Heart failure in chronic kidney disease

Dr Shirin Meshkinfar
nephrologist

HF and CKD represent concurrent chronic disease epidemics.
Both conditions have increasing incidence and prevalence in:

- older age
- hypertension
- diabetes mellitus
- cardiovascular
- kidney disease risk factors

having both conditions increases the risk of hospitalization, rehospitalization, need for intensive care or kidney replacement therapy, and death

patients with HF and CKD may fail to respond as predicted to conventional therapies or experience increased toxicity to them

DEFINITIONS

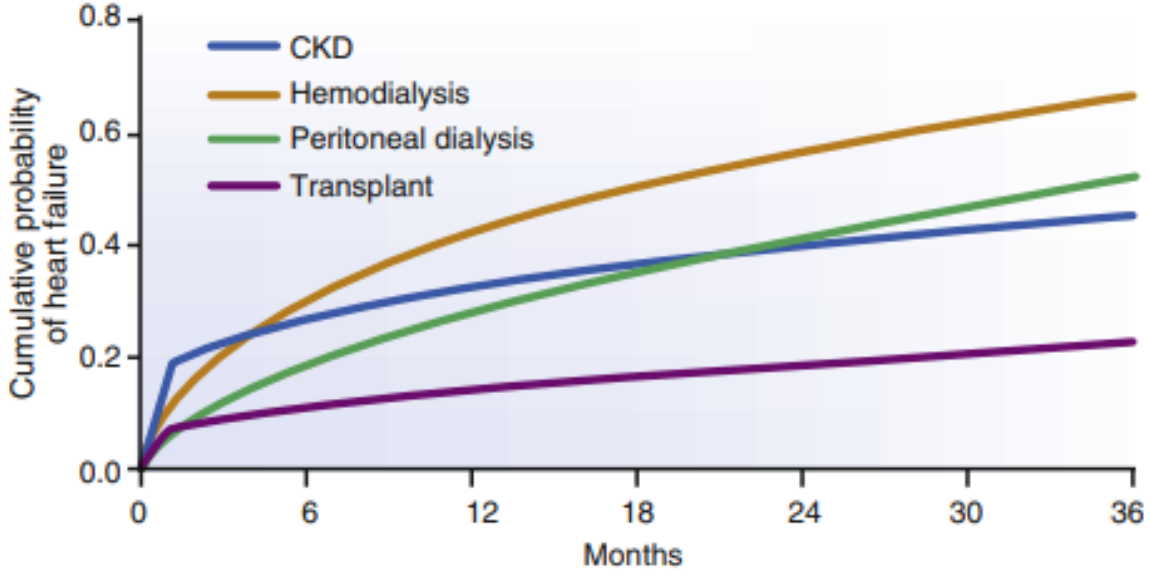
The 2016 European Society for Cardiology guidelines for managing HF define it on the basis of signs and symptoms owing to structural and/or functional cardiac abnormalities.
Subsets of HF include:

- preserved ejection fraction,>= 50% (HFpEF)
- reduced ejection fraction,< 40%(HFrEF)
- mid-range ejection fraction, 40% to 49% (HFmrEF)

CKD is defined on the basis of persistently reduced estimated glomerular filtration rate (eGFR) of <60ml/min per 1.73 m2 or at least 1 marker of kidney damage for > 3 months

EPIDEMIOLOGY

The incidence of de novo HF in known CKD is in the range of 17% to 21%. The emergence of HF varies depending on the degree of CKD and the modality of kidney replacement therapy, including transplantation



CKD: Incident general Medicare CKD patients, age 66 & older, 2001–2003 combined
ESKD: Incident ESKD patients, age 20 & older
Patients with CHF at baseline excluded. Probabilities unadjusted

Reduced eGFR is associated with increased risk of all-cause mortality, cardiovascular mortality, and hospitalization in patients with HFpEF or HFrEF

Elevated urine albumin is prognostic for HF outcomes, albeit to a lesser extent than reduced eGFR. Both reduced eGFR and albuminuria can develop as a result of HF

HF and CKD occur in a bidirectional fashion with considerable overlap.

- ✓ **The association of CKD with mortality in HFrEF is independent of: age, functional class, duration of HF, hemoglobin, or diabetes mellitus.**

- ✓ **Patients with CKD are less likely to receive guideline-directed medical therapy, likely because of concerns about hypotension, kidney function, and hyperkalemia**

two-thirds of HFrEF cases in the general population are due to ischemic cardiomyopathy and the remainder is due to nonischemic and/or idiopathic cardiomyopathy.

In HFpEF there appears to be a strong influence of age, obesity, diabetes mellitus, and poor fitness.

