Overall survival was also improved with high-dose HDF vs high-flux HDF after a median follow up of 30 months (figure 3). Additionally, the hazard ratios for non-cardiovascular death and infection-related hospitalizations were also lower in the HDF group.

However, the study's interpretation of cause-specific outcomes should be interpreted with caution due to inadequate power for these analyses.

	HDF (N)	Risk per 100/py	HD (N)	Risk per 100/py	Hazard ratio (95% CI)
Death from any cause	118	7,1	148	9,2	0,77 (0,65-0,93)
Cardiovascular death	31	1,9	37	2,3	0,81 (0,49-1,33)
Non-CV death	87	5,3	111	6,9	0,76 (0,59-0,98)
Infection + COVID Infection - COVID	38 23	2,3 1,4	54 33	3,6 2,1	0,69 (0,49-0,96) 0,82 (0,42-1,59)

Figure 2. Select primary and secondary outcomes. CI, confidence interval; HDF, haemodiafiltration; HD, haemodialysis.

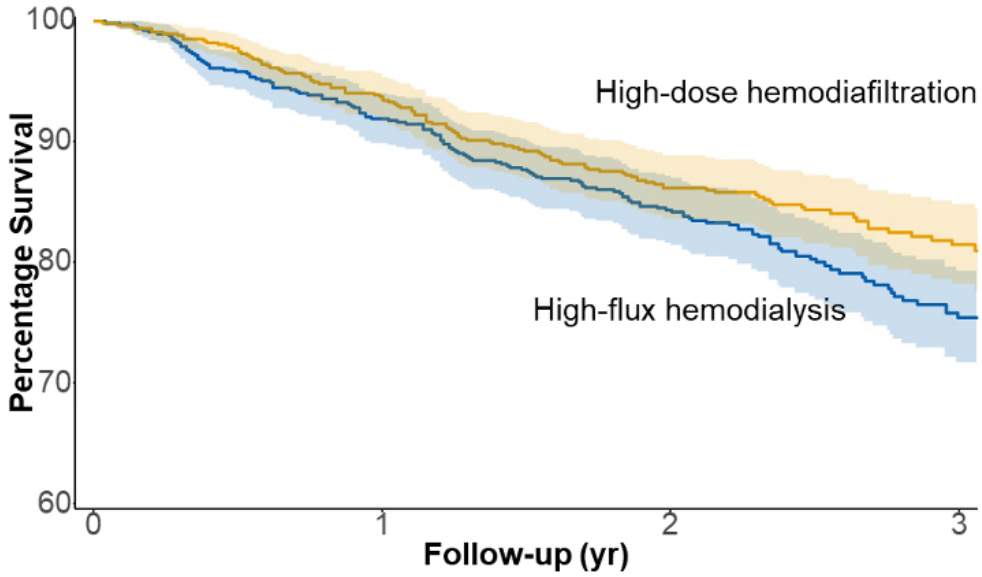


Figure 3. Overall survival across treatment groups (Kaplan Meier curve).

Conclusion

The CONVINCE trial provided evidence supporting the use of high-dose HDF in post-dilution mode with a convection volume of >23L per session for patients on haemodialysis. The trial demonstrated a beneficial effect of high-dose HDF in reducing all-cause mortality compared to standard high-flux HD. These findings may lead to wider acceptance of high-dose HDF as a treatment modality for patients with kidney failure resulting in kidney-replacement therapy. However, further analyses of patient-reported outcomes are ongoing, which are needed to provide a comprehensive assessment of the treatment impact from the patient perspective.

Further reading

1. Blankestijn PJ, et al. New Engl J Med 2023; 389: 700-709 .
2. Blankestijn PJ, et al. BMJ Open 2020;10:e033228.
3. Peters SAE, et al. Nephrol Dial Transplant 2016;31:978-984.
4. Vernooji RWM, et al. Nephrol Dial Transplant 2022;37:1006-13.

The sGC activator runcaciguat is associated with a strong reduction in albuminuria and good tolerability in CKD patients with or without an SGLT2 inhibitor: results of the CONCORD study

Ronald T. Gansevoort, The Netherlands

Introduction

Chronic kidney disease (CKD) poses a significant health burden, CKD patients are still at risk of progressive loss of kidney function towards a need for kidney function replacement treatment. Effective renal protective treatments are required to address these unmet needs. Soluble guanylate cyclase (sGC) activators have shown potential as renoprotective interventions in experimental models. The CONCORD study aimed to investigate the effects of the sGC activator runcaciguat on albuminuria, blood pressure, estimated glomerular filtration rate (eGFR), safety, and tolerability in CKD patients.

Trial Overview

The CONCORD study is a phase II trial that included CKD patients with and without type 2 diabetes (T2D). The patients were stratified into three groups: CKD with T2D and not treated with SGLT2 inhibitors, CKD with T2D and treated with SGLT2 inhibitors, and CKD without T2D and treated with runcaciguat at a maximum dose of 120mg once daily (figure 1).

Mean age was ~70 years, predominantly male, and all patients were white. Baseline urine albumin to creatinine ratio (UACR) levels differed slightly among groups.

The primary endpoint was change in spot morning void UACR from baseline, and the trial also assessed secondary and exploratory endpoints related to pre-dose plasma concentration of runcaciguat, blood pressure, eGFR, and safety parameters.

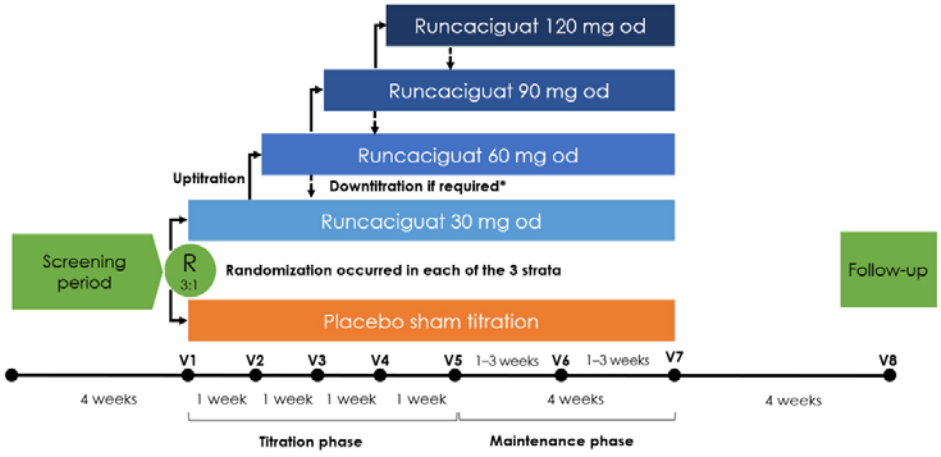


Figure 1. CONCORD trial design. *Down titration may be performed because of tolerability issues or due to safety concerns once. This dose is maintained until the end of treatment (V7). od, once daily; R, randomised.

Key Results

UACR Reduction

Runcaciguat demonstrated a reduction in albuminuria in all three patient groups with a significant reduction in two groups: CKD with T2D and no SGLT2 inhibitor and CKD with T2D and SGLT2 inhibitor (figure 2).

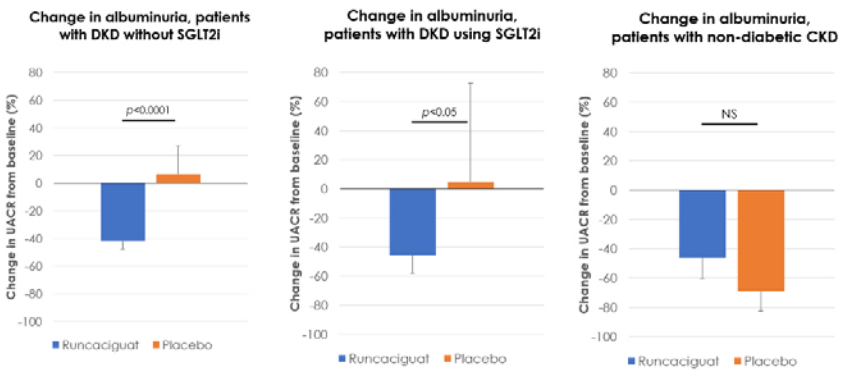


Figure 2. Primary endpoint: change in spot morning void urine albumin to creatinine ratio (UACR) from baseline across all three patient groups. Data show estimated mean percent change and 95% confidence interval (ANCOVA) for the Per-Protocol Set. DKD, Diabetic Kidney Disease; NS, not significant.

Blood Pressure and eGFR

Runcaciguat showed a small reduction in systolic blood pressure (SBP) and eGFR across patient groups. This suggests improvement in UACR is not driven by changes in blood pressure.

Safety and Tolerability

During the study, plasma concentrations of runcaciguat were measured at various time points in patients who reached the maximum dose level in the maintenance phase. ~80% of patients who completed the treatment phase reached the maximum runcaciguat 120 mg dose (figure 3).

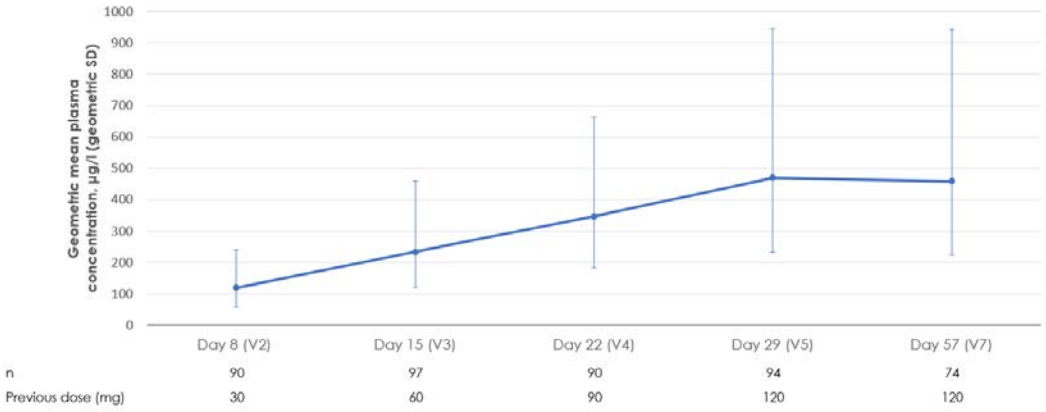


Figure 3. Geometric mean plasma concentrations of runcaciguat at various time points in patients who reached the maximum dose level in the maintenance phase.

Most treatment-emergent adverse events (TEAEs) were mild or moderate, and there were no overall safety concerns (table 1).

	All CKD	
Treatment-emergent adverse events	Runcaciguat n=184	Placebo n=59
(Serious) adverse events, %	69.0	52.5
Any study-drug related AE, %	32.6	20.3
Any SAE, %	6.5	8.5
Any SAE with outcome death, %	0.5	1.7
Maximum intensity for any (S)AE, %		
Mild, %	35.3	20.3
Moderate, %	27.7	27.1
Severe, %	6.0	5.1
(S)AE leading to discontinuing study drug, %	16.3	6.8

Table 1. Treatment-emergent adverse events across all CKD patients. AE, adverse event; SAE, serious adverse event.

Conclusion

The CONCORD study provides evidence for the potential of runcaciguat as a renoprotective intervention for CKD patients, with or without T2D and treated with or without SGLT2 inhibitors. The significant reduction in albuminuria, coupled with the generally well-tolerability profile, highlights the potential of runcaciguat in addressing the unmet need for novel kidney protective treatments.

References

1. Hahn MG et al. J Med Chemistry 2021;64:5323–5344.
2. Stasch JP et al. Curr Opin Pharmacol 2015;21:95–104.

Symposium 0.11
Late Breaking Clinical Trial II

Exercise During Haemodialysis in Patients with Chronic Kidney Failure

Gero von Gersdorff, Germany

Introduction

Chronic kidney disease (CKD) patients often experience muscle impairment and functional decline, making physical activity crucial for their well-being. However, the role of an intradialytic training program established for the entire dialysis unit remained unclear. The DiaTT trial aimed to investigate the impact of an intradialytic exercise program on patients with chronic kidney failure undergoing haemodialysis.

Trial Overview

The DiaTT trial is a multicentre, cluster-randomized, controlled trial conducted at 21 centres in Germany, with 10 centres assigned to the exercise intervention (n=578) and 11 centres to usual care (n=633). The intradialytic training therapy program comprised resistance exercises for major muscle groups and bed cycle-ergometer sessions, with monthly 5% increases in exercise intensity. The training was conducted three times per week in groups of 4-6 patients, with supervision and guidance by healthcare professionals.

Baseline Characteristics

The DiaTT trial included a diverse group of participants with CKD undergoing haemodialysis. The median age of the patients was 65.3 years, with 60% being male. Almost one-third of the patients had diabetes (29.4%) and heart failure (≥34.8%), 4.9% of patients had a lower extremity amputation.

Key Results:

Primary Outcome - 60-second sit-to-stand test (STS60) at 12 months

At 12 months, the STS60 repetitions improved in patients from 16.2 to 19.2 in the exercise group and declined from 16.2 to 14.7 in the usual care group (group difference, 3.85 repetitions; 95% confidence interval [CI], 2.22 to 5.48; P<0.0001) (figure 1).

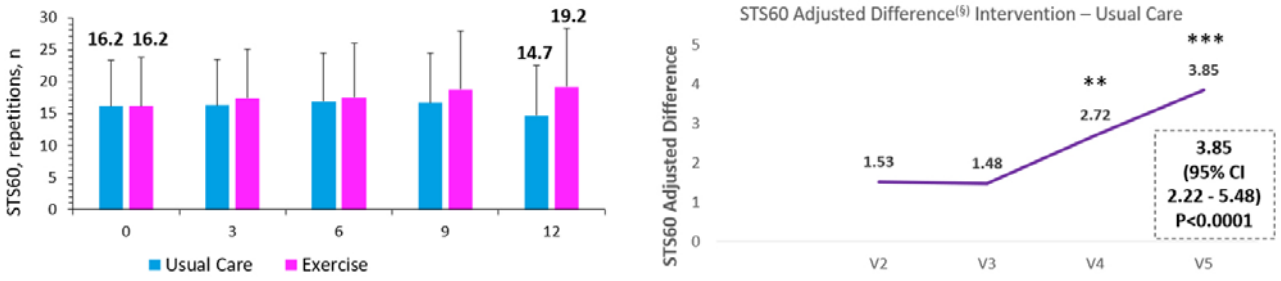


Figure 1. STS60 at 12 months, including adjusted difference between groups. **p<0/001; ***p<0.0001; §Determined in a mixed linear regression model including baseline physical function test, region, group and time*group interaction

Secondary Outcomes

The Six-Minute Walk Test (6MWT) and Timed Up and Go Test (TUG) showed better performance in the exercise group, indicating improved functional capacity. The Physical Component Summary score and Vitality subscale of the SF-36 questionnaire improved in the exercise group, indicating improved quality of life.

Hospitalization and Safety

Hospitalization rates were significantly lower in the exercise group, additionally patients spent a median of 3 days less in the hospital compared to usual care (figure 2).

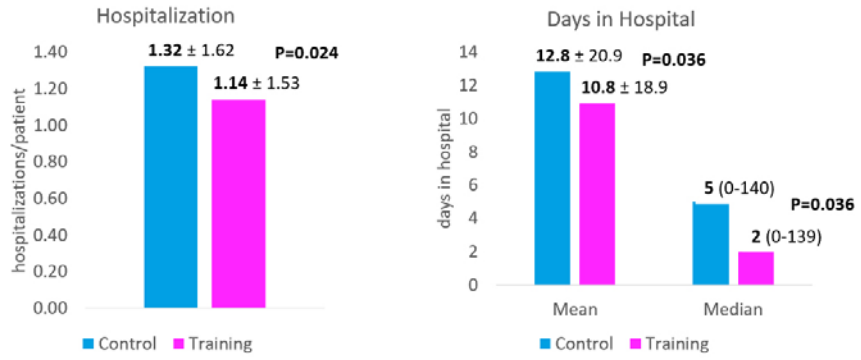


Figure 2. Hospitalisation rates and number of days spent in hospital across control (usual care) and training (exercise) groups.

The intradialytic exercise program was safe, with no significant increase in adverse events during dialysis sessions. Complications during dialysis therapy were similar between the groups (figure 3).

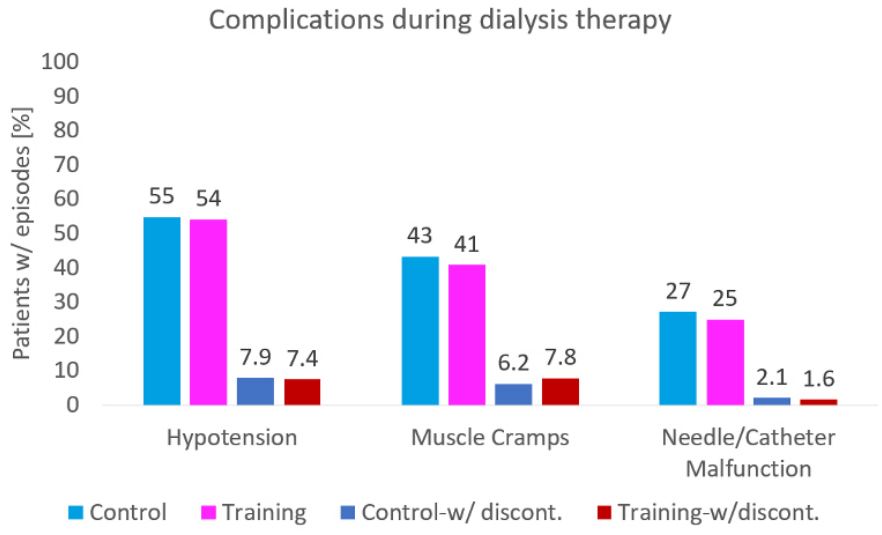


Figure 3. Complications during dialysis therapy across control (usual care) and training (exercise) groups.

Conclusion

The DiaTT Study demonstrated that a 12-month intradialytic exercise program significantly improved physical function, reduced hospitalization, and was safe for patients with CKD undergoing haemodialysis. Implementing the DiaTT training program received high interest and adherence from patients, was feasible and did not interfere with routine dialysis making it a potentially viable option for improving outcomes in dialysis units.

Further Reading

1. Anding-Rost K, et al. NEJM Evidence 2023;10.1056/EVIDoa2300057.
2. von Gersdorff G, et al. Methods Protoc 2021 Aug 31;4(3):60.

36-Week Efficacy & Safety of Atacicept 150 mg in the ORIGIN Randomized, Double-blind, Placebo-controlled Phase IIb Study in IgAN and Persistent Proteinuria

Richard Lafayette, USA

Introduction

IgA nephropathy (IgAN) is a chronic kidney disease characterized by the accumulation of immunoglobulin A (IgA) deposits in the glomeruli, leading to kidney damage and impaired function. Atacicept, as a dual inhibitor of B cells and plasma cells, may be a potential treatment option across multiple autoimmune diseases. The ORIGIN Phase IIb trial aims to assess the impact of atacicept on proteinuria reduction, stabilization of kidney function, and modulation of the immune response in high-risk IgAN patients.

Trial Overview

The ORIGIN Phase IIb trial is a multinational, double-blind, placebo-controlled trial evaluating the efficacy and safety of atacicept 150 mg in patients with IgAN and persistent proteinuria. The trial duration was 36 weeks. Participants received subcutaneous atacicept 25 mg, 75 mg, 150 mg, or placebo (figure 1). The primary efficacy endpoint was the reduction in UPCR at week 24. Secondary endpoints included urine protein-to-creatinine ratio (UPCR) at week 36, estimated glomerular filtration rate (eGFR) change up to week 96, and Gd-IgA1 change; safety was also assessed.

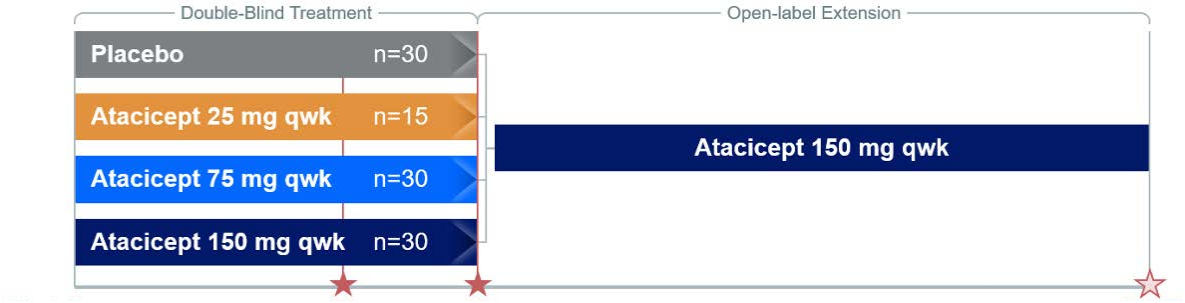


Figure 1. Overview of the ORIGIN Phase IIb multinational, randomized, placebo-controlled trial.

The trial enrolled patients aged ≥18 years with IgAN and high disease progression risk. The mean age was 39 years, with 59% male participants. The majority were White (53%) or Asian (44%). The baseline eGFR was 63 mL/min/1.73 m², and the UPCR was 1.6 g/g. Overall, the baseline characteristics were balanced among the treatment groups.

Key Results

Primary endpoint: reduction in proteinuria

Atacicept 150 mg demonstrated a significant reduction in UPCR at week 36 compared to placebo. Specifically, in the prespecified per-protocol (PP) analysis, patients receiving atacicept showed a significant 43% reduction in UPCR compared to 35% in the Intent-to-treat (ITT) group (figure 2).

