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Review article

Chronic kidney disease after lung transplantation in a changing era

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ABSTRACT

Lung transplant (LTx) physicians are responsible for highly complex post-LTx care, including monitoring of kidney function and responding to kidney function loss. Better survival of the LTx population and changing patient characteristics, including older age and increased comorbidity, result in growing numbers of LTx patients with chronic kidney disease (CKD). CKD after LTx is correlated with worse survival, decreased quality of life and high costs. Challenges lie in different aspects of post-LTx renal care. First, serum creatinine form the basis for estimating renal function, under the assumption that patients have stable muscle mass. Low or changes in muscle mass is frequent in the LTx population and may lead to misclassification of CKD. Second, standardizing post-LTx monitoring of kidney function and renal care might contribute to slow down CKD progression. Third, new treatment options for CKD risk factors, such as diabetes mellitus, proteinuria and heart failure, have entered clinical practice. These new treatments have not been studied in LTx yet but are of interest for future use. In this review we will address the difficult aspects of post-LTx renal care and evaluate new and promising future approaches to slow down CKD progression.

1. CKD in the changing LTx patient

Since the LTx programs took flight over 35 years ago, LTx treatment has been continuously evolving, resulting in better graft function and improved survival worldwide [1]. Post transplantation median survival is currently 8.9–11.8 years [1,2]. Improved donorlung optimizing technology and an increased donor and recipient pool, have contributed to the increased accessibility of this life saving treatment [3–5]. Similar to other solid organ transplantation (SOT) programs, also in LTx, patient characteristics are changing. Older age and more comorbidities are now accepted while listed. Currently 72% of the recipients is over 50 years old at the time of transplantation in contrast to 31% in the early years [6]. Major cardiovascular comorbidities were absolute contraindications for LTx in the past. At present, increasing numbers of patients who underwent minimal invasive coronary interventions, heart valve replacements and endovascular aortic repairs are considered for LTx [7]. Besides older age and cardiovascular disease, traditional CKD risk factors such as diabetes mellitus (DM), hypertension, dyslipidemia and previous smoking status are common in the LTx population. Pretransplantation DM is common and ranges from 21 to 29% for the total LTx population with a higher prevalence of 40–50% in cystic fibrosis (CF) patients [8–10].The prevalence of post-transplantation DM (PTMD) is high and currently increasing, probably related to older age, increasing weight and calcineurin inhibitor toxicity [11].The incidence

Abbreviations: ACR, Albumin creatinine ratio; AER, Albumin excretion rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration, Research Group; CLAD, Chronic lung allograft dysfunction; CNI, Calcineurin-inhibitor; ECMO, Extracorporeal membrane oxygenation; eGFR, Estimated glomerular filtration rate; ESRD, End-stage renal disease; GLP-1 agonist, Glucagon-like peptide-1 agonist; HRQoL, Health related quality of life; HTx, Heart transplantation; IMV, Invasive mechanical ventilation; KDIGO, Kidney disease: improving global outcomes; LAS, Lung allocation score; LCP tacrolimus, Extended-release tacrolimus; LTx, Lung transplantation; mGFR, Measured glomerular filtration rate; nonsteroidal MRA, Nonsteroidal mineralocorticoid receptor antagonist; mTORi, Mammalian target of rapamycin inhibitors; PCR, Protein creatinine ratio; PER, Protein excretion rate; PR tacrolimus, Prolonged-release tacrolimus; RAS, Renin-angiotensin-aldosterone system; SGLT2i, Sodium-glucose co-transporter-2 inhibitor; SOT, Solid organ transplantation.

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of PTDM is between 20% and 40% where a higher incidence is mostly driven by overrepresentation of CF patients in some cohorts [12,13]. From this we can conclude that diabetes mellitus after LTx, when considering the aggregate of DM and PTDM, is a very common comorbidity. In one recent single center cohort study total diabetes mellitus prevalence post-LTx was 60% for non-CF patients and 96% for CF patients [11]. The prevalence of dyslipidemia increased from 6% pre-LTx to 40.3% post-Ltx [14]. A positive smoking status was found in 62.7% of LTx patients with CKD stage G3 [15]. Listing patients with CKD has long been uncommon, but this too is changing. The pre-LTx prevalence of CKD is 6.4%–9.6% when using an eGFR <60 ml/min/1.73 m2 as the definition [15,16]. Underlying lung disease, especially COPD, is associated with worse renal outcome [17–19]. Furthermore caregivers have to realize that transplant patients are not equal to the average CKD patient. Compared to non-transplant CKD patients, solid organ recipients age faster with earlier, different and more severe vascular health issues, including renal failure [20,21].

