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POSITION PAPER

Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology

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Novel pharmacologic treatment options reduce mortality and morbidity in a cost-effective manner in patients with heart failure (HF). Undisputedly, the effective implementation of these agents is an essential element of good clinical practice, which is endorsed by the European Society of Cardiology (ESC) guidelines on acute and chronic HF. Yet, physicians struggle to implement these therapies as they have to balance the true and/or perceived risks versus their substantial benefits in clinical practice. Any worsening of biomarkers of renal function is often perceived as being disadvantageous and is in clinical practice one of the most common reasons for ineffective drug implementation. However, even in this context, they clearly reduce mortality and morbidity in HF with reduced ejection fraction (HFrEF) patients, even in patients with poor renal function. Furthermore these agents are also beneficial in HF with mildly reduced ejection fraction (HFmrEF) and sodium–glucose cotransporter 2 (SGLT2) inhibitors more recently demonstrated a beneficial effect in HF with preserved ejection fraction (HFpEF). The emerge of several new classes (angiotensin receptor–neprilysin inhibitor [ARNI], SGLT2 inhibitors, vericiguat, omecamtiv mecarbil) and the recommendation by the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF of early initiation

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and titration of quadruple disease-modifying therapies (ARNI/angiotensin-converting enzyme inhibitor + beta-blocker + mineralocorticoid receptor antagonist and SGLT2 inhibitor) in HFrEF increases the likelihood of treatment-induced changes in renal function. This may be (incorrectly) perceived as deleterious, resulting in inertia of starting and uptitrating these lifesaving therapies. Therefore, the objective of this consensus document is to provide advice of the effect HF drugs on renal function.

Keywords Heart failure • Pharmacological therapy • Renal function

Introduction

Novel pharmacologic treatment options reduce mortality and morbidity in a cost-effective manner in patients with heart failure (HF)[1] Undisputedly, the effective implementation of these agents is an essential element of good clinical practice, which is endorsed by the European Society of Cardiology (ESC) guidelines on acute and chronic HF.[2] Yet, physicians struggle to implement these therapies as they have to balance the true and/or perceived risks versus their substantial benefits in clinical practice.[3] Any worsening of biomarkers of renal function is often perceived as being disadvantageous and is in clinical practice one of the most common reasons for ineffective drug implementation.[4] Indeed, renin–angiotensin–aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and, angiotensin receptor–neprilysin inhibitors (ARNI) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, all influence renal function acutely and chronically.[5–9] Additionally, RAAS inhibitors can also induce hyperkalaemia, which is a frequent trigger of RAAS inhibitor non-use, down-titration and discontinuation.[10] However, even in this context, they clearly reduce mortality and morbidity in HF with reduced ejection fraction (HFrEF) patients, even in those with poor renal function. Furthermore these agents are also beneficial in HF with mildly reduced ejection fraction (HFmrEF) and SGLT2 inhibitors more recently demonstrated a beneficial effect in HF with preserved ejection fraction (HFpEF).[2,11] The emerge of several new classes (ARNI, SGLT2 inhibitors, vericiguat, omecamtiv mecarbil) and the recommendation by the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF of early initiation and titration of quadruple disease-modifying therapies (ARNI/ACE-I + beta-blocker + MRA and SGLT2 inhibitor) in HFrEF increases the likelihood of treatment-induced changes in renal function. This may be (incorrectly) perceived as deleterious, resulting in inertia of starting and uptitrating these lifesaving therapies. Therefore, the objective of this consensus document is to provide advice of the effect HF drugs on renal function and the implications during titration of therapies in patients with HF.

Kidney physiology in health and heart failure

The main tasks of the kidneys are to clear the blood of toxins and waste products, to maintain the body fluid and electrolyte homeostasis, produce essential renal hormones and preserve tissue perfusion. In order to perform these tasks the kidney needs to filter a sufficient amount of blood per time from the renal glomerular capillaries into the Bowman's space (glomerular filtration function). Afterwards, the kidney strictly regulates tubular water and solute reabsorption (renal tubular function). In normal circumstances glomerular filtration is closely intertwined with tubular function and vice versa.

Glomerular function

The glomerular filtration rate (GFR) is determined by the filtration equation and depends on the number of functional nephrons, the ultrafiltration coefficient (K_f) and the net Starling forces (P_{UF}).[12] Net Starling forces are determined by the hydrostatic and colloid osmotic pressure differences between glomerular capillaries and the Bowman's space (*Figure 1*). Mainly the hydrostatic capillary pressure drives net filtration, as the hydrostatic pressure in the glomerular capillaries are twice as high compared to any other capillary network.[13] This latter is achieved by the unique position of the glomerular capillaries in between the glomerular afferent arteriole (AA) and the efferent arteriole (EA).[14] In normal physiological conditions, GFR is kept relatively stable through autoregulation with a variable vasoconstriction of the AA and EA in the face of changes in renal blood flow (RBF) as depicted in *Figure 1B*. As such, the glomerulus maintains GFR and protects itself against hyper-filtration through a process of tubuloglomerular feedback (TGF; as discussed later reflects the tubular detection of chloride in the ultrafiltrate at the level of the macula densa, resulting in adenosine release and vasoconstriction of the AA).[15] How efficiently the individual nephron maintains GFR in normotensive individuals (single nephron GFR = snGFR) is mainly determined by the RBF and this relationship is not linear (*Figure 1C*).[16] In the setting of a low RBF, P_{UF} does not occur over the entire capillary length but reaches a filtration equilibrium (*Figure 1C*). The relationship between GFR and RBF also determines a parameter known as the filtration fraction (FF). The FF represents the amount of RBF, or better renal plasma flow (=[1-hematocrite] x RBF) being filtered in the Bowman's space (FF = GFR/RBF).[17] Importantly, the FF determines the amount of sodium and water which will be reabsorbed in the proximal parts of the tubules[16] (a process known as glomerulotubular balance). A final parameter in the filtration equation is the ultrafiltration coefficient K_f, which is the product of the hydraulic conductivity of the capillary (L_p) and the effective surface area for filtration (S_f).[18] The K_f of the renal glomeruli is significantly higher than

