REVIEW

The influence of heart failure on the pharmacokinetics of cardiovascular and non-cardiovascular drugs: a critical appraisal of the evidence

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Prescribing in heart failure (HF), a common disease state that predominantly affects the older population, is often a challenging task because of the dynamic nature of the condition, requiring frequent monitoring and medication review, the presence of various comorbidities, and the frailty phenotype of many patients. The significant alterations in various organs and tissues occurring in HF, particularly the reduced cardiac output with peripheral hypoperfusion and the structural and functional changes of the gastrointestinal tract, liver and kidney, might affect the pharmacokinetics of several drugs. This review critically appraises the results of published studies investigating the pharmacokinetics of currently marketed cardiovascular and selected non-cardiovascular drugs in HF patients and control groups, identifies gaps in the current knowledge, and suggests avenues for future research in this complex patient population.

Introduction

Heart failure (HF), commonly defined as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood, is a disabling condition that primarily affects the older population [1]. In the USA, the incidence of HF is 19.3 per 1000 subjects per year in those aged 65–69 years and 48.4 per 1000 subjects per year in those aged 80–84 years [2]. In the UK, epidemiological studies have reported an overall incidence of 3.4 per 1000 persons per year in those aged 55–64 years and 25.5 per 1000 persons per year in those aged 75–84 years [3]. Although the long-term mortality rates in HF patients have decreased over time, probably as a result of significant advances in early diagnosis and management, they remain unacceptably high. Data from the Framingham Heart Study show that, in patients with a new diagnosis of HF, the mortality rate is 20–30% at 1 year and 45–60% at 5 years [4].

The presence of comorbidities further increases the risk of mortality and reduces the quality of life in patients with HF [5]. Data from the American Heart Association Get With The Guidelines-Heart Failure (GWTG-HF) registry in 207 984 hospitalized HF patients showed that 30% had one, 27% had two and 25% had three or more comorbidities. The most common comorbidities were diabetes, chronic obstructive pulmonary disease (COPD) or asthma, and anaemia. In this study, the increasing number of comorbidities in HF was significantly

associated with longer hospital stay, in-hospital and 30-day mortality and readmission [6].

Several classes of drugs are routinely prescribed in HF to maintain cardiac function, prevent atherothrombotic events and arrhythmias, regulate water and sodium homeostasis and treat various comorbidities [7]. However, it is important to emphasize that there is a significant inter-individual variability in HF patient sub-types, disease severity and clinical progress. In addition to the traditional form of HF characterized by left ventricular dysfunction, reduced cardiac output and pulmonary congestion (HF with reduced ejection fraction), HF patients can also exhibit a preserved function of the left ventricle (HF with preserved ejection fraction) or an impaired function of the right ventricle, either isolated (right-sided HF, with predominant hepatic congestion, ascites and leg oedema) or combined with left ventricular dysfunction (bi-sided HF). Furthermore, there is a wide range of symptom severity (New York Heart Association functional class I–IV), even in the same patient, e.g. chronic stable HF vs. acute decompensated HF, and involvement of other key organs, particularly the kidney and the liver. These factors, together with advancing age [8, 9], can differently influence the pharmacokinetics, as well as the pharmacodynamics, of drugs for the treatment of HF and comorbid conditions, potentially limiting the generalizability of the results of studies conducted in HF patients with specific characteristics to other HF subgroups.

A number of excellent reviews of pharmacokinetics in HF have been published previously [10–15]. This updated review briefly discusses the main pathophysiological changes in HF that are likely to influence pharmacokinetics, critically appraises the results of published studies investigating the pharmacokinetics of currently marketed cardiovascular, and selected non-cardiovascular, drugs in HF patients and control groups, and discusses strategies for further research in the field.

Pathophysiological changes in HF potentially affecting pharmacokinetics

The state of systemic arterial hypoperfusion, venous congestion and neurohormonal activation occurring in HF negatively affects the integrity and the function of key organs, particularly the gastrointestinal tract, the liver and the kidney. A reduced (−29%) absorption of D-xylose with increased (+35%) permeability, bacterial growth, and wall thickness in the small and large intestine have been observed in HF patients when compared to healthy controls [16]. Recent evidence suggests that some of the structural and functional alterations of the gastrointestinal tract observed in HF might be, at least partly, accounted for by changes in the gut microbiome that favour local inflammation and fibrosis [17]. In a study investigating the presence of bacteria and fungi in faeces in HF patients and controls, the former group had a significantly higher number of *Campylobacter*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, and *Candida* species [18]. Studies have also reported a significant reduction in gastric emptying in mice with left ventricular dysfunction post-myocardial infarction. It has been proposed that the adverse effects on gastric emptying are mediated by the B-type natriuretic peptide [19].

Hepatic congestion is a common feature in patients with HF that is associated with laboratory abnormalities indicating cholestasis as well as reduced synthetic capacity. The latter leads to a prolongation of the prothrombin time and hypoalbuminaemia [20]. Hypoalbuminaemia in HF is also a consequence of increased losses through the gastrointestinal system and the kidneys [21]. In some cases, chronic hepatic congestion can progress to fibrosis and cirrhosis and also predisposes to acute ischaemic hepatitis, resulting from a sudden reduction in cardiac output and hepatic perfusion [22, 23].

