Heart failure treatments for patients with advanced renal impairment: the tide is not turning

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ABSTRACT

Introduction: Even though advanced chronic kidney disease (CKD) frequently aggravates heart failure (HF), these patients have traditionally been excluded from the majority of HF trials. We aim to provide updated estimates of the representation of patients with advanced CKD and the provision of indices of baseline renal function in HF randomized trials in general and landmark HF trials in particular.

Methods: Updated systematic review of MEDLINE (via PubMED) from inception to 31st December 2019 looking for randomized controlled trials on chronic HF published in the top three medical and cardiology journals and providing data on all-cause or cardiovascular mortality. Analyses conducted to assess the representativeness of advanced CKD patients from HF trials over time and the reporting of baseline renal function.

Results: 184 randomized trials with 320,906 participants included in this analysis. A total of 103 trials (60%) had exclusion criteria related with baseline renal function, which persisted over time - seen in 55.1% (27 of 49) of trials published from inception to 2000, 53.4% (39 of 73) in those published from 2001 to 2010 and 61.3% (38 of 62) of trials from 2011 (p=0.64). However, criteria for exclusion based on renal function have gradually become less restrictive. The more recent trials were more likely to provide indices of baseline renal function (28.6% from inception to 2000 versus 53.4% from 2001 to 2010 and 82.3% from 2011, p<0.001). Similar findings were observed when restricting these analyses to landmark HF randomized trials.

Conclusions: Patients with severe renal impairment remain underrepresented from HF trials even in modern days, although criteria have become less restrictive over time and the quality of renal function monitoring has gradually improved. Studies specifically designed

and executed in HF patients with impaired renal function and addressing evidence-based treatments and strategies are warranted.

INTRODUCTION

There is a well-documented association between chronic kidney disease (CKD) and heart failure (HF) (1). The presence of one condition accelerates the presentation and progression of the other, with worsening renal function negatively impacting on the prognosis of patients with HF (2) often described as the cardio-renal syndrome. In addition, HF treatments can affect renal function in a variety of ways. In patients with both HF and CKD, it may not be possible to reach target doses of guideline-directed medical therapy, resulting in failure to achieve the maximum prognostic benefit from these medications, while toxicity may be more likely to occur.

This intrinsic relationship between HF and CKD underscores the importance of studies on the treatment of HF patients who also have or develop CKD, but it is acknowledged that patients with severe renal dysfunction have in general been excluded from most of the landmark randomized HF studies. Although previous authors have encouraged greater enrolment of patients with CKD in HF trials, persistent exclusion of these patients from HF trials has been reported in three previous systematic reviews (3–5), the two most recent providing an update among clinical trials published between 2006 and 2013/14 in top medical journals (3,4). Reasons for the underrepresentation of severe CKD patients in HF trials include the anticipated difficulty in patient recruitment and retention, the potential for reduced treatment effect or increase in side effects, and, most importantly, the issue of competing risks of mortality. Heart failure trials are less likely to provide prognostic benefit in patients at much higher risk of noncardiovascular mortality despite cardiovascular death continuing to be the most common mortality cause in CKD patients. As a result, trialists and sponsors may quite understandably have concerns that the resulting

"dilution" of the overall treatment effect by competing mortalities may either deem a treatment not effective or would increase the costs of a trial.

The best treatment approaches for patients with CKD have remained therefore uncertain, and current ESC guidelines reflect the lack of evidence in patients with moderate to several renal dysfunction in their cautious recommendations ("An ACE inhibitor should only be used in patients with adequate renal function (creatinine ≤221 mmol/L or ≤2.5 mg/dL or eGFR ≥30 mL/min/1.73 m2) and a normal serum potassium level"), while highlighting the need for more data on this specific patient population.

We aim to provide updated estimates of the representation of patients with advanced CKD and the provision of indices of baseline renal function in HF randomized trials in general and landmark trials in particular.