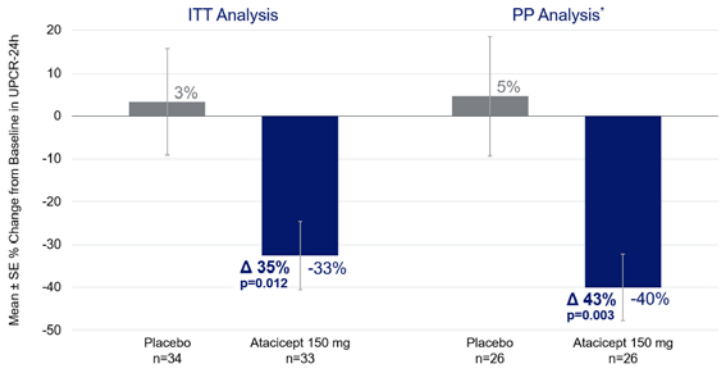


Figure 2. UPCR % Change with Atacicept 150 mg at Week 36. p-values, % changes from baseline and treatment differences were computed using FDA-endorsed mixed-effects modelling. *PP analysis excluding patients with protocol violations identified at week 36 data-cut prior to unblinding.

Secondary endpoints

The study showed that patients receiving atacicept had stable eGFR through week 36, demonstrating a statistically and clinically significant difference of 5.8 mL/min/1.73 m2 compared to placebo (figure 3). In addition, the atacicept 150 mg group achieved a 64% reduction from baseline at week 36 in Gd-IgA1 (p<0.0001).

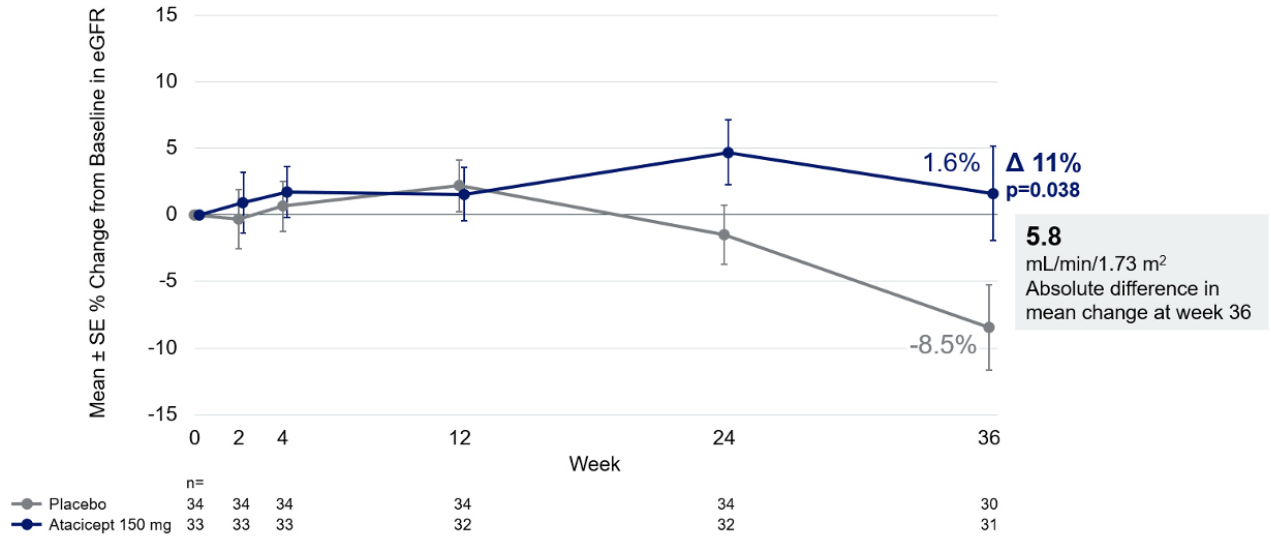


Figure 3. eGFR Change with Atacicept 150 mg Through Week 36

Safety Profile

Safety results indicated that atacicept was generally well-tolerated, with no notable increase in infection rate compared to placebo. Overall, there were no drug discontinuations or interruptions related to hypogammaglobulinemia. Serious treatment-emergent adverse events were observed in 3% of patients receiving atacicept 150 mg and in 9% of placebo patients.

Conclusion

The ORIGIN Phase IIb trial showed that atacicept 150 mg reduced proteinuria in IgAN patients at high risk of disease progression. It also demonstrated stable eGFR and a generally well-tolerated safety profile. A confirmatory Phase III trial (ORIGIN 3) evaluating self-administered Atacicept 150 mg versus placebo is currently enrolling.

Further Reading

1. Hiepe F, et al. Nat Rev Rheumatol 2011;3:170-178.
2. Gordon C, et al. Arthritis Rheumatol 2017;69:122-30.
3. Haselmayer P, et al. Eur J Immunol 2017;47:1075–1085.
4. Gordon C, et al. Rheumatol Adv Pract 2019;0:1-12.
5. Barratt J, et al. Nephrol Dial Transplant 2022;3 suppl 3, abstr FC051.
6. Barratt J, et al. ASN Kidney Week 2022, abstr SA-PO655.

GFR Slope as a Surrogate Endpoint for Kidney Failure in Clinical Trials: An Updated Meta-Analysis

Hiddo L Heerspink, The Netherlands

Introduction

The evaluation of therapies for chronic kidney disease (CKD) poses a significant challenge due to the reliance on late-stage clinical endpoints such as kidney failure and doubling of serum creatinine in randomized controlled trials (RCTs). However, the rate of glomerular filtration rate (GFR) decline, known as the GFR slope, plays a crucial role in the causal pathway leading to kidney failure across all kidney diseases. The GFR slope has emerged as a surrogate endpoint in some registration RCTs to assess drug efficacy. Therapies, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists (MRAs), have demonstrated potential benefits in slowing CKD progression in patients at various stages of the disease. These recent RCTs have provided an opportunity for a more comprehensive assessment of the GFR slope's validity as a surrogate endpoint, encompassing diverse populations and multiple interventions.

Study Overview

A meta-analysis was conducted to investigate the use of GFR slope as a surrogate endpoint in CKD RCTs. The systematic literature search included RCTs with follow-up periods longer than 12 months, measuring GFR and proteinuria, and with GFR greater than 15 mL/min/1.73 m^2 at baseline. RCTs were categorized based on intervention type and disease. The study included 66 RCTs with 186,312 participants. Baseline characteristics showed a mean age of 63.4 years and 35% of participants were female. The baseline eGFR was 68.0 mL/min/1.73m^2 and the baseline albumin-to-creatinine ratio (ACR) was 68 mg/g. The mean rate of GFR progression was -3.2 mL/min/1.73m^2. The total GFR slope, computed at 2 and 3 years, was evaluated along with the clinical endpoint defined as a composite of kidney failure with replacement therapy, sustained GFR <15mL/min/1.73m2 and doubling of serum creatinine (57% decline in GFR).

Key Results

Overall, the treatment effect on the total GFR slope at 3 years was -0.35 mL/min/1.73 m^2 per year. The total GFR slope treatment effect showed a strong association with the clinical endpoint overall and across subgroups based on disease type and CKD severity. The chronic GFR slope treatment effect demonstrated a moderate association with the clinical endpoint (figure 1).

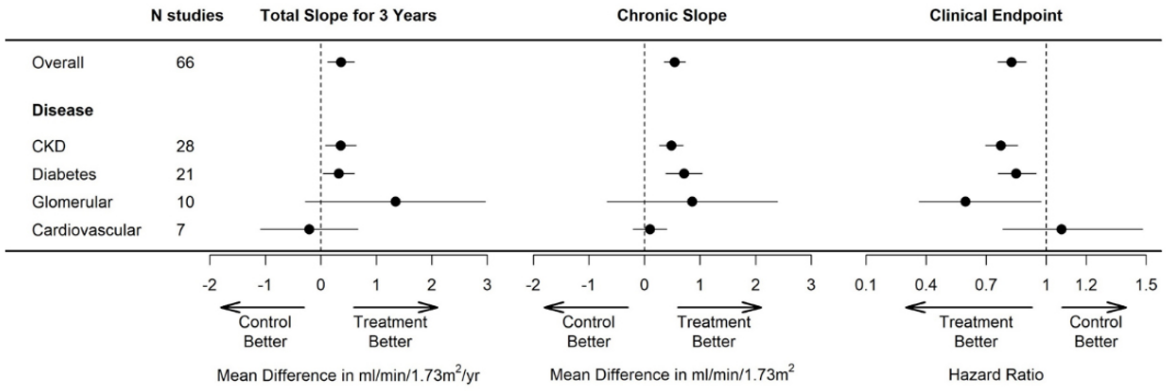


Figure 1. Treatment effects on total slope, chronic slope and the clinical endpoint.

Additionally, the minimum treatment effect on 3-year total GFR slope associated with a 97.5% probability of clinical benefit would be 0.44 and 0.79 mL/min/1.73 m2 per year in a large (n=1,600) and small (n=400) trial, respectively (Table 1). The findings were consistent across subgroups by disease type and CKD severity.

GFR slope	Observed Treatment effect on GFR slope	Large RCT‡		Small RCT‡	
		Median HR and 95% Bayesian Prediction Interval	PPV_{trial}	Median HR and 95% Bayesian Prediction Interval	PPV_{trial}
Total slope computed at 3 years	0.5	0.80 (0.66, 0.98)	0.98	0.80 (0.58, 1.12)	0.91
	0.75	0.74 (0.60, 0.89)	1.00	0.74 (0.53, 1.02)	0.97
	1	0.68 (0.54, 0.82)	1.00	0.68 (0.48, 0.93)	0.99
Threshold for treatment effect on GFR slope associated with 97.5% probability of clinical benefit		0.44		0.79	

Table 1. Converting Treatment Effect on 3-Yr Total Slope to Probability of Clinical Benefit; ǂ A large clinical trial corresponds to a samples size of ~1600, a small clinical trial corresponds to a sample size of ~400. Clinical benefit defined as a hazard ratio for the clinical endpoint <1.0.

Conclusion

The findings of this meta-analysis support the use of total GFR slope as a valid surrogate endpoint in RCTs evaluating therapies for CKD progression. The GFR slope can serve as an informative marker for regulatory approval, funding decisions, and informing healthcare professionals and patients about the benefits of interventions in slowing CKD progression and reducing the risk of kidney failure.

Further reading

1. Heerspink et.al. Lancet 2023:401(10388):1584-1594.
2. Komers R, et al. Kidney Int Rep 2020;5(4):494–502.
3. Clinicaltrials.gov. FIND-CKD. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05047263. Last accessed: August 2023.
4. Inker et.al. J Am Soc Nephrol 2019:30(9);1735-45.
5. Inker LA, et al. Nat Med. 2023; 29(7):1867-1876.

Symposium 0.6
Diabetes in CKD: the KDIGO Guideline Update

Highlights and Key Publications: KDIGO Diabetes and CKD Guideline Update 2022

Katherine R. Tuttle, USA

Introduction

Chronic kidney disease (CKD) is a significant complication of diabetes, leading to serious health issues and mortality. To address this, the KDIGO Diabetes and CKD Guideline was updated in 2022, to provide evidence-based recommendations on the management of diabetes and CKD to improve patient outcomes. The presentation highlighted key publications and studies related to the guideline update and highlights the benefits of additional treatments for kidney and cardiovascular protection in patients with diabetes and CKD.

Key Highlights and Publications

SGLT2 Inhibitors

Clinical studies CREDENCE, DAPA-CKD, and EMPA-KIDNEY demonstrated significant reductions in kidney failure or decline in estimated glomerular filtration rate (eGFR) and cardiovascular events (figure 1). The CREDENCE trial included adults with type 2 diabetes, an eGFR above 30 mL/min/1.73 m^2, and urine albumin-to-creatinine ratio (UACR) above 300 mg/g. The study found that canagliflozin significantly reduced the risk of kidney failure, substantial eGFR decline, or death from kidney or cardiovascular causes compared to the placebo group. Similarly, the DAPA-CKD trial, which included adults with or without type 2 diabetes, eGFR above 25 mL/min/1.73 m^2, and UACR above 200 mg/g, demonstrated similar results in patients treated with dapagliflozin versus placebo.

The EMPA-KIDNEY trial investigated the effects of empagliflozin in adults with or without type 2 diabetes, eGFR ranging from ≥45 to <90 mL/min/1.73 m^2, and UACR ≥200 mg/g or ≥20 to <45 mL/min/1.73 m^2 irrespective of albuminuria. The trial demonstrated a significant reduction in kidney failure, cardiovascular death, and substantial eGFR decline in the empagliflozin group compared to placebo.

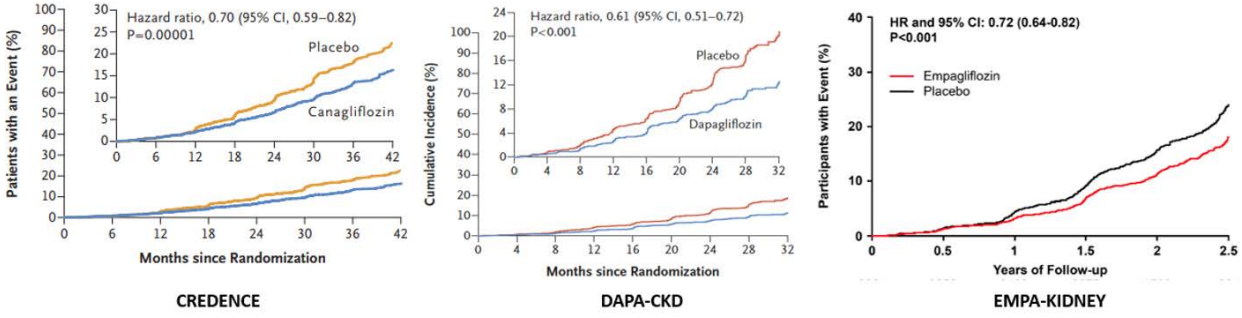


Figure 1. Primary outcomes: Substantial eGFR decline (40%, 50%, 57%), kidney failure, or death due to kidney or cardiovascular causes across SGLT2 inhibitor clinical studies CREDENCE, DAPA-CKD, and EMPA-KIDNEY, respectively. CI, confidence interval.

GLP-1 Receptor Agonists

Studies with GLP-1 receptor agonists, such as liraglutide and semaglutide, have shown cardiovascular benefits in type 2 diabetes patients, reducing major adverse cardiovascular events. Research has also suggested that GLP-1 receptor agonists may decrease macroalbuminuria and eGFR decline from early- to late-stage CKD.

The post-hoc analysis of SUSTAIN-6 and PIONEER-6 trials demonstrated that kidney function is stabilised by semaglutide. In the overall population and in eGFR subgroups, semaglutide was associated with a significant change in eGFR slope, compared with placebo (figure 2)

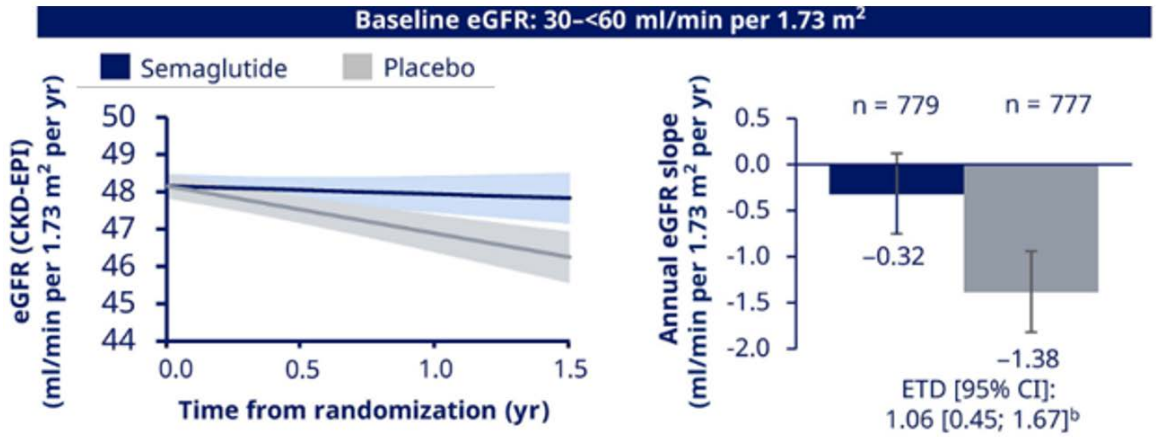


Figure 2. Annual change in estimated glomerular filtration rate (eGFR; model-based total annual eGFR slope) over time and from baseline to end of treatment in patients with baseline eGFR 30 - <60 mL/min/m2. ETD, estimated treatment difference; CI, confidence interval.

Next-Generation Dual Incretin Agonist: Glucose-Dependent Insulinotropic Polypeptide (GIP) and GLP-1

Tirzepatide, a dual GIP and GLP-1 receptor agonist has shown potential in reducing the risk of kidney disease endpoints. The SURPASS-4 trial demonstrated that tirzepatide reduced the incidence of composite kidney disease endpoints, including significant eGFR decline, renal death, progression to end-stage kidney disease (ESKD), and new-onset macroalbuminuria compared to insulin glargine.

Non-Steroidal Mineralocorticoid Receptor Antagonist

Finerenone, a non-steroidal mineralocorticoid receptor antagonist has also shown positive outcomes in patients with CKD and type 2 diabetes. Studies such as FIDELIO and FIGARO demonstrated that patients treated with finerenone had a lower risk of kidney failure, sustained decrease of ≥40% in the eGFR from baseline, or death from renal causes as well as a lower risk of cardiovascular events, including myocardial infarction, stroke, heart failure hospitalization, and cardiovascular death, when used in combination with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) (figure 3).

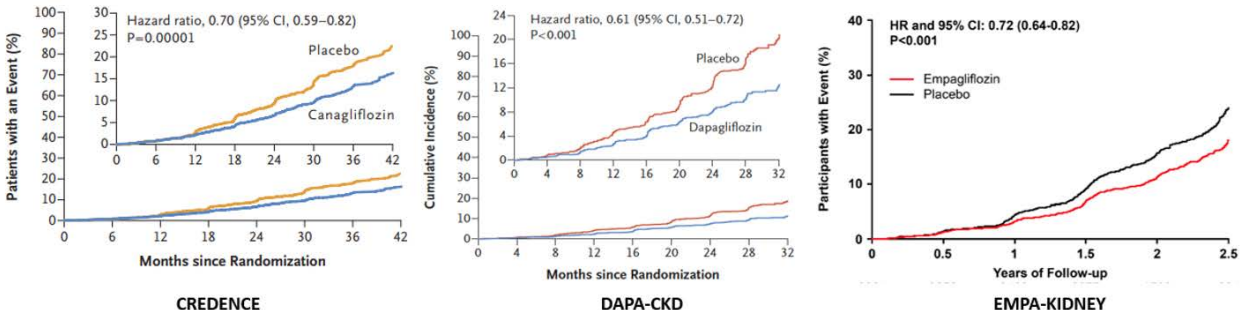


Figure 3. Primary composite outcome results from FIDELIO (the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes in the finerenone and placebo groups), and FIGARO (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) clinical trials. CI, confidence interval.

Conclusion

The updated evidence from these key publications underscores the potential benefit of incorporating SGLT2 inhibitors, GLP-1 receptor agonists, tirzepatide, and finerenone into the management of diabetes and CKD in clinical practice. Moreover, collaborative multidisciplinary care, involving nephrologists, endocrinologists, and primary care physicians, was noted as essential for effectively implementing these guideline-directed medical therapies to provide the best possible outcomes for patients with diabetes and CKD.

Further Reading

1. Bakris GL, et al. N Engl J Med 2020;383:2219-2229.
2. de Boer IH, et al. Diabetes Care 2022;45:3075-3090.
3. Ghuman J, Tuttle K. Kidney 360 2022;3:744-748.
4. Heerspink HJL, et al. N Engl J Med 2020;383(15):1436-1446.
5. Herrington W, et al. N Engl J Med 2023;388:117-127.
6. KDIGO Diabetes Work Group. Kidney Int 2022;102(5S):S1-S127.
7. Müller TD, et al. Mol Metab 2019;30:72-130.
8. Perkovic V, et al. N Engl J Med 2019;380:2295-2306.
9. Sattar N, et al. Lancet Diabet Endo 2021;9:653-652.
10. Tuttle KR, et al. CJASN 2022;17:1092-1103.

Implementation of KDIGO Guidelines for the European Context

Frederik Persson, Denmark

Introduction

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients with diabetes and chronic kidney disease (CKD) emphasizes the need for a comprehensive strategy to reduce the risks of kidney disease progression and cardiovascular complications. However, the implementation of these guidelines in the European context faces several barriers. This presentation highlights the challenges and potential future directions for improving the management of patients with diabetes and CKD in Europe.

Guidelines Are Here, but Challenges Remain

While guidelines provide valuable recommendations for clinical practice, their implementation can be challenging. In Europe, the public healthcare systems often do not incentivize healthcare providers to adhere to guidelines through pay-for-performance schemes. Additionally, screening for diabetes and CKD is not always prioritized, leading to delayed or missed diagnoses. Reimbursement policies for necessary tests and treatments can also vary between different countries, impacting patient access to proper care. Furthermore, the management of diabetes and CKD typically involves multiple medical specialties, leading to fragmented care and suboptimal outcomes.

Inertia in Screening and Treatment

One of the significant challenges in implementing guidelines is inertia, both in screening and treatment practices. Studies have shown that annual urine albumin-to-creatinine ratio (UACR) testing is not consistently performed in primary care settings across Europe, leading to underdiagnosis and delayed intervention. However, this is improving in countries such as Denmark. Furthermore, the use of cardioprotective glucose-lowering drugs in patients with diabetes and cardiovascular disease remains suboptimal (figure 1), indicating treatment inertia.