Kidney dysfunction and reduced glomerular filtration rate, also commonly observed in patients with HF in the form of chronic kidney disease and/or acute kidney injury, are secondary to reduced renal blood flow, the direct deleterious effects of HF risk factors (e.g. hypertension and diabetes) on the renal parenchyma, and the effects of nephrotoxic drugs [24]. There is also emerging evidence that a state of renal venous hypertension, resulting from cardiac congestion and increased central venous pressure, might significantly contribute to the development of renal fibrosis, causing a further reduction of renal perfusion and glomerular filtration [25].

Although the pathophysiological changes described above can potentially affect drug absorption, first-pass metabolism, protein binding, volume of distribution and clearance, there is a significant inter-individual variability in the presence and the severity of hepatic and renal dysfunction, singly or in combination, in the HF population. In a recent epidemiological study of 24 339 HF patients hospitalized in the UK, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease (CKD), 3.4% had stage 1, 30.9% stage 2, 52.2% stage 3, 11.3% stage 4, and 2.2% stage 5 CKD [26]. Similarly, studies have reported a significant variability in laboratory liver function tests and the histological evidence of liver fibrosis in patients with HF [27, 28]. Furthermore, significant temporal changes in hepatic and/or renal function can occur in the same patient, either progressively or as a result of acute cardiac or non-cardiac events, e.g. severe infections. In this context, the presence of significant fluid overload can lead to modifications of specific compartments, such as the pleural space (pleural effusion) and the peritoneal cavity (ascites), and/or a systemic expansion of the interstitial fluid volume (anasarca), with significant effects on the distribution of water-soluble drugs [29, 30]. Cardiac cachexia, a condition characterized by progressive weight loss due to reduced skeletal muscle and fat mass in patients with HF, might also influence pharmacokinetics [31]. Although no specific information is available on possible pharmacokinetic alterations in cardiac cachexia, a recent systematic review identified 14 pharmacokinetic studies in cachectic patients with cancer and human immunodeficiency virus infection. These studies, primarily investigating anti-cancer drugs, opioids, antiretrovirals and antibiotics, showed a reduced volume of distribution for both water-soluble and fat-soluble drugs, presumably reflecting the concomitant loss of fat and lean body mass, and a possible impairment in drug metabolism, particularly for drugs

metabolized by CYP3A4 [32]. The following sections will discuss the available evidence regarding the pharmacokinetics of currently marketed cardiovascular, and selected non-cardiovascular, drugs in studies conducted in HF patients and in control groups.

Methods

A literature search was conducted on Pubmed, Embase and Scopus, from inception to May 2018, using the following terms: generic names of individual cardiovascular and selected non-cardiovascular drugs, pharmacokinetics and heart failure. Inclusion criteria were: (1) English language; (2) human studies comparing pharmacokinetic data between HF patients and a control group or analysing the associations between the presence of HF and specific pharmacokinetic parameters by means of multivariate analysis, e.g. population pharmacokinetic studies; and (3) current marketing status. References in individual papers were screened and reviewed to identify additional studies. Grey literature was also searched by accessing Google Scholar. Current marketing status for each drug was verified using online resources [33]. Individual cardiovascular drugs and drugs used for the treatment of diabetes, COPD, asthma and anaemia were identified using the Anatomical Therapeutic Chemical (ATC) Classification System (2018 version) developed by the WHO Collaborating Centre for Drug Statistics Methodology (Oslo, Norway). Drugs for the treatment of diabetes, COPD, asthma and anaemia were selected on the basis that these conditions represent the most common comorbidities in patients with HF [6]. Cardiovascular drugs included those listed under ATC codes C01–10 (cardiac therapy, antihypertensives, diuretics, peripheral vasodilators, vasoprotectives, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system, and lipid lowering agents) and B01 (antithrombotic agents). Drugs for diabetes included those listed under code A10 (insulins and analogues, blood glucose lowering drugs excluding insulins, and other drugs used in diabetes), drugs for COPD and asthma those listed under code R03 (inhaled adrenergics and other inhaled drugs for obstructive airway diseases, adrenergics for systemic use, and other systemic drugs for obstructive airway disease), and drugs for anaemia those listed under code B03 (iron preparations, vitamin B_{12} and folic acid and other anti-anaemic preparations).

The following parameters were collected from each study: dose, route of administration, number of HF patients and controls, age, sex, New York Heart Association (NYHA) functional class, presence of significant renal and/or hepatic impairment, bioavailability, maximum concentration, concentration at steady state, time to reach maximum concentration, volume of distribution, clearance, elimination half-life and area under the curve. Information regarding the physicochemical characteristics (water solubility and Biopharmaceutics Classification System) and the pharmacokinetics of individual drugs in healthy groups (bioavailability, protein binding, volume of distribution, elimination half-life and main route of elimination) was also collected using established sources (Table S1) [33–36].

Results

A total of 59 studies (49 on cardiovascular drugs) investigating 36 drugs (31 cardiovascular) were identified (Tables 1–6). Twelve studies were published in the period 1970–1979 [37–48], 20 in the period 1980–1989 [49–68], 12 in the period 1990–1999 [69–80], 10 in the period 2000–2009 [81–90], and five in the period 2010–2018 [91–95].