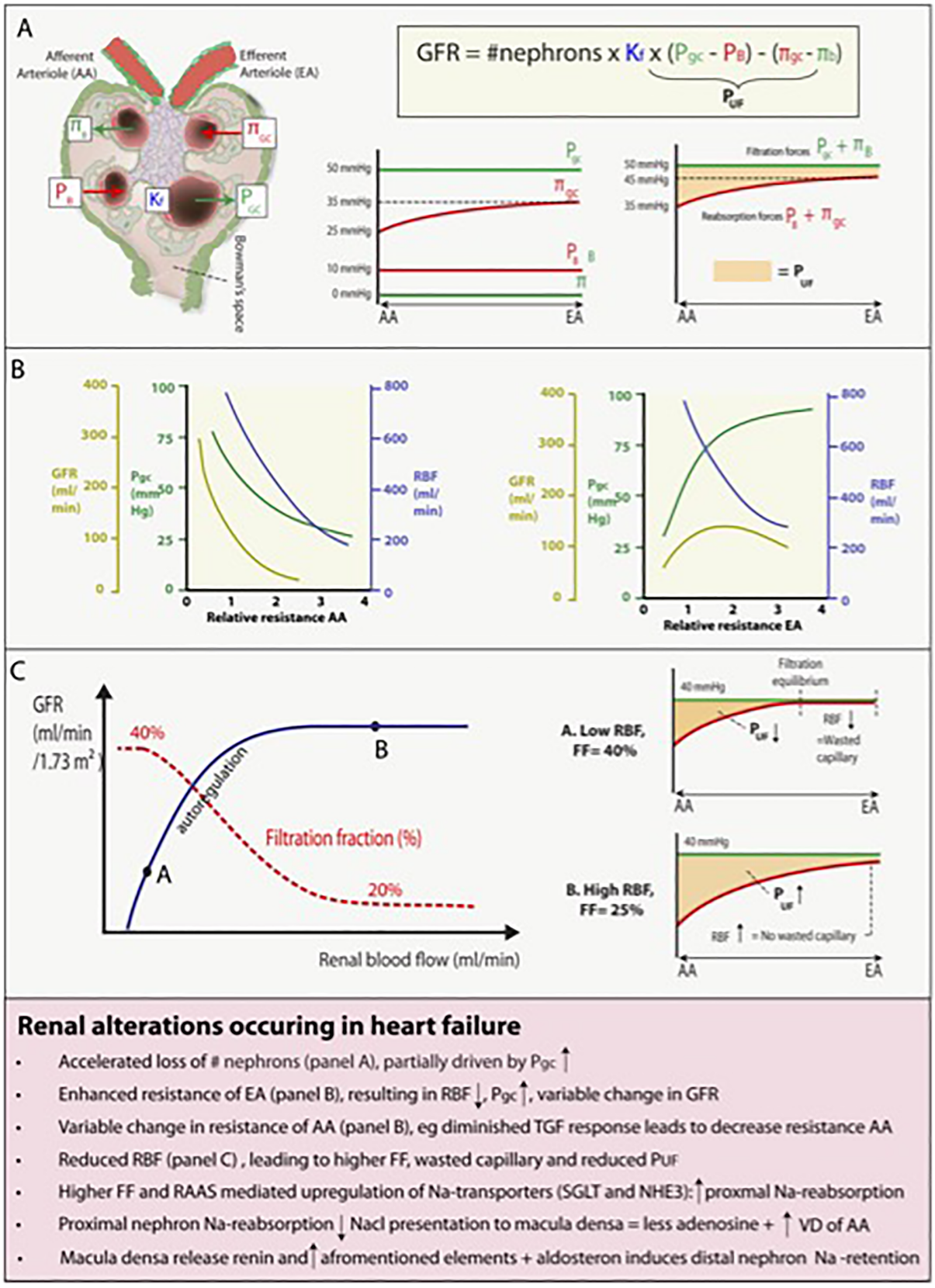


Figure 1 Legend on next page

other capillary beds and mesangial cell contraction can result in significant changes in the S_f component of K_f. All these aforementioned parameters will be influenced by HF (*Figure 1*) and therefore also by the pharmacological therapies used for the treatment of HF.[19]

Acute HF with alterations in central haemodynamics is often associated with acute changes in GFR.[3] In contrast, a progressive reduction in GFR in the setting of chronic HF (independent of a trigger) is largely thought to be a reflection of progressive loss of nephrons. The haemodynamic alterations in acute HF are a combination of impaired cardiac output, systemic venous congestion or elevated high central venous pressure, and systemic vasoconstriction or increased systemic vascular resistance, all with a variable effect on mean arterial pressure and potential alteration in abdominal pressures. The common effect of all these alterations is a drop in RBF. Acute changes in RBF will be counterbalanced by renal autoregulation that directly affects intraglomerular haemodynamics, hereby dampening the effect of these haemodynamic changes on GFR. Additionally, preservation of GFR in the face of a reduction in RBF results in an increased FF which will increase proximal nephron sodium and water absorption.[16] The theoretical maximum of FF depends mainly on the intraglomerular hydrostatic pressures, with higher pressures allowing higher FF. Also, medical therapies that influence intraglomerular hydrostatic pressures (e.g. through TGF such as SGLT2 inhibitors or loop diuretics, or mitigation of EA vasoconstriction with ACE-I/ARB/ARNI) will affect GFR and to some extent FF.

Renin–angiotensin system activation increases intraglomerular pressure by causing preferential vasoconstriction of the EAs. This may be necessary to maintain normal intraglomerular pressure when mean arterial pressure is low, but comes at the cost of a reduction in RBF. In addition, exaggerated neurohumoral activation despite normal or high blood pressure may cause intraglomerular hypertension, which leads to podocyte loss and accelerates kidney function decline over time. Indeed, in patients with chronic HF, the deterioration in GFR over time (slope) is greater as compared with healthy individuals.[20] Sympathetic nerve system activation aggravates the impact of angiotensin II (ATII) on RBF, as it promotes general vasoconstriction. In addition, it may transiently increase the S_f and hence the GFR through mesangial contraction, which puts more mechanical stress on the renal podocytes that constitute the most vulnerable part of the glomerular membrane, causing permanent structural damage.

Tubular function

Another unique feature of the renal microvasculature is the presence of two serially connected capillary beds (glomerular and peritubular capillary network). Changes in the relative resistance of the AA and EA keep the intraglomerular hydrostatic pressures high in comparison to the hydrostatic pressure in the peritubular capillary network.[14] Furthermore, glomerular filtration results in intravascular haemoconcentration across the glomerular capillary network with increased oncotic pressures over the length of the glomerular capillaries as a result in the peritubular capillary network favouring proximal nephron sodium, water and solute reabsorption (*Figure 1*). Additionally, a decrease in RBF will ultimately – through the preservation of GFR by autoregulation – result in an increased FF, which invokes the mechanism of glomerular tubular balance.[21] Glomerular tubular balance is the process of enhanced proximal nephron reabsorption in the setting of increased FF, a process which is independent of neurohormonal interference. Therefore, the haemodynamic alterations in HF resulting in a lower RBF result in a higher FF which will promote proximal nephron sodium avidity. Furthermore, neurohormonal activation occurring in HF worsens this proximal sodium reabsorption as it upregulates proximal nephron sodium transporters (e.g. sodium–glucose cotransporters or sodium–hydrogen exchanger).[22–24] The increased fractional sodium reabsorption in the proximal nephron results in diminished sodium and chloride presentation to the macula densa. The macula densa is an area of closely packed specialized cells lining the wall of the distal tubule which are sensitive to the concentration of sodium chloride in the tubular lumen and responsible for the TGF mechanism. When faced with a decrease in chloride delivery, (i) it decreases resistance of the afferent arterioles, which raises glomerular hydrostatic pressure and helps return the GFR toward normal, and (ii) it increases renin release from the juxtaglomerular cells of the afferent and efferent arterioles, which are the major storage sites for renin. Both the TGF and increased neurohumoral stimulation are hallmark features of HF. In normal physiologic conditions, the TGF protects the glomerulus from hyperfiltration, as hyperfiltration will result in enhanced sodium and chloride presentation to the macula densa. This results in adenosine release and vasoconstriction of the AA diminishing harmful elevations in glomerular hydrostatic pressures. Yet, the precise altered tubular sodium balance in HF with heightened proximal nephron sodium retention (also occurring in diabetes due to

Figure 1 Renal physiologic concept relevant to heart failure and guideline-directed medical therapy titration. (*A*) A drawing of the nefron with annotated element of the Starling filter equation. The two line charts in panel *A* represent the change in hydrostatic and colloid forces across the glomerular capillary from the afferent to efferent arteriole. Red lines indicate factors opposing filtration while green lines indicate factors driving filtration. Net Starling forces (P_{UF}) are highlighted by the yellow area. This illustrates how changing red and green lines can alter P_{UF}. (*B*) Interplay between renal blood flow (RBF), glomerular filtration rate (GFR) and relative resistance of afferent (AA) and efferent arterioles (EA), illustrating how changes in relative resistance (caused by heart failure or drug to treat heart failure) affect these components. (*C*) Relation between GFR and RBF and their interaction (filtration fraction), right-sided line charts indicate the effect of low versus high RBF on components of the starling filtration and net Net starling forces (P_{UF}). FF, filtration fraction; Pb, hydrostatic pressure in Bowman's space; Pgc, hydrostatic pressure in glomerular capillary; Πgc, oncotic pressure in glomerular capillary; πb, oncotic pressure in Bowman's space; RAAS, renin–angiotensin–aldosterone system; SGLT, sodium–glucose cotransporter; VD, vasodilatation.

sodium–glucose cotransporter upregulation), limit the effectiveness of TGF to protect the glomerulus from hyperfiltration.[25,26] As a result, HF patients are faced with intraglomerular hypertension which will further aggravate the loss of functional nephrons.