2. Impact of CKD on outcome in the LTx population

CKD after LTx is associated with high morbidity, mortality and costs [15,16,19,22]. Dialysis requirement early after LTx increases the adjusted hazard ratio for 1-year and 5-year mortality to 7.2 and 4.0 respectively [16]. For LTx patients an eGFR between 30 and 59.9 ml/min/173m^2 (mean eGFR 51 ml/min/1.73m^2) at time of listing is independently associated with post-LTx mortality compared to an eGFR >60 ml/min/173m^2 at time of listing. One-year post-LTx mortality differs significantly for patients with and without CKD pre-LTx (21.8% versus 12.7%). Interestingly, the association between mortality and pre-LTx eGFR was lost for patients younger than 45 years old [15]. This may be explained by a somewhat lower vulnerability to kidney failure related mortality in younger patients with a dominance of the competing lung transplantation related mortality. In addition, the used eGFR equation in the younger group is less applicable than in the older group. Pediatric eGFR formulas can be more accurate in adult in the age group 18–25 years [23]. However, this was not assessed in this study. In another large cohort study the relative risk of death in non-renal SOT increased to 4.55 in patients with stage 4 and 5 CKD post-transplantation [22].

LTx in general leads to significantly improved Health Related Quality of Life (HRQoL), but lower scores are reported with allograft dysfunction [24,25]. HRQoL in CKD patients without LTx is worse with higher CKD stage [26]. When considering costs, LTx-costs are high, on average $196,000 per-person per year in the USA for patients surviving the first year [27]. In the presence of CKD expenses increase significantly. CKD patients in the Western world are responsible for high health care costs, which increase with progressive disease (Table 1) [26]. How long-term QoL and costs for LTx patients are influenced by the presence or absence of CKD has not been described for this specific patient group. Decreased HRQoL and increased costs in the presence of CKD however, have to be taken into account.

Table 1
CKD general features.

Trajectory worldwide	By 2040 a 100% rise in number of years of life lost for the CKD population is forecasted, making CKD the 5th cause of years of life lost by disease [100]
CKD Definition (KDIGO guideline)	An abnormality of kidney structure or function, present for >3 months, with implications for health [28]
CKD Staging (KDIGO guideline)	5 categories based on the estimated Glomerular Filtration Rate (eGFR) and albuminuria (A) [28,101] Stage 1 with normal or high eGFR (eGFR >90 ml/min/1.73m^2), with or without albuminuria Stage 2 Mild CKD (eGFR = 60–89 ml/min/1.73m^2), with or without albuminuria Stage 3A Mild to moderate CKD (eGFR = 45–59 ml/min/1.73m^2), with or without albuminuria Stage 3B Moderate to severe CKD (eGFR = 30–44 ml/min/1.73m^2), with or without albuminuria Stage 4 Severe CKD (eGFR = 15–29 ml/min/1.73m^2), with or without albuminuria Stage 5 End Stage CKD (eGFR <15 ml/min/1.73m^2), with or without albuminuria
CKD stage with high risk for progressive CKD correlated with (cardiovascular) mortality and ESRD (KDIGO guideline)	Stage G3a or G3b in combination with albuminuria >300 mg/g or 30 mg/mmol, or stage 4/5 with or without albuminuria [28]
Annual costs in Western world for CKD stage 1–3	$1600 to $25,037[26]
Annual costs in the Western world for CKD stage 5/ESRD	$20,110 to $100,593[26]
CKD-EPI creatinine-cystatin C eq. (2021)	$135 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-0.544} \times \min(Scys/0.8, 1)^{-0.323} \times \max(Scys/0.8, 1)^{-0.778} \times 0.9961^{Age} \times 0.963$ [if female] where Scr is serum creatinine (in mg/dl), Scys is serum cystatin C (in mg/l), κ is 0.7 for females and 0.9 for males, α is −0.219 for females and −0.144 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Age (years)
AKI definition (KDIGO guideline)	Increase in Scr by ≥0,3 mg/dl (≥ 26,5 μmol/l) within 48 h; or Increase in Scr to ≥1.5 times baseline within the prior 7 days; or Urine volume < 0.5 ml/kg/h for 6 h [36]

KDIGO=Kidney Disease: improving Global Outcomes, nonprofit organization for developing and implementing evidence-based clinical practice guidelines in kidney disease, ESRD = end stage renal disease, Scr = serum creatinine, CKD-EPI=Chronic kidney Disease Epidemiology Collaboration, research group.