Positive inotropes and vasopressors

The pharmacokinetics of six drugs (digoxin, enoximone, adrenaline, noradrenaline, isoprenaline and levosimendan) were investigated in 11 studies (Table 1). Digoxin clearance was mildly, albeit significantly, lower (between −6% and −32%) in HF patients vs. controls in four studies [49, 69, 91, 92]. However, no significant between-group differences in digoxin clearance were reported in two other studies [37, 81]. Given the key role of renal function in influencing the elimination of digoxin (Table S1), it is important to emphasize that renal function was not significantly altered in HF patients in two of the six studies assessing digoxin clearance. Notably, in these two studies the clearance of digoxin was either minimally reduced (−6%) [91] or not significantly different from that of controls [37]. This suggests that the clearance of digoxin is unlikely to be significantly affected in HF patients with preserved renal function. When compared to controls, patients with HF had a reduced clearance (−58%) and a mildly longer half-life (+21%) of enoximone, although no statistical analyses were reported [50]. A reduced clearance (between −26% and −56%) of adrenaline, noradrenaline and isoprenaline and a marked increase in steady state concentrations (between +49% and +204%) of adrenaline and noradrenaline [70–72] were observed in HF patients. By contrast, the pharmacokinetics of levosimendan, a drug with a short half-life that is predominantly metabolized in the liver and the small intestine (Table S1) [96], was not significantly affected by HF [73].

Diuretics

Four diuretics (bumetanide, furosemide, hydroflumethiazide and metolazone) were investigated in six studies (Table 2). Studies of the loop diuretics bumetanide and furosemide provided conflicting results. There were no significant differences between HF patients and controls in bioavailability, volume of distribution, clearance and elimination half-life of both drugs after intravenous administration [51, 52]. By contrast, bumetanide clearance was significantly lower (−44%) in HF patients after oral administration [51]. In another study, HF patients had a significantly longer elimination half-life of both bumetanide (+144%) and furosemide (+70%) administered orally [53]. Finally, a study reported a significant reduction (−50%) in furosemide clearance in HF patients after intravenous administration, although the volume of distribution and the elimination half-life were similar to that of controls [38]. The results of this study, conducted in patients with preserved renal function, require further confirmation as the clearance of furosemide, primarily mediated by the kidney (Table S1), was similar in HF patients with renal dysfunction and in controls in another study [52]. There was a significant reduction (−52%) in volume distribution and a shorter (−42%) half-life of the thiazide diuretic

Table 1

Pharmacokinetic studies of positive inotropes and vasopressors in patients with heart failure and controls

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Digoxin, 0.75 mg, oral [37]	HF: n = 12, NYHA n/a, age 61 ± 4 years, 10M/2FC: n = 9, age 60 ± 16 years, 7M/2F	No	n/a	n/a	↓ (−36%)	n/a	↑	n/a	↑	n/a	↑
Digoxin, 0.19 mg day^{-1}, oral, [69]	PPK: n = 385, age 60 ± 13 years, 207M/178F HF subgroup: n = 77, NYHA and age n/a, 43M/34F	Yes	No	n/a	n/a	n/a	n/a	n/a	↓ (−19%)	n/a	n/a
Digoxin, 0.21 mg day^{-1}, oral [49]	HF: n = 10, NYHA n/a, age 76 ± 5 years, M/F n/aC: n = 9, age 77 ± 11 years, M/F n/a	Yes	n/a	n/a	n/a	↑ (+40%)	n/a	n/a	↓ (−32%)	n/a	n/a
Digoxin, n/a, oral [81]	PPK: n = 106, age n/a, 43M/63F HF subgroup: n = 14, NYHA, age and M/F n/a	Yes	No	n/a	n/a	n/a	n/a	n/a	↑	n/a	n/a
Digoxin, 3.8 μg kg^{-1} day^{-1}, oral [91]	PPK: n = 94, age 74 ± 6 years, 60M/34F HF subgroup: n = 41, NYHA, age and M/F n/a	No	n/a	n/a	n/a	n/a	n/a	n/a	↓ (−6%)	n/a	n/a
Digoxin, n/a, oral [92]	PPK: n = 122, age 75 ± 8 years, M/F n/a HF subgroup: n, NYHA, age and M/F n/a	Yes	No	n/a	n/a	n/a	n/a	↓ (−10%)	↓ (−10%)	n/a	n/a
Enoximone, 1–2 mg kg^{-1} (75 mg in controls), oral [50]	HF: n = 7, NYHA III-IV, age 51 years, M/F n/a HF subgroup: n = 2, age and M/F n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↑^{a} (−58%)	↑^{a} (+21%)	n/a
Adrenaline, 1-h i.v. infusion^b [70]	HF: n = 42, NYHA III-IV, age 50 ± 1 years, 39M/3FC: n = 31, age 41 ± 5 years, 31M/0F	n/a	n/a	n/a	n/a	↑ (+49%)	n/a	n/a	↓ (−34%)	n/a	n/a
Noradrenaline, 1-h i.v. infusion^c [70]	HF: n = 42, NYHA III-IV, age 50 ± 1 years, 39M/3FC: n = 31, age 41 ± 5 years, 31M/0F	n/a	n/a	n/a	n/a	↑ (+121%)	n/a	n/a	↓ (−26%)	n/a	n/a
Noradrenaline, 0.5-h i.v. infusion [71]	HF: n = 7, NYHA III-IV, age 49 ± 3 years, 6M/1FC: n = 6, age 38 ± 3 years, 6M/0F	n/a	n/a	n/a	n/a	↑ (+204%)	n/a	n/a	↓ (−43%)	n/a	n/a
Noradrenaline, 0.5-h i.v. infusion [72]	HF: n = 8, NYHA III-IV, age 56 ± 4 years, 8M/0FC: n = 9, age 38 ± 2 years, 9M/0F	n/a	n/a	n/a	n/a	↑ (+111%)	n/a	n/a	↓ (−56%)	n/a	n/a