In 25% of cases of HFpEF in the general population, there is superimposed cardiac ischemia; however, its role in the development of HFpEF is unknown. All-cause mortality in HFpEF with CKD is elevated

PATHOPHYSIOLOGY

In CKD and ESKD, risk factors for HF include:

- long-standing hypertension with often worsened blood pressure (BP) control as CKD worsens

- salt and water retention causing excessive preload
- cardiomyopathic factors including left ventricular (LV) hypertrophy and fibrosis

- CKD- and ESKD-specific factors that affect afterload: increased arterial stiffness and high output shunting through arteriovenous fistulae or grafts

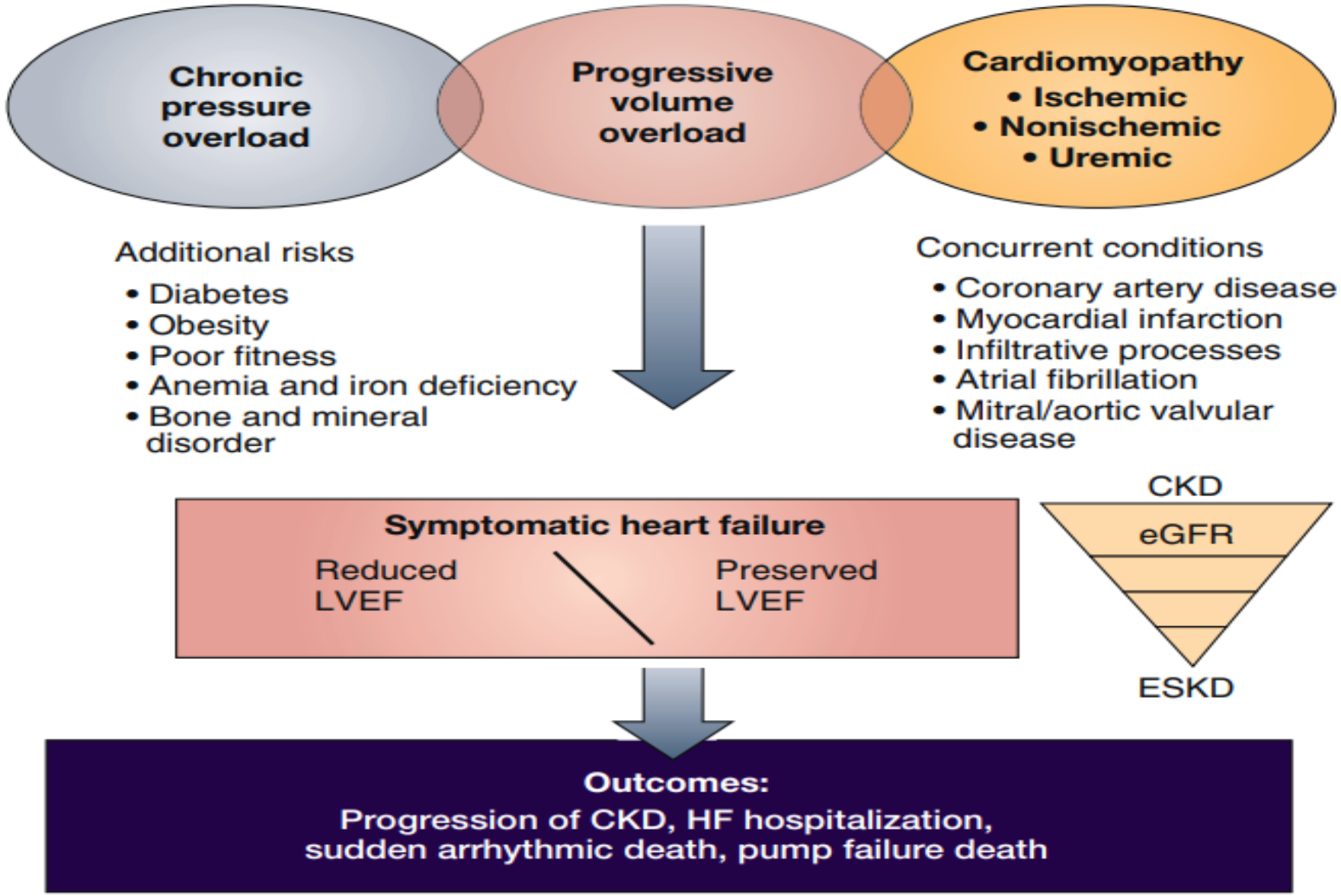
- load-independent factors (neurohormonal activation, impaired iron utilization, anemia, demand ischemia, profibrotic factors [e.g., fibroblast growth factor 23 {FGF-23}], inflammation, etc

➢ Arteriovenous fistulae or grafts:

- worsen right ventricular hypertrophy
- increase pulmonary pressures
- associate with significant right ventricular dilatation
- reduce right ventricular function

which are closely linked to survival

Pathophysiology of heart failure in CKD progressing to ESKD



DIAGNOSIS

- There are no accepted definitions or criteria for HF diagnosis in CKD, and intravascular and extravascular volume overload can occur in the absence of structural heart disease, especially in patients with dialysis-dependent CKD

- Echocardiography can support the diagnosis of HF by providing information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and filling pressures

HFpEF in nondialysis CKD

- As in the general population without CKD, the diagnosis of HFpEF in patients with nondialysis CKD is difficult and should be supported by multiple objective measures including impaired cardiac function with rest and exercise

- Echocardiography with assessment using the American Society of Echocardiography grade of diastolic function (grades 1–4) should be performed.

- Biomarkers such as B-type natriuretic peptide (BNP) or N-terminal pro-BNP have a high negative predictive value.