3. CKD definitions used in LTx

The prevalence of CKD after LTx is high, but actual numbers reported are variable, often due to the differences in CKD definitions. For the CKD definition used in clinical care and staging criteria see Table 1. Table 2 shows the prevalence of common metabolic and endocrine complications in the overall CKD population, and possible interventions. In non-SOT CKD patients, endocrine and metabolic function starts to be compromised from an estimated Glomerular Filtration Rate (eGFR) lower than 60 ml/min/1.73m^2 [28]. CKD is a well-known and major independent predictor for progressive decline in kidney function, end-stage renal disease (ESRD), cardiovascular events and mortality [29–31]. So, identifying patients at risk is crucial. Accurate identification will offer physicians better insight for personalized post-LTx care and select patients in which renal protective measures have to start early, even though creatinine levels are not (yet) alarmingly increased. In LTx research, patients with CKD are identified in different ways. Measured GFR (mGFR), absolute eGFR decline, high stage CKD or ESRD are used to single out subjects. In this context, comparing outcomes is difficult. mGFR studies in LTx have shown a mean mGFR loss of 54% 6 months after LTx and 55% 1 year after LTx [32,33]. Importantly, significant difference between pre-LTx mGFR and pre-LTx eGFR was found (mean mGFR±SD 106 ± 5 versus mean eGFR±SD 122 ± 4 ml min/1.73m^2), where only pre-LTx mGFR, but not pre-LTx eGFR, was significantly associated with high risk of developing CKD (stage ≥3) post-LTx. From these small studies we may conclude that renal function loss is high in the post-transplantation period, but also that with eGFR we fail to identify high risk patients before LTx. One year after LTx mGFR and eGFR did not differ significantly [33]. Larger studies are warranted to confirm these findings. When defining CKD as stage G3 or higher,

Table 2
CKD complications by GFR category.

Complication	GFR category (ml/min/1.73m^2)					
	G1 eGFR ≥ 90	G2 eGFR 89–60	G3a eGFR 59–45	G3b eGFR 44–30	G4 eGFR 29–15	Treatment options
Anemia	4.0%	4.7%	12.3%	22.7%	51.5%	Iron Erythropoietin stimulating agent
Hypertension	18.3%	41.0%	71.8%	78.3%	82.1%	Dietary salt restriction Antihypertensives
Acidosis	11.2%	8.4%	9.4%	18.3%	31.5%	Bicarbonate
Hyperphosphatemia	7.2%	7.4%	9.2%	9.3%	23.0%	Dietary interventions Phosphate binders
Hypoalbumenemia	1.0%	1.3%	2.8%	9.0%	7.5%	Dietary interventions
Hyperparathyrodism	5.5%	9.4%	23.0%	44.0%	72.5%	Target hyperphosphatemia and vitamin D deficiency calcimimetics
Osteodystrophy with bone fracture risk (HR) [102]	?	1.41 (NS)	1.37	1.70	1.99	Target hyperparathyroidism, vitamin D deficiency, hyperphosatemia and osteoporosis

Adapted from the KDIGO guideline 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease [28]. (e)GFR = (estimated) glomerular filtration rate, HR = hazard ratio, NS = not significant.

66–69% of LTx patients fulfill the definition one year post-LTx [33,34] and 80% two years post-LTx [17]. A typical course for LTx is large renal function loss within the first 2 years after LTx and slower progression thereafter [35]. Contrary to CKD trials, the KDIGO definition for CKD diagnosing, staging and identifying high risk patients (Table 1) are not often used in LTx trials measuring renal outcome. Data on CKD progression in LTx is scarce. Unraveling this subgroup with CKD should start with using the same definitions as in CKD trials, and also focus on intervention possibilities to slow down progressive CKD.