(continues)

Table 1
(Continued)

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Isoprenaline, 0.5-h i.v. infusion [72]	HF: n = 8, NYHA III–IV, age 56 ± 4 years, 8M/0FC: n = 9, age 38 ± 2 years, 9M/0F	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↓ (−43%)	n/a	n/a
Levosimendan, 0.50 mg, oral[f] and i.v.[g] [73]	HF: n = 8, NYHA II, age 54 years, 8M/0FC: n = 8, age 54 years, 8M/0F	No	No	↑	→[a]	n/a	→[a]	↑	↑	↑	↑

AUC, area under the curve; C, controls; CL, clearance; C_{max}, maximum plasma/serum concentration; C_{ss}, concentration at steady state; F, bioavailability; F, female; HF, patients with heart failure; M, male; n/a not available/reported; NYHA, New York Heart Association functional class; PPK, population pharmacokinetics study; T_{max}, time to reach the maximum plasma/serum concentration; $t_{1/2}$, elimination half-life; V_D, volume of distribution
*, significant; ↑, significantly increased; ↓, significantly decreased; →, not statistically different;
[a] no statistical analysis performed;
[b] [N-$methyl$-^{3}H] adrenaline (0.5–1.0 μCi min^{-1});
[c] [7-^{3}H] noradrenaline (0.5–1.0 μCi min^{-1});
[d] [ring-2,3,6-^{3}H] noradrenaline (15 μCi m^{-2} over 5 min followed by 1.05 μCi min^{-1} m^{-2});
[e] d,l-[7-^{3}H(N)]isoprenaline (15 μCi m^{-2} over 5 min followed by 1.05 μCi min^{-1} m^{-2});
[f] ^{13}C^{15}N-labelled;
[g] ^{14}C-labelled

hydroflumethiazide in HF patients [39]. By contrast, the clearance of the thiazide diuretic metolazone in HF patients was similar to that of controls. The absence of significant renal dysfunction in HF patients in this study might explain the lack of significant changes in metolazone clearance, which primarily occurs through the elimination of the unchanged drug in urine (Table S1) [40].

Vasodilators and beta-blockers

The pharmacokinetics of nine drugs (carvedilol, metoprolol, nifedipine, bosentan, hydralazine, nicorandil, isosorbide-5-mononitrate, isosorbide dinitrate and prazosin) were investigated in 10 studies (Table 3). There were no significant differences in the pharmacokinetics of the beta-blockers carvedilol and metoprolol between HF patients and controls, barring a significantly shorter (−44%) elimination half-life of carvedilol in HF [82, 83]. These findings, in HF patients without significant hepatic or renal dysfunction, are not unexpected given that both carvedilol and metoprolol undergo significant metabolism in the liver (Table S1). HF did not significantly affect the pharmacokinetics of the calcium channel blocker nifedipine, the endothelin receptor antagonist bosentan, and the direct vasodilating agent hydralazine, drugs that are also significantly metabolized in the liver (Table S1) [54, 55, 93]. By contrast, patients with HF had a significantly greater volume of distribution (+39%) and higher clearance (+94%) of the vasodilator nicorandil, administered intravenously, when compared to controls [84]. Studies investigating the effects of HF on the pharmacokinetics of nitrates showed reduced peak concentrations (−28%) and a significantly longer time to reach peak concentrations (+72%) and, to a lesser extent, elimination half-life (+29%) with isosorbide-5-mononitrate [74]. No significant changes in bioavailability or clearance were observed with isosorbide dinitrate [56]. The most significant pharmacokinetic changes in this group of drugs was observed with the alpha-1 blocker prazosin, with significant reductions (−54%) in clearance, a marked prolongation in elimination half-life (between +153% and +160%), and a greater area under the curve (between +111% and +127%) in HF patients [41, 57]. The mechanisms responsible for these alterations are unknown given that prazosin is extensively metabolized in the liver and its metabolites are almost completely excreted in the bile (Table S1) [97]. Furthermore, liver function was preserved in one study but unknown in another [41, 57].