Prognostic role of glomerular filtration rate changes in heart failure

Glomerular filtration rate is a stronger predictor of clinical outcome than left ventricular ejection fraction in HF patients.[27] A large meta-analysis encompassing over one million patients with chronic HF, illustrated that the presence of chronic kidney disease (CKD; defined as a GFR <60 ml/min/1.73 m^2) is associated with a doubling in the risk of all-cause mortality.[28] However, as explained previously, the GFR is the net result of the total number of functioning nephrons, the ultrafiltration coefficient (K_f) and the net Starling forces (P_{UF}) across the glomerular capillaries. Importantly, the prognostic relevance of GFR deterioration is especially relevant if it reflects permanent loss of functioning nephrons. As such, one needs to understand the pathophysiologic mechanism behind GFR changes in order to understand their potential relation with clinical outcome. As such, an increase in serum creatinine (often termed 'worsening renal function' [WRF]) in the setting of acute HF is not always associated with adverse clinical outcomes[29–31] as it is often a reflection of the altered haemodynamic state if acute HF.[32] Indeed, no study has documented that WRF in acute HF is associated with functional nephron loss. Instead, the combination of elevated central venous pressure, with or without low cardiac output/low blood pressure and elevated intra-abdominal pressures form the basis for a reduction in RBF leading to a decrease in GFR.[33–35] Importantly, relieve of congestion in acute HF is associated with better outcomes despite a temporarily decrease in GFR.[36,37] Yet, therapies used to alleviate congestion in acute HF also influence glomerular haemodynamics.[38] For instance, the macula densa is lined with the NKCC receptor (which is also inhibited by loop diuretics) to assess chloride content in the ultrafiltrate.[15] Likely as a result of the effect of chloride delivery to the macula densa, treatment with loop diuretics can cause a decrease in GFR that is likely driven by increased macula densa mediated renin release. However, as loop diuretics also relieve congestion, this drop in GFR is not indicative of poor prognosis.[39,40] Indeed, numerous studies in acute HF have documented that an increase in creatinine in combination with effective decongestion (good diuretic response, relieve of congestion) is actually associated with a better prognosis, despite an elevation in creatinine.[39,41] A previous position paper from this cardiorenal working group has already proposed to evaluate creatinine changes during decongestion in light of the decongestive effectiveness.[3]

In contrast to acute HF, in the setting of chronic HF, an unprovoked decrease in the GFR is often clinically relevant as it mostly reflects a permanent loss of functioning nephrons (e.g. due to intraglomerular hypertension or chronic hypoperfusion damage).[42] Progressive nephron loss results in an accelerated decline of GFR over time leading to the premature development of end-stage kidney disease or experiencing a major adverse renal event.[28] Additionally, CKD is associated with the highest population attributable risk (how much the development of a certain endpoint is related to a certain risk factor) to develop HF-related mortality.[43] In healthy individuals, the average annual decline in estimated GFR (eGFR) has been shown to be 0.6–1 ml/min/1.73 m^2 per year after the age of 30–50.[44] In comparison, patients with chronic HF in the GISSI-HF trial experienced a slope in decline of GFR around 2.57 ml/min/1.73 m^2 per year.[45] Importantly, HF itself remained independently associated with a more pronounced decline in GFR over time, even after adjustment for other well-known risk factors associated with progression towards CKD.[45] Additionally, a more rapid decline – often seen in diabetes mellitus – in GFR is associated with a higher risk for adverse events.[46] Not surprisingly, assessment of GFR slopes is becoming a frequent trial endpoint in randomized controlled trials (RCT) assessing the impact of HF therapies, serving as a proxy for development of end-stage kidney disease.[9,47,48] Indeed, it is generally accepted that a reduction in annual GFR decline by 0.5–1.0 ml/min/1.73 m^2 per year is associated with a 0.7 lower risk to develop end-stage kidney disease. However, one needs to interpret these changes carefully. First, changes in GFR in clinical practice are often provoked, for instance initiation of SGLT2 inhibitors and RAAS inhibitors are thought to reduce intraglomerular pressures, hereby resulting in a haemodynamic-related drop in GFR.[5,7–9,47,49,50] However, this drop in GFR is not reflective of progressive nephron loss. In contrast, the sustained reduction in intraglomerular pressures is associated with attenuation of the loss of glomerular function over time.[51,52] As such, the early part of the slope is obscured by the glomerular haemodynamic effect of these agents, despite already leading to a reduction in major adverse cardiac or renal events. Indeed, eGFR slope analysis might be less straightforward for drugs that have an acute effect on GFR. However, just excluding this acute drop generates a new post-randomization baseline which induces potential bias. Second, for reliable slope calculations, sufficient follow-up of eGFR assessments during at least 3–5 years is often not the case in most HF drug RCTs.[53,54] These elements need to be taken into account when using annual eGFR decline as surrogate endpoint for development of end-stage kidney disease. However, development of end-stage kidney disease is relative uncommon in modern HF trials which will be elaborated later.

Renal effects of established guideline-recommended heart failure therapies

Guideline-directed medical therapy (GDMT) forms the backbone of the treatment of HF patients. Given the essential positioning of the kidney in the pathophysiology of HF, GDMT will also impact indices of renal function. Despite observational data illustrating that HF is associated with a more pronounced decline in eGFR over time,[45] there is limited to no trial evidence that older established therapies (ACE-I, ARB, beta-blockers or MRAs) alter this slope in the setting of HF. Additionally renal endpoints

(e.g. sustained drop in eGFR, development of end-stage kidney disease or renal death) were not typically assessed in the landmark trials with ACE-I/ARBs, beta-blockers or MRAs. However, the nephro-protective effects of ACE-I/ARB in the setting of CKD are well established.[55] This section discusses the potential mechanisms of ACE-I/ARBs, beta-blockers and MRAs on renal physiology and the clinical trial evidence. An overview of the landmark RCTs, including their inclusion criteria in relation to baseline renal function and percentage of patients with CKD are reflected in *Table 1*. A full name of trial acronyms can be found in online supplementary *Appendix S1*.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Effects of angiotensin II on renal pathophysiology

Angiotensin II can cause pressure-induced glomerular damage through its effect on inducing systemic hypertension and glomerular hypertension through predominant vasoconstriction of the EA.[56] This mechanism might be particularly important in hypertensive HF patients, especially when other risk factors for glomerular hypertension (diabetes, CKD, obesity) are present.[20] Additionally, through extreme arteriolar vasoconstriction ATII can cause ischaemia-related damage, a mechanism which might be more dominant in patients with advanced HF and hypoperfusion.[57] Furthermore, ATII stimulates renal fibroblasts to become myofibroblasts leading to mesangial cell proliferation. Additionally, ATII stimulates mesangial cells to contract, aggravating further stress on the podocytes and filtration barrier.[58] By the activation of several growth factors, ATII increases glomerulosclerosis and platelet activation potentially amplifying intrarenal atherosclerotic process and progressive vascular obstruction. ATII also exerts effects on renal tubuli increasing the expression of proximal nephron sodium transporters.[23]

Trial evidence of renal effects of ACE-I and ARB

Post-hoc analysis of landmark ACE-I trials as well as real-world observational studies illustrate a beneficial effect of ACE-inhibition, even if patients had CKD at baseline as well as in patients who experienced a drop in eGFR after initiation of ACE-I.[59,60] Although 33% of patients in SOLVD had an increase in serum creatinine of >0.5 mg/dl, the benefits on outcome were well maintained, even in patients with more advanced CKD.[61] Therefore, the treatment benefit of ACE-I is well preserved if patients develop an acute drop in eGFR. Similar data are available for ARBs.[62] In addition, baseline CKD should not preclude the utilization of ACE-I/ARBs as their treatment effects are maintained as demonstrated by several renal sub-analysis of the landmark trials (CONSENSUS, SOLVD, SAVE, ATLAS, Val-HeFT, CHARM-Added, CHARM-Alternative and HEAAL).[63] However, post-hoc analysis of the landmark ACE-I trials in HF show that ACE-I do not reduce the slope of GFR decline in comparison to patients assigned to placebo, but the short duration of follow-up and early assessment of eGFR limit the interpretation of slope changes.[64,65] In contrast, in patients with diabetes (with or without HF), ACE-I and ARBs do reduce the slope of GFR decline over time in trials of similar duration, which probably relates to the fact that diabetes is associated with more intraglomerular hypertension.[68] Also, in these studies the acute drop in eGFR with initiation of ACE-I/ARB predict the slowing in annual eGFR slope decline. Such observation has not been documented with ACE-I/ARBs in HF.[67] Despite these favourable effects, specific studies investigating the effect of RAAS inhibitors in patients with both HF and advanced CKD (GFR <15 ml/min/1.73 m^2) are limited and their safety should be confirmed in observational studies with longer term follow-up. In CKD stage 5, the KDIGO guidelines still indicate the use of ACE-I and ARBs with moderate evidence for ACE-I/ARB if CKD stage 5 and dialysis and weak evidence supporting their use in patients with CKD stage 5 not on dialysis.[55] We are aligned with KDIGO guideline recommendation to use ACE-I/ARB also in more advanced CKD stages (stage 4–5). However, careful renal function and potassium monitoring and starting at a low dosage is warranted, with consideration of the use of potassium binders according to local reimbursement criteria if appropriate.[55]