4. CKD in LTx beyond traditional risk factors

Although all mentioned pre- and post-LTx risk factors are important and increasing contributors to CKD progression, two aspects are considered major factors for huge and permanent renal loss post-LTx: acute kidney injury (AKI) and calcineurin-inhibitor (CNI) nephrotoxicity. Table 3 shows risk factors before, during and after LTx. AKI is defined by a serum creatinine increasing within the first 48 h or 7 days and/or acute decline in urine output [36]. For the full definition see Table 1. The incidence of AKI is 52.5–68.8% early after transplantation, with need of renal replacement therapy in 8.1%-9.3% of cases [37,38]. Mean mGFR declined from 103 to 65 (+/−18) and 53 (+/−16) ml/min/1.73m^2 at 1 and 3 weeks post-Ltx [39]. Specific risk factors for AKI early after Ltx are hypercapnia/hypoxemia related renin-angiotensin-aldosterone system (RAS) activation, duration of cardiopulmonary bypass, poorly controlled hemodynamics peri- and postoperative due to complications, and CNI exposure [37,38,40]. Eventually, postoperative AKI in LTx increase the relative risk (RR 4.56) for developing CKD stage 4 or 5 [22]. Large studies and registries looking into AKI outcome mainly come from non-Tx cohorts, but could however be of interest for the LTx-population. The 2021 data from the United States Renal Data System for healthcare beneficiaries show CKD stage 3 or higher in 33.3% at 12 months after an AKI episode [41]. In a recent published prospective study in which 769 AKI patients participated, the finding of post-AKI albuminuria 3 months after an AKI episode was associated with higher risk of kidney disease progression defined as halving of eGFR or ESRD [42]. Considering the high incidence of AKI after LTx, it would be relevant to investigate the correlation between AKI, albuminuria and renal outcome in this population and consequently whether early treatment intervention alters the CKD course.

Immunosuppressive regimes in LTx have changed in the last decades. Data from the International Thoracic Organ Transplant Registry show that >90% of patients currently use tacrolimus while in the 90's > 75% of patients used cyclosporine [6]. The main advantage of tacrolimus over cyclosporine is less acute rejection and chronic lung allograft dysfunction (CLAD). Tacrolimus is therefore now considered the cornerstone of treatment in LTx. Unfortunately, renal outcome has not improved for LTx patients in the tacrolimus era [43]. When compared to other SOT programs, LTx patients need higher tacrolimus dosages to prevent acute rejection, with increased risk of drug toxicity including renal toxicity [44]. Chronic CNI nephrotoxicity is a well-studied clinical and pathological finding in non-renal SOT. Both hemodynamic changes in the kidneys and direct toxic effects are crucial for causing ongoing damage [45]. That CKD after non-renal SOT is the outcome of multiple renal hits has been shown in kidney biopsy studies. Pathological findings

Table 3
peri-transplantation risk factors for progressive CKD after lung transplantation.

Risk factors for progressive CKD	Pre-LTx	Per-Tx	Post-Tx
Immunosuppressants: CNI [35,40,46]		X	X
Acute kidney injury, including RRT [22,34,37,38]	X	X	X
Higher LAS score [16,103]	X		
Older age [22,28,34,35,104]	X		
Sex (male>female) [22,28,34]	X		
Decreased eGFR [15,22,28,34,35,104]	X		
Higher level of albuminuria [28,65]	X		X
Diabetes mellitus [15,22,28]	X		X
Hypertension [22,28,34,46]	X		X
Smoking history [15,28,35,105]	X		
Dyslipidemia [28]	X		X
Pulmonary hypertension [103]	X		
Heart failure [106]		X	X
Underlying lung diagnosis (COPD>other diagnosis) [17–19,104,105]	X		
Primary renal disease	X	X	X
Re-transplantation [103]	X		
Longer duration of ECMO or IMV [103]	X	X	
Longer duration of cardiopulmonary bypass [103]		X	
Longer duration of ICU stay [16]		X	
Immunosuppressants (other than CNI): mTORi [35]		X	X
Comedication with nephrotoxic agent [34,40]*	X	X	X
Comedication with CYP3A4 inhibitors increasing the risk for supra-therapeutic tacrolimus levels [107]**		X	X
Increased fluctuation of pharmacokinetics for CNI metabolism and associated AKI risk [108]		X	X
CMV infection [104]			X
BK infection [109]			X

CNI = calcineurin inhibitors, RRT = renal replacement therapy, LAS = lung allocation score, eGFR = estimated glomerular filtration rate, COPD = chronic obstructive pulmonary disease, ECMO = extracorporeal membrane oxygenation, IMV = invasive mechanical ventilation, IC = intensive care unit, mTORi = mammalian target of rapamycin inhibitors, CMV = cytomegalovirus, BK virus = Polyomavirus hominis1, B.K. initials of the first renal transplant patient in which it was first isolated.

* commonly used in LTx patients: amphotericin B, aminoglycosides, (val) aciclovir, (val)ganciclovir, vancomycine,

** Azole antifungal agents, macrolide antibiotics, (HIV) protease inhibitors.

characteristic for AKI, diabetes mellitus, hypertension, acute and chronic CNI toxicity were found in varying and coexisting combinations [45,46].

Table 3 lists the peri-transplantation risk factors for progressive CKD post-transplantation. Addressing all risk factors simultaneously in each phase of LTx, is what makes renal care complex.