- ✓ The effect of worsening eGFR on levels of BNP and especially N-terminal pro-BNP relates to both impaired renal clearance and underlying cardiac abnormality

- ✓ Obesity can lead to modestly lower levels of BNP and N-terminal pro-BNP in those with HF

- ➢ **Cystatin C provide better estimates of eGFR than does creatinine because of its relative independence of muscle, hepatic, and dietary contributions of creatinine**

- In critically ill patients, invasive assessment of hemodynamics including measurement of the pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, and LV end-diastolic pressure may be required to distinguish HFpEF from other diagnoses such as obesity-associated deconditioning, primary pulmonary hypertension, high output from arteriovenous shunting, and lung disease

- Cardiopulmonary stress testing with measurement of the peak oxygen consumption can be a helpful for assessing the degree of functional impairment and discerning between cardiac and pulmonary dyspnea.

HFrEF in nondialysis CKD

The diagnosis of HFrEF in the population with nondialysis CKD parallels that of the population without CKD.

Monitoring of HFrEF in CKD includes the usual standards of care:

- evaluating sodium, potassium, creatinine (eGFR), albumin-to-creatinine ratio, BNP or N-terminal pro-BNP, troponin I or T, and galectin-3 levels
- some select cases may justify advanced physiological measurements such as pulmonary artery pressure monitoring and/or bioimpedance techniques.
- Changes in volume status can be detected on physical examination, chest radiography, and lung ultrasonography.

HFpEF or HFrEF in dialysis-dependent CKD

- In patients on dialysis, symptoms typical of HF, such as paroxysmal nocturnal dyspnea, orthopnea, dyspnea, fatigue, ascites, and dependent edema, may be intermittent
- It is important to consider other causes of dyspnea, such as chronic obstructive pulmonary disease, pulmonary hypertension, anemia, or obstructive sleep apnea.
- Patients with dialysis-dependent HF should undergo the same evaluation as patients with nondialysis-dependent HF
- In the setting of dialysis, the role of natriuretic peptides is unclear.
- Newly discovered HFrEF in patients undergoing dialysis should prompt full risk stratification for an ischemic versus nonischemic etiology

there may be additional evaluation or considerations for dialysis-dependent patient:

Chest radiograph :

- radiographic signs are specific but only moderately sensitive in diagnosing HF.
- The chest radiograph can be used to screen for other sources of dyspnea, such as pulmonary and diaphragmatic abnormalities.
- Prompt resolution of radiographic findings of interstitial infiltrates after dialysis and/or ultrafiltration supports extracellular fluid overload as a cause of signs and symptoms of HF.

Echocardiography:

- Measurements of LV ejection fraction, LV hypertrophy, right ventricular ejection fraction, chamber dimensions, and valvular function are fundamental in managing ESKD

when possible, imaging should be carried out when patients on dialysis are close to dry weight, and preferably on a nondialysis day for patients on hemodialysis

- indicators for LV dysfunction include: reduced LV ejection fraction, LV diastolic volume index of >86 ml/m2 or LV systolic volume index of >37 ml/m2 .

Electrocardiography:

- Electrocardiography can be used to detect rhythm disturbances or evidence of prior myocardial damage or pericardial disease.

TREATMENT

Prevention of incident HF

Hypertensive and glycemic control

- ✓ **Tight BP control, defined as targeting systolic BP to< 120 mm hg, reduces incident HF with LV ejection fraction >=35%,even in the presence of CKD.**
- ✓ **In patients with CKD and diabetes, poor glycemic control is a risk factor for developing HF and improved glycemic control is associated with a reduced risk of HF**

- In the RENAAL (Reduction in End Points in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) diabetic nephropathy trial, a risk reduction of 32% was observed for the first hospitalization for HF in the losartan patient group versus the placebo group

Clinical Trial › N Engl J Med. 2001 Sep 20;345(12):861-9. doi: 10.1056/NEJMoa011161.

Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy

B M Brenner [1], M E Cooper, D de Zeeuw, W F Keane, W E Mitch, H H Parving, G Remuzzi, S M Snapinn, Z Zhang, S Shahinfar, RENAAL Study Investigators

sodium glucose cotransporter 2 inhibitors have been shown to not only slow the progression of CKD in such patients but also reduce the risk of hospitalizations for HF in both those with and without a history of HF

Whether glycemic control has a direct effect in preventing HF is unclear, as sodium-glucose cotransporter 2 inhibitors also lead to reductions in BP and body weight, promote diuresis, and have strong off-target effects on the cardiac Na/H exchanger.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D. for the EMPA-REG OUTCOME Investigators

November 26, 2015
N Engl J Med 2015; 373:2117-2128
DOI: 10.1056/NEJMoa1504720

In the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study, empagliflozin resulted in a 39% relative risk reduction in hospitalization for HF in patients with type 2 diabetes mellitus and CKD G3a or higher and/or urine albumin-to-creatinine ratio >300 mg/g

A similar effect was seen with canagliflozin and dapagliflozin

Randomized Controlled Trial > Circulation. 2018 Jan 9;137(2):119-129.
doi: 10.1161/CIRCULATIONAHA.117.028268. Epub 2017 Sep 13.

Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease

Christoph Wanner [1], John M Lachin [2], Silvio E Inzucchi [3], David Fitchett [4], Michaela Mattheus [5], Jyothis George [5], Hans J Woerle [5], Uli C Broedl [5], Maximilian von Eynatten [5], Bernard Zinman [6], EMPA-REG OUTCOME Investigators

Affiliations + expand

PMID: 28904068 DOI: 10.1161/CIRCULATIONAHA.117.028268

Treatment of existing HF

- ✓ There are no proven treatments for HFpEF, including in the setting of CKD
- ✓ it cannot be assumed that drugs with proven efficacy in HFrEF have the same benefits in HFpEF
- ✓ Therapy for HFrEF can cause eGFR to vary, so when eGFR declines from >60 to<60 (i.e., CKD G3a or higher) it can be unclear if this truly represents CKD versus a transient decline due to hemodynamic and neurohormonal factors.
- ✓ Identification of true kidney injury versus transient azotemia would dramatically aid in decisions on diuretics and other agents in goal-directed medical therapy

Medications that can reduce adverse outcomes associated with HFrEF include:

- **angiotensin converting enzyme inhibitors (ACEis)**
- **angiotensin II receptor blockers (ARBs)**
- **angiotensin receptor neprilysin inhibitors**
- **b-blockers**
- **mineralocorticoid receptor antagonists (MRAs)**

b-Blockers

it seems reasonable to use b-blockers for managing HFrEF in patients with CKD, except for b-blockers that have significant renal excretion and have the potential for over exposure: atenolol, nadolol, or sotalol.

- ✓ **Atenolol can be used as part of the management approach for hypertension and coronary disease if given 3 times per week in ESKD during hemodialysis.**

- ✓ **consideration should be given to the potential for dialyzability of certain b-blockers, as a 1.4-fold increased mortality risk was observed in the group treated with highly dialyzable b-blockers such as metoprolol.**

Angiotensin blockade

- Both ACEis and ARBs can lead to decreased GFR in patients with HFpEF or HFrEF

- ARBs can be considered for those who are ACEi intolerant

- The superiority of captopril was maintained in patients with CKD. Other trials of ACEis and ARBs reported similar results in patients with CKD

- **The angiotensin receptor neprilysin inhibitor LCZ696(sucabitril valsartan sodium hydrate) has also demonstrated a hemodynamic effect in preserving GFR, with 1 study reporting smaller eGFR decline in patients with HFpEF on LCZ696 versus valsartan after 36 weeks of treatment.**

- **urinary albumin-to-creatinine ratios showed increases with LCZ696 versus valsartan**

✓ **Azotemia alone in the setting of diuresis should not necessarily result in changes to or withdrawal of ACEis or ARBs because their removal may lead to worse outcomes**

Diuretics

- Thiazide diuretics are a mainstay of BP control in the general population and commonly advanced to loop diuretics in the setting of CKD

- Important considerations in patients hospitalized for decompensated HF on a twice daily, chronic oral loop diuretic regimen include (i) dosing, (ii) duration, and (iii) whether to change from oral to i.v

- Increased i.v. doses of furosemide and continuous infusions may be used to relieve congestion.

- **The Diuretic Optimization Strategies Evaluation (DOSE-AHF) study demonstrated that a high-dose strategy could improve dyspnea scores, weight change, and net fluid loss at 72 hours whereas a low-dose group was less likely to convert from i.v. to oral and more likely to require a dose increase**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 3, 2011 VOL. 364 NO. 9

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O'Connor, M.D., for the NHLBI Heart Failure Clinical Research Network*

There was an increased frequency of early increased serum creatinine level of >=0.3 mg/ dl in the high-dose group, but no appreciable difference in kidney function over 60 days between any of the study groups.

- **Torsemide may have an advantage over furosemide, with longer half-life, better bioavailability, and potential for reducing myocardial fibrosis**

MRAs

patients randomized to the highest dose of finerenone experienced
a decrease in the secondary composite endpoint of death, cardiovascular hospitalization, or emergency department visit for worsening HF without worsening hyperkalemia or kidney function.