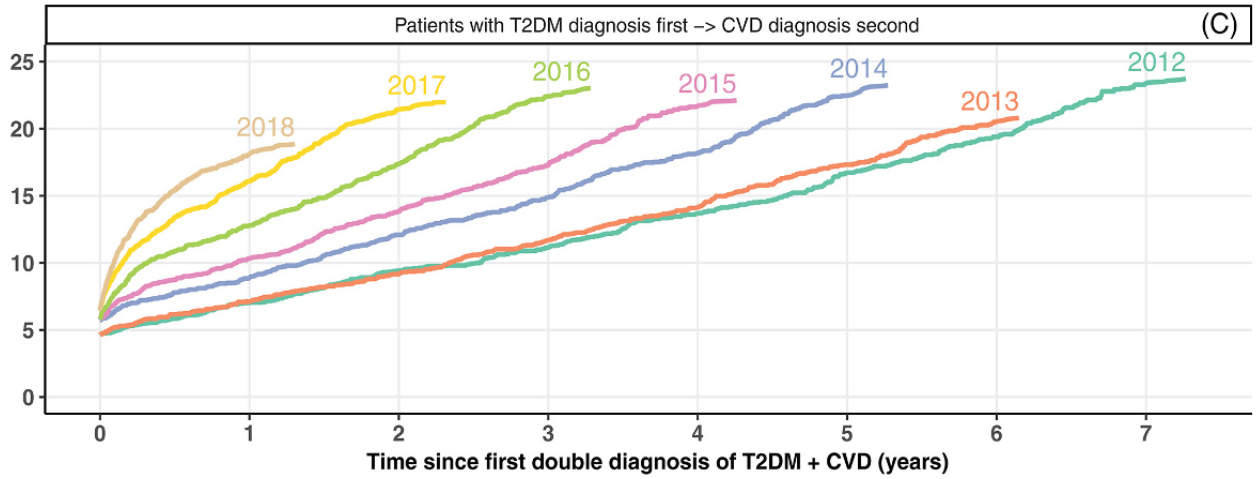


Figure 1. Real-world use of cardioprotective glucose-lowering drugs in patients with type 2 diabetes and cardiovascular disease: A Danish nationwide cohort study, 2012 to 2019. Prevalent users of cardioprotective GLDs are included in graph at time = 0. T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease.

Approaches to Management of Patients with Diabetes and CKD

The Chronic Care Model, exemplified by the Steno Diabetes Fusion Clinic, offers a patient-centred and integrated approach to care. By joint focus on diabetes and CKD, patients benefit from fewer visits and collaborative care, leading to improved patient outcomes and user satisfaction (figure 2). However, such approaches require more administrative efforts to ensure optimal coordination among healthcare providers.

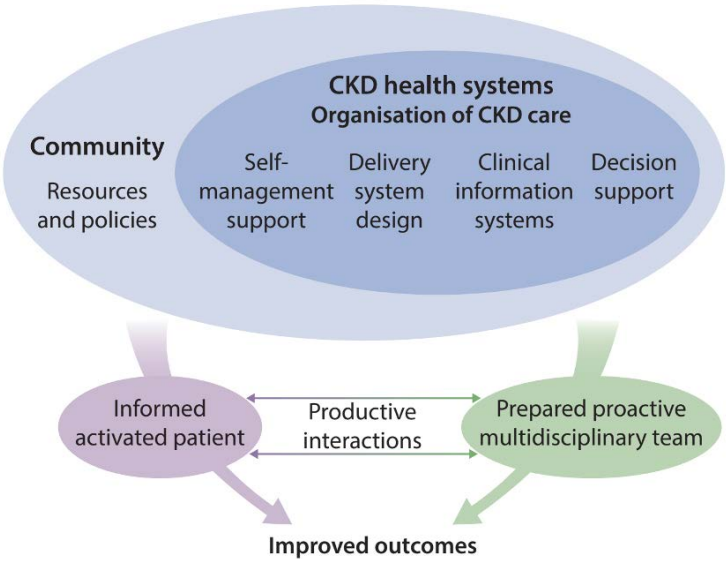


Figure 2. Chronic Care Model: approaches to management of patients with diabetes and CKD.

Evidence for Improving Quality of Care is Needed

Improved evidence is needed to drive successful implementation. This includes diversifying screening approaches, considering the role of general practice in early detection and management, and promoting nonpharmacological care options. Deprescribing, or the careful withdrawal of medications that may no longer be beneficial, can also improve patient outcomes. Shared decision-making between patients and healthcare providers is crucial in tailoring treatment plans to individual needs.

Precision Evidence for Personalized Treatment

To further enhance management strategies precision medicine approaches are needed, however additional evidence is required. Biopsy studies such as BEAT-DKD, KPMP, and PRIMETIME, which focus on identifying and validating biomarkers of disease progression and treatment responses, as well as imaging and multiomic studies can help to understand the complex interplay of genetic and environmental factors in diabetes and CKD. This can lead to a better characterised CKD with diabetes population and ultimately improve outcomes through optimal treatment selection with personalised care (figure 3).

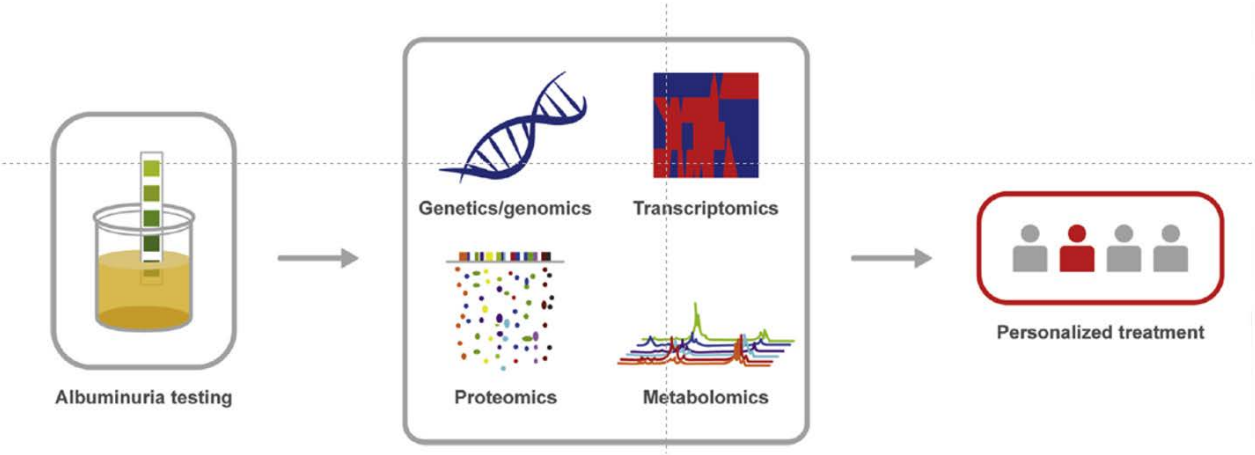


Figure 3. From albuminuria testing to personalized treatment.

Conclusion

Implementing the KDIGO guideline for patients with diabetes and CKD in the European context faces significant challenges due to the diversity of healthcare systems and medical specialties involved. Overcoming inertia in screening and treatment practices, adopting a holistic, multidisciplinary approach, and sharing precision medicine evidence may be key to achieving more comprehensive care and improving patient outcomes overall.

Further Reading

1. Eckardt K-U, et al. 2023. KDIGO conference Report.
2. Funck MD, et al. Diabetes Obesity Metabolism 2020;23(2):520-529.
3. Lamprea-Montealegre JA, et al. Diabetes Care 2022;1;45(12):2900-2906.
4. Møller M, et al. BMJ Open 2023;13:e072216.
5. Persson F, and Rossing P. Kidney int Suppl 2018;8(1):2-7.
6. Persson F, et al. Primary Care Diabetes 2021;44(8):1894-1897.
7. Stempniewicz N, et al. Diabetes Care 2021;44:2000-2009.

ADA/KDIGO and ADA/EASD Consensus Reports

Peter Rossing, Denmark

Introduction

In this presentation, the key findings, and recommendations from the American Diabetes Association (ADA)/Kidney Disease: Improving Global Outcome (KDIGO) and ADA/European Association for the Study of Diabetes (EASD) consensus reports on managing chronic kidney disease (CKD) in patients with type 2 diabetes were presented.

Key findings and recommendations: The ADA/KDIGO consensus report

Screening for CKD in People Living with Diabetes

The ADA/KDIGO consensus report emphasizes the importance of regular screening for CKD in individuals with type 2 diabetes. Testing for albuminuria (measured by urine albumin-to-creatinine ratio, (UACR)) and estimated glomerular filtration rate (eGFR) should be undertaken at least once a year. However, only 50% of patients are currently tested within this timeframe, indicating a need for improved screening practices (figure 1).

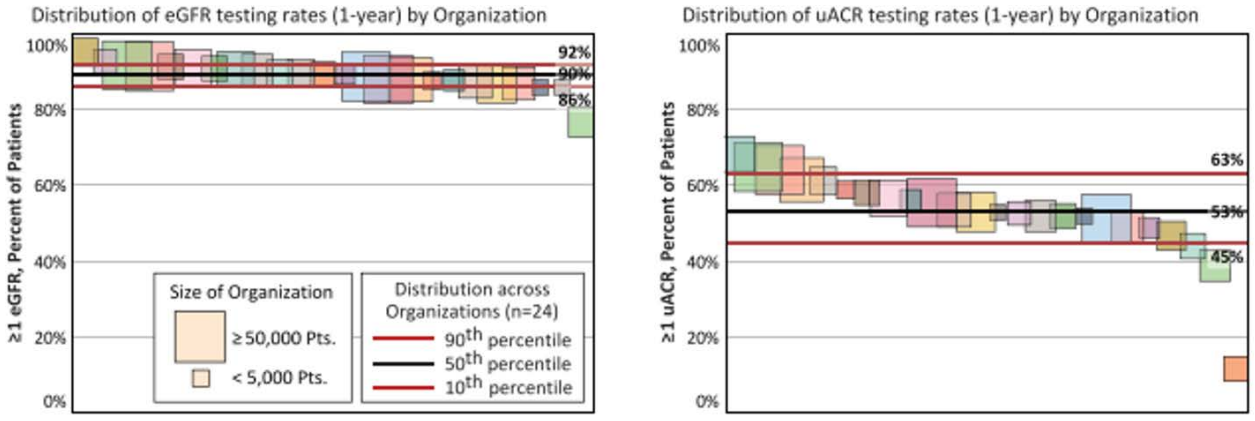


Figure 1. Distribution of eGFR and UACR testing rates among patients with type 2 diabetes and CKD, over 1 year across 24 US healthcare organizations.

Lifestyle Interventions in Patients with Diabetes and CKD

Lifestyle interventions, such as individualized diets rich in vegetables, fruits, whole grains, fibre, legumes, and plant-based proteins, with reduced intake of processed meats, refined carbohydrates, and sweetened beverages, are essential. Moderate-intensity physical activity for at least 150 minutes per week is also encouraged, along with weight loss for patients with obesity and CKD. The consensus report also recommends implementing a structured self-management educational program for the care of people with diabetes and CKD.

GLP-1 Receptor Agonists and SGLT2 Inhibitor treatment

GLP-1 RA and SGLT2 inhibitors are recommended as treatment options for patients with type 2 diabetes and CKD.

SGLT2i can be continued even at lower levels of eGFR, once initiated. Clinical studies demonstrated significant reductions in kidney failure or decline in estimated glomerular filtration rate (eGFR) and cardiovascular events with SGLT2 inhibitors.

Studies with GLP-1 receptor agonists, such as liraglutide and semaglutide, have shown cardiovascular benefits in type 2 diabetes patients, reducing major adverse cardiovascular events. A GLP-1 receptor agonist with proven cardiovascular benefit is recommended for patients with type 2 diabetes and CKD who do not meet their individualized glycemic target with metformin and/or an SGLT2 inhibitor or because they are unable to use these drugs.

Nonsteroidal Mineralocorticoid Receptor Antagonist treatment

The FIDELITY study, a pooled analysis of FIDELIO-DKD and FIGARO-DKD trials, demonstrated that finerenone, a nonsteroidal mineralocorticoid receptor antagonist, reduced the risk of cardiovascular events and CKD progression in patients with type 2 diabetes and CKD. For patients with type 2 diabetes, eGFR ≥25 mL/min/1.73 m2, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAS inhibitor, it is recommended to consider finerenone.

Improved outcomes: a holistic approach for patients with diabetes and CKD

An overall holistic approach to improve outcomes in patients with type 2 diabetes and CKD is recommended. This should ideally consider individual factors related to the patient's lifestyle, choice of first-line drug therapy, include regular reassessment of biomarkers and risk factors, as well as additional risk-based therapy (figure 3).

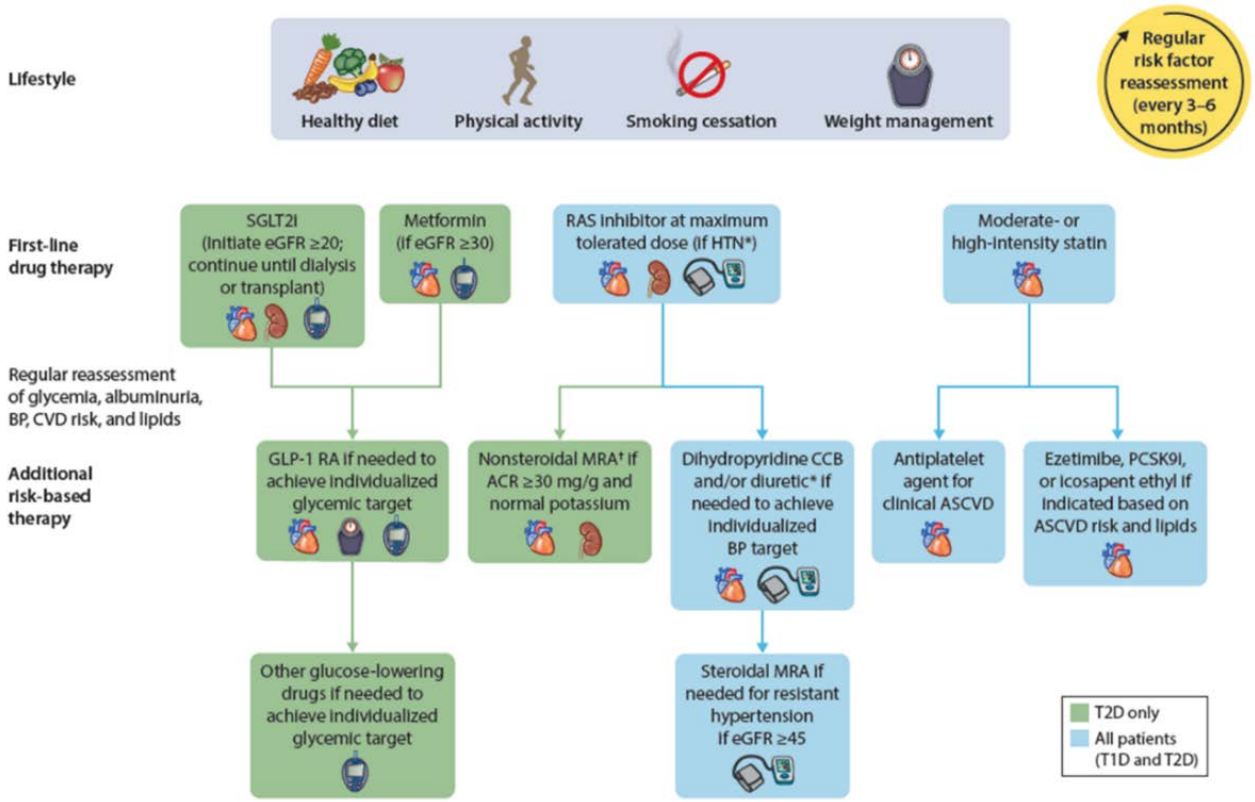


Figure 3. Holistic approach for improving outcomes in patients with diabetes and CKD.

Key findings and recommendations: The ADA/EASD consensus report

The second half of this presentation focused on the ADA/EASD recommendations for the management of Hyperglycaemia in Type 2 Diabetes, which was co-chaired by John B. Buse and Melanie J. Davies.

To implement effective diabetes care, clinicians must adopt practical strategies, including promoting integrated care with a cohesive team and leveraging technology when appropriate. Individualizing care through patient involvement in decision-making is crucial. Emphasizing diabetes self-management education alongside drug treatments and facilitating access to local resources and. encouraging healthy behaviours and weight management requires shared decision-making, self-monitoring, and thorough discussions on hypoglycaemia risks.

Staying updated on glucose-lowering therapies and co-morbidities such as CKD, avoiding therapeutic inertia, and considering combination therapies are also important to consider. Prioritizing organ-protective treatments such as SGLT2is and GLP-1 RAs is recommended for patients with specific conditions. Careful insulin positioning, preferring GLP-1 RAs, and basal insulin, and adopting continuous glucose monitoring for insulin patients are recommended. Continuous education, team-based approaches, and quality improvement interventions should be considered to deliver improved outcomes for patients with type 2 diabetes (figure 4).

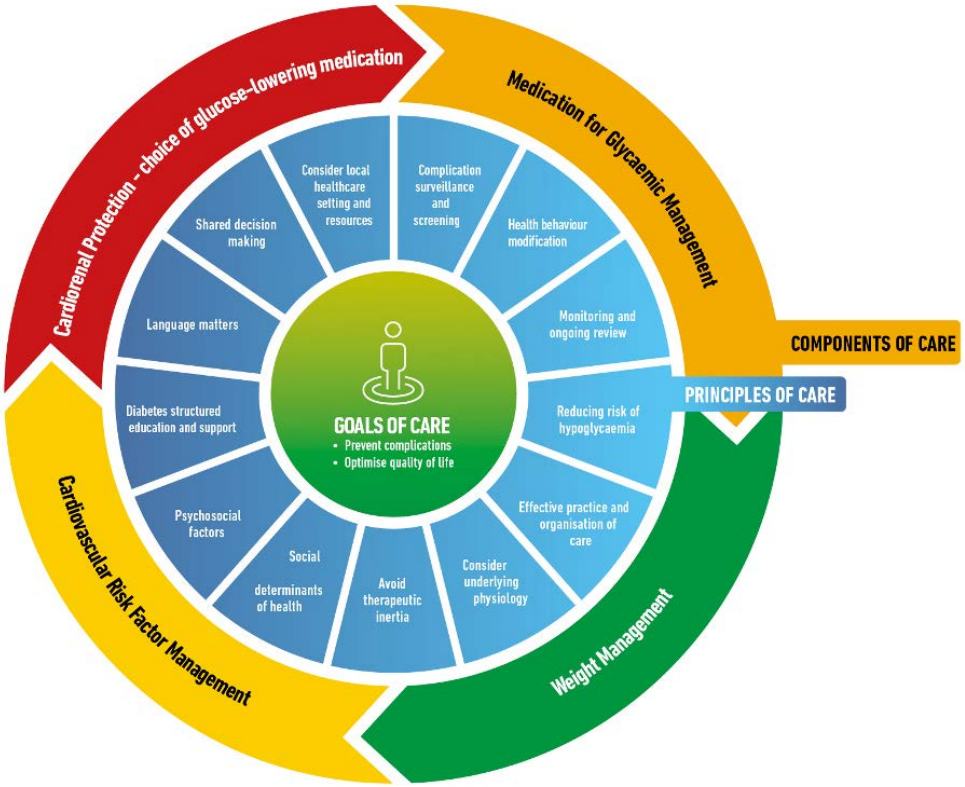


Figure 4. Holistic person-centred approach to type 2 diabetes management

Conclusion

The ADA/KDIGO and ADA/EASD consensus reports provide evidence-based guidelines for managing CKD in patients with type 2 diabetes. Early screening, lifestyle interventions, and the use of specific medications, such as SGLT2i, GLP-1 RA, and nonsteroidal MRAs, have been shown to significantly improve cardiovascular and kidney outcomes in CKD patients with type 2 diabetes. Moreover, this presentation highlights the importance of a comprehensive and organized approach to patient care to tackle barriers to implementation and improve patient outcomes.

Further Reading

1. Agarwal R, et al. Eur Heart J 2022;43:474–484.
2. Boer IH, et al. Diabetes Care 2022;45(12):3075-3090.
3. Brenner BM et al. N Engl J Med 2001; 345(12):861–869.
4. Davies MJ et al. Diabetes Care 2022;45(11):2753–2786.
5. Filippatos G, et al. ESC 2021; abstract 7161.
6. Heerspink HJL et al. N Engl J Med 2020;383:1436-46.
7. Lewis EJ et al. N Engl J Med 2001; 345(12):851–860.
8. Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5.
9. Stempniewicz N, et al. Diabetes Care 2021;44:2000-2009.
10. Tuttle KR et al. JAMA Netw Open 2019;2:e1918169.

Symposium 4.6
Hypertension in dialysis patients: how to measure it and how to treat in 2023?

Blood pressure target in haemodialysis patients: approach to an unsolved dilemma

Indranil Dasgupta, United Kingdom

Introduction and objectives

The management of blood pressure (BP) in haemodialysis (HD) patients presents various uncertainties and challenges. This includes the definition of hypertension, the optimal BP measurement method, and the best approach to controlling BP. This presentation aimed to summarise the key findings and data related to these uncertainties in current BP management in HD patients.

Key results

Definition of hypertension and BP targets

The definition of hypertension in HD patients remains unclear, and consensus guidelines have previously only focused on the non-dialysis chronic kidney disease (CKD) population. Guidelines such as the Kidney Disease Outcomes Quality Initiative (KDOQI) 2005 and the UK Kidney Association 2011 suggest pre-HD BP targets of <140/90 mmHg or <130/80 mmHg; in younger patients (<40 years old) without comorbidities the pre-HD systolic BP (SBP) target is 130-160 mmHg.

However, there is a lack of randomised controlled trials (RCTs) to establish precise targets for treatment; ongoing research is recommended.