Mineralocorticoid receptor antagonists

Effects of aldosterone on renal pathophysiology

Aldosterone results in mesangial cell proliferation, podocyte injury, sclerotic changes and arteriolar hyalinosis.[68] In hypertensive animal studies, treatment with an ACE-I diminishes renal damage, but this process is reversed by infusion of aldosterone. This underscores the independent detrimental effects of aldosterone beyond ATII which is clinically relevant (in HF and diabetes) and known as aldosterone escape.

Trial evidence of renal effects of MRA

Further suppression of the RAAS axis with MRA beneficially influences the outcome in HFrEF patients (*Table 1*).[6,69] Importantly, a post-hoc analysis of the EPHESUS and EMPHASIS-HF trial illustrated that the presence of an eGFR <60 ml/min/1.73 m^2 did not influence the benefit on the primary endpoint of HF hospitalization and cardiovascular mortality.[50,70] Similarly to ACE-I and ARB initiation, an analysis from the EPHESUS trial indicated that MRA initiation causes an acute drop in GFR which is maintained throughout MRA administration, although the absolute drop is minor (adjusted mean difference of −1.40 ml/min/1.73 m^2).[50] Additionally, MRA did not influence the slope of GFR decline in the EPHESUS trial.[50] However, more recently, finerenone (a non-steroidal, selective MRA) was shown to reduce the slope decline in GFR in patients with type 2 diabetes and diabetic kidney disease (least square mean change in GFR after 4 months: −2.66 mg/dl per year vs. −3.97 mg/dl per year).[71] The differential effect on slope might indicate that diabetes is perhaps associated with more intraglomerular hypertension, or reflects the differential follow-up duration between trials (21 months eplerenone vs. 31 months finerenone).[50,71] Currently, there is no recommendation for MRA if eGFR <30 ml/min/1.73 m^2 as safety and efficacy data are lacking.

Table 1 **Landmark pharmacological agents trials for management of heart failure with reduced ejection fraction**

Trial	*N*	Design	Primary outcome	Mean LVEF	Renal function exclusion	CKD	RR primary outcome (95% CI)
CONSENSUS	253	Enalapril vs. Pl	ACM	NA	Cr >3.4 mg/dl	NA	0.70 (0.54–0.89)
SOLVD-Treatment	2569	Enalapril vs. Pl	ACM	25%	Cr >2.0 mg/dl	36%	0.84 (0.73–1.06)
SOLVD-Prevention	4228	Enalapril vs. Pl	ACM	28%	Cr >2.0 mg/dl	21%	0.92 (0.79–1.08)
SAVE	2331	Captopril vs. Pl	ACM	31%	Cr >2.5 mg/dl	33%	0.81 (0.68–0.97)
AIRE	2006	Ramipril vs. Pl	ACM	NA	NA	NA	0.73 (0.60–0.89)
TRACE	1749	Trandolapril vs. Pl	ACM	NA	Cr >2.3 mg/dl	40%	0.78 (0.67–0.91)
NETWORK	1532	Enalapril 2.5 vs. 5 vs. 10 mg BID	ACM, HFH or WHF	NA	Cr >2.3 mg/dl	NA	1.20 (0.86–1.68)
ATLAS	3164	Lisinopril high vs. low dose	ACM	23%	Cr >2.5 mg/dl	NA	0.92 (0.82–1.03)
Val-HeFT	5010	Valsartan vs. Pl	ACM	27%	Cr >2.5 mg/dl	58%	1.02 (0.88–1.18)
CHARM-Added	2548	Candesartan vs. Pl	CV death or HFH	28%	Cr >3.0 mg/dl	33%	0.85 (0.75–0.96)
CHARM-Alternative	2028	Candesartan vs. Pl	CV death or HFH	30%	Cr >3.0 mg/dl	43%	0.77 (0.67–0.89)
HEAAL	3846	High-dose vs. low-dose losartan	ACM or HFH	33%	Cr >2.5 mg/dl	NA	0.90 (0.82–0.99)
MDC	383	Metoprolol vs. Pl	ACM	22%	NA	NA	0.68(0.38–106)
CIBIS	641	Bisoprolol vs. Pl	ACM	25%	Cr >3.4 mg/dl	NA	0.80 (0.56–1.15)
US Carvedilol	1094	Carvedilol vs. Pl	ACM	22%	Clinical important renal disease	NA	0.35 (0.20–0.61)
MERIT-HF	3991	Metoprolol vs. Pl	ACM	28%	NA	37%	0.66 (0.53–0.81)
CIBIS-II	2289	Bisoprolol vs. Pl	ACM	28%	Cr >3.4 mg/dl	43%	0.66 (0.54–0.81)
COPERNICUS	2289	Carvedilol vs. Pl	ACM	20%	Cr >2.8 mg/dl	61%	0.65 (0.52–0.81)
CAPRICORN	1959	Carvedilol vs. Pl	ACM	33%	Renal impairment	61%	0.77 (0.60–0.98)
COMET	3029	Carvedilol vs. metoprolol	ACM	26%	NA	NA	0.83 (0.74–0.93)
SENIORS	2128	Nebivelol vs. Pl	ACM or CV hospitalization	36%	Significant renal disease	42%	0.86 (0.74–0.99)
RALES	1663	Spironolactone vs. Pl	ACM	25%	Cr >2.5 mg/dl	48%	0.70 (0.60–0.82)
EMPHASIS-HF	2737	Eplerenone vs. Pl	CV death or HFH	26%	eGFR <30 ml/min/1.73 m^2	33%	0.66 (0.56–0.78)

ACM, all-cause mortality; BID, bis in die; CI, confidence interval; CV, cardiovascular; Cr, creatinine; CKD, chronic kidney disease (eGFR <60 ml/min/1.73 m^2); eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; NA, not available; Pl, placebo; RR, relative risk; WHF, worsening heart failure.
BEST trial is not reflected as not guideline-indicated agent (missed primary endpoint). EPHESUS not reflected as it is a high-risk acute coronary syndrome trial.
Full description of trial acronyms is available in online supplementary *Appendix S1*.