METHODS

We performed an updated systematic review of MEDLINE (via PubMED) from inception to 31st December 2019 looking for HF randomized controlled trials published in the top three medical and three cardiology journals as ranked by impact factor. These included the *New England Journal of Medicine*, *The Lancet*, the *Journal of the American Medical Association*, the *European Heart Journal*, *Circulation* and the *Journal of the American College of Cardiology*. It was thought that these six journals would have included the overwhelming majority of HF trials published from inception until modern days, including all of the landmark trials. For validity purposes, the latest American and European guidelines on the management of chronic HF patients were also carefully assessed to look for randomized studies which were not identified by the original search (6,7).

Studies were included if they **(i)** focused on chronic HF, including acutely decompensated HF patients, or post-myocardial infarction patients with severe left ventricular systolic dysfunction, **(ii)** reported all-cause or cardiovascular mortality data and **(iii)** provided a minimum follow-up duration of 6 months. Exclusion criteria included the absence of mortality data, studies on acute HF patients with no previous history of HF, follow-up duration of less than 6 months and post-hoc analyses of randomized trials.

The following data was extracted from each study: publication year, trial design with exclusion criteria, exclusion threshold of patients with CKD, primary endpoint results and data on all-cause or cardiovascular mortality, demographics, heart failure severity, mean left ventricular ejection fraction, patient comorbidities, indices of baseline renal function and medication. A group of so-called “landmark trials” were selected for a separate analysis. Landmark trials were defined as those with the largest impact on guideline recommendations and daily clinical practice in the field of HF. Three investigators (SB, RD and RP) independently performed this selection from the complete list of trials. For a study to be considered a “landmark trial”, it had to be selected by at least two investigators.

For each study, we obtained the total length of follow-up in patient-years and the number of all-cause deaths (whenever available) in control groups and then calculated the rate of mortality per 100 patient-years of follow-up. Studies providing data only on cardiovascular mortality were excluded from this analysis. The association between year of publication and all-cause mortality rates in control groups was assessed according to the presence or absence of criteria for exclusion based on renal function. This analysis was performed using SPSS v.26 and carried out through linear regression modelling using weighted least squares, such that larger studies, as determined by the total number of patient-years of follow-up, were given greater weight in determining the regression

coefficients. Trend line graphs were subsequently constructed in Microsoft Excel 2013 to illustrate the change in mortality rates over time, according to the presence or absence of exclusion criteria.

We conducted analyses to answer 5 different questions: **First**, has there been a change in the underrepresentation of advanced CKD patients from HF trials over time? **Second**, has there been an increase in the reporting of baseline renal function in HF trials? **Third**, what were the results of sub-group analyses based on renal function in landmark HF trials? **Fourth**, were the mortality rates of studies excluding advanced CKD patients significantly different from those where these patients were not excluded? **Finally**, were there significant differences in average baseline renal function between trials excluding versus those not excluding advanced CKD patients, as would be expected?

RESULTS

Our analysis included a total of 184 randomized trials (8–191) (**supplementary table**), of which 23 were manually retrieved from the latest European or American HF guidelines (169–191) (**Figure 1**). These studies included 320,906 participants, corresponding to approximately 756,349 patient-years of follow-up. A total of 103 trials (60%) had exclusion criteria related to baseline renal function (9,11,14,15,18,20–22,24,25,27,28,31–33,35–38,40,44,45,47,49–60,64,65,69–71,76–79,82,84–89,91,92,94–98,100,101,106–108,110,111,116,120,124,126,127,129,132,134,136–139,141,144,147,149–151,153–157,161,163,164,166,167,170–172,179,182,185,186,188,190,191), of which the most common was the exclusion of patients with an estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2 (seen in 35 trials). Patient exclusion based on specific renal markers has persisted over time (**Figure 2**) - seen in 55.1% (27 of 49) of trials published from inception to