BP measurement techniques

Routine peri-dialysis BP is commonly used but is imprecise and influenced by patient-related factors such as white-coat effect and suboptimal conditions. Standardised out-of-centre BP measurements, such as ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM), have shown better prognostic accuracy in predicting cardiovascular outcomes and mortality. However, HBPM requires motivated patients to avoid the risk of noncompliance while ABPM has limited patient acceptability and is more complex to implement in clinical practice

Approaches to BP control

The optimal approach to controlling BP in HD patients is uncertain. Non-pharmacological strategies, such as volume control, are recommended as a first-line approach. Pharmacotherapy is often necessary, but the choice of antihypertensive medications for HD patients may need to be individualised based on patient characteristics and comorbidities.

Relationship between BP and cardiovascular and mortality risk

There is a linear relationship between BP levels and cardiovascular risk in the general population. Intensive BP control has shown improved cardiovascular and mortality outcomes in HD patients, as demonstrated in the SPRINT trial (figure 1). However, the relationship between peri-dialysis BP and mortality follows a U- or J-shaped curve, suggesting that both low and high BP levels are associated with increased risk (figure 2). Factors contributing to this relationship include imprecision of BP readings, patient-related factors, comorbidities, fluid volume status, and attempts to lower BP that may lead to intradialytic hypotension.

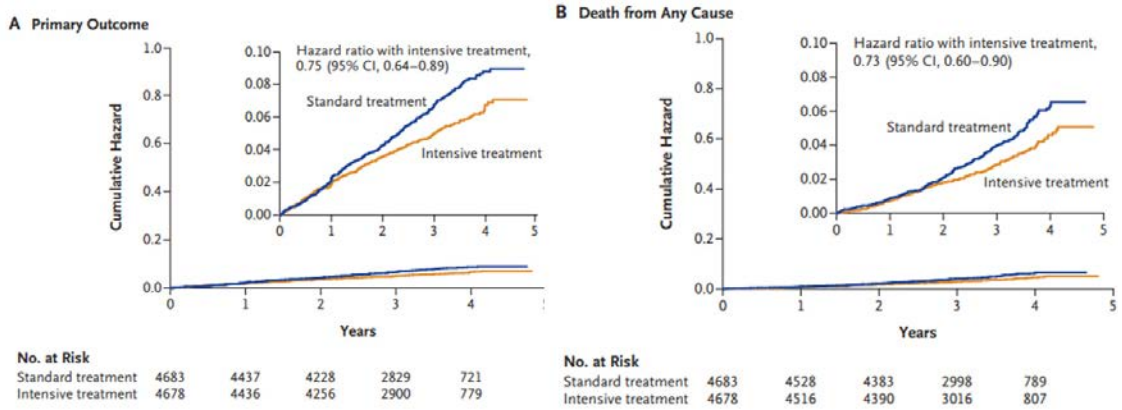


Figure 1. (a) Outcome and death from any cause – shown are the cumulative hazards for the primary outcome (a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) and (b) for death from any cause; CI, confidence interval.

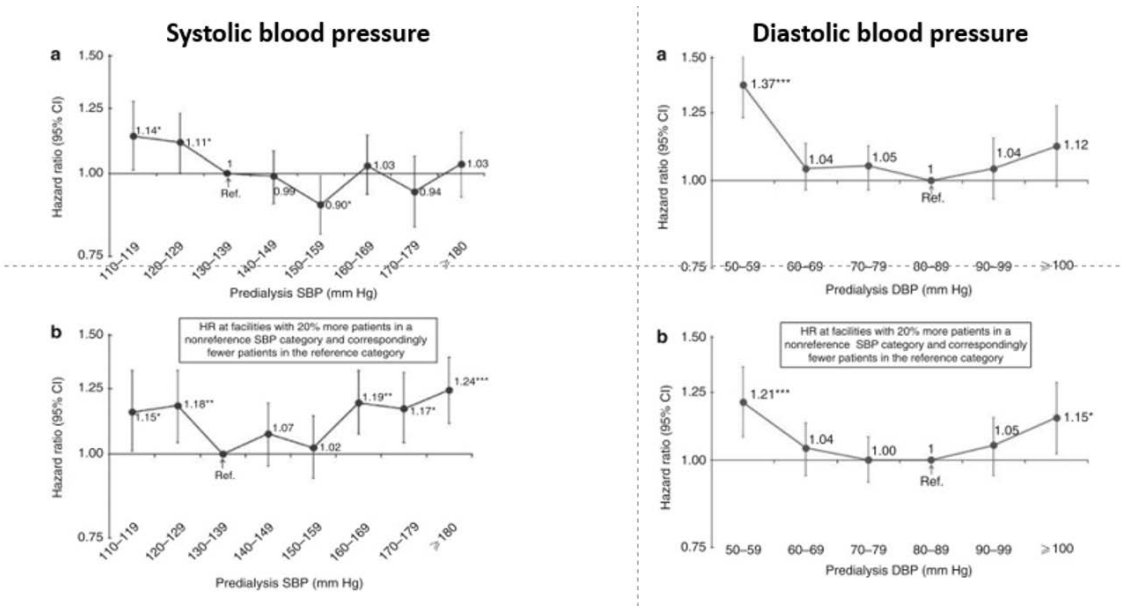


Figure 2. Predialysis systolic blood pressure (SBP) and mortality (fully adjusted model). (a) Mortality by patient-level predialysis SBP categories (fully adjusted). (b) Mortality by facility level predialysis SBP categories (fully adjusted). CI, confidence interval; HR, hazard ration.

Conclusion

Managing BP in HD patients remains an unresolved dilemma. The lack of RCT data and the complexities involved in BP measurement techniques contribute to the uncertainties in defining hypertension and determining optimal BP targets.

The determination of BP targets in HD is closely tied to the method of BP measurement employed; although routine peri-dialytic BP measurement is imprecise, it is likely to continue guiding treatment in many healthcare centres. Based on current evidence, the suggested pre-HD SBP target is 130-160 mmHg or lower depending on age and comorbidities. Out-of-centre BP measurements, ABPM and HBPM, offer greater prognostic accuracy; based on current evidence, the suggested SBP target is 120-130 mmHg. However, it should be noted that actively attempting to lower BP can have detrimental effects, including increased mortality, vascular access thrombosis and hospitalisation.

Therefore, there is a need for a well-designed RCT with sufficient statistical power to compare "lower" versus "higher" BP targets (e.g., 110-130 mmHg vs 140-160 mmHg), using HBP or standardized out-of-centre BP measurements – such a study may necessitate international collaboration.

Further reading

1. Doulton, TWR, et al. Semin Dial. 2020;33:223– 235
2. Fuchs FD, et al. Hypertension. 2020;75:285–292
3. The SPRINT Research Group. N Engl J Med. 2015; 373:2103-2116
4. Robinson BM, et al. Kidney Int. 2012;82(5):570-80
5. Pappaccogli M, et al. Neph Dialysis Transplant. 2019;34(9):1612–1615
6. Rahman M, et al. Am J Kidney Dis. 2002;39(6):1226-30
7. Agarwal R, et al. Am J Nephrol. 2008;28(2): 210–217
8. Agarwal R, et al Clin J Am Soc Nephrol. 2006;1(3):389-98
9. Bansal N, et al. Hypertension. 2017;70(2):435–443
10. Miskulin DC, et al. J Am Soc Nephrol. 2018;29(1):307-316

Dialysis and home dialysis in the pandemic years

Helena Rydell, Sweden

Introduction and objectives

This presentation examined the impact of dialysis and home dialysis on patients during the COVID-19 pandemic. The objectives were to assess the prognosis of patients on dialysis, determine the effect of vaccinations and identify risk factors for a worse prognosis with COVID-19. Other objectives include to outline preventive strategies in dialysis units, investigate the risks associated with ongoing renal transplantations during the pandemic, analyse the incidence of chronic kidney disease (CKD) after acute kidney injury (AKI) and its impact on renal replacement therapy (RRT) as well as to assess the long-term effects of COVID-19 on patients on dialysis.

Key results

Prognosis and COVID-19 vaccination effectiveness in patients on dialysis

Patients on dialysis have a poor prognosis when infected with COVID-19. All-cause mortality was greater among dialysis and transplant patients compared to the general population. Data from a Swedish nationwide cohort study showed a COVID-19-related mortality rate was 10% higher for dialysis patients and 22% for kidney transplant patients during the first pandemic year (figure 1). Vaccination against COVID-19 has demonstrated effectiveness in reducing hospitalisations and mortality in patients on dialysis.

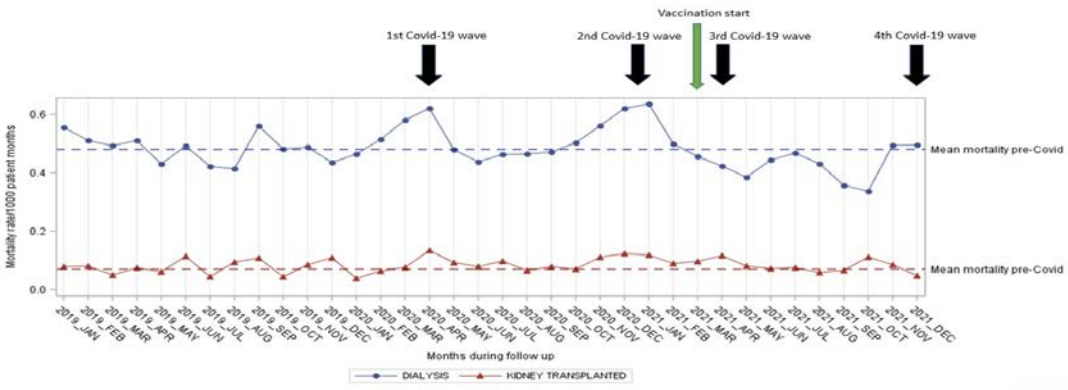


Figure 1. All-cause mortality in dialysis and kidney transplanted patients before and after vaccination for COVID-19 between January 2019 to December 2021.

Risk factors for COVID-19 hospitalisation and mortality

A nationwide cohort study identified age, advanced CKD stage, cardiovascular diseases, chronic pulmonary disease, diabetes, and the use of certain medications (systemic corticosteroids, other immunosuppressants, insulin and proton pimp inhibitors) as significantly associated with an increased risk of COVID-19 hospitalisation and mortality in patients with CKD.

Prognosis with home dialysis

Home dialysis modalities, including peritoneal dialysis (PD) and home haemodialysis (HHD), have not been associated with a significantly higher or lower risk of COVID-19 infection or mortality compared to in-centre dialysis. However, there are some studies showing a lower risk of infections with PD or HHD compared with in-centre haemodialysis. Moreover, PD has shown comparable outcomes to extracorporeal dialysis (intermittent haemodialysis or continuous kidney replacement therapy) for AKI management in COVID-19 patients.

Preventive strategies in dialysis units

During the initial wave of COVID-19, 73 European haemodialysis centres implemented stringent preventive measures, including enhanced infection control protocols, frequent testing, and the provision of adequate personal protective equipment (PPE). There was a decrease in SARS-CoV-2 infection rates among healthcare personnel in centres that prioritized the use of masks and protective shields. However, infection rates among patients did not show a similar decline.

An additional study found a significant risk of infection due to shared healthcare transport, especially as COVID-19 can be asymptomatic. Minimizing shared healthcare transport may help mitigate the risk of COVID-19 outbreaks in haemodialysis units.

Risk with ongoing renal transplantations during the pandemic

Ongoing renal transplantations during the pandemic may increase the risk of 28-day mortality in kidney transplant and dialysis patients and are primarily driven by the risk factors age and frailty. probably related to the impact of immunosuppressive drugs.

Acute Kidney Injury (AKI)

COVID-19 patients who develop AKI during hospitalisation are at a heightened risk of experiencing a decline in their estimated glomerular filtration rate (eGFR) at day 90 post-infection (table 1). Survivors of COVID-19 with hospital-acquired AKI are susceptible to long-term kidney complications, highlighting the importance of ongoing monitoring and management.

90-day outcomes	All groups, *n* (%)
Patients	1215
eGFR decline from baseline	
>30%	95 (7.8)
>40%	63 (5.2)
>50%	135 (11.1)

Table 1. eGFR decline of hospitalised AKI patients at 90 days.

Long-Term impact and recovery from COVID-19

Most dialysis patients who contract COVID-19 ultimately recover and regain their previous mental and functional status within a three-month period (figure 2).

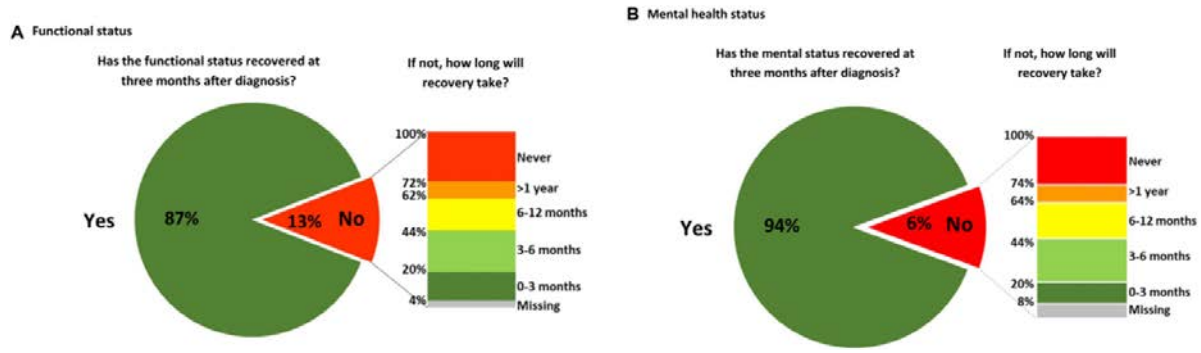


Figure 2. Functional and mental health status in HD patients at 3 months after a COVID-19 diagnosis, as judged by the treating nephrologist.

Conclusion

Patients on dialysis and renal transplantation face a higher all-cause mortality, COVID-19-related hospitalisation, and mortality compared to the general population. However, vaccination against COVID-19 significantly reduces the risk of hospitalisations and mortality among dialysis patients. Risk factors such as advanced CKD stage, cardiovascular diseases, chronic pulmonary disease, diabetes, and certain medications were associated with worse prognosis in patients with CKD.

Home dialysis was associated with a lower risk of infections but showed comparable mortality rates to in-centre dialysis. The risk of ongoing renal transplantations during the pandemic was associated with increased mortality and COVID-19 patients who develop AKI are at risk of long-term kidney complications.

These data emphasise the need for ongoing monitoring and management. Further research is needed to understand the long-term effects of COVID-19 in patients on dialysis and to develop strategies for optimising clinical outcomes in this vulnerable population.

Further reading

1. Gansevoort RT, Hilbrands LB. Nat Rev Nephrol. 2020;16(12):705-706
2. Fatima K, et al. Med Infect Dis. 2022:28;7(3):37
3. Jeffrey P, et al. CJASN. 2021;16(9):1410-1412
4. Hsu CM, et al. J Am Soc Nephrol. 2021;32(7):1569-1573
5. Noordzij M, et al. Clin Kidney J. 2023;16(4):662–675
6. Rincón A, et al. Clin Kidney J.2020;13(4):542–549
7. Lu J, et al. Nephrol Dial Transplant. 2023:1-10
8. Hemmelder MH, Nephrol Dial Transplant. 2022;37(6):1140-1151
9. Lumlertgul, N, et al. Ann Intensive Care. 2022;12:118
10. Sourial MY, et al. Perit Dial Int. 2023;43(1):13-22

Assessing fluid volume in haemodialysis with lung ultrasound - can it be the new standard of care?

Pantelis A. Sarafidis, Greece

Introduction and objectives

Fluid volume management is a concern in the care of haemodialysis (HD) patients given the consequence such as hypertension/hypotension, cardiovascular dysfunction, and associated mortality (figure 1). In addition, defining "dry weight" remains a challenge due to the absence of universally accepted standard measurement. The current model for assessment of fluid status in HD metrics may have issues with accurately assessing and maintaining optimal fluid balance, highlighting that fluid volume management remains a complex challenge.

The objective of this presentation is to provide an overview of the role of lung ultrasound in assessing fluid volume in haemodialysis and its potential to become the new standard of care, while exploring its applications, advantages, and findings from relevant studies.

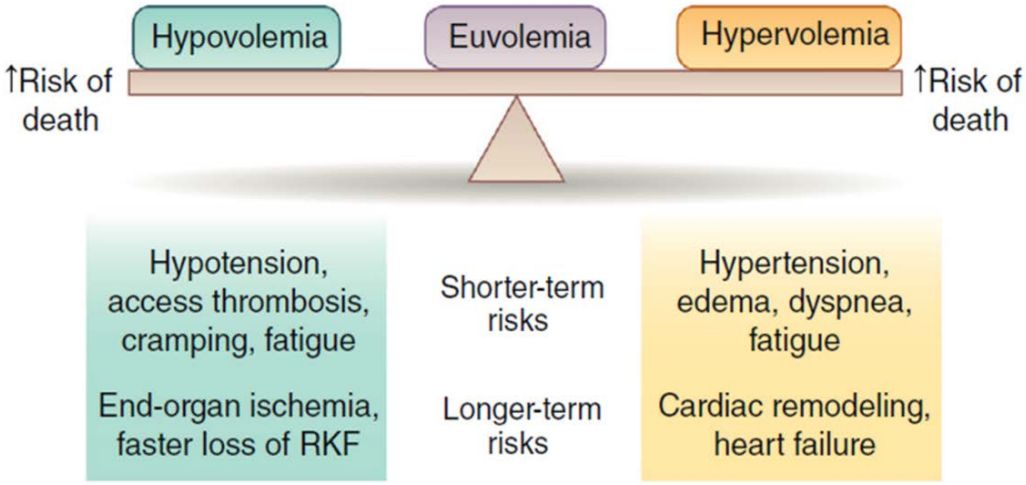


Figure 1. Consequence of fluid depletion (hypovolemia) or overload (hypervolemia) in haemodialysis patients.

Lung Ultrasound: A Novel Diagnostic Paradigm

Lung ultrasound has gained prominence as a potential breakthrough for assessing fluid status. The technique capitalizes on the "comet-tail" artifact, which allows distinction between normal pulmonary parenchyma and presence of oedema or alternative lung conditions. It's potential to estimate lung water content has been studied in observational investigations. These studies have underscored that lung water excess correlates more strongly with cardiac parameters, such as heart failure, rather than mere hydration status.

A simpler technique in dialysis

Lung ultrasound is increasingly used to estimate lung water in dialysis patients. A common method involves a score based on ultrasound findings called US-B lines which are measured at 28 locations between the ribs. In a study of 303 haemodialysis patients this method's effectiveness was compared to a simplified version using only eight of those locations. The goal was to determine how well these scores could predict death and cardiovascular events in this patient group.

The 8- and the 28-sites scores were highly inter-related (figure 2) indicating that the 8-sites score has almost the same ability to predict outcomes as the reference score. Moreover, while the 28-sites score takes 3 minutes to complete, the 8-sites score only takes 1.30 minutes, making it more practical for daily use in haemodialysis units.

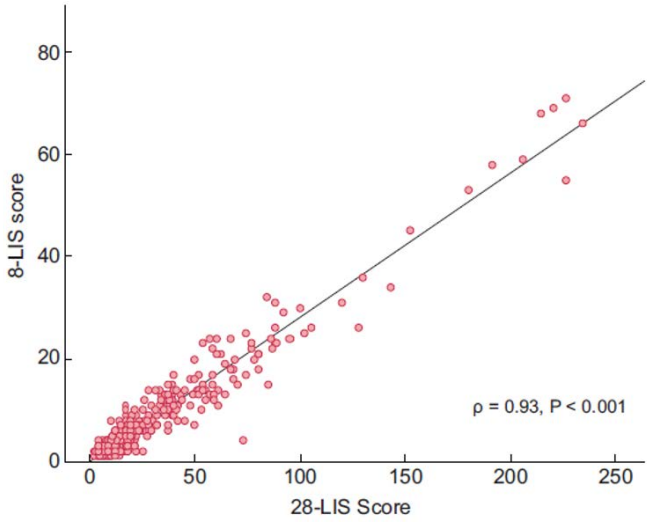


Figure 2. Correlation between 28- and 8-site scores in the study populations. LIS, lung intercostal spaces.

Clinical Trials and Lung Ultrasound

The LUNG WATER by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy (LUST) trial aimed to investigate the impact of ultrasound-guided extra-vascular lung water (LW-US) measurements on guiding dry-weight adjustments and ultrafiltration intensity in high-risk ESRD patients with cardiomyopathy. The trial's primary composite endpoint encompassed all-cause mortality, nonfatal myocardial infarction, and hospitalizations related to heart failure or acute coronary syndrome. The trial included ESRD patients with a history of cardiovascular events. Out of 367 enrolled patients, 183 received ultrasound-guided care (Lung-US guided), and 180 received standard usual care. During a mean follow-up of 1.49 years, the primary composite end point did not significantly differ between the two study arms (HR 0.88; 95% CI 0.63-1.24; P=0.47) (figure 2). Yet, post hoc analysis demonstrated risk reductions in recurrent decompensated heart failure (IRR 0.37; 95% CI 0.15–0.93; P=0.035) and cardiovascular events (IRR 0.63; 95% CI 0.41–0.97; P=0.038).