European Heart Journal (2016) **37**, 2105–2114
doi:10.1093/eurheartj/ehw132

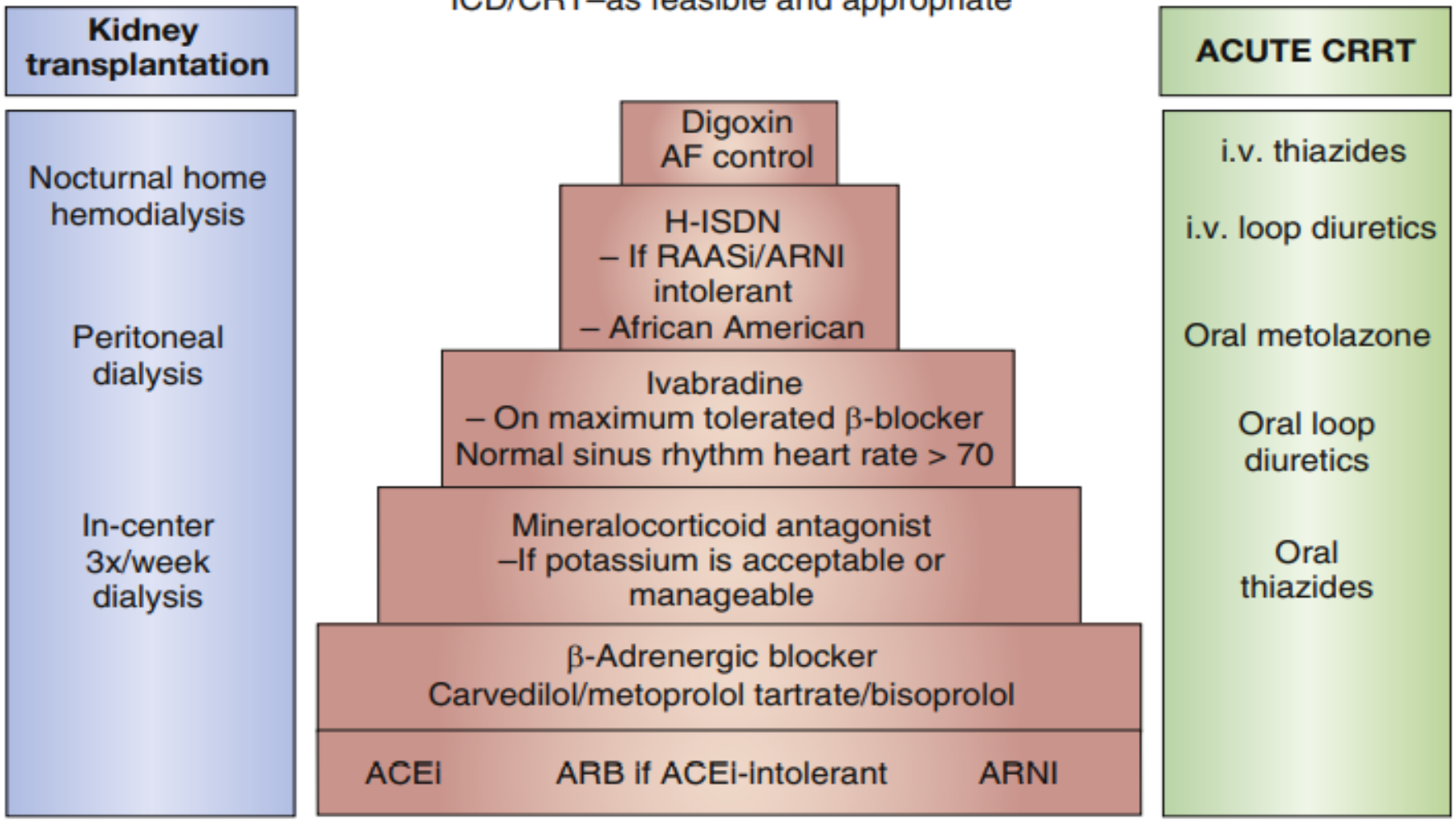
FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease

Gerasimos Filippatos[1]*, Stefan D. Anker[2], Michael Böhm[3], Mihai Gheorghiade[4], Lars Køber[5], Henry Krum[6†], Aldo P. Maggioni[7], Piotr Ponikowski[8], Adriaan A. Voors[9], Faiez Zannad[10], So-Young Kim[11], Christina Nowack[11], Giovanni Palombo[12], Peter Kolkhof[13], Nina Kimmeskamp-Kirschbaum[14], Alexander Pieper[15], and

Other considerations

Avoid AKI (e.g., radiocontrast, NSAIDs, aminoglycosides, vancomycin, lithium)
Treat iron-deficiency anemia
Treat vitamin B and thiamine deficiencies
Optimize CKD-MBD measures
ICD/CRT–as feasible and appropriate