Beta-blockers

Effects of adrenergic activation on renal pathophysiology

The kidney contains both α and β-adrenergic receptors. Mainly α-adrenergic activation in the kidney result in vasoconstriction of the AA and EA and reduces RBF.[72,73] Furthermore, sympathetic activation triggers granular cells to release renin, resulting in higher levels of ATII. Furthermore, adrenergic activation stimulates several segments of the renal tubuli to enhance sodium absorption from the ultrafiltrate, further contributing to renal sodium avidity occurring in the setting of HF.[73]

Trial evidence of renal effects of beta-blockers

Beta-blockers significantly reduce mortality and morbidity in HFrEF patients (*Table 1*). Contrary to RAAS inhibitors, beta-blockers do not cause an acute reduction in eGFR and they also do not alter the slope of eGFR decline over time.[74] However, a meta-analysis of the CAPRICORN and COPERNICUS trials with carvedilol did show a higher transient increase in serum creatinine (4.6% in carvedilol treated patients vs. 1.8% in placebo treated patients; $p < 0.001$), without hyperkalaemia or development of end-stage kidney disease.[75] This rise in serum creatinine might be explained by the more pronounced α-adrenergic blocking effect of carvedilol in comparison to other beta-blockers. Importantly while no treatment interaction is observed with CKD and the use of ACE-I/ARB, a post-hoc analysis from the MERIT-HF trial across GFR strata (<45, 45–60, and >60 ml/min/1.73 m^2) suggests that patients with the lowest GFR strata actually had the highest relative risk reduction effect of metoprolol (p-value for interaction = 0.095).[76] An individual patient data meta-analysis of 10 beta-blocker trials, however, did not support a larger relative risk reduction in patients with eGFR <30 ml/min/1.73 m^2.[77] Additionally, the discontinuation rate of beta-blockers tended also to be the highest in patients with more advanced CKD.[78] Moreover, a trial in HFrEF patients on dialysis indicates that carvedilol also reduces morbidity and mortality in patients with end-stage kidney disease.[79] Nevertheless, it is important to remember that carvedilol is not dialyzable (and bisoprolol and nebivolol to a limited extent) while more water soluble beta-blockers (being metoprolol and atenolol) are removed by dialysis, so dose of metoprolol might need to be adjusted (atenolol is not advised in HF).[2,80]

Renal effects of novel guideline-recommended heart failure therapies

Several new agents have become available over the last years reducing morbidity and mortality in HFrEF and potentially also in HFmrEF and HFpEF, which include SGLT2 inhibitors and ARNI. In comparison to the older agents (ACE-I, ARB, beta-blockers and MRA), novel HF therapies such as ARNI and SGLT2 inhibitors do positively affect the slope of eGFR in dedicated HF trials in which renal endpoints were often formally assessed allowing also to comment on the kidney effects of these agents. Such data (both in HFrEF and HFmrEF/HFpEF trials) is reflected in *Table 2*.[9,81,82] In general, it is important to emphasize that renal events are relatively infrequent in modern HF trials, therefore these agents are often not formally powered to assess hard renal endpoints such as a sustained drop in eGFR and/or development of end-stage kidney disease or renal death. An overview of all landmark trials with novel agents in HFrEF are reflected in *Table 3*, including their exclusion criteria in relation to baseline renal function and the proportion of patients with CKD, allowing to comment on the efficacy of these agents for HF endpoints in the setting of CKD. A visual representation of the effect of the drugs on the GFR slope is reflected in *Figure 2*.

Sacubitril/valsartan

Effects of natriuretic peptides on renal pathophysiology

Natriuretic peptides are secreted from cardiomyocytes in response to augmented filling pressure and wall stress. Through the generation of cyclic guanosine monophosphate (cGMP), natriuretic peptides promote diuresis and natriuresis, increase GFR, decrease systemic sympathetic activities, plasma volume and blood pressure.[83] Atrial natriuretic peptide (ANP) increases GFR through its vasodilating effects on the AAs, both directly through calcium channel pathways,[84] and through reversal of norepinephrine-induced and endothelin-mediated vasoconstriction.[85] Furthermore, ANP directly increases the glomerular capillary ultrafiltration coefficient (K_f) by inducing relaxation of the contractile intraglomerular mesangial cells in the space between capillary endothelium and podocytes.[51,85] Sacubitril inhibits the breakdown of natriuretic peptides leading to their enhanced beneficial effects.[86]

Trial evidence of renal effects of ARNI

As the major RCTs with ARNI in HFrEF and HFpEF compared sacubitril/valsartan either with enalapril or valsartan, the incremental effects observed on renal endpoints in these trials related to the beneficial effects incurred by elevated levels of natriuretic peptides (or potential other substrates of neprilysin). In sub-analyses of the PARADIGM-HF, PARAMOUNT and PARAGON-HF trials, sacubitril/valsartan reduced the risk of renal events (sustained 50% reduction in GFR or developing end-stage kidney disease) in addition to cardiac events in both HFrEF and HFpEF (*Table 2*).[81,82,87] Additionally, sacubitril/valsartan slowed the annual decline in eGFR both in HFrEF and HFpEF despite a small increase in urinary albumin concentrations (UACR).[81,82,87] The latter might be explained by the effect on the glomerular capillary ultrafiltration coefficient (K_f) and tubular protein reabsorption and therefore does not reflect enhanced glomerular loss, as increases in UACR were not associated with renal adverse events in patients treated with sacubitril/valsartan (suggesting no permanent nephron loss).[51,85] As such, in diabetic nephropathy and chronic CKD, sacubitril/valsartan is particularly beneficial in reducing cardiac events and renal decline.[88] In addition, combining sacubitril/valsartan with MRAs appeared to reduce the incidence of hyperkalaemia, therefore therapeutic optimization with ARNI could potentially enhance tolerability of an MRA.[89] However, in the UK HARP-III trial, a double-blind trial that randomized patients with GFR of 20–60 ml/min/1.73 m^2 to ARNI versus irbesartan, ARNI had similar effects on kidney function and albuminuria compared to irbesartan.[90]

Table 2 Renal outcomes with angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter 2 inhibitors in heart failure

Trial	*N*	Design	ESKD events	≥40% or 50% reduction in eGFR	Effect on renal endpoint
Angiotensin receptor–neprilysin inhibitors					
PARADIGM-HF	8442	Sac/val vs. enalapril	Sac/val: 8 (0.2%) Enalapril: 16 (0.4%)	Sac/val: 32 (0.8%) Enalapril: 41 (1.0%)	HR 0.63 (95% CI 0.42–0.95) for ESKD+ ≥50% eGFR decline
PARAGON-HF	4822	Sac/val vs. valsartan	Sac/val: 7 (0.3%) Valsartan: 12 (0.5%)	Sac/val: 27 (1.1%) Valsartan: 60 (2.5%)	HR 0.50 (95% CI 0.33–0.77) for ESKD+ ≥50% eGFR decline or renal death
Sodium–glucose cotransporter 2 inhibitors					
DAPA-HF	4744	Dapagliflozin vs. placebo	Dapagliflozin: 16 (0.7%) Placebo: 16 (0.7%)	Dapagliflozin: 14 (0.6%) Placebo: 23 (1.0%)	HR 0.71 (95% CI 0.44–1.16) for ESKD+ ≥50% eGFR decline or renal death
EMPEROR-Reduced	3730	Empagliflozin vs. placebo	No breakdown ESKD vs. 40% eGFR drop Empagliflozin: 30 (1.6%) Placebo: 58 (3.1%)		Rate of eGFR decline: group difference 1.7 ml/min/year
EMPEROR-Preserved	5988	Empagliflozin vs. placebo	No breakdown ESKD vs. 40% eGFR drop Empagliflozin: 108 (3.6%) Placebo: 112 (3.7%)		Rate of eGFR decline: group difference 1.4 ml/min/year

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; Sac/val sacubitril/valsartan.

Table 3 Landmark pharmacological trials with novel agents for the management of heart failure with reduced ejection fraction