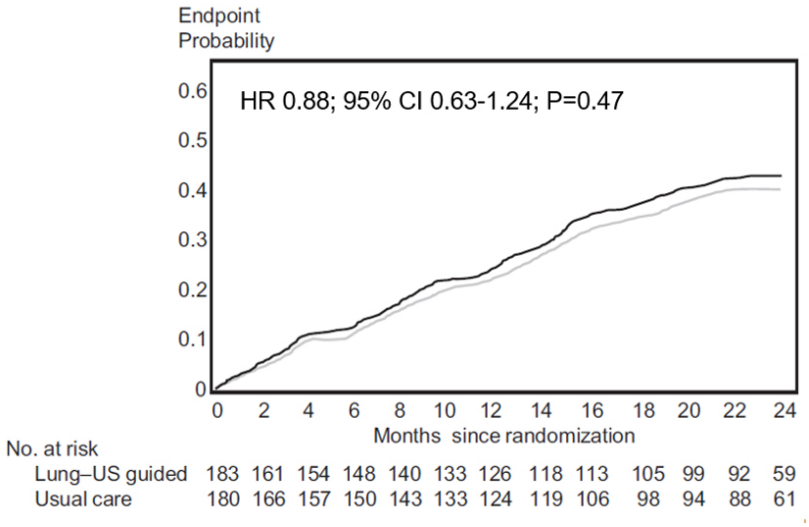


Figure 2. Primary endpoint: composite of all-cause death, nonfatal myocardial infarction, or decompensated heart failure. HR, hazard ratio.

Conclusion

Fluid volume assessment remains a pivotal facet of haemodialysis care with a need for more precise and objective techniques. Lung ultrasound can precisely quantify volume excess in a critical area and is characterized by its ease of learning, speed, portability, and comparatively lower technical complexity compared to other ultrasound procedures. However, it should be noted that its application is not limited to water-specific assessments. The diagnostic and prognostic value of lung ultrasound in dialysis is substantiated by observational studies. Furthermore, randomized controlled trials (RCTs) support its utility in regulating blood pressure and improving echocardiography parameters. Notably, RCTs suggest that strategies guided by lung ultrasound could potentially contribute to reducing the recurrence of cardiovascular events.

Further Reading

1. Sarafidis et al. Nephrol Dial Transplant. 2017 Apr 1;32(4):620-640
2. Canaud et al. Br J Nephrol 2019;41(4):550-9
3. Donadio C, et al. Medicine (Baltimore) 2015; 94:e473.
4. Gargani L, et al. Cardiovasc Ultrasound 2014; 12:25
5. Loutradis C, et al. Am J Kidney Dis 2020;75(1):11-20.
6. Loutradis C, et al. Kidney Int. 2019 Jun;95(6):1505-1513
7. Sarafidis PA, et al. Nephrol Dial Transplant 2017;32:620-640.
8. Tan TN, et al. BMC Nephrol 2022;23(1):44.
9. Torino et al. Clin J Am Soc Nephrol 2016;11(11):2005-2011.
10. Ziskin MC, et al. J Ultrasound Med 1982;1:1-7

Symposium 5.1
Deceased donor selection: new approaches and solutions

Ethical Issues in Deceased Donor Kidney Transplantation

Mehmet Sukru Sever, Türkiye

Introduction

Kidney transplantation is a critical intervention for patients with end-stage renal disease, but it poses numerous ethical challenges that require careful consideration and resolution. This presentation outlines the ethical issues surrounding kidney transplantation, focusing on controversies related to deceased donors, definitions of death, public concerns, and adherence to the dead donor rule. Additionally, it explores the complexities of donor families' involvement, the allocation criteria for deceased donor kidneys, and the ethical implications of these aspects (figure 1).

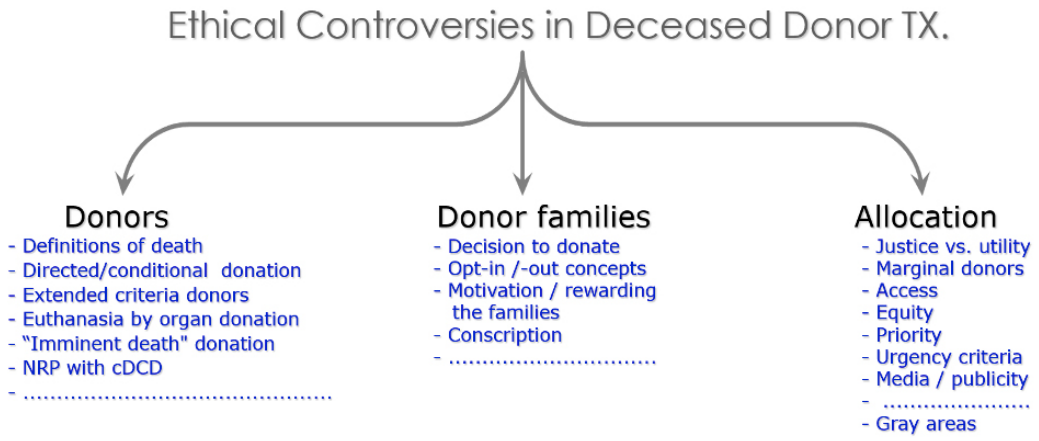


Figure 1. Ethical controversies surrounding deceased donor kidney transplantation. TX, transplant.

Donors

Definitions of Death

The determination of death in the context of kidney transplantation is a crucial ethical consideration. Brain death, defined as the cessation of all functions of the entire brain, including the brainstem, is a widely accepted definition. However, there is confusion at the public level due to medical reports of patients diagnosed as "brain dead" but maintaining organ functions for extended periods while remaining permanently unconscious and reliant on ventilators. The public's understanding and perception of brain death play a significant role in the acceptance of deceased organ donation. Achieving uniformity in brain death determination across different countries is essential to avoid discrepancies in declaring death and ensure the legitimacy of organ removal.

Dead Donor Rule

The Dead Donor Rule presents a deontological ethical stance focused on preserving public trust in the organ-procurement system and safeguarding the sanctity of life while preventing harm to living individuals. However, its implementation raises ethical debates as it may limit the procurement of transplantable organs, particularly in situations where determining death is complex. This rule's conflict with fundamental ethical principles, such as autonomy, utility, and nonmaleficence, continues to be a subject of academic scrutiny. The dissemination of these ethical controversies could potentially lead to a decrease in organ donation rates. To mitigate misunderstandings, it is essential to provide clear, straightforward, and transparent information about deceased organ donation and its ethical considerations, fostering a better understanding among the public.

Conditional Donation and Directed Donation

Ethical debates surround conditional donation, where organ donation is restricted based on factors such as race or lifestyle. Directed donation involves specifying a particular individual to receive the organ. The challenge lies in ensuring that organ allocation is fair, transparent, and not influenced by discriminatory factors.

Donor Families

Decision to Donate

The decision to donate a deceased person's organs often involves the donor's family, making it an ethical matter of utmost sensitivity. Different systems, such as opting-in (informed consent) and opting-out (presumed consent), have been proposed for consent for organ donation. While opt-out systems may increase donation rates, ethical concerns arise regarding informed consent, particularly related to contradiction on choice of donation; where families almost always make final decision, despite consent from the donor.

Motivation and Rewarding the Families

A contentious ethical issue pertains to whether financial incentives, such as an honorarium, could be justified to motivate donor families for organ donation. While most stakeholders accept financial incentives (figure 2) which may increase donation rates, ethical considerations may persist.

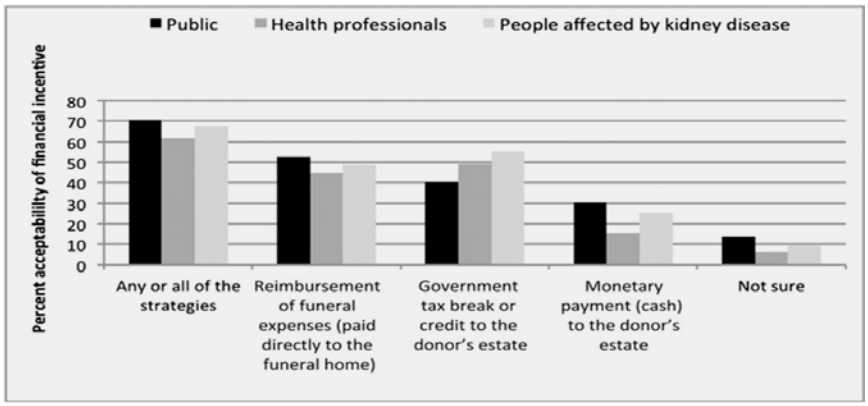


Figure 2. Canadian web-based survey (2011): Percent acceptability of financial incentive to increase organ donation among central public and healthcare professionals.

Allocation

There are thousands of people waiting for an organ from a limited pool of donors (figure 3). Developing ethically and legally approved organ allocation systems is a must to improve this process and ultimately patient outcomes.

Justice vs. Utility

Allocating deceased donor kidneys involves striking a balance between justice and utility (figure 3). Ethical allocation strategies must prioritize the worst-off patients while promoting fairness, transparency, and social usefulness. Nevertheless, decisions must also consider factors such as graft outcomes, cost, and efficiency, raising complex ethical dilemmas.

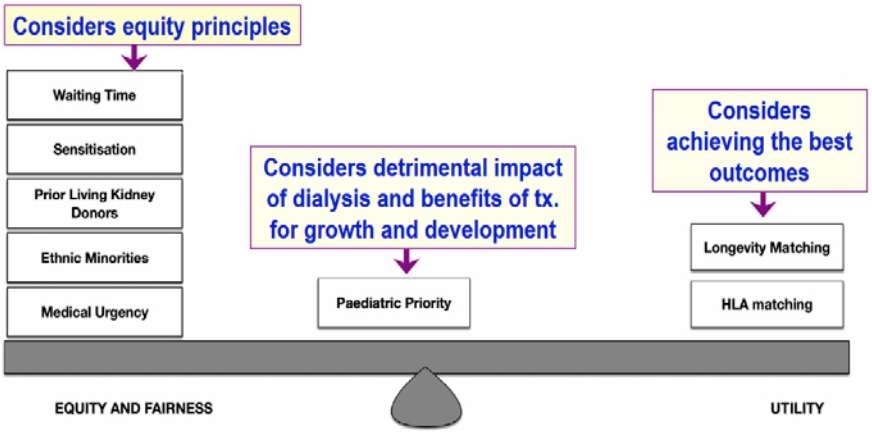


Figure 3. Factors considered to strike the balance between principles of utility and equality in allocation systems.

Grey Areas in Allocation

Furthermore, various grey areas in the field of kidney transplantation remain subject to controversy such as, determining the priority of individuals who experience first transplant failure due to non-adherence to prescribed medications and priority allocation when several organs are available. Moreover, certain key issues were noted but not thoroughly discussed, including the inclusion of foreign individuals in waiting lists, the exclusion of patients based on social support considerations, and racial/ethnic disparities, among others.

Conclusion

The selection of donors, the involvement of donor families, and the equitable allocation of deceased donor kidneys are critical aspects which have notable ethical implications. Navigating through these ethical controversies is essential for the medical community to optimize organ donation and benefit patients in need, all while upholding public trust in the organ procurement process. This presentation highlights that a comprehensive approach combining utilitarian considerations with deontological and ethical principles offers the optimal strategy to increase organ donation and ultimately improve patient outcomes.

Further Reading

1. Barnieh L, et al. Clin J Am Soc Nephrol 2012;7:1956–1963.
2. Bernat JL. New Engl J Med 2013; 369:1289-91.
3. Goss AL, Creutzfeldt CJ. Neurol Clin 2022;40:59.
4. Jenkins and Moorlock. Clinical Ethics 2022;1–10.
5. Lee D et al. Nephrology 2019;24:591-8.
6. Pennings G. J Appl Philos 2007;24:41-49.
7. Truog RD. New Engl J Med 2013; 369:1287-9.
8. Wijdicks E. Brain 2012:135;1321.
9. Yeung MY et al. Semin Nephrol 2022;42:151274.
10. Zalewska K. Introduction to Selection and Allocation Policies 2015. Available from: http://odt.nhs.uk/pdf/introduction_to_selection and_allocation_policies.pdf. Last accessed: August 2023.

New Approaches to Improve Graft Viability and Implementation

Gabriel C. Oniscu, Sweden

Introduction

One of the key challenges with organ transplantation is that demand exceeds the available supply, leading to unequal access and high waiting list mortality. To address these challenges, transplant centres are exploring innovative strategies to enhance graft viability and increase the availability of suitable donor organs. This presentation delves into potential solutions, with a primary focus on machine perfusion strategies and promising therapeutic interventions.

To expand the pool of available organs, transplant centres are now considering more complex donors. This includes exploring organs from extended criteria donors and those donated after circulatory death (DCD). While these donors present challenges in terms of organ quality, they offer an opportunity to save more lives and increase the availability of organs.

Key Strategies to Improve Graft Viability and Implementation

Machine perfusion is emerging as a potential approach to enhance organ preservation and viability. Different machine perfusion strategies, such as hypothermic machine perfusion (HMP), subnormothermic machine perfusion (SMP), and normothermic machine perfusion (NMP), have been developed to assess and maintain organ function outside the human body. These techniques provide a more accurate evaluation of organ viability and hold the potential to increase the utilization of previously discarded organs.

Donation after DCD has gained attention as an alternative source of organs. A recent study demonstrated that the use of normothermic perfusion in the donor (NRP) significantly improves kidney transplant outcomes. Notably, graft failure was reduced by 50%, and instances of delayed graft function were reduced. Moreover, there was an improvement in estimated glomerular filtration rate (eGFR) of 6.3 mL/min/1.73 m^2 at the end of the first year (table 1).

Graft outcomes	NRP Kidney transplants (N=210)	Non NRP kidney transplants (N=5744)
12-month graft failure N (%)	7 (3%)	368 (6%)
Immediate function	155 (73.8%)	3413 (59.4%)
Delayed Graft Function N (%)	**49 (23.3%)**	**1793 (31.2%)**
Primary non-function N (%)	4 (1.9%)	175 (3.1%)
Mean eGFR at one year (ml/min/1.73m²)	**56.4**	**45.6**
Unknown/missing data on function	2 (1%)	363 (6.3%)

Table 1. Kidney graft outcomes in NRP kidney transplants vs non-NRP kidney transplants in organs recovered from donors after DCD. Data from the United Kingdom (UK).

Other strategies explored encompassed donor hypothermia, which demonstrated inferiority to machine perfusion methods, as well as hypothermic oxygenated perfusion and normothermic machine perfusion.

Despite positive results, several questions remain unanswered such as determining the optimal perfusion type, timing during the transplant process, perfusion duration, and the most suitable perfusate composition.

Implementing Sustainable Organ Perfusion Services

While there is potential of sustainable organ perfusion services for donor organs, implementation is considered complex, requiring key factors to be addressed such as a dedicated core team, education and training, institutional support, a drive for innovation within the healthcare system, robust infrastructure, seamless integration of technologies etc. (figure 1).

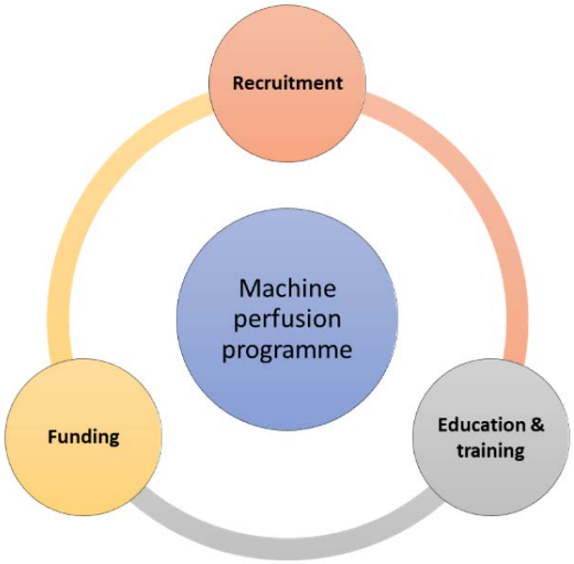


Figure 1. Key themes for the implementation of a sustainable organ perfusion service

Conclusion

The increasing demand for organ transplantation necessitates innovative solutions to improve graft viability and optimize organ utilization. Strategies involving machine perfusion and therapeutic interventions have the potential to improve transplantation outcomes. While organ perfusion is established in clinical practice, determining the most suitable strategy for different organs remains a challenge. Nevertheless, there is rapid progress in understanding graft injury and identifying mitigating strategies.

Further Reading

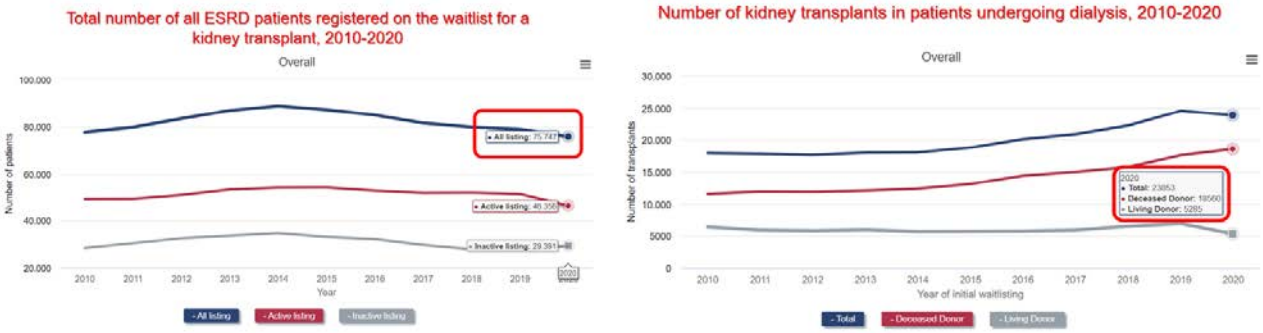
1. Arcolino FO, et al. Am J Transplant 2022;22:2791–2803.
2. Husen P, et al. JAMA Surg 2021;1;156(6):517-525.
3. Jochmans I, et al. Lancet 2020;21;396(10263):1653-1662
4. Malinoski D, et al. N Engl J Med 2023;2;388(5):418-426.
5. Oniscu GC, et al. Am J Transplant 2014;14(12):2846-54.
6. Oniscu GC, et al. Transplantation 2023;1;107(2):438-448.
7. Stewart DE, et al. Am J Transplant 2016;16(6):1834-47.
8. Hosgood, S.A., et al. Nat Med 2023;29:1511–1519.

Deceased Donor Selection: How to Select the Right Donor for the Right Recipient - Guidelines and Other Considerations

Piergiorgio Messa, Italy

Introduction

The Kidney Disease Improving Global Outcomes (KDIGO) guideline emphasizes any end-stage renal disease (ESRD) patient, with a life expectancy long enough, should be evaluated for being included in the kidney transplant (KTx) waiting list, since KTx is the best treatment option for replacing the failed kidney function. However, the demand for kidneys far exceeds the supply of available organs, with the number of patients on the waiting list far higher than the number of organs available each year (figure 1).



This scarcity necessitates careful selection of deceased donors to maximize the chances of graft success and recipient survival. This presentation delves into the process of deceased donor selection for kidney transplantation, exploring guidelines, considerations, and emerging tools for enhancing the efficacy of this vital procedure and its limitations.

Figure 1. The total number of ESRD patients on a kidney transplant waiting list (left) and the number of kidney transplants undertaken in the same time period (right). Data from the United States Renal Data System 2022.

Key Considerations for Deceased Donor Selection

Equity and Efficiency

The principle of equitable allocation underscores providing equal opportunity to all waitlisted patients to receive the most suitable organ. Simultaneously, efficient allocation ensures that organs are appropriately matched to recipients, avoiding under-utilization or misassignment (figure 2).

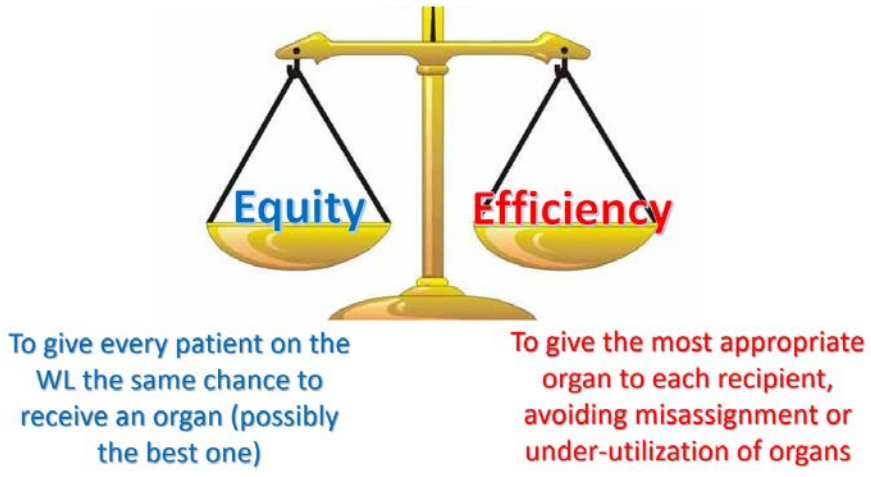


Figure 2. Equity and efficiency as key considerations for deceased donor selection. WL, waiting list.

The models currently used to achieve the best possible match between donor and recipient are based on immunological and non-immunological criteria.

Overview of current models for choosing the right donor for the right recipient

Immunological Donor/Recipient Matching

Compatibility between donors and recipients in terms of human leukocyte antigen (HLA) and ABO blood group plays a pivotal role in graft success. Guidelines emphasize the significance of HLA matching to minimize the risk of rejection and improve long-term outcomes. Allocations transitioning from local to national and international levels have increased access to organs and improved matching. Moreover, paired-donation and donor exchange programs broaden the living donor pool, enhancing the likelihood of finding suitable matches and optimizing transplant outcomes.

Non-Immunological Donor/Recipient Matching

Apart from the specific programs of priority assignment to some categories of ESRD patients who have an urgent need for a kidney transplant, many non-immunological aspects have been considered for the best possible matching between the expected duration of the graft in itself and the expectation of survival of the graft recipient after KTx.

Expanded Criteria Donors (ECD) vs. Standard Criteria Donors (SCD)

The ECD/SCD classification system guides allocation decisions based on donor characteristics. However, concerns exist about discarding potentially viable organs due to classification, propelling the search for more nuanced allocation strategies.