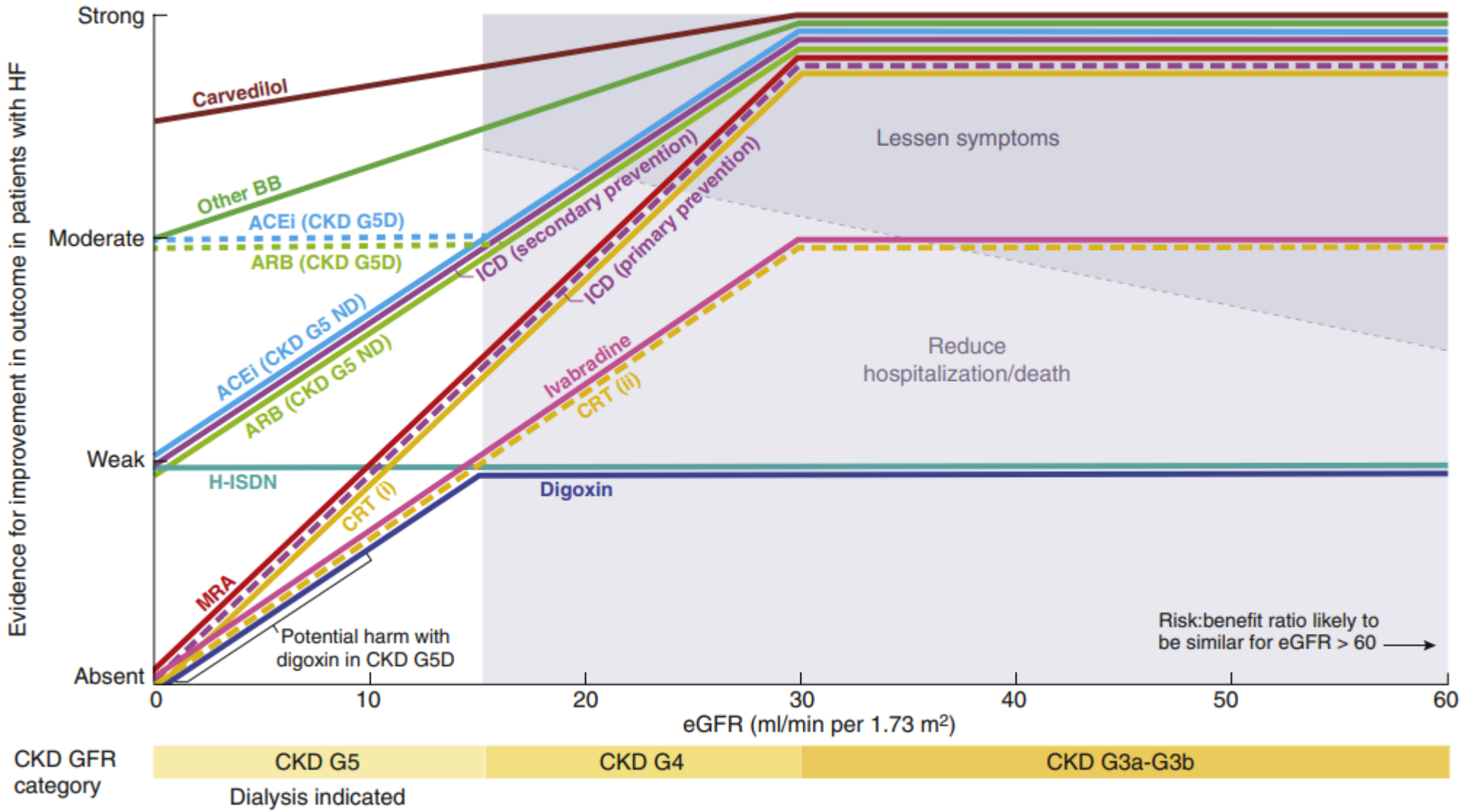
LV assist devices

- Renal dysfunction is common in patients referred for mechanical circulatory support (MCS)
- there are no diagnostic tests to distinguish irreversible from reversible forms of renal dysfunction in such patients
- most patients, experience early improvement in kidney function with MCS, this improvement is often transient
- Venous congestion, right ventricular dysfunction, and reduced pulsatility are potential mechanisms involved in resurgence of renal dysfunction after MCS.

there is no clearly preferred method of kidney replacement therapy in MCS

- ✓ **peritoneal dialysis :has advantages in MCS and non-MCS HF with sustained daily ultrafiltration, fewer volume-related preload issues, home accessibility, and reduced cost.**

- ✓ **Patients with ESKD undergoing MCS have significantly worse outcomes than do those without ESKD**



CRT (i) = QRS > 120 ms, LBBB QRS morphology, EF ≤ 35%
or QRS > 130 ms, EF ≤ 30%
CRT (ii) = QRS > 150 ms

Loop diuretics (p.o./i.v.) (furosemide, bumetanide, torsemide) and thiazide diuretics (metolazone [p.o.], chlorothiazide [i.v.]) = benefit uncertain

Adjunctive and emerging approaches

- ✓ improved diagnosis and treatment of sleep apnea, obesity management, nutrition management, physical activity, sodium restriction (and possibly fluid restriction), may be helpful in reducing symptoms and improving functioning for patients with HF and CKD.

- ✓ In the setting of atrial fibrillation, permissive rate control and cardioversion are reasonable strategies

Treatment of CKD-related conditions and dialysis

Iron deficiency and anemia

- Erythropoiesis-stimulating agents have no effect on the prevention or treatment of HF in patients with CKD.
- for patients with chronic HF and iron deficiency with or without anemia, treatment with i.v. ferric carboxymaltose improves symptoms, functional capacity, and quality of life.
- hospitalizations for HF and mortality were significantly decreased in the iron-treated group
- Patients with HF and CKD can be considered for receiving parenteral iron given the proven safety record in patients with advanced CKD

Mineral and bone disorders

- ✓ cinacalcet treatment has been associated with modest reductions in the time to first episode of HF in patients on hemodialysis

Macro- and micronutrients

- ✓ Maintenance of lean tissue through adequate macronutrient intake of protein, essential amino acids, and essential fatty acids is viewed as desirable, and adequate levels of micronutrients including water- and fat-soluble vitamins, trace minerals, and cofactors are also considered to be important