2000, 53.4% (39 of 73) in those published from 2001 to 2010 and 61.3% (38 of 62) of trials from 2011 (p=0.64). **Table 1** lists all renal parameters used as exclusion criteria in these 103 trials. There were an additional 18 trials with exclusion criteria which would have led to the exclusion of patients with more advanced CKD, particularly those with end-stage renal failure, although a specific renal threshold was not given (e.g. *"any other conditions thought to limit survival or ability to participate in a long-term trial"*, "*coexisting noncardiac disease resulting in a life expectancy of less than 3 years", "concomitant serious disease"* or *"life-limiting comorbidity")* (**table 1**). Although criteria for exclusion based on renal function persisted over time, they have, however, become gradually less restrictive – three fourths (9 of 12) of studies excluding only those patients with end-stage renal disease on chronic dialysis were published between 2014 and 2019 (22,25,31,40,45,64,90,94,98,116,136,167); moreover, 5 out of 6 studies excluding patients with estimated GFR or creatinine clearances below < 25 mL/min/1.73 m^2 or 15 ml/min, respectively, were published since 2014 (47,87,89,110,127,137), and the more restrictive criteria of estimated GFR < 30 mL/min/1.73 m^2 was seen most often in the first half of this study (25 out of the 35 studies with this exclusion criteria) (11,14,20,21,33,35–37,44,52–60,65,70,71,82,85,86,91,92,101,106,108,120,141,147,151,154,163,166) (**Figure 3**). Conversely, more recent trials were more likely than older ones to provide indices of baseline renal function such as mean/median serum creatinine or creatinine clearances, or proportion of patients allocated to each CKD severity stratum (28.6% from inception to 2000 versus 53.4% from 2001 to 2010 and 82.3% from 2011, p<0.001) (**Figure 2**). The average renal function in studies providing baseline indices was better in trials with compared with those without exclusion criteria, but the differences were smaller than expected (mean creatinine 110.3 vs. 118.7 µmol/L, p=0.049; mean eGFR 65.8 vs 58.2 mL/min/1.73 m^2,

p=0.026). All-cause mortality rates in control groups were similar between studies with versus those without exclusion criteria (**Figure 4**). There was a small trend towards a reduction in all-cause mortality rates over time in studies with exclusion criteria (unadjusted R^2 =0.051, p=0.045), while no such trend was seen in studies without exclusion criteria (unadjusted R^2 =0.024, p=0.20).

Similar findings were observed when restricting these analyses to landmark randomized trials (11,12,14,21,26–29,43–45,53,58,61,67,72,76–79,82,95,96,108,109,125,126,132,134,139,141,147–151,157,158,160,162,163) (**Figure 5** and **table 2**): there was a persistent underrepresentation of advanced CKD patients, but indices of baseline renal function were increasingly reported over time. Exclusion criteria based on renal parameters were seen in 13 of 15 landmark studies of renin-angiotensin system (RAS) inhibitors versus 13 of 25 studies of different drugs or cardiac electronic devices. There was a trend towards a higher prevalence of renal exclusion criteria in landmark trials compared with the remaining studies (67.5% vs. 53.5%, p=0.1), whereas indices of baseline renal function were reported in a relatively similar proportion of cases (50% vs. 58.3%, p=0.35). **Table 2** provides data on the mean renal function of patients included in the 40 landmark trials (whenever provided), while **table 3** includes the results of sub-group analyses based on renal function, which were available for only 14 of the 40 landmark trials. None of these sub-group analyses focused on patients with severe renal dysfunction, with 60 mL/min/1.73 m^2 representing the most commonly used threshold. With the exception of the CONSENSUS trial (82), where patients with more advanced CKD appeared to derive higher benefit from randomisation to angiotensin converting enzyme inhibitors, the effect size was in general similar across subgroups of renal function.

DISCUSSION

Our analysis shows that there has been no significant change in paradigm over the last decades concerning the exclusion of patients with severe renal dysfunction from HF trials, although criteria for patient exclusion have become slightly less restrictive in the contemporary era. Patients with more advanced CKD, particularly those with severe or end-stage renal failure, have been and continue being persistently excluded from HF trials. This is usually the result of specific criteria based on a renal function threshold, but occasionally occurs due to more ambiguous "non-renal" criteria. This contradicts the greater emphasis on patients with CKD in more recent HF guidelines and the call for high-quality data on these patients. It further highlights the fact that clinical decisions on patients with advanced renal impairment are persistently taken from extrapolation of data collected from patient populations with normal renal function or only milder forms of renal dysfunction.