Antiarrhythmics

Seven antiarrhythmics (cibenzoline, disopyramide, ibutilide, lidocaine, mexiletine, procainamide and quinidine) were investigated in 17 studies (Table 4). No significant differences in the pharmacokinetics of cibenzoline, disopyramide and ibutilide were observed between HF patients and controls with preserved renal and liver function [58, 59, 85]. Studies on lidocaine reported a significant reduction in volume of distribution (−33%) and clearance (between −36% and −37%) and a significantly longer elimination half-life (between +62% and +628%) in HF patients [42, 43, 60]. By contrast, other studies did not report any significant differences in volume of distribution and elimination half-life of lidocaine between HF patients and controls [42, 60]. The

Table 2

Pharmacokinetic studies of diuretics in patients with heart failure and controls

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Bumetanide, 3 mg, oral and i.v. [51]	HF: $n=6$, NYHA III-IV, age 60 ± 12 years, 5M/1FC: $n=4$, age 30 ± 7 years, 4M/0F	Yes	No	→	→	n/a	→	→	→[a]↓ (−44%)	→	n/a
Bumetanide, 1-2 mg, oral [53]	HF: $n=20$, NYHA I-IV, age 33–74 years, 14M/4FC: $n=10$, age n/a, 10M/0F	Yes	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↑ (+144%)	n/a
Furosemide, 40–80 mg, oral [53]	HF: $n=20$, NYHA I-IV, age 33–74 years, 14M/4FC: $n=10$, age n/a, 10M/0F	Yes	n/a	↑	n/a	n/a	n/a	n/a	n/a	↑ (+70%)	n/a
Furosemide, 40 mg, oral and i.v. [52]	HF: $n=17$, NYHA, age and M/F n/aC: $n=8$, age 22–27 years, 5M/3F	Yes	n/a	↑	n/a	n/a	n/a	↑	↑	↑	n/a
Furosemide, 40 mg, i.v. [38]	HF: $n=6$, NYHA n/a, age 69 ± 24 years, M/F n/aC: $n=8$, age 52 years, 6M/2F	No	n/a	n/a	n/a	n/a	n/a	↑	↓ (−50%)	↑	n/a
Hydroflumethiazide, 25 mg, oral [39]	HF: $n=9$, NYHA I-III, age 65 ± 11 years, 9M/0FC: $n=5$, age 29 ± 1 years, 4M/1F	No	n/a	n/a	n/a	n/a	n/a	↓ (−52%)	↑	↓ (−42%)	↑
Metolazone, 2.5 mg, oral [40]	HF: $n=3$, NYHA and age n/a, 2M/1FC: $n=3$, age n/a, 3M/0F	No	n/a	n/a	n/a	n/a	n/a	n/a	↑	n/a	n/a

AUC, area under the curve; C, controls; CL, clearance; C_{max}, maximum plasma/serum concentration; C_{ss}, concentration at steady state; F, bioavailability; F, female; HF, patients with heart failure; M, male; n/a not available/reported; NYHA, New York Heart Association functional class; T_{max}, time to reach the maximum plasma/serum concentration; $t_{1/2}$, elimination half-life; V_D, volume of distribution;

*, significant; ↑, significantly increased; ↓, significantly decreased; →, not statistically different;

[a]No significant differences in clearance between heart failure patients and controls after i.v. dose, clearance in heart failure patients was significantly lower than controls after oral dose;

[b]no statistical analysis reported

Table 3

Pharmacokinetic studies of vasodilators and beta-blockers in patients with heart failure and controls

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Carvedilol, 0.09 mg kg⁻¹, oral [82]	HF: $n = 15$, NYHA n/a, age 6 ± 6 years, 11M/4FC: $n = 9$, age 30 ± 5 years, 3M/6F	No	No	n/a	→	n/a	→	n/a	n/a	↓ (−44%)	→
Metoprolol, 40–120 mg day⁻¹, oral [83]	PPK: $n = 34$, age 70 ± 8 years, 21M/13FHF subgroup: $n = 5$, NYHA II-III, age and M/F n/a	No	No	n/a	n/a	n/a	n/a	→	→	n/a	n/a
Nifedipine, 20 mg, oral [54]	HF: $n = 12$, NYHA, age and M/F n/aC: $n = 5$, age and M/F n/a	n/a	n/a	n/a	→	n/a	→	n/a	n/a	→	→
Bosentan, 2.3 ± 0.8 mg kg⁻¹, oral [93]	PPK: $n = 46$, age 4 ± 5 years, 29M/17FHF subgroup: $n = 24$, NYHA, age and M/F n/a	No	No	n/a	n/a	n/a	n/a	n/a	→	n/a	n/a
Hydralazine, 50 mg, oral [55]	HF: $n = 7$, NYHA III-IV, age 61 ± 6 years, 3M/4FC: $n = 8$, age 57 ± 8 years, 7M/1F	No	No	n/a	→	n/a	→	n/a	n/a	→	→
Nicorandil, 200 μg kg⁻¹ –24 mg i.v. bolus, 50–200 μg kg⁻¹ h⁻¹ i.v. infusion [84]	Population PK: $n = 105$, age n/a, 76M/29FHF subgroup: $n = 94$, NYHA II-IV, age n/a, 65M/29F	n/a	n/a	n/a	n/a	n/a	n/a	↑ (+39%)	↑ (+94%)	n/a	n/a
Isosorbide-5-mononitrate, 20 mg, oral [74]	HF: $n = 8$, NYHA n/a, age 72 ± 5 years, 6M/2FC: $n = 9$, age 60 ± 12 years, 6M/3F	No	n/a	n/a	↓ (−28%)	n/a	↑ (+72%)	n/a	n/a	↑ (+29%)	→
Isosorbide dinitrate, 5 mg (s.l.), 30 mg (oral) [56]	HF: $n = 9$, NYHA II-III, age 63 ± 9 years, 8M/1FC: $n = 8$, age 58 ± 7 years, 6M/2F	n/a	n/a	↑	n/a	n/a	n/a	n/a	→	n/a	n/a
Prazosin, 5 mg, oral [57]	HF: $n = 9$, NYHA III-IV, age 62 years, 6M/3FC: $n = 5$, age 39 years, 2M/3F	No	No	n/a	→	n/a	→	n/a	↓ (−54%)	↑ (+153%)	↑ (+127%)
Prazosin, 2-5 mg, oral [41]	HF: $n = 9$, NYHA II-IV, age 57 years, 8M/1FC: $n = 10$, age 27 years, 10M	n/a	n/a	n/a	n/a	n/a	↑	n/a	n/a	↑ (+160%)	↑ (+111%)