Mode of dialysis

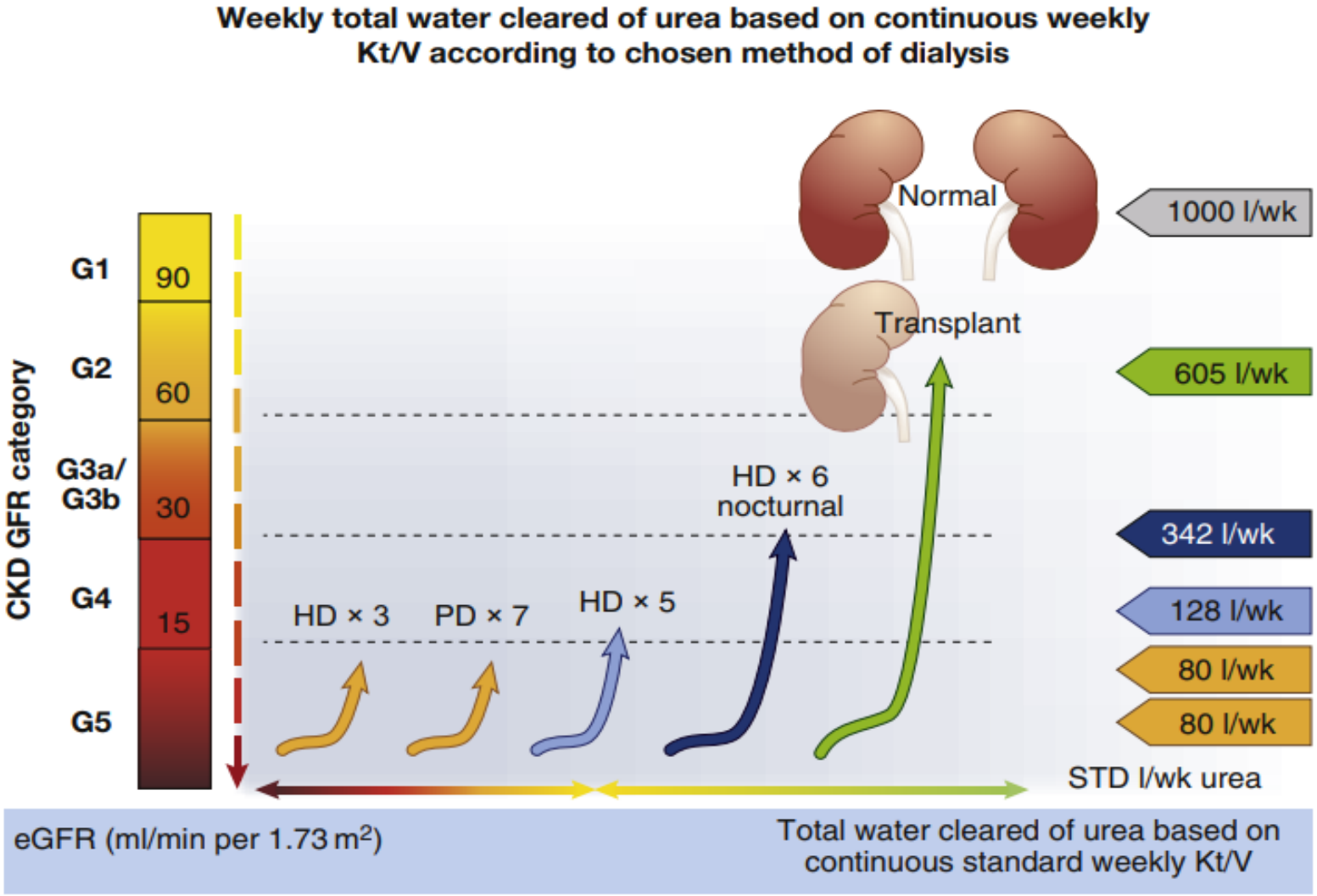
There are no studies of interventions that use the development of de novo HFrEF or HFpEF as an outcome in the population on dialysis

It has not been feasible to randomize patients to modality type

Increasing the frequency of dialysis sessions, as in short daily hemodialysis, reduces LV mass and lowers the risk of cardiovascular death and hospitalizations.

Patients under going home dialysis have a markedly reduced risk of hospitalization for HF and cardiovascular mortality (41% lower risk of HF, fluid overload, and cardiomyopathy).

home nocturnal hemodialysis 6 times per week is next best after kidney transplantation and normal functioning kidneys for clearance of urea from water



- Recurrent dialysis-induced ischemic injury is associated with regional wall motion abnormalities and the development and worsening of HF, and therefore conditions of the dialysis treatment itself may influence HF

- Evidence from a small study suggests dialysate cooling may slow the progression of hemodialysis-associated cardiomyopathy by reducing recurrent ischemic injury.

- there are no RCTs to inform the benefits of peritoneal dialysis versus hemodialysis.

- **Management of the sodium concentration in dialysis solutions requires careful consideration in dialysis dependent patients with HF, as it may present an additional sodium load**

- **residual kidney function are desirable, as this can mitigate some of the significant hemodynamic and fluid shifts that occur with volume removal during dialysis**

PATIENTS WITH A KIDNEY TRANSPLANT

Incidence and prevalence of HF in recipients of kidney transplant

- ✓ The prevalence of HF/LV systolic dysfunction in patients referred or wait-listed for transplantation may be as high as 25%
- ✓ HF at the time of transplantation is associated with a higher risk of mortality, cardiovascular events, and graft failure.

Several risk factors like:

- ✓ increased age
- ✓ Sex
- ✓ Increased BMI
- ✓ CVD before KTx
- ✓ MI after KTx
- ✓ Smoking history
- ✓ Diabetes
- ✓ Anemia
- ✓ Hypoalbuminemia
- ✓ Increased duration of dialysis before KTx
- ✓ Deceased donor kidney
- ✓ Increased donor age
- ✓ Graft failure, allograft rejection

have been shown to be associated with clinical HF after transplantation .De novo HF is also associated with lower graft survival.

Diagnosis and screening of HF in recipients of kidney transplant

- ✓ There is little or no evidence of whether to obtain a screening echocardiogram to assess LV function for all transplant candidates.
- ✓ it is reasonable to obtain an echocardiogram if there are symptoms of HF, history of cardiovascular disease, or hemodynamic instability on dialysis
- ✓ The approach to de novo HF in transplant recipients is the same as that for the general population, including evaluation for coronary artery disease.