Although we could reasonably speculate that the underrepresentation of severe CKD patients from HF trials could be related to the known contraindications of renin-angiotensin-aldosterone system (RAAS) inhibitors, exclusion based on renal parameters was not restricted to studies specifically assessing these drugs, but rather seen in almost half of all landmark trials on HF devices and drugs other than RAS inhibitors. Several clinical issues arise from this lack of data: **first**, dosing recommendations for CKD patients with HF have to be based on pharmacokinetic modeling rather than indices of safety and efficacy as demonstrated in clinical trials; **second**, beneficial drugs may be withhold from HF patients with CKD on the basis of a paucity of safety data; **third**, the true effect of landmark drugs or cardiac electronic devices on the outcome of HF patients with severe renal impairment remains mostly unknown, with data obtained only from observational studies, which is far from ideal. Examples include the lack of randomized data on the efficacy of angiotensin

converting enzyme inhibitors or implantable-cardioverter defibrillators (ICD) on patients on dialysis. However, there is reasonable evidence from observational data that substantial renal dysfunction should not be a contraindication to the judicious use of RAAS inhibitors in symptomatic HF patients, as long as they have an adequate follow-up plan to careful monitor renal function (192). Furthermore, treatment with RAAS inhibitors has been shown to confer significant renal benefits in patients with diabetic nephropathy, protecting against the deterioration of renal function (193,194). As such, the exclusion of more advanced CKD patients from studies on RAAS inhibitors may not be warranted.

Increased mortality risk from renal impairment appears to be mostly due to death from HF progression (195), with the adequacy of renal function seen as a primary determinant of compensation in patients with heart failure. Renal impairment may mediate worsening HF by enhanced RAS and sympathetic activity and pro-inflammatory stimulus (192). As such, the need for safe and effective HF treatment in patients with advanced CKD cannot be overstated. Some authors have previously come forward with suggestions to overcome the underrepresentation of CKD patients on cardiovascular trials (196). These include **i)** the possibility of exclusion of patients with severe renal dysfunction from the primary efficacy analysis, allowing a separate analysis for this sub-group, **ii)** patient exclusivity extensions, **iii)** the mobilization of patients for increased demand for access to trials on advanced CKD, and **iv)** use of existing infrastructures for reducing the burden of the trial participation on patients. An additional possibility could be the novel registry-based randomized clinical trial concept (197), which involves the use of national registries as online platforms for randomization, case-record-forms and follow-up data. By using the infrastructure of a population-based registry, patient enrolment and data collection would be significantly facilitated and accelerated.

Conversely, our analysis confirms and expands on the findings of a previous systematic review (3) on the heightened focus on the monitoring of kidney function within cardiovascular trials in general and HF in particular, with a reassuring increase in reporting of baseline measures of renal function seen over time, with particular emphasis on the reporting of the eGFR. However, the use of serum creatinine levels for exclusion was still seen in 36 trials (almost as many as the 43 which used eGFR-based criteria), which may seem inappropriate given the availability of superior methods to estimate renal function. This had already been highlighted before (4). Notwithstanding, since January 2015 most of the studies with exclusion criteria used eGFR thresholds for excluding patients or end-stage renal disease (**figure 4**).

Caution is needed not to conclude on the inappropriateness of patient exclusion in each study based on our results, as such analysis was not conducted. Our study has shown that severe CKD patients have been persistently excluded from HF trials over the last four decades, but whether the exclusion was clinically justified is complex and not the purpose of this study. Still, the fact that the average renal function seen in studies without renal exclusion criteria was relatively similar to that seen in studies with exclusion criteria suggests that, even in the former, physicians were still excluding these patients on the basis of ambiguous non-renal criteria or the simple perception that these patients would have reduced likelihood of survival for the duration of trial. This persistent underrepresentation of severe CKD from HF trials remains worrisome and should urge trialists to not only increase the representativeness of severe CKD in future HF randomized studies but also improve and extend outcome analyses to the sub-groups with more advanced renal impairment. The thresholds used over time for sub-group analyses based on renal function, as seen in **table 3**, had in general little value for obtaining outcome data in patients with

severe CKD, as they rarely focused on those who did have severe renal impairment. Moreover, as mortality rates in the control groups were not significantly different between studies with versus those without exclusion criteria, trialists should be reassured that more lenient criteria for patient selection based on renal function may remain a safe approach.