Kidney Donor Profile Index (KDPI) and estimated post-transplant survival score (EPTS)

Emerging tools such as the KDPI and EPTS entail continuous evaluation of both donor and recipient, based on multiple parameter evaluation. KDPI offers insight into the projected post-transplant longevity of the kidney, while EPTS estimates the duration of benefit for the recipient. These metrics are quantified on a scale of 0 to 100%, with lower scores indicating longer estimated transplant function and longevity of benefit, respectively. However, limitations exist also within this model. The assessment of the KDRI through C-statistics yields notably low values (0.60-0.65). Moreover, there exists significant geographic diversity in the influence of variables shaping KDPI values. The threshold for KDPI values exceeding 85%, which is the value usually utilized in clinical practice, presents a parallel concern to the ECD/SCD model bias, potentially leading to the unwarranted discard of kidneys positioned above this threshold (figure 3).

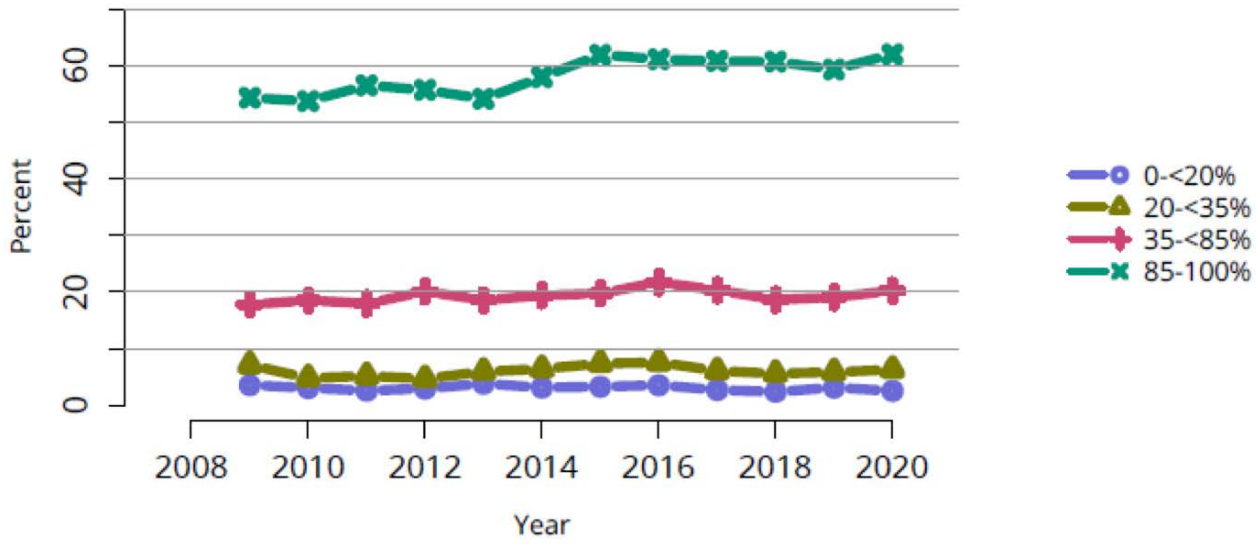


Figure 3. Percent of kidneys recovered for transplant which were not transplanted by KDPI.

Emerging Tools and Considerations

Pre-Transplant Renal Biopsy and Novel Prognostics

Exploring the role of pre-transplant renal biopsy as a predictive tool introduces an additional layer of evaluation for donor-recipient compatibility, it is to be underlined that the histological assessment for the purposes of assigning the organ to be transplanted has been found to increase the number of organs discarded.

The incorporation of novel prognostic tools based on omics technologies holds potential to enhance matching accuracy and predict graft outcomes. Additionally, the analysis of biochemical markers through liquid biopsy presents a potential solution to the constraints posed by conventional histological evaluations.

Conclusion

Deceased donor selection for kidney transplantation is a complex process that aims to optimize graft success and recipient survival while ensuring equitable distribution of available organs. All the available organ assignment models are far from being ideal in achieving the efficacy and equity criteria. Furthermore, an as-yet unacceptable number of organs that could be effectively utilized in patients with a relatively reduced life expectancy (e.g. elderly patients) are discarded. So, in producing graft allocation scoring systems, for better achieving the goal of giving the right kidney to the right recipient, also the estimate of the expected survival of the recipient remaining on the waiting list should be taken into account.

Further Reading

1. Aubert O, et al JAMA Int Med 2019;179(10):1365-1374.
2. Archer KJ, et al. Am J Transplant 2022;22(11):2515-2528.
3. Chadban SJ, et al. Transplantation 2020;104:S1–S103.
4. Colvin M, et al. OPTN/SRTR 2020 Annual Report. Am J Transplant 2022. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajt.16977. Last accessed: August 2023.
5. Husain SA et al Am J Transplant 2022;22:1603–1613.
6. Jadav P, et al. Curr Opin Nephrol Hypertens 2021;30(6):571-576.
7. Lenain R, et al. Am J Kidney Dis 2021;79(2):164-174.
8. Miller J, et al. Am J Transplant 2023;23(5):636-641.
9. Schutter R et al. Neph Dial Transplant 2023;3:787-796.
10. USRDS Annual Report 2022. Available from: https://usrds-adr.niddk.nih.gov/2022 . Last accessed: August 2023.

Symposium 7.4
Contemporary AKI management

Prediction of AKI: biomarkers, clinical models or both?

Greet De Vlieger, Belgium

Introduction and objectives

Acute Kidney Injury (AKI) is a common complication that often goes undiagnosed until at the time of initial harm to the kidney, potentially leading to worse outcomes. With no curative treatment, the ability to predict AKI has become crucial for timely preventive interventions. This presentation aims to explore the use of biomarkers, clinical models, or a combination of both for predicting AKI, highlighting key findings from relevant studies.

Key Results

Biomarkers and Clinical Models for AKI Prediction

Studies have identified markers such as tissue inhibitor metalloproteinase-2 (TIMP-2), insulin-like growth factor-binding protein (IGFBP7) and neutrophil gelatinase-associated lipocalin (NGAL) as potential indicators of AKI development. These biomarkers have been found to have varying levels of accuracy in predicting AKI, with TIMP-2 x IGFBP7 demonstrating an area under the receiver operating characteristic curve (AUC) of 0.80 and NGAL showing an AUC of 0.74 (figure 1).

Combining biomarkers and clinical models may enhance AKI prediction. Studies have demonstrated that integrating biomarker measurements with clinical models can improve accuracy, with the combined approach achieving AUC values as high as 0.87 (figure 1). This suggests that leveraging both biomarkers and clinical data can have a synergistic effect in predicting AKI.

	Clinical model	Biomarker	Both
TIMP-2 x IGFBP7			
Sapphire	0.81	0.80	0.87
TOPAZ	0.70	0.86	0.86
Jia et al		0.66	0.75
NGAL			
AKIPredictor	0.77	0.74	0.80

Figure 1. AKI prediction model based on clinical and biomarker data across multi-centre studies (AUC data presented)

Challenges for the use of Clinical Models for AKI Prediction

Machine-learning-based clinical prediction models have gained attention in AKI research. These models utilize various patient data points and algorithms to generate predictions. A review of published AKI prediction models across all clinical sub-settings outlined that across 150 studies – differences in design, population, AKI definition, and model performance assessments were apparent. Additionally, existing models have shown good accuracy, but their lack of external validation and high risk of bias limit their clinical utility (Table 1).

Subgroup	No. of studies	AUC (95% CI)	Between-group *P* value
Clinical settings			
Nephrotoxins	29	0.81 (0.78-0.84)	
Postoperation	64	0.81 (0.79-0.83)	.11
ICU	21	0.82 (0.78-0.86)	
General hospitalization	36	0.77 (0.75-0.80)	
AKI definition			
Self-defined	36	0.82 (0.80-0.85)	
KDIGO	76	0.79 (0.77-0.81)	.15
Others	38	0.80 (0.77-0.83)	
Risk of bias			
Low	24	0.79 (0.76-0.82)	.29
High	26	0.80 (0.79-0.82)	
Study design			
Retrospective	124	0.80 (0.78-0.81)	.31
Prospective	26	0.82 (0.78-0.86)	
Region			
North America	56	0.78 (0.76-0.80)	
Asia Pacific	60	0.83 (0.81-0.85)	.002
Others	34	0.79 (0.76-0.82)	
AKI frequency			
10%	56	0.79 (0.77-0.81)	
10%-20%	43	0.82 (0.79-0.84)	.26
20%	51	0.80 (0.77-0.82)	
Development methods			
Logistic regression	110	0.80 (0.78-0.81)	.56
Machine learning	40	0.81 (0.78-0.84)	
Predictor numbers			
<15	108	0.80 (0.79-0.82)	
15	32	0.80 (0.77-0.83)	.76
Not reported	10	0.78 (0.71-0.85)	
Overlap			
No/probably no	118	0.89 (0.78-0.81)	.35
Yes/probably yes	32	0.81 (0.78-0.84)	
Predictor availability			
Yes/probably yes	116	0.80 (0.78-0.81)	.38
No/probably no	34	0.81 (0.78-0.84)	

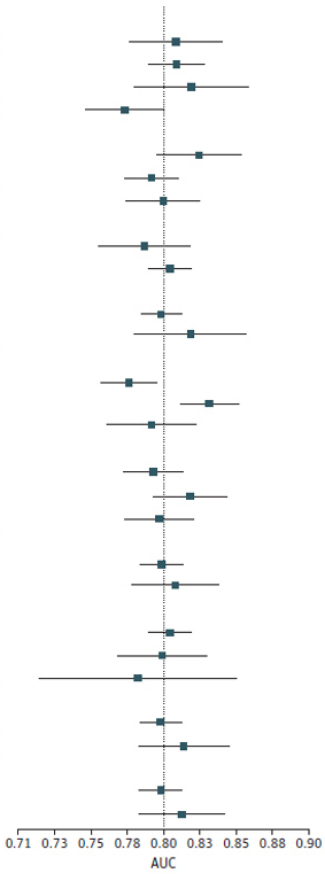


Table 1. Characterization of Risk Prediction Models for Acute Kidney Injury AKI – a review of 150 studies. AKIN, Acute Kidney Injury Network; CM, contrast medium; H-L test, Hosmer-Lemeshowtest; ICU, intensive care units; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury and Failure, Loss and End-Stage Kidney Disease.

Conclusion

Predicting AKI is essential for timely interventions. Machine-learning-based clinical models hold potential, but their lack of validation and potential biases limit their application. Combining biomarkers and models can enhance accuracy however key challenges to implementation include external validation and real-world implementation. Future research should focus on AKI sub-phenotyping using machine-learning tools, identifying relevant biomarkers or clinical features for tailored prediction models. Additionally, machine-learning algorithms can uncover complex patterns in large datasets, potentially improving AKI prediction accuracy in the future.

Further reading

1. Bihorac A, et al. Am J Respir Crit Care Med 2014;189:8
2. Desanti De Oliveira B, et al. Nat Rev Nephrol 2019;15:599–612.
3. Feng Y, et al. JAMA Netw Open 2023;6(5):e2313359.
4. Flechet M, et al. Intensive Care Med. 2017;43(6):764-773
5. Forni LG, et al. J Crit Care 2022;71:154066
6. Kashani K, et al. Crit Care 2013;17:R25
7. Koyner JL, et al. Crit Care Med 2018;46(7):1070-1077
8. Menger J, et al. Crit Care 2022;26(1):268.
9. Ostermann, M., et al. Intensive Care Med 2023;49:219–222
10. Pan HC, et al. Crit Care 2022;26:349

Artificial intelligence: Can it guide management of AKI patients?

Jay L. Koyner, USA

Introduction and objectives

Artificial Intelligence (AI) has emerged as a powerful tool in healthcare, including the management of Acute Kidney Injury (AKI). This presentation explores the potential of AI in assisting clinical decision-making and improving patient outcomes in AKI. The key findings from relevant studies are presented, focusing on clinical decision support systems, the role of AI in AKI, and the importance of combining AI with biomarkers.

Key Results

Clinical Decision Support Systems

AI-powered clinical decision support tools have shown potential in identifying high-risk AKI patients and prompting timely interventions. Studies have reported reduced mortality rates and improved patient outcomes when these tools are integrated into healthcare practices.

Clinical decision support (CDS) systems utilize AI algorithms to analyse patient data, identify patterns, and provide evidence-based recommendations to healthcare providers. One notable CDS tool is ICE-AKI, a clinical prediction rule developed to stratify patients based on their risk of developing AKI or the presence of EARLY-AKI . ICE-AKI has demonstrated effectiveness in predicting AKI risk and prompting early interventions to prevent its progression as ICE-AKI – decreased mortality in the at-risk group (figure 1). Additionally, medication alerts powered by AI have proven valuable in reducing nephrotoxic drug exposure and mitigating AKI incidence in both adult and pediatric patients. These alerts have demonstrated success in several studies particularly around the discontinuation of non-steroidal anti-inflammatory drugs (NSAIDs), vancomycin, piperacillin-tazobactam, renin-aldosterone agents and proton pump inhibitors (PPIs).

	Intervention Site			Control Site		
	Before	After	OR (95% CI), P-value	Before	After	OR (95% CI), P-value
CA-AKI Cases	n = 670	n = 755		n = 491	n = 586	OR (95% CI), P-value
In-patient mortality	23%	23%	1·01 (0·79–1·29), 0·95	19%	17%	0·86 (0·63–1·17), 0.34
AMBER (APS ≥5)	n = 2,057	n = 2,351		n = 1,810	n = 1,851	
In-patient Mortality	14%	11%	0·78 (0·66–0·94), 0·008	10%	10%	0·96 (0·78–1·20), 0·74

Figure 1. In-patient mortality cases with CA-AKI and in those flagged as high-risk on admission by the CPR. CA-AKI, community-acquired AKI; OR, odds-ratio, CPR, electronic clinical prediction rule.

AI Phenotyping in AKI

AKI is a heterogeneous condition with varying aetiologies and clinical presentations. AI phenotyping aims to identify distinct subtypes of AKI based on complex patient data, enabling more precise pathologic diagnosis and tailored treatment plans. AI algorithms can analyse large datasets, including genetic profiles, biomarker levels, and electronic health records, to uncover previously unrecognized patterns in AKI development and progression. This approach enhances the understanding of the disease and may lead to targeted interventions that improve outcomes for specific AKI subpopulations.

An example presented was in patients with acute interstitial nephritis (AIN). These patients often present without typical clinical features, leading to a delay in diagnosis and treatment. The inclusion of novel biomarkers with a validated diagnostic model, electronic health record (EHR), to identify patients at risk of AIN, showed an improved area under the receiver operating characteristics curve (AUC) versus EHR alone (figure 2). Using biomarkers specific to a biopsy proven injury pattern is future of AKI diagnostics and care.

Model	Setting	AUC
EHR	Yale, training set	**0.78** (0.73, 0.83)
EHR	Yale, test set	**0.73** (0.64, 0.81)
EHR	Indiana, validation set	**0.74** (0.69, 0.79)
EHR + biomarkers	Yale AIN study	**0.84** (0.76, 0.91)

Figure 2. Model performance: AUC improved with addition of urine diagnostic biomarkers IL-9 and TNF-ŧ . area under the receiver operating characteristics curve (AUC); electronic health record (EHR).

Conclusion

AI has the potential to greatly impact the management of AKI patients. However, the implementation of AI in AKI care is not without challenges. Prospective validation of AI tools, especially concerning different AKI phenotypes, is essential to ensure their clinical utility and effectiveness. Further research and prospective validation of AI tools are necessary to determine their clinical utility in different AKI contexts, particularly with earlier diagnosis.

Further reading

1. Churpek MM, et al. JAMA Netw Open 2020;3(8):e201289
2. Goldstein SL, et al. Pediatrics 2013; 132:e756-e767
3. Lyons PG, et al. JAMA Intern Med 2023;183(6):611–612
4. Mohammed Al-Jaghbeer, et al. J Am Soc Nephrol 2018;29(2):654-660
5. Selby NM, et al. J Am Soc Nephrol 2019;30(3):505-515.
6. Sohaney R, et al. Am J Kidney Dis. 2021 Feb;77(2):300-302.
7. Wilson P, et al. BMJ 2021;372:m4786
8. Moledina DG, et al. Nephrol Dial Transplant. 2021, 36(10):1851-1858
9. Moledina DG, et al. Nephrol Dial Transplant. 2022; 37(11):2214-2222.

As climate changes, Europe gets ready for subtropical AKI

Vivekanand Jha, India

Introduction

Climate change is a worldwide phenomenon with implications for public health. It is a global concern, as average temperatures have reached record levels even in temperate regions like Europe. Amidst these challenges, Acute Kidney Injury (AKI) is a significant public health issue. This condition affects millions of people globally and is linked to high morbidity and mortality rates. Given the potential impact of climate change on AKI due to rising temperatures, it is important to prioritize research and raise awareness to address this often-neglected disease.

Key Results

AKI in the Tropics

AKI in tropical regions and developing countries exhibits distinctive pathophysiological characteristics compared to temperate climates, with a greater estimated burden in these regions (figure 1). Tropical AKI is intricately linked to local ecosystems and cultural practices, making it a complex and multifactorial condition. The presentation and clinical outcomes of tropical AKI are substantially influenced by health system-level factors, such as limited access to healthcare, inadequate resources, and varying treatment practices.

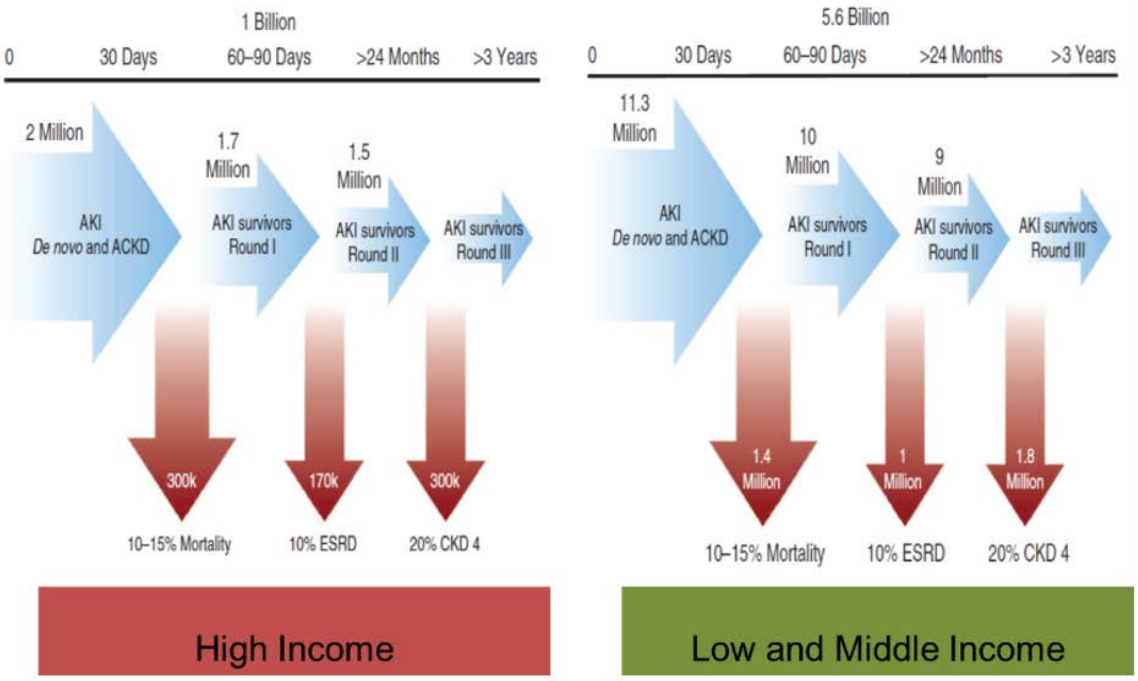


Figure 1. Estimated burden of AKI with progression to CKD and death in developed (high-income) and developing (low-income) regions.

Climate Change and AKI challenges

Climate change exacerbates the challenges in managing AKI in tropical regions. Rising temperatures and increased humidity create a conducive environment for various infections and contribute to the prevalence of AKI.

As climate change continues to progress, this has direct implications for AKI, as changes in the prevalence and distribution of infectious diseases impact the incidence and severity of AKI, leading to changes in the distribution and activity of disease-carrying vectors, such as mosquitoes, which can indirectly affect the incidence of AKI (figure 2). Mosquito-borne diseases like malaria and dengue can lead to AKI as severe complications. Additionally, water-borne diseases that flourish in warmer climate such as cholera and leptospirosis, can also contribute to AKI cases.

This is compounded in tropical regions due to an increased likelihood of poverty, fragile ecosystems, high population growth and under-resourced health and social security systems. Addressing AKI in these regions requires a comprehensive approach that considers not only medical interventions but also social and environmental determinants.

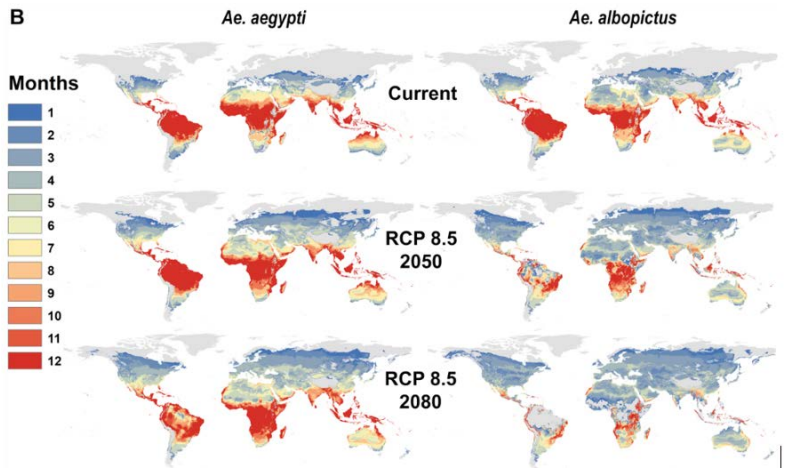


Figure 2. Predicted mean monthly temperatures under current climate and future scenarios for 2050 and 2080 for Ae. aegypti and Ae. Albopictus (mosquito species) in a worst-case scenario (based on a business-as-usual fossil fuel emissions scenario of representative concentration pathway (RCP) 8.5).