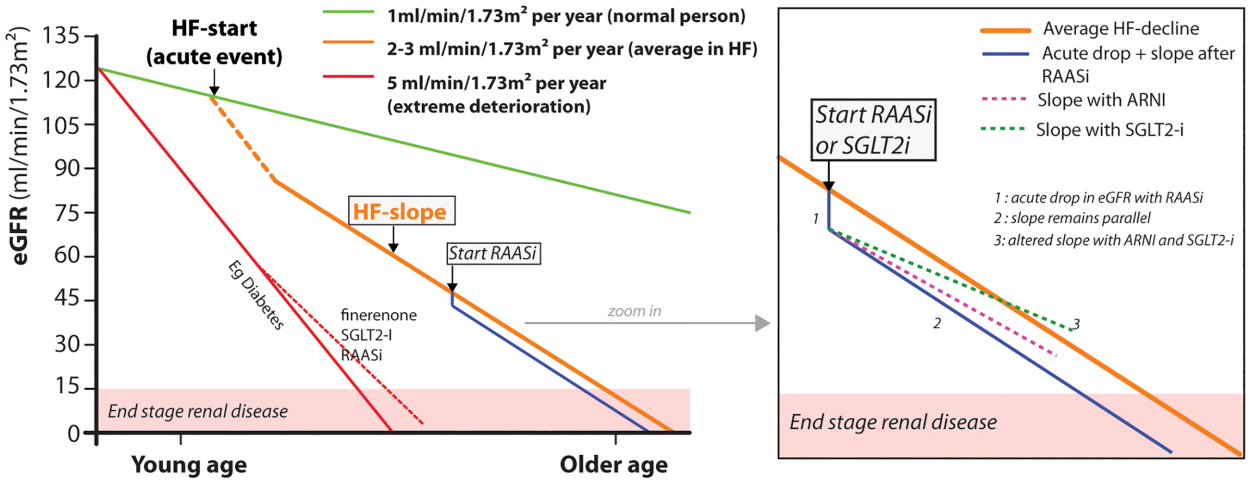
Trial	*N*	Design	Primary outcome	Mean LVEF	Renal function exclusion	CKD	RR primary outcome (95% CI)
Angiotensin receptor–neprilysin inhibitors							
PARADIGM-HF	8442	Enalapril vs. Sac/val	CV death or HFH	29%	eGFR <30 ml/min/1.73 m^2	33%	0.80 (0.73–0.87)
Sodium–glucose cotransporter 2 inhibitors							
DAPA-HF	2373	Dapagliflozin vs PI	WHF or CV death	31%	eGFR <30 ml/min/1.73 m^2	41%	0.74 (0.65–0.85)
EMPEROR-Reeduced	1863	Empagliflozin vs. PI	WHF or CV death	27%	eGFR <20 ml/min/1.73 m^2	53%	0.75 (0.65–0.86)
SOLOIST-WHF	1222	Sotagliflozin vs. PI	Total WHF and CV death	35%	eGFR <30 ml/min/1.73 m^2	NA	0.67 (0.52–0.85)
Agents considered in selected HFrEF patients							
SHIFT	6558	Ivabradine vs. PI	CV death or HFH	29%	Severe renal disease	NA	0.82 (0.75–0.90)
VICTORIA	5050	Vericiguat vs. PI	CV death or HFH	29%	eGFR <15 ml/min/1.73 m^2	54%	0.92 (0.82–0.98)
GALACTIC-HF	8256	Omecamtiv mecarbil vs. PI	CV death or HFH/WHF	27%	eGFR <15 ml/min/1.73 m^2	53%	0.92 (0.86–0.99)

ACM, all-cause mortality; BID, bis in die; CI, confidence interval; CKD, chronic kidney disease (eGFR <60 mL/min/1.73 m^2); Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; NA, not available; PI, placebo; RR, relative risk; Sac/val, sacubitril/valsartan; WHF, worsening heart failure.

Sodium–glucose cotransporter 2 inhibitors

Effects of SGLT2 on renal pathophysiology

In normal circumstances, all glomerular filtered glucose is reabsorbed in the proximal nephron. The high capacity, low affinity SGLT2 is located almost exclusively in the S1 and S2 segments of the proximal tubules. Residing there at the luminal membrane of proximal tubular cells, it is responsible for approximately 90% of glucose reabsorption. The remaining glucose is reabsorbed by a related transporter that is predominant in the S3 segment of the proximal tubules, i.e. the sodium–glucose cotransporter 1, which has lower capacity but higher affinity for glucose. Importantly, several pathologic conditions including HF, diabetes and obesity



Key messages

1. Acute drop in GFR with RAASi, ARNI and SGLT2-i does not diminishes treatment effect
2. A reduction in slope deterioration in HFrEF with ARNI and SGLT2-i is associated with reduced hard renal endpoints

Figure 2 Effect of drugs on renal slope. ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2-i, sodium–glucose cotransporter 2 inhibitor. Adapted from Mullens *et al.*[3]

are associated with upregulation of the SGLT2. This upregulation explains why much higher blood glucose levels are needed before occurrence of glycosuria in diabetic patients.[22–24] SGLT2 hyperactivity also implies increased proximal tubular reabsorption of sodium as well as chloride – the latter is following sodium, driven by the lumen negative potential present in the S1 and S2 segments of the proximal tubules. Therefore, less chloride will be presented to the macula densa, which in turn stimulates an increase in GFR through dilatation of the AA (TGF).[26] This mechanism is responsible for the phenomenon of glomerular hyperfiltration, often observed early on in diabetes and in patients with HF. Mice models of SGLT2 knock-out have implicated SGLT2 in the progression of CKD.[91]

Trial evidence of renal effects of SGLT2 inhibitors

In patients with HFrEF, a meta-analysis of the DAPA-HF and EMPEROR-Reduced trials demonstrated a significant reduction in the composite renal endpoint with the use of a SGLT2 inhibitor (hazard ratio 0.69, 95% confidence interval 0.62–0.78; p <0.0001), without evidence for heterogeneity between trials in the treatment effect on the pre-defined composite renal endpoint (time to first occurrence of any of the components of 50% or higher sustained decline in eGFR, end-stage kidney disease, or renal death).[92] Both dapagliflozin and empagliflozin cause an acute drop in GFR after initiation, but subsequently both dapagliflozin (−1.09 vs. −2.85 ml/min/1.73 m^2; p <0.001) and empagliflozin (−0.55 vs. −2.28 ml/min/1.73 m^2 per year; p <0.001) treatment attenuated the annual decline in eGFR.[7,9,93,94] Moreover, the presence of CKD at baseline did not influence the treatment effect of dapagliflozin or empagliflozin on the primary (cardiac) endpoints or secondary renal endpoints.[93,94] The consistent beneficial effect of SGLT2 inhibitors on glomerular function (also observed in diabetes and CKD trials) is likely in part related to the diminishment in proximal nephron sodium reabsorption leading to restoration of TGF and a decrease in intraglomerular hydrostatic pressures (although TGF is more a minute to minute regulator of GFR). Some discussion remains on the precise mechanism of reduction in intraglomerular pressures being predominantly driven by EA vasodilatation or AA vasoconstriction.[26,95–97] While the effect of SGTL2 inhibitors is consistent in HFrEF both in patients with versus without baseline diabetes, those with diabetes tend to have a more pronounced acute drop in eGFR, potentially reflecting the higher intraglomerular pressures.[98] The EMPERIAL trial documented a similar pattern (acute drop in GFR) in patients with HFpEF.[99] More recently the EMPEROR-Preserved trial also showed that empagliflozin attenuated the annual decline in eGFR in patients with HFpEF (−1.25 vs. −2.62 ml/min/1.73 m^2 per year; p <0.001), while it did not significantly reduce the combined renal endpoint, in contrast to findings in EMPEROR-Reduced.[100]

Next to the beneficial effect observed on glomerular function, SGLT2 inhibitors also cause a significant reduction in cardiac filling pressure,[101,102] which is probably related to several mechanisms. A reduction in plasma volume (and potentially also interstitial volume)[103,104] and a change in the end-diastolic pressure–volume relationship (left ventricular stiffness)[105,106] have been postulated. Additionally, SGLT2 inhibitors have also shown to induce significant glucosuria and other studies also demonstrated significant

natriuresis leading to the lower intravascular volume and interstitial volume.[104,107–110] Also, as the site of sodium reabsorption which is being inhibited is proximal to the macula densa, little compensatory neurohormonal/sympathetic nervous system activation is observed with these agents. Finally, the addition of SGLT2 inhibitors leads to a reduction of the proportion of patients developing hyperkalaemia.[111] Therefore, appropriate use of these agents might enhance tolerability of MRA.

Renal effects of heart failure agents recommended or to be considered in selected patients

Beyond the well-established disease-modifying agents presented above, several other agents are considered in selected patients to further modify the disease trajectory (ivabradine, vericiguat, omecamtiv mecarbil) or to relieve congestion (diuretics) and interact with renal function. An overview of landmark trials with these agents in stable HFrEF is reflected in *Table 3*, including their exclusion criteria in relation to baseline renal function and the proportion of patients with CKD.

Ivabradine

A sub-analysis from the SHIFT trial indicated that ivabradine is equally effective in reducing the primary endpoint of HF hospitalization and cardiovascular death in patients with or without renal dysfunction.[112] Though a higher heart rate in patients included in SHIFT was associated with an increased risk for WRF, ivabradine itself did not alter the eGFR over time in comparison to the placebo group.