HF treatment in recipients of kidney transplant

- ✓ transplant recipients with HF should be treated as they would be treated in the general population.
- ✓ In some patients with a kidney transplant, management of HF is complicated by persistent, severe hyperkalemia, which may prevent the use of ACEis, ARBs, and MRAss
- ✓ concern about reduction in eGFR should not automatically lead to withholding of otherwise beneficial treatments of HFrEF.

A unique exacerbating factor may be the ongoing presence of an "unnecessary" arteriovenous fistula.

the ligation of which should be considered:

- ✓ **in recipients with symptoms of HF**
- ✓ **a high cardiac output hemodynamic profile**
- ✓ **high arteriovenous fistula flow (1.5–2.0 l/min and arteriovenous fistula flow > 30% cardiac output).**

Effects of kidney transplantation on cardiac structure and function

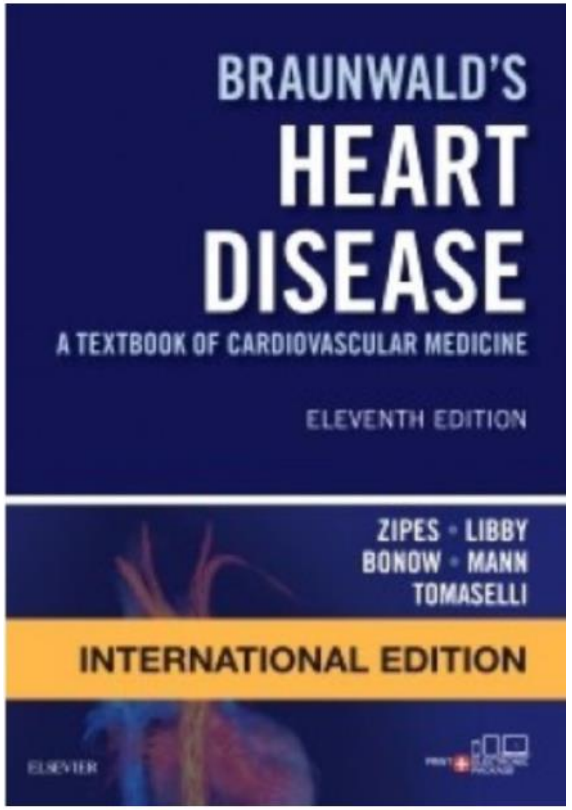
- ✓ Reports have documented reversal of clinical cardiac dysfunction and improvement in echocardiographic parameters after kidney transplantation, supporting the notion of a potentially reversible “uremic cardiomyopathy
- ✓ Reversal is less likely in patients who have been dialyzed for long periods of time
- ✓ Transplant candidates should thus not be excluded solely on the basis of LV systolic dysfunction and, in some circumstances, should be considered for priority wait-listing

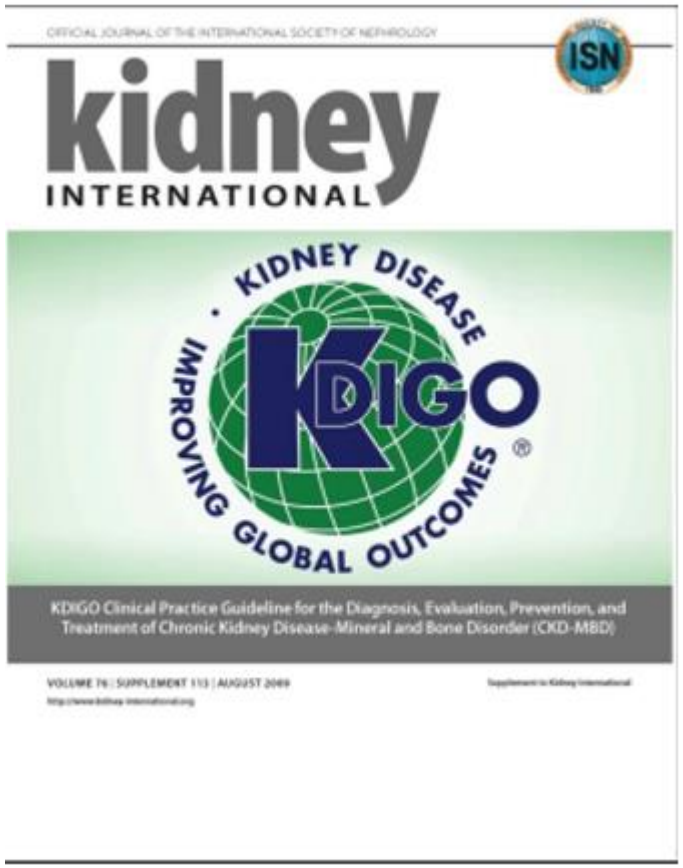
Simultaneous kidney-heart transplant

- **Patients with severe HF who are dependent on chronic dialysis may benefit from a simultaneous kidney-heart transplant.**

In an analysis of U.S. registry data, 5-year post transplant survival was higher in dialysis-dependent patients with end stage HF who received a simultaneous kidney-heart transplant compared with heart transplant alone

Refrence:





e KDIGO website http:// kdigo.org/conferences/heart-failure-in-ckd


THANK YOU