5. Assessment of kidney function in lung transplantation in daily practice

eGFR is most commonly used in clinical practice and the recommended approach for initial CKD evaluation in the current guideline [28], but can be unreliable in LTx due to specific patient characteristics. In this section we explain why.

Kidney function is represented by the Glomerular Filtration Rate (GFR). Direct GFR measurement cannot be done. Instead, the urinary clearance of an ideal filtration marker is used to estimate GFR. An ideal marker is endogenously produced in the body at a constant rate and exclusively cleared by the kidneys. Unfortunately, no such marker is available for daily use. The most accurate filtration markers are intravenously administered markers such as inulin, iohexol or radiolabeled ^{51}Cr-EDTA and ^{99}Tc-pentetic acid [47]. Measuring GFR with these markers has the best performance, but is not routinely used or available because of their presumed inconvenience and high costs. In the current KDIGO CKD guideline mGFR is suggested to be used when more accurate GFR measurement will impact on treatment decisions [28]. Creatinine has been widely adopted as the standard filtration marker for GFR assessment in day-to-day clinical practice because of its constant release into the circulation under normal physiologic conditions, filtration qualities, ease to measure and low costs [28,48,49]. Creatinine is a metabolic end product of muscle catabolism. Its release in the circulation is proportional to muscle mass and intake of creatine rich food [49]. Age, sex, nutritional status, body morphology and specific medication affect serum creatinine. Mathematical creatinine-based equations have been developed to correct for some physical aspects in a stable clinical state. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating GFR is recommended for daily use in all adult CKD patients, but other kidney function measurement can be better applicable in specific populations [28]. Until recently the 2009 eGFR equation was used, which incorporated correction for sex and race. The new 2021 equation excludes race to promote health equality [50]. Expeditious implementation of the new equation is recommended in the United States. The possibility of shifting patients to different CKD stages in comparison to the 2009 equation has to be taken into account when interpreting CKD-EPI 2021 eGFR results [51].

Muscle mass in patients with a respiratory disease before and after transplantation is highly influenced by disease, interventions and medication [52–55]. In a cohort of 37 LTx patients low muscle mass was present in 80% at one month and in 33% at 2 years after transplantation [56]. The low and fluctuating muscle mass makes creatinine a less reliable filtration marker in this population. Another endogenously easy accessible filtration marker is cystatin C, which is produced at a constant rate by all nucleated cells in the human body and is freely filtered by the kidneys [49]. Cystatin C is recommended for GFR estimation in populations with low muscle mass because of its independence of muscle mass, sex and age [28]. Cystatin C is however influenced by medication such as prednisolone, inflammation and diabetes mellitus, all common in SOT [55,57,58]. To overcome these limitations both creatinine and cystatin C have been incorporated in equations for GFR estimation, including the 2021 Eq. [50]. In lung [59,60], liver [61] and kidney transplant patients [62] combining both markers for estimating GFR outperforms equations based on creatinine alone. In a recent study comparing mGFR to several new and older eGFR equations with or without cystatin C in 32 LTx patients, the 2021 CKD-EPI combined equations showed the lowest bias [60]. In the largest population based prospective cohort study (n = 440,526) the combined use of Cystatin C and creatinine resulted in a more accurate estimation of GFR, earlier detection of CKD and risk of cardiovascular disease [63,64]. This could be of importance for prognostic and therapeutic aspects in specific populations including those with higher cardiovascular risk and low muscle mass. Numerous studies focused on comparing mGFR to eGFR using different equations and markers to estimate GFR in different renal populations. A 30% margin of error compared to the mGFR is usually accepted for assessment of equations for eGFR. Experts opinion state this margin to be extremely wide and a 10% margin would be better to diagnose patients correctly [47]. Health professionals involved in LTx renal care should appreciate LTx patients to be different from the general CKD population and consider more accurate assessment with mGFR for confirmation of the initial diagnosis and the combined creatinine-cystatin C equation in the out-patient setting.

Creatinine clearance in a 24 h urine sample can also be considered, especially for patients with low muscle mass. Accurate urine collection is essential for interpreting results. Urinary creatinine represents the creatinine that is filtered but also creatinine that is actively secreted in the renal tubules, resulting in a 15–20% overestimation of GFR. Tubular excretion increases with decreasing renal function, resulting in a larger overestimation in advanced CKD.