AUC, area under the curve; C, controls; CL, clearance; C_{max}, maximum plasma/serum concentration; C_{ss}, concentration at steady state; F, bioavailability; F, female; HF, patients with heart failure; M, male; n/a, not available/reported; NYHA, New York Heart Association functional class; PPK, population pharmacokinetics study; T_{max}, time to reach the maximum plasma/serum concentration; $t_{1/2}$, elimination half-life; V_D, volume of distribution;

*, significant; ↑, significantly increased; ↓, significantly decreased; →, not statistically different

Table 4

Pharmacokinetic studies of antiarrhythmics in patients with heart failure and controls

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Cibenzoline, 80 mg, oral and i.v.[a] [58]	HF: $n=6$, NYHA II–III, age 57 ± 8 years, 6M/0FC: $n=5$, age 58 ± 11 years, 5M/0F	No	No	↑	↑	n/a	↑	↑	↑	↑	↑
Disopyramide, 150 mg i.v. bolus, 18–24 mg h⁻¹ i.v. infusion [59]	HF: $n=13$, NYHA n/a, age 52–89 years, M/F n/aC: $n=22$, age 48–90 years, M/F n/a	No	No	n/a	n/a	↑	n/a	↑	↑	↑	n/a
Ibutilide, 1 mg, i.v. [85]	HF: $n=6^b$, NYHA II–III, 53 ± 17 years, 3M/3FC: $n=10^b$, age 61 ± 19 years, 8M/2F	No	No	n/a	↑	n/a	n/a	↑	↑	↑	↑
Lidocaine, 50–100 mg, i.v. [42]	HF: $n=8$, NYHA n/a, age 44–73 years, M/F n/aC: $n=10$, age 24–57 years, 9M/1F	Yes	Yes	n/a	n/a	n/a	n/a	↓ (−33%)	↓ (−37%)	↑	n/a
Lidocaine, 100 mg i.v. bolus, 1.4 mg min⁻¹ i.v. infusion [43]	HF: $n=7$, NYHA n/a, age 61 ± 13 years, 7M/0FC: $n=6$, age 50 ± 4 years, 6M/0F	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↑ (+628%)	n/a
Lidocaine, n/a i.v. bolus, i.v. infusion 14–42 µg kg⁻¹ min⁻¹ [60]	HF: $n=11$, NYHA n/a, age 73 ± 14 years, M/F n/aC: $n=24$, age 60 ± 15 years, M/F n/a	No	No	n/a	n/a	n/a	n/a	↑	↓ (−36%)	↑ (+62%)	n/a
Mexiletine, n/a, oral [86]	PPK: $n=584$, age n/a, 412M/172F HF subgroup: $n=210$, NYHA I–IV, age 60 ± 15 years, 157M/53F	n/a	No	n/a	n/a	n/a	n/a	n/a	↓ (−33%)	n/a	n/a
Mexiletine, n/a, oral [61]	PPK: $n=58$, age 66 ± 12 years, 50M/8FHF subgroup: $n=27$, NYHA, age and M/F n/a	n/a	Yes	n/a	n/a	n/a	n/a	↑	↑	n/a	n/a
Procainamide, 750 mg, i.v. [75]	HF: $n=9$, NYHA II–III, age 57 ± 12 years, 6M/3FC: $n=7$, age 53 ± 10 years, 4M/3F	No	No	n/a	↑	n/a	n/a	↑	↑	↑	↑
Procainamide, i.v. infusion 25 mg min⁻¹ [62]	HF: $n=15$, NYHA n/a, age 66 ± 12 years, 14M/1FC: $n=10$, age 59 ± 14 years, 9M/1F	No	n/a	n/a	↑	n/a	n/a	↑	↑	↑	n/a

(continues)

Table 4
(Continued)