Implications for temperate regions

The impact of climate change on environmental conditions has significant implications for temperate regions such as European countries, particularly concerning changes in biodiversity and the occurrence of vector-borne diseases. The altered environmental landscape provides favourable habitats for disease-carrying vectors, leading to potential disease outbreaks. Additionally, climate-induced migrations can play a role in disease transmission, necessitating the development of targeted strategies to address the increasing risk of vector-borne diseases in Europe. These observations underscore the urgency for scientific and public health communities to proactively adapt and implement measures to mitigate the potential threats posed by climate change on disease dynamics globally to reduce potential vector-borne disease risk (figure 3).

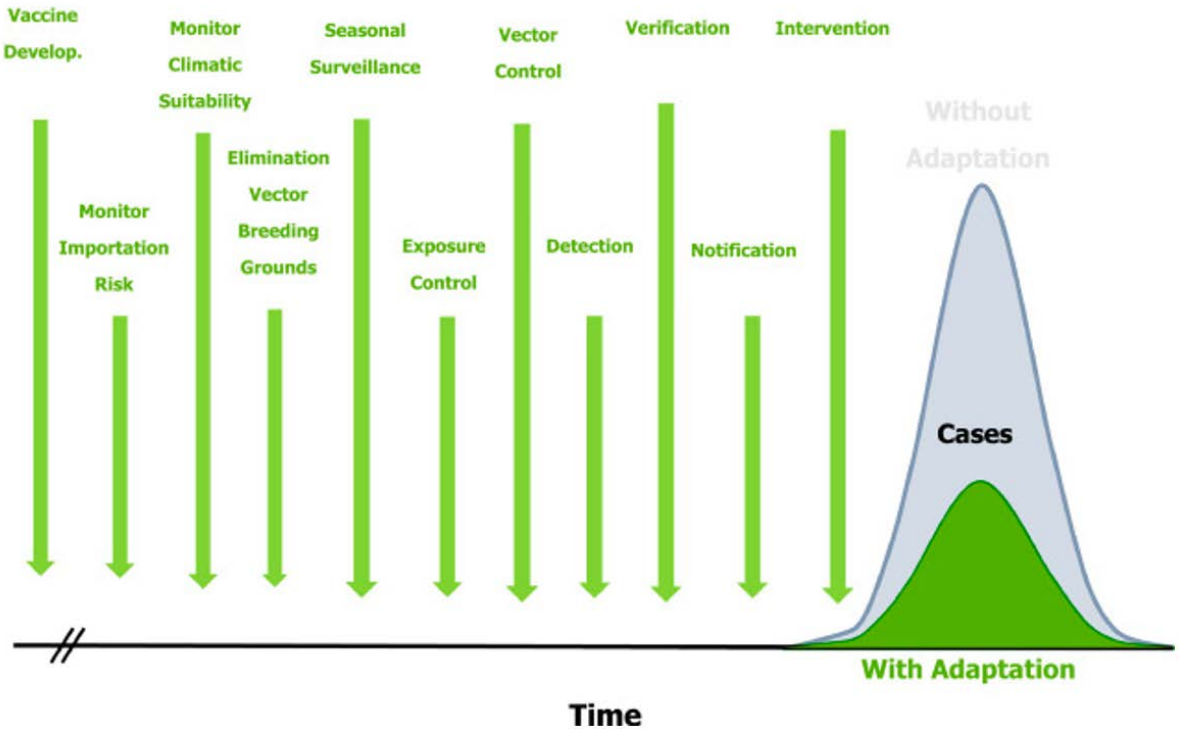


Figure 3. Climate change adaptation options for vector-borne diseases in Europe (with vs without adaptation).

Conclusion

The impact of climate change poses significant challenges for managing AKI in tropical regions, and as climate change progresses, it could become a greater concern in temperate regions as well. AKI's unique nature in tropical areas, influenced by climate, living conditions, and culture, calls for targeted research and community engagement. Climate change's influence on vector-borne diseases also affects AKI incidence and severity. To enhance prevention, management, and outcomes, addressing climate change implications for AKI through research, healthcare strengthening, and community awareness are key. Embracing proactive measures will bolster health resilience against environmental challenges in both tropical and temperate regions, including Europe.

Further reading

1. Lewington AJ, et al. Kidney Int 2013 Sep;84(3):457-67
2. Naqvi R, et al. Pak J Med Sci 2015;31:1472–1475
3. Ryan SJ, et al. PLoS Negl Trop Dis 2019;13(3):e0007213
4. Semenza JC. Nat Immunol 2020;21(5):484-487
5. Williams J. Geography 2021;106(3):136-142
6. Wu X, et al. Environ Int 2016;86:14-23

Symposium 0.5
Nephrology Pearls

End Stage Kidney Disease and Dialysis

Christian Combe, France

Introduction

End-stage kidney disease (ESKD) is a critical condition that requires renal replacement therapy, such as dialysis or transplantation, to sustain patients' lives. This presentation provides a comprehensive overview of recent advancements and critical considerations in the field of dialysis and ESKD.

Advancements and key considerations in patients with ESKD treated by dialysis

Genetics in Dialysis

Recent research has explored the impact of genetics on peritoneal dialysis outcomes; AQP1 rs2075574 variants have been associated with peritoneal ultrafiltration rates and risk of the composite of death or technique failure (i.e., transfer to haemodialysis) in patients treated by peritoneal dialysis (table 1). The TT genotype is associated to a higher risk of treatment failure and death.

Variable	Overall	CC	CT	TT	P Value†
Peritoneal water transport					
Discovery phase					
No. of patients	433	184	199	50	—
Net ultrafiltration during baseline 3.86% glucose–based PET — ml	611±280	626±283	625±282	506±237	0.02
Validation phase					
No. of patients	985	383	459	143	—
Daily net ultrafiltration — ml	488±633	563±641	463±629	368±603	0.003
Outcomes					
No. of patients	898	384	400	114	—
Death or technique failure — no. (%)	419 (47)	162 (42)	191 (48)	66 (58)	0.01
Technique failure — no. (%)	280 (31)	105 (27)	136 (34)	39 (34)	0.10
Death from any cause — no. (%)	139 (15)	57 (15)	55 (14)	27 (24)	0.03

Table 1. AQP1 genotype, ultrafiltration rates and outcomes in patients treated by peritoneal dialysis.

The Impact of COVID-19 on patient outcomes

The COVID-19 pandemic had a significant impact on dialysis patients. Multiple waves of the virus affected patients' mortality rates, with the initial waves being associated with the highest mortality. Moreover, a study from the European Renal Association COVID-19 Database (ERACODA) demonstrated excess COVID-19 related mortality in patients who received a kidney transplant vs those treated with haemodialysis, suggesting unique vulnerabilities among these populations.

Vaccination Coverage and Infections

Consequently, the effectiveness of vaccination against COVID-19 is a critical concern for dialysis patients. Vaccination coverage in dialysis patients showed variations between 2020 and 2021 (across the first to third wave of the virus). Using Bayesian multivariable spatiotemporal models, the association between vaccine exposure and severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) severe infections (with hospital admission) in dialysis patients from simultaneous incidence in the general population were estimated. The incidence of severe infections in dialysis patients was greater than the general population overall. Moreover, there were proportional dynamics across both groups during the first two pandemic waves. The relative incidence in dialysis patients dropped in early 2021 after the beginning of the vaccine policies, suggesting a protective effect against severe forms of COVID-19 in dialysis patients (figure 1).

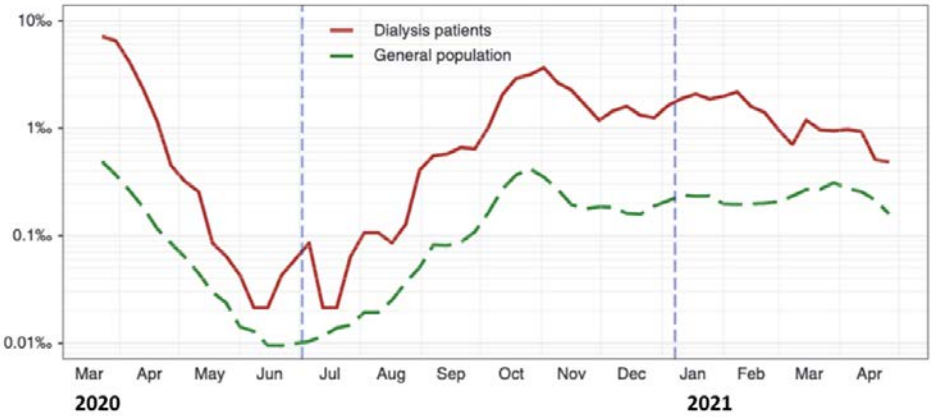


Figure 1. Nationwide vaccination coverage and SARSCoV-2 severe infections in patients needing maintenance dialysis and in the general population (adults aged ≥25 years).

Anticoagulation in Patients Treated by Haemodialysis

Research conducted in Belgium evaluated the use of rivaroxaban in patients with atrial fibrillation on haemodialysis (>80 years). Survival free of fatal and non-fatal cardiovascular events were greater with rivaroxaban versus VKA. Moreover, other anticoagulation treatments were evaluated; an apixaban study showed that clinically relevant bleeding events were significantly more frequent than stroke or systemic embolism, indicating the need for careful assessment of the risks and benefits of anticoagulation in this population.

Haemodialysis Techniques

In a Swiss prospective single-centre observational cohort study, incremental dialysis had an increased survival rate compared to standard haemodialysis and peritoneal dialysis (figure 1).

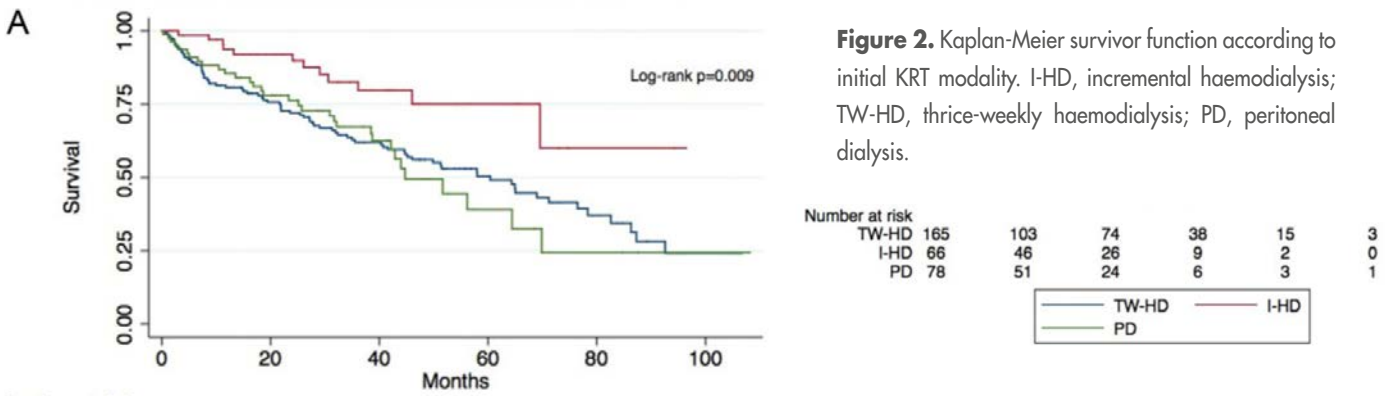
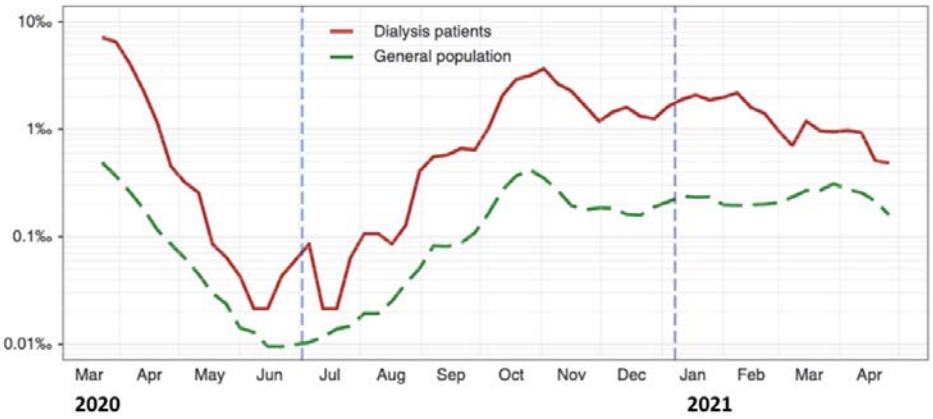


Figure 2. Kaplan-Meier survivor function according to initial KRT modality. I-HD, incremental haemodialysis; TW-HD, thrice-weekly haemodialysis; PD, peritoneal dialysis.

A randomized controlled trial in the UK demonstrated that incremental haemodialysis was associated with lower costs and could be a feasible approach, potentially benefiting specific patient groups. However, it was noted that worldwide the safety and feasibility of incremental dialysis must be proven before widespread use can be implemented.

Cooler dialysate temperatures have been investigated to prevent intradialytic hypotension, a common issue during haemodialysis. A Canadian trial examined the pragmatic implementation of cooler dialysate temperatures and its impact on hypotension and mortality. Results showed a reduction in intradialytic hypotension without an associated increase in mortality. Additionally, as concerns were previously raised regarding the safety of citric acid-containing dialysate in the press and the potential association with higher mortality rates; a Dialysis Outcomes and



Practice Patterns Study (DOPPS) in haemodialysis patients (n=11,306) was undertaken - no association between citric acid-containing dialysate and mortality was found.

Conclusion

Advancements in dialysis for ESKD patients have significantly impacted patient care. Genetic influences on dialysis outcomes, COVID-19 vaccination implications, anticoagulation therapy considerations, and innovative techniques such as incremental dialysis and cooler dialysis baths collectively contribute to improving patient outcomes. While progress has been made, the complexity of ESKD necessitates ongoing research and a personalized approach to treatment.

Further Reading

1. Carriazo S, et al. Nephrol Dial Transplant 2022;37:2253-2263.
2. De Vriese AS, et al. J Am Soc Nephrol 2021;32:1474-83.
3. El Karoui K, et al. Clin J Am Soc Nephrol 2022;17:395-402.
4. Goffin E, et al. Nephrol Dial Transplant 2021;36:2094-2105.
5. Jaques DA, et al. Nephrol Dial Transplant 2022;37:2514-2521.
6. Morelle J, et al. N Engl J Med 2021;385:1570-80.
7. Pokorney SD, et al. Circulation 2022;146:1735–1745.
8. Reinecke H, et al. Circulation 2023;147:296–309.
9. Ureña-Torres PA, et al. Kidney 360 2021;2:666-673.
10. Vilar E, et al. Kidney 2022;101:615-625.

Basic Science and Translational Nephrology:

Nicole Endlich, Germany

Introduction

In more than 75 % of chronic kidney disease patients, the podocytes are remarkably often damaged. Depending on the glomerulopathy, changes in the podocyte foot processes are found to varying degrees. In the past, it was only possible to study podocyte foot process morphology by electron microscopy (EM) since the size of the tiny foot processes is below the optical resolution of a light microscope. However EM has several limitations, notably, it is time-consuming with a subjective analysis and therefore limited reproducibility. This presentation provides an overview of Super-Resolution Microscopy (SRM), a new light microscopy technique which can overcome these limitations.

Super-Resolution Microscopy

Super-Resolution Microscopy: overview

SRM overcomes the optical resolution limit of 200 nm formulated by Ernst Abbe for a light microscope. The term SRM covers different techniques like photo-activated localization microscopy (PALM), (direct) stochastic optical reconstruction microscopy [(d)STORM], stimulated emission depletion (STED), and structured illumination microscopy (SIM). Notably, SIM has the lowest optical resolution (85-100 nm in x,y-plane; 300 nm in the z-plane) (figure 1).

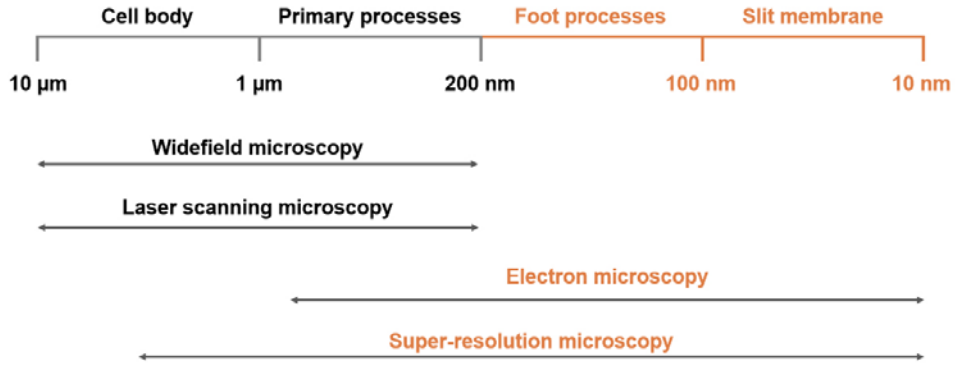


Figure 1. Optical resolution of SRM versus other techniques

SRM has high-resolution imaging capabilities, especially in multiple stainings, which provide clarity in visualizing complex cellular structures (figure 2).

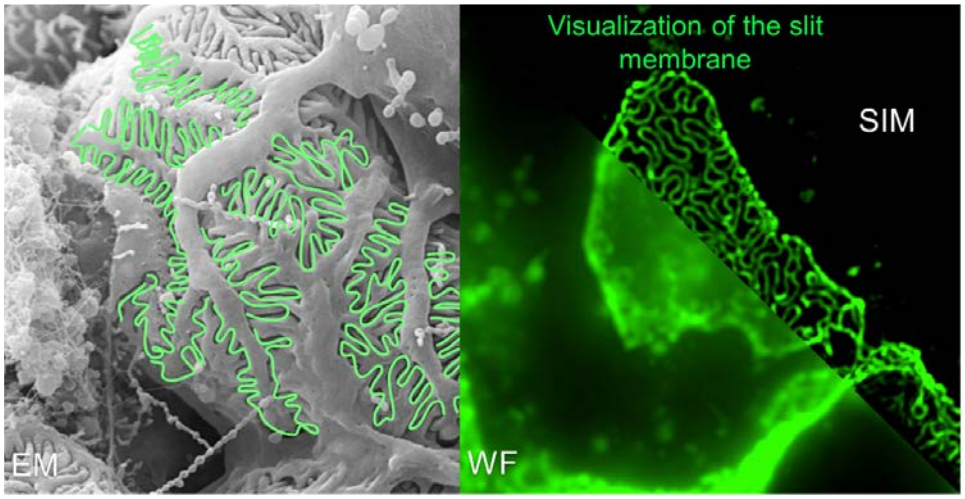


Figure 2. Visualisation of filtration slit membrane by EM (left) and SIM (right). WF, widefield.

SRM enables the use of standard preparation procedures, immunofluorescence staining and classical mounting media. Furthermore, 3-dimensional structured illumination microscopy (3D-SIM) can be performed with a resolution in the z-plane of 300 nm on so called optical sections. Podocyte Exact Morphology Measurement Procedure (PEMP) allows the quantification of changes of the foot process morphology by measuring the filtration slit density (FSD) (figure 2).

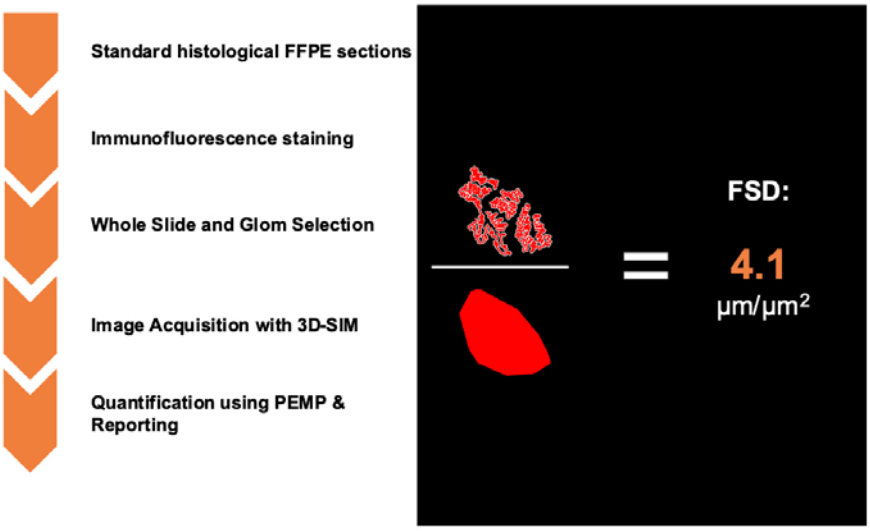


Figure 2. SRM technique overview including PEMP; FFPE, formalin-fixed and paraffin-embedded.

Super-Resolution Microscopy: application

SRM is suitable for different disease models and all glomerulopathies and species. SRM can provide high-resolution, providing insights into various aspects of kidney health, such as:

- Biomarker Claudin 5: This biomarker aids in predicting prognosis and personalized diagnosis, offering valuable information about the progress of disease.
- Discovery of New Biomarkers: SRM supports the identification and validation of new biomarkers, which fuels ongoing research and validation in the field of nephrology.
- Independent mRNA Quantification: Unlike traditional methods that rely on specific antibodies, SRM can be combined with the quantification of mRNA on single mRNA levels independently, offering a versatile approach to gene expression analysis.
- Measurement of GBM and Cell Evaluation: SRM allows precise measurement of the glomerular basement membrane (GBM) and evaluation of endothelial and mesangial cells, providing insights into the structural health of the kidney.