Urinary albumin excretion is the second key element in renal disease evaluation, and part of the CKD classification because of its link to renal outcome [65]. An early morning urine sample is the worldwide standard to calculate a ratio to urinary creatinine concentration; the albumin creatinine ratio (ACR). A positive result ($\geq$30 mg/g or $\geq$ 3 mg/mmol) needs to be confirmed with a second early morning sample or 24 h urine collection. Referral to a nephrology specialist is recommended when albuminuria is severely increased (ACR >300/mg/g or 30 mg/mmol) [28]. 'Typical' CKD course in LTx is fast eGFR decline within the first 2 years after transplantation and more gradual thereafter with low ACR [66,67]. Increasing ACR and/or rapid eGFR decline can be clues for causes and diseases other than AKI and CNI nephrotoxicity with therapeutic and prognostic consequences. Referral to a specialist in kidney care is recommended in specific circumstances. Table 4 shows general referral criteria for CKD patients according to the KDIGO guideline for CKD evaluation and management. For LTx patients, however, some criteria can be less straightforward. When interpreting eGFR and rapid progression, physicians must take into account the patients (changing) physique. In the peri-transplantation period muscle mass is often low. Regaining normal muscle mass after LTx is time-consuming if reached at all. Creatinine based eGFR is not accurate for estimating renal function in this time period and will overestimate. Not seldom it can take years before stable muscle mass is reached and creatinine based eGFR is better on target. Many LTx patients fulfill the definition of rapid CKD progression within the first 2 years after transplantation, where again their changing muscle mass have to be taken in to account. Criteria for subgroups of CKD, including LTx, do not exist. Important to conclude is that

Table 4
Referral criteria for CKD patients to a renal care specialist.

AKI or abrupt sustained fall in GFR
eGFR <30 ml/min/1.73m^2
a consistent finding of significant albuminuria (ACR $\geq$300 mg/g [$\geq$30 mg/mmol] or AER $\geq$300 mg/24 h, approximately equivalent to PCR $\geq$500 mg/g [$\geq$50 mg/mmol] or PER $\geq$500 mg/24 h)
Rapid progression of CKD (>5 ml/min/1.73 m2/year)
Urinary red cell casts
CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
persistent abnormalities of serum potassium
recurrent or extensive nephrolithiasis
hereditary kidney disease

Adapted from the KDIGO guideline 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease [28].
AKI = acute kidney injury, eGFR = estimated glomerular filtration rate, ACR = albumin creatinine ratio, AER = albumin excretion rate, PCR = protein creatinine ratio, PER = protein excretion rate, CKD = chronic kidney disease.

renal function in clinical practice is an estimation and cannot be directly measured. LTx patients are at risk for overestimation of eGFR when using creatinine as a filtration marker due to patient factors.

6. Reno- and cardiovascular protective treatment goals in lung Tx

Management of CKD patients in general aim to slow the progression of CKD and cardiovascular disease, reduce symptoms and metabolic complications. Similar treatment goals could apply for SOT patients, including LTx patients, nevertheless considering patients specific prognosis.

No official LTx guideline and no prospective data are available in LTx to define targets or drug preference for vascular comorbidities post LTx. In 2017, Adegunsoye et al. published a paper addressing, among others, therapy targets for vascular complications after LTx based on non-LTx population guidelines [68]. Renal protective management is currently a fast moving field with exciting recent breakthroughs in slowing CKD progression for the non-Tx CKD population. New drug classes with renal benefit include sodium-glucose co-transporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) agonists and nonsteroidal mineralocorticoid receptor antagonists (MRA). Guidelines on hypertension management, diabetes mellitus management and renoprotection in CKD have been published in 2020 and 2021 and could offer additional insights [69–71]. Another update for diabetes management in CKD is expected soon, incorporating new high-quality trials and to guide clinicians in the new therapies. These novel treatment strategies will be discussed below.

CKD management is conducted according to a step-up approach and includes targeting risk factors such as lipids, blood pressure, diabetes mellitus and proteinuria [69].

6.1. Lipids

Targeting lipids is advised for CKD and kidney transplant patients [72,73]. Statins are the first line drug choice. With most SOT patient currently using tacrolimus instead of cyclosporine, interaction with statins may be less of a problem than it was in the past. However, dose restriction with advanced CKD may be necessary [72].

6.2. Blood pressure

In stable kidney transplant patients the standardized office blood pressure target is <130/80 mmHg. A dihydropyridine calcium channel blocker or a RAAS-inhibitor are considered first-line drug choices in hypertension, with the preference for RAAS-inhibition when ACR ≥ 300 mg/g [≥30 mg/mmol] for prevention of CKD progression [28,71]. Therapy should be targeted to an ACR <300 mg/g [<30 mg/mmol]. When using a RAS-inhibitor a maximum of 30% eGFR decline is acceptable due to normal physiological renal hemodynamics which correlate with long-term renal protection [74,75].