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Procainamide, n/a, oral and i.v. [63]	PPK: $n = 39$, age 60 ± 14 years, 34M/5FHF subgroup: $n = 24$, NYHA I, age and M/F n/a	No	No	n/a	n/a	n/a	n/a	↑	↓[c] (−17%)	n/a	n/a
Procainamide, 500 mg, oral [44]	HF: $n = 20$, NYHA n/a, age 55 years, 13M/7FC: $n = 20$, age 24 ± 1 years, 10M/10F	No	No	n/a	n/a	n/a	n/a	n/a	n/a	↑[d] (+114%)	n/a
Procainamide, 700–1000 mg i.v. bolus, 3–5 mg min⁻¹ i.v. infusion [64]	PPK: $n = 20$, age 61 ± 9 years, 16M/4FHF subgroup: $n = 6$, NYHA n/a, age 63 ± 6 years, 4M/2F	Yes	No	n/a	n/a	n/a	n/a	n/a	↓ (−49%)	n/a	n/a
Quinidine, 1000–1500 mg, oral (both steady-state and not steady-state) [76]	PPK: $n = 60$, age 65 years, 46M/14FSubgroup with HF: $n = 41$, NYHA, age and M/F n/a	Yes	Yes	n/a	n/a	n/a	n/a	n/a	↓[e] (−46%)	n/a	n/a
Quinidine, 400 mg, oral and i.v. [65]	HF: $n = 8$, NYHA II–IV, age 60 ± 13 years, 4M/4FC: $n = 10$, age 54 ± 12 years, 6M/4F	No	No	↑	↑	n/a	↑ (+127%)	↓ (−34%)	↓ (−32%)	↑	n/a
Quinidine, 600–840 mg, oral and i.m. [45]	PPK: $n = 39$, age and M/F n/a HF subgroup: $n = 20$, NYHA, age and M/F n/a	n/a	n/a	n/a	n/a	n/a	n/a	↓[f] (−72%)	n/a	↑	n/a
Quinidine, dose 100–2000 mg, oral [46]	HF: $n = 8$, NYHA, age and M/F n/aC: $n = 9$, age and M/F n/a	No	No	n/a	n/a	↑	n/a	n/a	n/a	↑	n/a

AUC, area under the curve; C: controls; CL, clearance; C_{max}, maximum plasma/serum concentration; C_{ss}, concentration at steady state; F, bioavailability; F, female; HF, patients with heart failure; M, male; n/a not available/reported; NYHA, New York Heart Association functional class; PPK, population pharmacokinetics study; T_{max}, time to reach the maximum plasma/serum concentration; $t_{1/2}$, elimination half-life; V_D, volume of distribution

*, significant; ↑, significantly increased; ↓, significantly decreased; →, not statistically different;

[a] $^{15}N_2$-cibenzoline;

[b] Sample size calculation performed;

[c] No significant effect of heart failure on miscellaneous metabolic clearance (CL_0);

[d] Plasma procaine half-life assessed *in vitro*;

[e] Severe heart failure or liver failure;

[f] No statistical analysis performed

Table 5

Pharmacokinetic studies of renin-angiotensin system inhibitors in patients with heart failure and controls

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Enalapril, 2.5–40 mg, oral [66]	HF: $n = 8$, NYHA III-IV, age 53 ± 9 years, 4M/4FC: $n = 5$, age 52 ± 13 years, 4M/1F	No	No	n/a	n/a	n/a	↑[a] (+67%)	n/a	↓[a] (−75%)	↑[a] (+130%)	n/a
Fosinopril, 10 mg oral, 7.5 mg i.v. [77]	HF: $n = 10$, NYHA II-III, age 65 ± 10 years, 8M/2FC: $n = 10$, age 65 ± 10 years, 8M/2F	No	No	↑	↑	n/a	↑	↑	↑	↑	↑
Irbesartan, 75 mg, oral and i.v. [88]	HF: $n = 10^{b}$, NYHA II-III, age 63 ± 9 years, 9M/1FC: $n = 10^{b}$, age 62 ± 11 years, 9M/1F	No	No	↑	↑	n/a	↑	↑	↑	↑	↑
Lisinopril, 5 mg, oral [67]	HF: $n = 6$, NYHA n/a, age 78 ± 9 years, M/F n/aC: $n = 6$, age 29 ± 7 years, M/F n/a	No	No	n/a	n/a	n/a	n/a	n/a	↓ (−74%)	n/a	↑ (+127%)
Perindopril, 4–16 mg, oral [87]	HF: $n = 10$, NYHA III-IV, age 64 ± 8 years, 7M/3FC: $n = 6$, age 25 ± 3 years, 6M/0F	n/a	n/a	n/a	→[c] ↑[d] (+220%)	n/a	↑[c] (+137%) →[d]	n/a	n/a	↑[c] (+360%) ↓[d] (−9.2%)	↑[c] (+300%) →[d]

AUC, area under the curve; C, controls; CL, clearance; C_{max}, maximum plasma/serum concentration; C_{ss}, concentration at steady state; F, bioavailability; F, female; HF, patients with heart failure; M, male; T_{max}, time to reach the maximum plasma/serum concentration; n/a not available/reported; NYHA, New York Heart Association functional class; $t_{1/2}$, elimination half-life; V_D, volume of distribution

*, significant; ↑, significantly increased; ↓, significantly decreased; →, not statistically different;

[a]No statistical analysis performed;

[b]Sample size calculation performed;

[c]Perindopril;

[d]Perindoprilat

Table 6

Pharmacokinetic studies of other classes of drugs in patients with heart failure and controls