Vericiguat

Vericiguat stimulates the activity of soluble guanylyl cyclase (sGC). sGC is a ubiquitously distributed intracellular enzyme which mediates nitric oxide biological effects by the conversion of guanosine triphosphate into cGMP.[113] In the kidney, sGC is expressed in various types of renal cell (glomerular arterioles, granular cells, descending vasa recta, fibroblasts, podocytes) and its activation is able to modulate renal blood flow, to regulate the function of glomerular and tubular compartments and to reduce inflammation and renal fibrosis.[114]

On the basis of this background, sGC stimulators and activators have been proposed as a therapeutic strategy potentially also useful to preserve renal function.[114] However, data in humans on the renal effects of sGC stimulators are scarce. More recently, vericiguat was tested in the VICTORIA-HF trial, in selected symptomatic HFrEF patients.[115] Interestingly, among the trial's inclusion criteria, the minimum GFR value was >15 ml/min/1.73 m^2. At the time of the enrolment, the median GFR was 58.4 ml/min/1.73 m^2, with 10.2% of patients having a GFR <30 ml/min/1.73 m^2 and 42.7% between 31 and 60 ml/min/1.73 m^2[116] (*Table 3*). There was no interaction between baseline GFR and the effect of vericiguat on clinical outcome. Vericiguat therapy also had no effect on the incidence of WRF or change in eGFR over time.[116]

Omecamtiv mecarbil

Omecamtiv mecarbil modifies cardiac contractility though selectively binding to cardiac myosin, increasing the power stroke at the start of systole through the number of myosin heads binding to the actin filaments. Omecamtiv mecarbil is metabolized by multiple enzymes, including enzymes from the cytochrome P450 family, and excreted in stool and urine. In a phase I study of 31 participants, the pharmacokinetics of omecamtiv mecarbil were not significantly affected by renal impairment, and no major tolerability issues with omecamtiv mecarbil were reported.[117] Recently, the GALACTIC-HF trial randomized 8256 patients (inpatients and outpatients) with symptomatic chronic HFrEF to receive omecamtiv mecarbil or placebo[118] (*Table 3*). The trial included patients with a median GFR of 59 (interquartile range 44–74) ml/min/1.73 m^2. The population also included patients at the lower range of the GFR spectrum (stage 4: 15–29; $n = 523$, 6.3%). Omecamtiv mecarbil did not affect renal function (positively or negatively), or potassium as measured by creatinine at 24 and 48 weeks of follow-up when compared to placebo. Finally, omecamtiv mecarbil effect was consistent across most pre-specified vital sign and laboratory parameter subgroups, including GFR. The finding that omecamtiv mecarbil (a drug that can improve cardiac output) does not improve eGFR is indicative that on a population level in HF eGFR is not heavily dependent on cardiac output.

Diuretics

Diuretics are recommended in selected HF patients with signs of congestion or volume overload.[2] A detailed description of the use and pharmacology of diuretics in HF (acute and chronic) has been previously reviewed by this cardio-renal working group, and falls beyond the scope of the manuscript.[3,119] However, diuretics can have acute and potentially chronic effects on kidney function. Diuretics can cause an acute reduction in GFR which relates to their ability to induce sympathetic nervous system activation, RAAS activation, changes in proximal tubular pressures, renal interstitial pressures, renal pelvis pressures, changes in volume status and TGF. Loop diuretics are the preferred diuretics in the treatment of acute HF, and are often associated with an increase in creatinine (WRF, typically defined as an increase in serum creatinine >0.3 mg/dl). The occurrence of WRF often triggers inappropriate discontinuation and dose reduction of loop diuretics, leading to incomplete decongestion.[3] Incomplete decongestion at the time of discharge is strongly associated with HF readmission or all-cause mortality. WRF occurs in about 18% of patients treated with loop diuretics in recent acute HF trials.[120] Importantly, WRF occurring in the setting of a good diuretic response is a normal kidney response to decongestive therapy and is associated with better outcome (also termed pseudo-WRF).[120,121] This underscores the importance of measuring diuretic response in the setting of acute HF. The 2021 ESC HF guidelines therefore advise to measure diuretic response by measuring urinary sodium concentration (UNa) and urine output (UO) after administration of a loop diuretic on the first day of admission.[2] Such approach helps to identify patients with good diuretic response

Table 4 Initiation of heart failure drugs in relation to baseline chronic kidney disease status

Drug	Evidence across GFR strata according to baseline eGFR enrolment criteria	Acute drop GFR	Impact on GFR slope in HF trial	CKD treatment interaction	Treatment effect with CKD
	ESKD / 15–30 / 30–60 / >60				
ACE-I/ARB	Moderate evidence if dialysis, weak evidence if not on dialysis	Yes	No (beneficial effect of around 1–2 ml/min/1.73 m^2 per year in CKD trials)	No	Relative benefit: ~ Absolute benefit: ↑
Beta-blockers		No	No	Yes (potentially but some conflicting results)	Relative benefit: ~ Absolute benefit: ↑
MRA		Yes	No	No	Relative benefit: ~ Absolute benefit: ↑
ARNI		Yes	Yes (around 0.5 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
SGLT2-i	>20	Yes	Yes (around 1–2 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
Ivabradine		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Vericiguat		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Omecamtiv mecarbil		No	No	No	Relative benefit: ~ Absolute benefit: ↑

A decrease in eGFR over time does not automatically mean RAASi/SGLT2-i need to be downtitrated or discontinued

Dark green, strong evidence; light green, moderate evidence; red, not advised; light grey, no data. ACE-I, angiotensin-converting enzyme inhibitor; ABR, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease (eGFR <60 ml/min/1.73 m^2); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2-i, sodium–glucose cotransporter 2 inhibitor.

(UNa >50–70 mmol/L after 2 h or UO >600 ml after 6 h). The ongoing PUSH-HF trial and ENACT-HF study are assessing the feasibility and safety of protocol-driven diuretic administration in acute HF and determine whether such approach is associated with better clinical outcome.[122,123]

In the chronic HF setting, observational data indicate that higher doses of loop diuretics are associated with a more rapid decline in GFR over time. However, such observational data are heavily influenced by selection bias as the sickest patients with intrinsic more rapid decline in GFR are often prescribed the highest doses of loop diuretics. There are insufficient data as to whether there are differences amongst loop diuretics (furosemide, bumetanide or torsemide) in relation to chronic changes in GFR. The ongoing TRANSFORM-HF study (NCT03296813) is assessing in HF patients with a recent acute HF episode if after discharge torsemide versus furosemide has a different effect on all-cause mortality.

Importance of guideline-directed medical therapy in chronic kidney disease

Observational data indicate that the proportion of patients using either a beta-blocker, ACE-I/ARB/ARNI or MRA decreases with increasing severity of renal dysfunction.[124] Additionally, the proportion of patients taking all three of these agents after discharge from an acute HF admission is only 15% if patients have an eGFR between 45–60 ml/min/1.73 m^2 and only 5% if eGFR is between 30–45 ml/min/1.73 m^2.[124] Limited data are available about the prescription pattern of SGTL2 inhibitors in relation to baseline renal function. Many, classes of different GDMT can safely be initiated in patients with lower GFR as reflected in *Table 4*. While some agents lead to an acute drop in eGFR, these acute changes are most often only transient and for ARNI and SGLT2 inhibitors the annual eGFR slope decline is further diminished. In none of the RCTs with the agents reflected in *Table 4*, statistical interaction was found between presence of CKD and the treatment effect on the primary endpoint. Therefore, in terms of relative risk reduction these agents are equally effective in patients with CKD. Because patients with CKD actually are at the highest baseline risk for cardiovascular death or HF hospitalizations, the absolute risk reduction effect is even more pronounced in HF patients with CKD.