6.3. Novel therapies for CKD with and without diabetes

Current treatment choices and targets for diabetic patients with CKD are highly depended on patient characteristics such as age, comorbidities and risk of hypoglycemia. That is why a single HbA1c target cannot be used for the whole CKD patient group. Also individual treatment goals such as HbA1c target, lowering CVD risk/CKD progression, weight loss or avoidance of hypoglycemia should guide the physician to specific drugs. Metformin is still considered a cornerstone treatment in diabetics. In SOT patients, gastro-intestinal side effects of metformin in combination with mycophenolate mofetil can be limiting. Metformin dose should be reduced for stage 3b CKD patients (eGFR <45 ml/min/1.73m^2) and is contra-indicated in stage 4–5 CKD. The current KDIGO guideline Diabetes in CKD recommend metformin for kidney transplant patients with an eGFR ≥30 ml/min/1.73m^2, like for non-transplanted patients with type 2 diabetes [69]. In LTx metformin can be considered for diabetes treatment based on safety data in kidney and heart transplantation [76,77] bearing in mind contra-indications such as in CF.

The protective effect of sodium-glucose co-transporter-2 inhibitors (SGLT2i) on renal and.

cardiovascular outcome in diabetic and also non-diabetic CKD patients is one of the major steps forward in CKD treatment in this era. The CREDENCE trial in 2019 [78], DAPA-CKD trial in 2020 [79] and EMPA-KIDNEY trial in 2022 (not yet published, but stopped early because of positive results) are large-scale trials with overwhelming efficacy on major kidney and cardiovascular outcome. All participants received a stable dose of RAS-inhibitors, and only in de EMPA-KIDNEY trial a subgroup (15%) of patients did not. Nephroprotective action is mainly through reduction of intrarenal pressure, in combination with a modest glucose-lowering and blood-pressure-lowering effect. Current renal indications are CKD (eGFR ≥30 ml/min/1.73m^2) with or without DM, and possibly in the near future CKD without albuminuria or lower eGFR [80]. SGLT2 inhibitors are now the first-line choice combined with metformin in patients with CKD and type 2 diabetes mellitus [69]. Although overall well tolerated, prescribers of SGLT2 inhibitors have to familiarize themselves with their effects, side-effects and how to incorporate with other therapies for diabetes and CKD [80]. Clinicians should also realize the evidence is for patients on RAS-inhibitors. At this point in time transplant patients have been excluded from the large trials. SGLT2 inhibitors appeared to be safe in the first placebo-controlled trial in 44 kidney transplant patients with diabetes mellitus and a short follow up time [81]. Results from soon to start large RCTs investigating SGLT2 inhibitors in kidney and heart transplant patients (RENAL LIFECYCLE trial; NTC05374291, DAPARHT trial; NTC05321706), will hopefully add in position of these drugs for transplant patients, including for LTx. Glucagon-like peptide-1 (GLP-1) receptor agonists have shown important risk reduction of major cardiac events (MACE) in diabetic patients. Although CKD patients have been included in most large trials, the primary endpoint was mostly MACE with secondary renal endpoints. A large ongoing RCT with primary renal endpoints is currently awaited (FLOW trial, NCT03819153). A 2021 meta-analysis with >60.000 patients with DM showed a risk reduction of 21% for a composite renal outcome (development of new severely increased albuminuria, decline in eGFR, rise in serum creatinine, progression to renal failure or death from renal disease), compared to placebo [82]. For CKD patients with type 2 diabetes adding a GLP-1 receptor agonist is recommended if glycemic targets are not achieved, while on metformin and SGLT2 inhibitor treatment [69]. Research in SOT is limited to small observational studies and series from which no conclusions can be drawn at this point in time [83].

The third novel drug class for CKD patients with type 2 diabetes are the selective nonsteroidal MRAs. Two complementary landscape trials have been published recently (FIDELIO DKD and FIGARO-DKD), which together included over 13.000 CKD patients within the whole spectrum (stage 1–4 and moderate to severe albuminuria) with diabetes and on maximum tolerated RAS inhibition. Nonsteroidal MRAs showed a risk reduction for a composite renal endpoint (renal failure, 40% eGFR decline from baseline or death from renal causes; hazard ratio, 0.82; 95% confidence interval, 0.73 to 0.93; $p = 0.001$) and MACE (hazard ratio, 0.71; 95% confidence interval, 0.76 to 0.98; $p = 0.03$). The effects were independent from SGLT2 inhibitors and GLP-1 antagonists use, and combined therapy has been suggested. The main disadvantage for these drugs is the increased risk for hyperkaliemia [84,85]. These drugs have not yet been studied in SOT patients.