Conclusion

SRM can potentially accelerate research and drug discovery, while revolutionising kidney transplantation and personalised medicine. By analysing the unique cellular and molecular characteristics of an individual's kidney tissue, clinicians can offer more accurate diagnoses and select treatments tailored to the patient's profile. This personalized approach can lead to better treatment/outcomes and enhanced patient well-being.

Further Reading

1. Artelt N, et al. Front Med 2018;5:292.
2. Dalbøge, LS, et al. Biomedicines 2022;10:166.
3. Lukosz W, & Marchand M. Optica Acta 1963;10:241–255.
4. Siegerist F, et al, Scientific Reports 2017;7:11473.
5. Siegerist F, et al., J Cell Mol Med 2022;26:3513–3526.
6. Tesch F, et al. J Cell Mol Med 2021;25(16):7631-7641.

Epidemiology and Clinical Nephrology

Pietro Manuel Ferraro, Italy

Introduction

In the field of Nephrology various research efforts have been undertaken to enhance the understanding of prevalent kidney diseases and their management. This presentation summarizes the key findings and implications of recent evidence in the field of clinical Nephrology.

Nephroprotective effects of SGLT-2 inhibitors

In the EMPA-KIDNEY trial, a total of 6,609 patients were randomized to receive either empagliflozin 10 mg or placebo. The study followed these patients for a median duration of 2 years. The primary outcome was the occurrence of either progression of kidney disease or death resulting from cardiovascular causes; this was lower in the empagliflozin group and demonstrated statistical significance (13.1% vs 16.9% in the empagliflozin vs placebo group, respectively). Secondary outcomes such as hospitalization due to heart failure were also lower with empagliflozin (4.0% vs 4.6% in the empagliflozin vs placebo group, respectively) but did not reach statistical significance (figure 1).

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21

Figure 1. EMPA-KIDNEY trial primary and secondary outcomes.

Other studies demonstrated generally improved safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis versus placebo. In addition a collaborative meta-analysis of large placebo-controlled trials showed that SGLT-2 inhibitors were generally better in terms of nephroprotective effects, when compared to placebo.

Nephroprotective effects of new MRAs

The combined Phase III trials FIDELIO-DKD and FIGARO-DKD investigated cardiovascular and kidney outcomes in different stages of chronic kidney disease (CKD) among patients with type 2 diabetes. The FIDELITY analysis aimed to pool patient-level data from these trials to assess the safety and effectiveness of finerenone compared to placebo across various CKD stages. The main efficacy outcomes were a composite of cardiovascular and kidney events. Among 13,026 patients with a median follow-up of 3 years, the composite cardiovascular outcome was 13% lower and the composite kidney outcome 22% lower in patients treated with finerenone (figure 2).

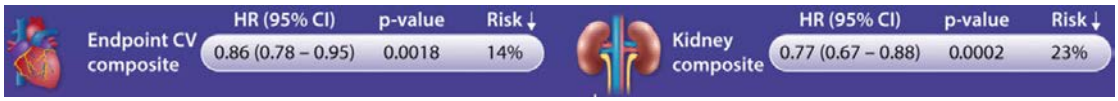


Figure 2. FIDELITY pooled analysis primary composite cardiovascular and kidney outcomes.

Additionally, in participants with stage 4 CKD and type 2 diabetes the kidney composite outcome at 2 years was 37% lower with finerenone.

Sparsentan in IgA nephropathy

In a prespecified interim analysis from a randomised clinical trial of patients with IgA nephropathy (IgAN), 404 participants were randomly assigned to either sparsentan (n=202) or irbesartan (n=202) groups. Over 36 weeks, sparsentan demonstrated a significantly greater reduction in the primary outcome – urine protein-to-creatinine ratio (-49.8%) compared to irbesartan (-15.1%), resulting in a 41% relative reduction between groups (figure 3).

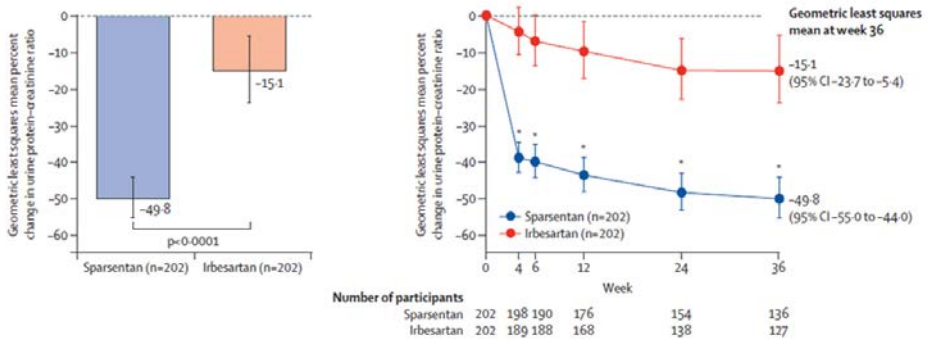


Figure 3. Primary outcome in IgAN patients treated with sparsentan or irbesartan.

Treatment-emergent adverse events were similar for both groups. No severe edema, heart failure, hepatotoxicity, or edema-related discontinuations were observed.

RAS-i discontinuation in advanced CKD

A multicentre, open-label trial to investigate the effects of discontinuing renin-angiotensin system (RAS) inhibitors in patients with advanced and progressive chronic kidney disease (eGFR, <30 mL/min/1.73 m2). The study aimed to assess the primary outcome of eGFR after 3 years, excluding values post renal-replacement therapy. Secondary outcomes included ESKD, composite eGFR decrease, hospitalization, blood pressure, exercise capacity, and quality of life. Among 411 patients over 3 years eGFR was 12.7 mL/min/1.73 m² (discontinuation group) vs. 13.3 mL/min/1.73 m² (continuation group) (figure 4). Additionally, ESKD or renal-replacement therapy initiation was undertaken by 68% (discontinuation group) vs. 63% (continuation group) of patients.

6. Tesch F, et al. J Cell Mol Med 2021;25(16):7631-7641.

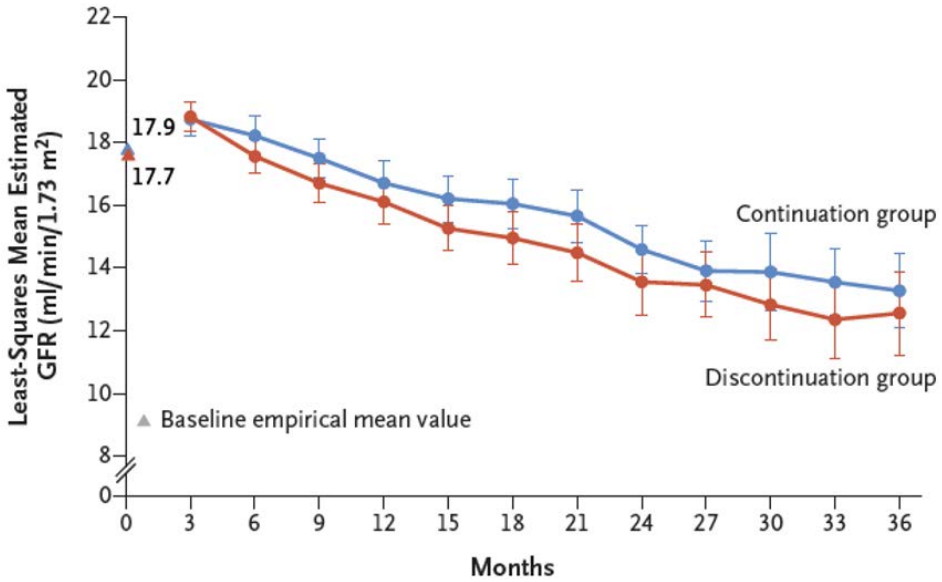


Figure 4. Estimated glomerular filtration rate at 3 years.

Equations for GFR estimation

A cross-sectional study (n=3,223) from 4 US community-based cohorts to quantify individual-level inaccuracy in GFR estimatation was undertaken. Participants had an average age of 59 years, including 32% Black individuals and 55% women, with a mean measured GFR (mGFR) of 68 mL/min/1.73 m2. Disparities were seen in CKD staging between mGFR and eGFRCR. For those with eGFRCR of 45-59 mL/min/1.73 m2, 36% had mGFR over 60, and 20% had mGFR under 45 mL/min/1.73 m2. Among eGFRCR 15-29 mL/min/1.73 m2, 30% had mGFR above 30 mL/min/1.73 m2, and 5% had mGFR under 15 mL/min/1.73 m2.

Thiazides for kidney stone recurrence

A clinical trial investigated the efficacy of hydrochlorothiazide in reducing the recurrence of kidney stones in patients (n=416) with a history of recurrent calcium-based kidney stones, treated with different doses of hydrochlorothiazide or a placebo. The primary outcome was a composite measure of symptomatic or radiologic stone recurrence; the incidence of recurrence did not appear to differ substantially among patients receiving hydrochlorothiazide once daily at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily, but there was a significantly lower incidence of radiological recurrence among those treated with hydrochlorothiazide 50 mg daily. Adverse effects such as hypokalaemia, gout, new-onset diabetes, skin allergy, and elevated creatinine were more common with hydrochlorothiazide compared to placebo. Certain study design characteristics might at least partly explain this study findings.

Conclusion

These recent clinical studies have provided additional insights into the advancement of kidney disease management. They highlight the potential of new treatments like SGLT-2 inhibitors and finerenone, while revealing challenges in discontinuing RAS inhibitors and accurate GFR estimation.

Further Reading

1. Agarwal R, et al. EHJ 2022;43(6):474–484.
2. Bhandari S, et al. N Engl J Med 2022; 387:2021-2032.
3. Dhayat NA, et al. N Engl J Med 2023;388(9):781-791.
4. Herrington, WG, et al. Lancet Diabetes Endocrinol 2022;10(6):416-427.
5. Herrington, WG, et al. N Engl J Med 2023; 388:117-127.
6. Heerspink JL, et al. The Lancet 2023;401:1584-1594.
7. Sarafidis P, et al. Clin J Am Soc Nephrol 2023;18(5):602–12.
8. Wheeler DC, et al. Nephrol Dial Transplant 2022;37(9):1647-1656.
9. Shafi T, et al. Annals of Internal Medicine. Available from: https://doi.org/10.7326/M22-0610. Last accessed: August 2023.

Kidney Transplantation

Rachel Hellemans, Belgium

Introduction

Renal transplantation is a pivotal treatment for end-stage renal disease (ESRD) patients. This presentation explores key aspects along the patient journey to renal transplantation such as recipient evaluation, allocation, early complications, and long-term outcomes. These elements substantially impact transplant outcomes and overall recipient health.

Recipient Evaluation: Obesity and coronary artery disease screening

Obesity and coronary artery disease are important factors to consider in renal transplantation. While obesity increases the risk of complications following transplantation, survival rates are generally better compared to remaining on dialysis. According to clinical guidelines from the DESCARTES Working Group of ERA, delaying waitlisting or transplantation solely due to increased body mass index (BMI) in individuals with a BMI of 30-35 kg/m² and end-stage kidney disease (ESKD) is not recommended, as long as they are otherwise suitable candidates for kidney transplantation. Additionally, patients in this category should receive support for weight loss and have their nutritional status monitored by a multidisciplinary team.

In a study encompassing 79,334 adults who received their first kidney transplant in the US between 2000 and 2014, researchers aimed to assess the impact of pre-transplant testing for coronary heart disease. However, the results indicated no significant link between testing and the occurrence of death or myocardial infarction within the initial 30 days post-transplant. This implies that the established practice of pre-transplant coronary testing might not substantially influence the reduction of adverse outcomes shortly after kidney transplantation.

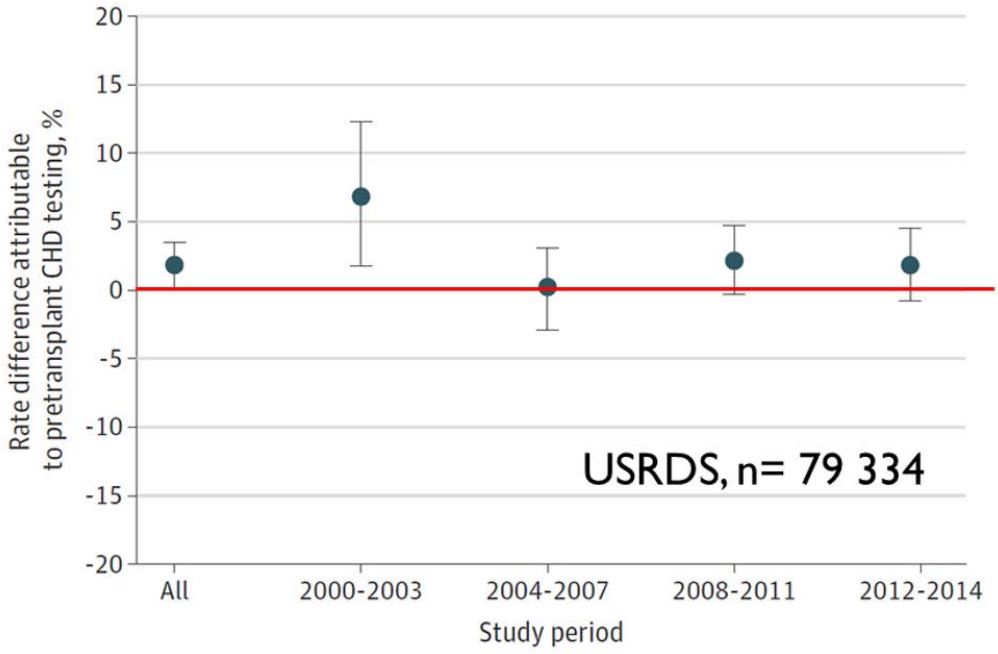


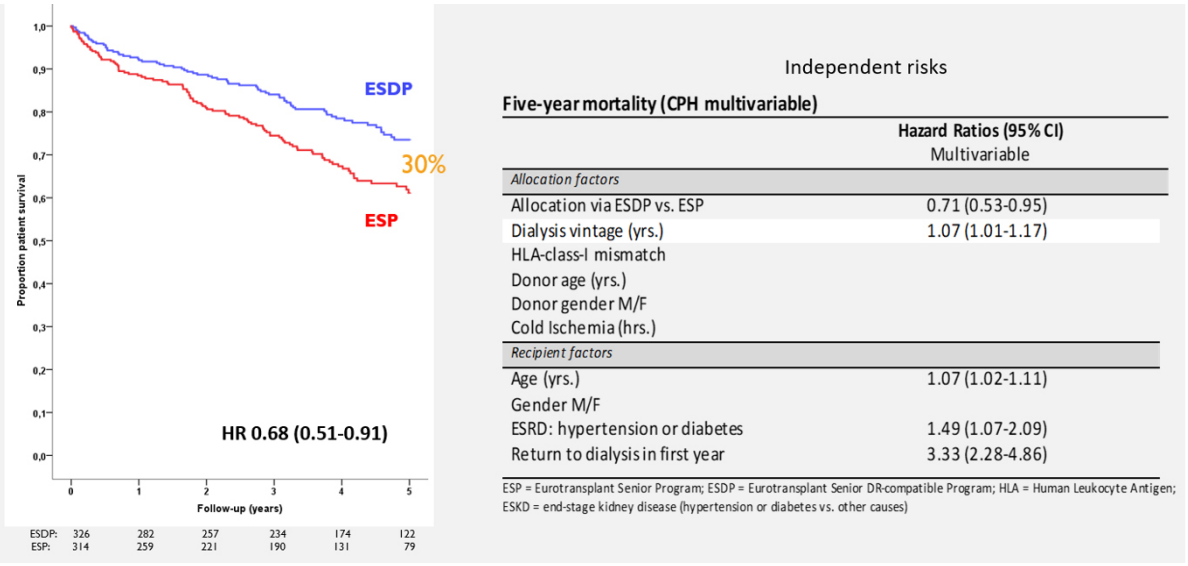
Figure 1. Rate difference attributable to pretransplant coronary heart disease (CHD) testing (rate of death or acute MI within 30 days after kidney transplantation). USRDS, United States Renal Data System.

Allocation: DR matching

The Eurotransplant senior program (ESP) allocates kidneys from 65+ aged donors to recipients aged 65 and older, utilizing regional allocation and omitting HLA matching for shorter cold ischemia times.. The existing ESP program allocates kidneys first to the candidates with the longest waiting time.

A recent study examined the impact of an alternative allocation policy within the ESP program, based on HLA-DR antigen matching. This Eurotransplant Senior DR-compatible Program study (ESDP) used paired allocation of 65+ DBD donor kidneys, where one kidney was allocated based on DR matching (n=336), while the contralateral kidney was allocated by the regular ESP program (n=326.

Matching for HLA-DR antigens demonstrated significant benefits. It was associated with ~30% better 5-year patient survival and a lower five-year risk of mortality (hazard ratio 0.71; 95% confidence interval 0.53-0.95) (figure 2), as well as a ~40% lower chance of kidney graft failure loss at 1 year.



Independent risks

Five-year mortality (CPH multivariable)

	Hazard Ratios (95% CI) Multivariable
Allocation factors	
Allocation via ESDP vs. ESP	0.71 (0.53-0.95)
Dialysis vintage (yrs.)	1.07 (1.01-1.17)
HLA-class-I mismatch	
Donor age (yrs.)	
Donor gender M/F	
Cold Ischemia (hrs.)	
Recipient factors	
Age (yrs.)	1.07 (1.02-1.11)
Gender M/F	
ESRD: hypertension or diabetes	1.49 (1.07-2.09)
Return to dialysis in first year	3.33 (2.28-4.86)

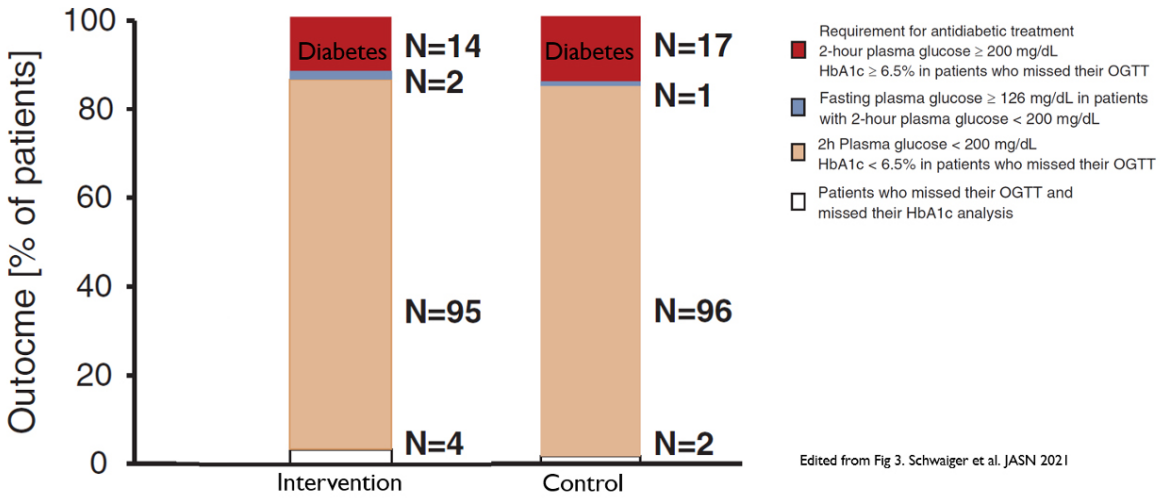
ESP = Eurotransplant Senior Program; ESDP = Eurotransplant Senior DR-compatible Program; HLA = Human Leukocyte Antigen; ESKD = end-stage kidney disease (hypertension or diabetes vs. other causes)

Figure 2. Five-year patient survival and mortality (ESDP vs ESP).

Early complications: post-transplant diabetes mellitus

A multicentre randomized trial investigated preventive strategies for diabetes mellitus following kidney transplantation in non-diabetic kidney transplant recipients (n= 263). These participants were divided into two groups; in the intervention group, participants received early postoperative basal insulin therapy if their evening glucose levels reached or exceeded 140 mg/dl. While in the control group, patients were administered short-acting insulin once their fasting glucose levels crossed the threshold of 200 mg/dl.

The primary objective of the study was to assess the efficacy of these approaches in preventing the onset of post-transplant diabetes mellitus (PTDM). At the one-year mark, PTDM rates were ~12% in the intervention group and ~15% in the control group. The analysis did not reveal a statistically significant difference in terms of reducing the risk of PTDM between the two groups (figure 3).



No significant benefit on PTDM risk (Intention-to-treat analysis): 12% versus 15% (N.S.)) at 1 year

Figure 3. Percent of patients with PTDM (intention-to-treat analysis). N.S, not significant.

Long-term outcomes: screening for HLA antibodies

Conducted across 13 UK transplant centres, a trial enrolled 2,037 participants between 2013 and 2016. The study explored unblinded HLA antibody testing, performed every 8 months. Individuals with HLA antibodies received adherence interviews and personalized optimization of medications including tacrolimus, mycophenolate mofetil, and steroids. This was compared against usual care, which included blinded HLA antibody testing at the same intervals. The intervention did not result in a delay of graft failure. Additionally, no significant improvements were observed in glomerular filtration rate (GFR) or proteinuria.

Conclusion

Renal transplantation encompasses multiple factors influencing outcomes. Effective HLA antibody screening, managing PTDM, optimizing DR matching, addressing obesity, and CAD screening are all components of successful transplant management.

Further Reading

1. Cheng XS, et al. JAMA Intern Med 2023;183(2):134–141.
2. de Fijter J, et al. Kidney Int 2023. Availabe from: https://kidney-international.org/article/S0085-2538(23)00419-2/fulltext. Last accessed: August 2023.
3. Schwaiger E, et al. J Am Soc Nephrol 2021;32(8):2083-2098.
4. Stringer D, et al. eClinicalMedicine 2023;56:101819.