Renal approach to titrating quadruple therapy

Clearly, novel disease management strategies are needed to effectively implement several classes of GDMT in eligible patients despite the presence of CKD. Yet, fear of WRF, hypotension and hyperkalaemia are major reasons for underdosing or discontinuation of GDMT.[125] As stated before, the temporal drop in GFR after initiation of these drugs is not reflected by structural damage (*Table 3*). Indeed, this drop is not associated with adverse clinical outcome (often referred to as pseudo-WRF), which has been illustrated by several landmark trials on ACE-I/ARB/ARNI and MRAs showing that even a 20%–30% deterioration in GFR is

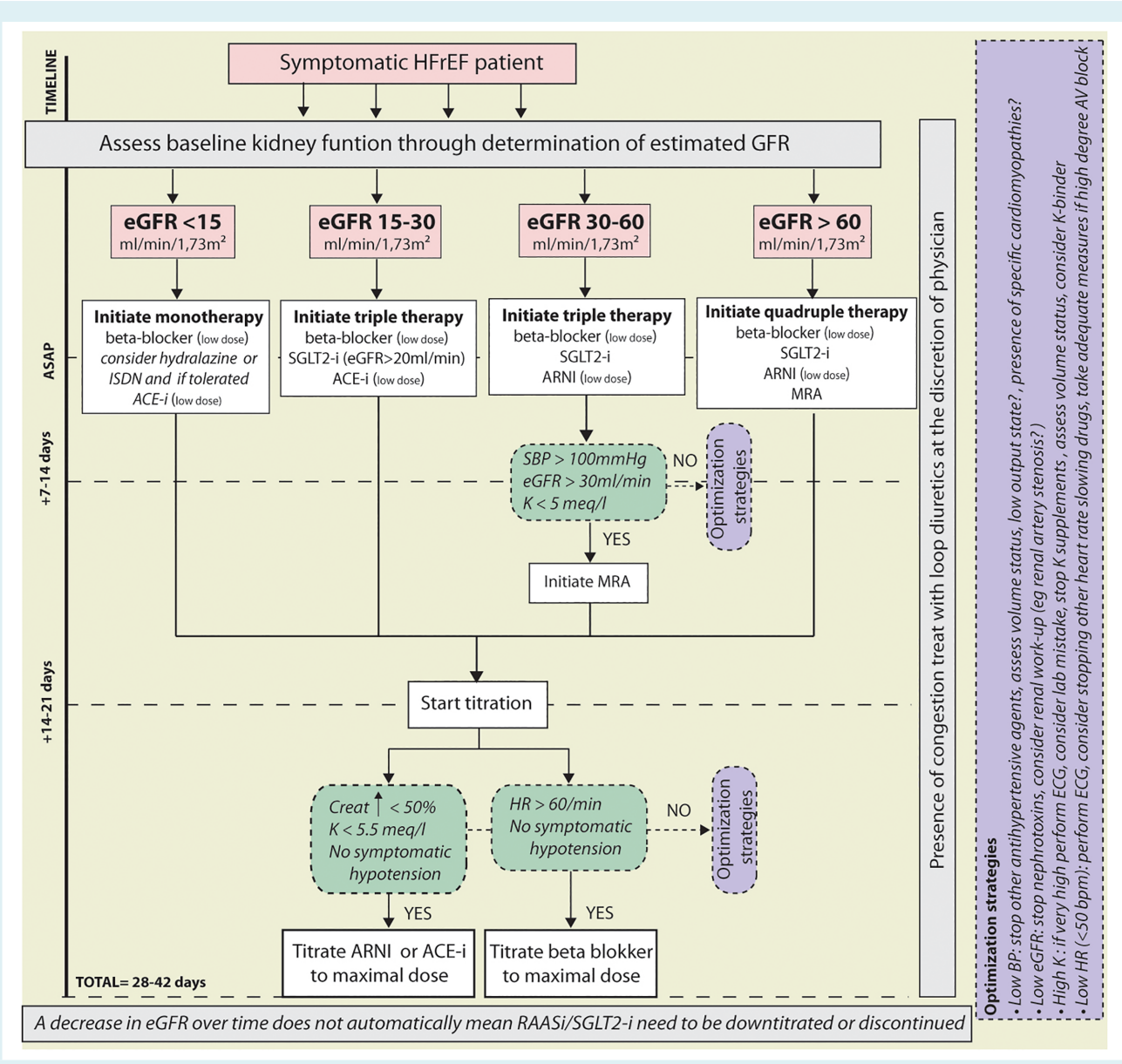


Figure 3 Renal-based approach to initiation and titrating of multilevel guideline-directed medical therapy (GDMT). Proposed flowchart for titrating GDMT in the setting of chronic kidney disease. During titration the lower threshold of blood pressure should be individualized based on the presence of activity limiting hypotension rather than pure blood pressure values itself. ACE-i, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; AV, atrioventricular; BP, blood pressure; Creat, creatinine; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HR, heart rate; ISDN, isosorbide dinitrate; K, potassium; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SBP, systolic blood pressure; SGLT2-i, sodium–glucose cotransporter 2 inhibitor.

not associated with a diminishment in treatment effect of these agents. Therefore, practice guidelines and a previous position paper from this working group propose to tolerate an increase of serum creatinine up to 50% if serum creatinine remains below 3.00 mg/dl and eGFR above >25 ml/min/1.73 m^2 when titrating ACE-I/ARB/ARNI. Surely, close monitoring of such patients is warranted. In contrast, only if serum creatinine rises by >50% or above 3.5 mg/dl treatment should be discontinued with re-challenge when possible (e.g. after treatment of other predisposing factors such as infection, hyper/hypovolaemia, blood loss/anaemia, etc.). Next to changes in renal function, hyperkalaemia is a frequent reason for drug discontinuation. The prevalence differs according to definitions used and ranges from 0.4% to 10% in landmark trials with ACE-I/ARB/ARNI/MRA.[63] Generally, dose reduction of these agents is advised if potassium is between 5.5 mEq/L and 6 mEq/L and temporarily termination if potassium is above 6 mEq/L, with reinstitution of the drug only when the potassium drops below 5.5 mEq/L. The use of new potassium binders

(patiromer and sodium zirconium cyclosilicate) may enable a persistent use of RAAS inhibitors in patients presenting hyperkalaemia, as acknowledged by the latest ESC HF guidelines.[2] Close laboratory assessment is needed when titrating GDMT. In the landmark MRA trials, potassium was checked after 7 days (and again after 72 h if dose reduction was needed as described above). In the ACE-I/ARB/ARNI and SGLT2 inhibitor trials, laboratory assessment of creatinine, urea, eGFR and electrolytes was typically done after 14 days during drug titration and every 4 months thereafter. However, in clinical practice, individualization according to the KDIGO stage should be considered, with more frequent analysis in CKD stage 5 or stage 4 with macro-albuminuria. Nevertheless, contemporary data illustrate that such frequent laboratory follow-ups are hardly performed in clinical practice.[126,127]

Figure 3 provides a proposed scheme suggested by this working group for initiating and titrating quadruple therapy, taking into account important cardio-renal elements.[125] Several other elements underscoring the importance of simultaneous titration include the difference in mode of action, the early incurred benefit on hard endpoints, and the already achieved effect even in low doses. In addition, certain drugs enhance tolerability of others. For instance, hyperkalaemia occurred less frequently in patients receiving ARNI in the PARADIGM-HF trial or dapagliflozin in the DAPA-HF trial.[8,111] Therefore, combining several drugs leads to larger improvement in endpoints than sequential uptitration of individual classes.

Finally, while most evidence for quadruple therapy is derived from trials in HFrEF, secondary analysis have also confirmed the effectiveness of these agents in HFmrEF and dedicated trials such as TOPCAT, PARAGON-HF and EMPEROR-Preserved indicate the potential role of MRA, ARNI and SGLT2 inhibitors in the setting of HFpEF. Many patients with HFpEF will also require a beta-blocker for rate control in atrial fibrillation. Therefore experience with titrating quadruple therapy might also be important beyond HFrEF also in HFmrEF and HFpEF.

Conclusion

Chronic kidney disease is common in HF and numerous of the pathophysiologic processes in HF coincide with the progress of CKD. Kidney dysfunction is the most important reason that GDMTs are incompletely implemented. A better understanding of the impact of GDMT on indices of kidney function will help to understand the incurred renal benefits of these agents which hopefully enhances the penetration of these life-saving therapies in a broader population of HF patients.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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