We acknowledge some limitations of our study. We restricted our literature search to six high-impact medical and cardiology journals and it is possible that some randomized studies may have been missed by this search strategy. However, all of the HF landmark trials were identified, and the analysis of the latest European and American HF guidelines further identified the remaining (potentially relevant) trials which had not been identified in the original literature search. Therefore, we are confident our results are generalizable. Also, in our literature search we excluded all trials which did not report data on cardiovascular or all-cause mortality. Although this led to the exclusion of a number of studies with endpoints such as the number of hospitalizations, quality of life, surrogate clinical or echocardiographic measures, our objective was to focus on treatments with the largest potential impact on survival, and trials driving the creation of guideline recommendations. Finally, as there is no formal definition of a landmark trial, our sub-group analysis of landmark trials is limited by some subjectivity in trial selection. This analysis was, however, deemed important as landmark trials are the main drivers of guideline recommendations and it was important to determine if the trends seen in the overall literature were also present.

CONCLUSIONS

Patients with severe renal impairment remain underrepresented from HF trials even in modern days, although criteria have become slightly less restrictive over time and the

quality of renal function monitoring has gradually improved. Studies specifically designed and executed in HF patients with impaired renal function and addressing evidence-based treatments and strategies are required.

FIGURE LEGENDS

Figure 1 – Literature search and study selection.

Figure 2 – Time trends on the utilization of renal function markers as exclusion criteria (top) and the availability of indices of baseline renal function (bottom).

Figure 3 – Distribution of exclusion criteria over time.

Figure 3 - Trend line graphs illustrating the time-trend variation of all-cause mortality rates among heart failure patients included in studies with (left) and without (right) exclusion criteria based on renal function. The area of each circle represents the size of each study, as assessed by the number of patient-years of follow-up.

Figure 5 – Time trends on the utilization of renal function markers as exclusion criteria (top) and the availability of indices of baseline renal function (bottom): analysis restricted to landmark trials (as seen in Tables 2 and 3).

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TABLE 1 – Renal markers used as exclusion criteria, as strictly mentioned in study protocols

	N
eGFR < 30 mL/min/1.73 m^2	35
Serum creatinine > 3.0 mg /dL	14
Patients on dialysis	10
Serum creatinine > 2.5 mg/dL	7
eGFR < 20 mL/min/1.73 m^2	3
Serum creatinine > 250 µmol/L (2.83 mg /dL)	5
Serum creatinine > 3.0 mg /dL or BUN > 70 mg/dL	3
End-stage renal disease/failure *	2
Serum creatinine > 220 µmol/L	2
Serum creatinine > 200 µmol/L	2
eGFR < 40 mL/min/1.73 m^2	1
eGFR < 40 mL/min/1.73 m^2 at screening or eGFR < 35 mL/min/1.73 m^2 at randomization	1
eGFR < 30 mL/min/1.73 m^2 or serum creatinine > 2.5 mg/dL	1
eGFR < 25 mL/min/1.73 m^2 or patients on dialysis	1
eGFR < 20 mL/min/1.73 m^2 or patients on dialysis	1
Serum creatinine > 5.1 mg/dL or dialysis	1
Serum creatinine ≥ 3.5 mg/dL or renal replacement therapy	1
Serum creatinine ≥ 3.0 mg/dL or chronic haemodialysis	1
Serum creatinine ≥ 3.0 mg /dL	1
Serum creatinine > 2.7 mg/dL	1
Serum creatinine > 2.5 mg/dL or BUN > 50 mg/dL	1
Serum creatinine > 2.49 mg/dL	1
Serum creatinine > 265 µmol/L	1
Serum creatinine > 221 µmol/L	1
Serum creatinine > 130 µmol/L	1
Patients on dialysis or creatinine clearance < 15 ml/min	1
Patients on dialysis or previous renal transplant	1
Clinically important renal disease *	1
Severe renal impairment *	1
Advanced kidney disease (pre-dialysis or dialysis) *	1
TOTAL	**103**
Additional criteria potentially leading to the exclusion of patients with more advanced CKD	**N**
Any other serious systemic disease that might complicate management and reduce life expectancy	2
A serious disease other than heart disease that was likely to be fatal within three years	1
Any clinically significant disease other than congestive HF	1
Any other conditions thought to limit survival or ability to participate in a long-term trial	1
Coexisting noncardiac disease resulting in a life expectancy of less than 3 years	1
Concomitant serious disease	1
Disease likely to limit 5-year survival	1
Life-expectancy ≤ 2 years	1
Limited life-expectancy as determined by enrolling physician	1
Noncardiac illness with a life expectancy of less than 3 years or noncardiac illness imposing substantial operative mortality	1
Other conditions likely to limit life expectancy	1
Other life-threatening conditions	1
Recognised contraindications to ACEi	1
Severe medical or psychiatric comorbid condition	1
Significant renal dysfunction beyond that which could be expected from CHF alone (undefined)	1
Life-limiting comorbidity	1
Severe concomitant non-cardiac disease	1
TOTAL	**18**