6.4. CNI-sparing regimes

Randomized controlled trials to investigate CNI-sparing regimes to preserve renal function in LTx are very limited. An RCT with 130 LTx patients showed early renal benefit for quadruple therapy by adding a

mammalian target of rapamycin (mTORi) inhibitor, in order to reduce tacrolimus dose [86]. In another RCT with 5 years follow up for 92 lung and 190 heart transplant (HTx) patients randomized for triple or quadruple therapy, a significantly better mGFR was found only for HTx patients using quadruple therapy [87]. In larger RCTs in liver and HTx testing CNI-sparing regimes, results on renal outcome vary. RCTs in liver transplantation showed significantly better renal function after 24 months in the mTORi group, but also more proteinuria, a possible predictor for renal function decline in the future [88,89]. In HTx, lowering tacrolimus dose by introducing mTORi did not improve renal function up to 8 years of follow up [90].

Belatacept is a selective T-cell costimulation antagonist of which its place is yet to be determined in SOT. Case series suggest renal benefit with belatacept and low or no CNI in LTx patients with renal failure, however hard conclusions cannot be drawn from this [91,92]. Another strategy in reducing CNI exposure is optimizing its blood levels. Immediate release (IM) tacrolimus, the current standard tacrolimus formula used worldwide, is so-called short acting and is dosed twice daily. Disadvantage of this formula are high peak levels twice a day. Newer tacrolimus formulas are known to have a more stable blood levels [93,94]. Two once-daily formulas have the potential to optimize efficacy and reduce toxicity; prolonged-release (PR) tacrolimus (Advagraf® Astagraf XL®, Astellas Pharma Inc., Tokyo, Japan) and extended-release (LCP) tacrolimus (Envarsus®, Chiesi Pharmaceuticals, Parma, Italy). Bioavailability is increased with lower peaks and up to 30% lower dose needed for LCP tacrolimus in comparison to both IM and PR tacrolimus in renal and lung transplant patients [94–96]. Switching from IM to LCP tacrolimus in stable LTx patients is safe within a short follow-up period, however long-term data and randomized trials are lacking [94,97]. In kidney transplant patients once-daily tacrolimus was non-inferior in efficacy and safety compared to IM tacrolimus in randomized studies [98,99]. With limited RCTs in non-renal SOT the position of the new once-daily formulas for these patients is currently not known. Randomized studies comparing once versus twice daily tacrolimus in liver and lung transplantation are ongoing.

7. Conclusion and future research possibilities

The prospects for LTx patients continue to improve. Nowadays the focus is shifting from short term survival to long term health outcome. In this context CKD is one the most frequently recognized complications after LTx with implications for patients health and survival. Uniformity in CKD definition in LTx research is low. Attempts at slowing down CKD progression have to start early when irreversible kidney damage is less extensive. Hence identification of the proper CKD stage in LTx patients is important, but can be difficult. LTx patients are considered an exceptional population in which serum creatinine based assessment can overestimate GFR, especially when creatinine production is not in a steady state. Misclassification, under-treatment and medication dosing errors are realistic consequences. In the perioperative phase, the mGFR deviated most from eGFR which has to be taken into account. The evidence using cystatin C in estimating GFR, and the introduction of new eGFR equations has changed clinical practice already in some parts of the world. LTx caregivers should reflect on the implications of possibly changes in renal care in the future. Ultimately, slowing down CKD progression in LTx is the goal. Minimizing the exposure to nephrotoxic medication including tacrolimus and agents with interaction is standard care for LTx physicians, and will remain a very important aspect in renal protection. The optimal timepoints to start treatment for blood pressure, proteinuria and lipids are not dependent on CKD stage. Therapy has to start when appropriate, in which early intervention is usually beneficial for long term vascular outcome. In SOT and non-SOT patients new promising therapies are under investigation and several have entered clinical care. Randomized trial results have to be awaited. To our knowledge no studies have been done to position SGLT2 inhibitors, GLP-1 agonists or selective nonsteroidal MRAs in LTx care, which would nevertheless be interesting. Finally, including a renal care specialist in the medical team is often necessary. LTx tailored referral criteria or a multidisciplinary approach would better help to identify the right patients for the right type of medical care. In conclusion, LTx patients with CKD have to be considered highly complex vascular patients, hard to identify correctly, and with high risk for progressive CKD and cardiovascular disease. With competing and increasing non-vascular health issues, addressing all makes LTx care complex and probably more so in the future.

Declaration of Competing Interest

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