Legends: BUN – Blood urea nitrogen; eGFR – Estimated glomerular filtration rate; HF – Heart failure

* Undefined in the study protocol

TABLE 2 – Renal thresholds used for patient exclusion and indices of baseline renal functional in landmark heart failure trials.

Landmark trial	Drug or device	Renal markers used as exclusion criteria	Indices of baseline renal function
V-HeFT I, 1986	Vasodilator therapy	-	-
Consensus, 1987	ACEi – Enalapril	eGFR < 30 mL/min/1.73 m^2	Mean serum creatinine: 128 µmol/L
V-HeFT II, 1991	ACEi - Enalapril versus ISDN/Hydralazine	-	-
SOLVD, 1991	ACEi – Enalapril	eGFR < 30 mL/min/1.73 m^2	Mean serum creatinine: 1.2 mg/dL
SAVE, 1992	ACEi - Captopril	eGFR < 30 mL/min/1.73 m^2	-
AIRE, 1993	ACEi – Ramipril	-	-
TRACE, 1995	ACEi - Trandolapril	eGFR < 30 mL/min/1.73 m^2	-
US Carvedilol HF Trials Program, 1996	Beta-blockers - Carvedilol	*Clinically important renal disease*	-
DIG, 1997	Digoxin	Serum creatinine > 3.0 mg /dL	-
CIBIS-II, 1999	Beta-blockers - Bisoprolol	eGFR < 30 mL/min/1.73 m^2	-
MERIT-HF, 1999	Beta-blockers - Metoprolol XL	-	-
RALES, 1999	MRA -Spironolactone	eGFR < 30 mL/min/1.73 m^2	-
Val-HeFT, 2001	ARB - Valsartan	eGFR < 30 mL/min/1.73 m^2	-
MADIT-II, 2002	Implantable cardioverter-defibrillator	-	-
Copernicus, 2002	Beta-blockers - Carvedilol	eGFR < 30 mL/min/1.73 m^2	Mean serum creatinine: 134 µmol/L
EPHESUS, 2003	MRA -Eplerenone	Serum creatinine > 2.5 mg/dL	Mean creatinine clearance: 78.5 ml/min
COMET, 2003	Carvedilol vs. Metoprolol	-	-
CHARM-Preserved 2003	ARB - Candesartan	eGFR < 30 mL/min/1.73 m^2	-
CHARM-Alternative 2003	ARB – Candesartan	eGFR < 30 mL/min/1.73 m^2	-
CHARM-Added 2003	ARB - Candesartan	eGFR < 30 mL/min/1.73 m^2	-
VALIANT 2003	ARB vs. ACEi	Serum creatinine > 2.5 mg/dL	Mean serum creatinine: 1.1 mg/dL

	and ARB + ACEi vs. ACEi alone		
DEFINITE 2004	Implantable cardioverter-defibrillator	-	-
COMPANION 2004	Cardiac resynchronization therapy with or without defibrillator	-	-
SENIORS 2005	Beta-blockers - Nebivolol	Serum creatinine > 250 µmol/L	Mean serum creatinine: 102.8 µmol/L
SCD-HeFT 2005	Implantable cardioverter-defibrillator	-	Mean serum creatinine: 1.1 mg/dL
CARE-HF 2005	Cardiac resynchronization therapy	-	Mean eGFR: 61 mL/min/1.73 m^2
CORONA 2007	Rosuvastatin	Serum creatinine > 2.5 mg/dL	Mean serum creatinine: 102.8 µmol/L Mean eGFR: 58 mL/min/1.73 m^2
Beautiful 2008	Ivabradine	-	-
REVERSE 2008	Cardiac resynchronization therapy	Serum creatinine > 3.0 mg /dL	Mean eGFR: 87.5 mL/min/1.73 m^2
MADIT-CRT 2009	Cardiac resynchronization therapy	Serum creatinine > 3.0 mg /dL	Mean serum creatinine: 1.2 mg/dL
SHIFT 2010	Ivabradine	eGFR < 30 mL/min/1.73 m^2	Mean eGFR: 74.7 mL/min/1.73 m^2
RAFT 2010	Cardiac resynchronization therapy	-	Mean eGFR: 60.2 mL/min/1.73 m^2
EMPHASIS-HF 2011	MRA - Eplerenone	eGFR < 30 mL/min/1.73 m^2	Mean serum creatinine: 115 µmol/L Mean eGFR: 70.8 mL/min/1.73 m^2
STITCH 2011	Coronary artery bypass grafting	-	Proportion of chronic renal insufficiency (undefined): 8%
WARCEF 2012	Warfarin vs. Aspirin	-	-
Echo CRT 2013	Cardiac resynchronization therapy	Serum creatinine > 2.5 mg/dL	-
TOPCAT 2014	Aldosterone antagonists / Spironolactone	eGFR < 30 mL/min/1.73 m^2 or serum creatinine > 2.5 mg/dL	Mean serum creatinine: 1.1 mg/dL Mean eGFR: 65.4 mL/min/1.73 m^2
PARADIGM-HF 2014	Angiotensin Receptor-Neprilysin Inhibitors	eGFR < 30 mL/min/1.73 m^2	Mean serum creatinine: 1.13 mg/dL
DANISH 2016	Implantable cardioverter-defibrillator	Patients on dialysis	Mean eGFR: 74 mL/min/1.73 m^2
DAPA-HF 2019	Dapagliflozin	eGFR < 30 mL/min/1.73 m^2	Mean eGFR: 65.7 mL/min/1.73 m^2

Legends: ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin receptor blocker; eGFR – Estimated glomerular filtration rate; MRA – Mineralocorticoid receptor antagonist

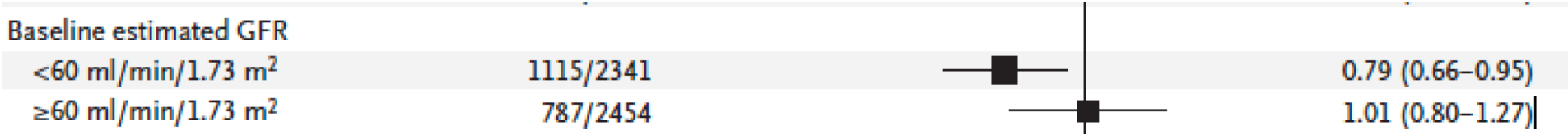
TABLE 3 – Sub-group analyses based on renal function in landmark heart failure trials. Data obtained from the original papers, separately published papers with subgroup analyses (note that randomisation no longer adhered), supplementary appendices or previously published trial rationale/designs.

Landmark trial	Drug or device	Sub-group analysis based on renal function	Results
Consensus, 1987	ACEi – Enalapril	Effect on crude 6-month mortality Serum creatinine ≤ 120 > 120	 Reduction in mortality 24%, p = 0.12 Reduction in mortality 52%, p = 0.002
RALES, 1999	MRA - Spironolactone	Effect on all-cause mortality Serum creatinine < 1.2 mg/dL ≥ 1.2 mg/dL	 Favoured Spironolactone in both groups (no effect size provided)
EPHESUS, 2003	MRA - Eplerenone	Effect on time to death from any cause Serum creatinine concentration < 1.1 mg/dL ≥ 1.1 mg/dL	 P-value = 0.03, greater benefit in <1.1 mg/dL
VALIANT 2003	ARB vs. ACEi and ARB + ACEi vs. ACEi alone	Valsartan group vs. captopril Effect on all-cause mortality Serum creatinine concentration ≤ Median > Median Valsartan + captopril vs. captopril group Effect on all-cause mortality Serum creatinine concentration ≤ Median > Median	 P-value for interaction = 0.32 P-value for interaction = 0.93
CARE-HF 2005	Cardiac resynchronization therapy	Effect on composite of death from any cause or an unplanned CV hospitalisation Estimated GFR < 60.3 ml/min/1.73m^2	 HR 0.67 (0.5–0.89)

		≥ 60.3 ml/min/1.73m^2	HR 0.57 (0.4–0.8)
CORONA 2007	Rosuvastatin	Effect on composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke Estimated GFR < 51 mL/min/1.73 m^2 ≥ 51 mL/min/1.73 m^2	Generally treatment group is first group 15.8% vs. 16.3% 9.5% vs. 10.5% 16.3% vs. 15.8% 10.5% vs. 9.5%
REVERSE 2008	Cardiac resynchronization therapy	Effect on HF clinical composite response Estimated GFR < 82.7 mL/min/1.73m^2 ≥ 82.7 mL/min/1.73m^2	 OR 0.73 (0.39–1.38) OR 0.67 (0.37–1.21)
RAFT 2010	Cardiac resynchronization therapy	Effect on composite of death or hospitalisation for HF Estimated GFR < 60 mL/min/1.73 m^2 ≥ 60 mL/min/1.73 m^2	 P-value for interaction = 0.70
EMPHASIS-HF 2011	MRA - Eplerenone	Effect on hospitalisation for HF or death from CV causes Estimated GFR < 60 mL/min/1.73m^2 ≥ 60 mL/min/1.73m^2	 P-value for interaction = 0.50
WARCEF 2012	Warfarin vs. Aspirin	Effect on time to composite end point of ischaemic stroke, intracerebral haemorrhage or death from any cause Estimated GFR *High* *Low*	 HR 0.83 (0.65–1.08, p = 0.17) HR 0.98 (0.79–1.22, p = 0.84) P-value for interaction = 0.36
TOPCAT 2014	MRA - Spironolactone	Effect on composite of death from CV causes, aborted cardiac arrest or hospitalisation for HF Estimated GFR Less than the median At or above the median	 HR 0.92 (0.76–1.11) HR 0.85 (0.66–1.08)

		Estimated GFR < 60 mL/min/1.73m2 ≥ 60 mL/min/1.73m2	P-value for interaction = 0.62 HR 0.95 (0.77–1.17) HR 0.82 (0.66–1.02) P-value for interaction = 0.34
PARADIGM-HF 2014	Angiotensin Receptor-Neprilysin Inhibitors	Effect on cardiovascular death Estimated GFR < 60 mL/min/1.73 m^2 ≥ 60 mL/min/1.73 m^2	P-value for interaction = 0.73
DANISH 2016	Implantable cardioverter-defibrillator	Effect on all-cause death Estimated GFR < 73 mL/min/1.73 m^2 ≥ 73 mL/min/1.73 m^2	HR 0.88 (0.64-1.21) HR 0.82 (0.55-1.23) P-value for interaction = 0.86
DAPA-HF 2019	Dapagliflozin	Effect on composite of hospitalisation for HF or death from CV causes Estimated GFR < 60 mL/min/1.73m2 ≥ 60 mL/min/1.73m2	HR 0.72 (0.59–0.86) HR 0.76 (0.63–0.92)

PARAGON-HF 2019?



Legends: ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin receptor blocker; CV – Cardiovascular; eGFR – Estimated glomerular filtration rate; HF – Heart failure; HR – Hazard ratio; MRA – Mineralocorticoid receptor antagonist; OR – Odds ratio.