Drug, dose, route of administration, reference	Study group, size, NYHA class, age and sex	Renal disease*	Hepatic disease*	F	C_{max}	C_{ss}	T_{max}	V_D	CL	$t_{1/2}$	AUC
Theophylline, n/a, i.v. [47]	PPK: n = 57, age n/a, 27M/30F HF subgroup: n = 3, NYHA n/a, age 63 ± 8 years, 2M/1F	n/a	No	n/a	n/a	n/a	n/a	→	↓ (−43%)	n/a	n/a
Theophylline, n/a, oral and i.v. [78]	PPK: n = 204, age 60 years, 113M/91FHF subgroup: n = 24, NYHA, age and M/F n/a	No	No	n/a	n/a	n/a	n/a	n/a	↓ (−25%)	n/a	n/a
Theophylline, 700 mg, oral [79]	HF: n = 11, NYHA II-III, age 77 years, 5M/6FC: n = 15, age 75 years, 8M/7F	n/a	n/a	n/a	↑	n/a	↑ (+81%)	↑	↓[a] (−69%)	↑[a] (+267%)	n/a
Theophylline, n/a, oral [80]	HF: n = 16, NYHA II-IV, age 67 ± 9 years, 11M/5FC: n = 16, age 61 ± 10 years, 13M/3F	No	No	n/a	n/a	n/a	n/a	n/a	↓ (−43%)	n/a	n/a
Theophylline, 208 mg, i.v. [68]	HF: n = 50, NYHA III-IV age 20–72 years, 30M/20FC: n = 20, age and M/F n/a	n/a	n/a	n/a	n/a	n/a	n/a	↑	↓ (−62%)	↑(+84%)	n/a
Theophylline, n/a, i.v. [48]	HF: n = 200, age n/a, 95M/105F HF subgroup: n = 51, NYHA, age and M/F n/a	Yes	Yes	n/a	n/a	n/a	n/a	n/a	↓[b] (−37%)	n/a	n/a
Conivaptan, 20–40 mg, oral and i.v. [89]	HF: n = 58, NYHA, age and M/F n/aC: n = 145, age and M/F n/a	Yes	No	n/a	↑	↑	n/a	n/a	→	↑	↑
Tolvaptan, 5–240 mg, oral [94]	PPK: n = 745, age 61 ± 7 years, 484M/261FHF subgroup: n = 628, NYHA I-IV, age 64 ± 13 years, M/F n/a	n/a	Yes	n/a	n/a	n/a	n/a	↓ (−40%)[c] (−49%)[d]	↓ (−42%)[c] (−55%)[d]	n/a	n/a
Dabigatran, 110–150 mg, oral [95]	PPK: n = 9522, age 71 ± 9 years, 6190M/3332FHF subgroup: n = 3039, NYHA I-IV, age and M/F n/a	Yes	n/a	n/a	n/a	n/a	n/a	↑	↓ (−7%)[e]	n/a	↑ (+7%)[e]
Darbopoetin, 0.75–5 s μg kg^{-1}, s.c. and i.v. [90]	HF: n = 33, NYHA II-IV, age n/a, 17M/16FC: n = 30, age n/a, 17M/13F	Yes	n/a	→	↑	n/a	↑	n/a	→	→	↑

AUC, area under the curve; C, controls; CL, clearance; C_{max}, maximum plasma/serum concentration; C_{ss}, concentration at steady state; F, bioavailability; F, female; HF, patients with heart failure; M, male; n/a not available/reported; NYHA, New York Heart Association functional class; PPK, population pharmacokinetics study; T_{max}, time to reach the maximum plasma/serum concentration; $t_{1/2}$, elimination half-life; V_D, volume of distribution

*, significant; ↑, significantly increased; ↓, significantly decreased; →, not statistically different;

[a]Significant difference in males only;

[b]Moderate–severe heart failure vs. controls and subjects with mild heart failure;

[c]NYHA class I–II;

[d]NYHA class III-IV;

[e]NYHA class II-IV vs. controls and subjects with NYHA class I

clearance of mexiletine was significantly reduced (−33%) in HF patients in one study [86], but not in another [61]. No significant pharmacokinetic changes in HF patients were observed with procainamide in four studies, barring a significant reduction (between −17% and −49%) in clearance in two studies [62–64, 75]. Another study reported a significant increase (+114%) in the half-life of procainamide; however, this parameter was estimated by measuring plasma procaine half-life *in vitro* [44, 98]. Studies on quinidine reported a significant increase in the time to reach peak concentrations (+127%) and a significant reduction in volume of distribution (−32%) and clearance (between −34% and −72%) in HF patients. However, there were no significant differences in either bioavailability, maximum serum concentrations, steady-state concentrations or elimination half-life [45, 46, 65, 76].

Renin-angiotensin system inhibitors

Five drugs (enalapril, fosinopril, lisinopril, perindopril and irbesartan) were investigated in five studies (Table 5). An increase in the time to reach peak concentrations (+67%) and elimination half-life (+130%), and a reduced clearance (−75%), were observed with oral enalapril in HF patients. However, no statistical analyses between HF patients and controls were reported in this study [66]. A significant reduction (−74%) in clearance, with an increase (+127%) in the area under the curve, was observed in HF patients with preserved renal function receiving oral lisinopril [67]. Notably, lisinopril is excreted unchanged almost entirely in the urine (Table S1). Patients with HF treated with oral perindopril had similar peak concentrations, a significantly longer time to reach peak concentrations (+137%) and elimination half-life (+360%), and a significantly greater area under the curve (+300%) when compared to controls [87]. However, analysis of the active metabolite perindoprilat yielded different results, with a significant increase in peak concentrations (+220%), a similar time to reach peak concentrations and area under the curve, and a significantly shorter elimination half-life (−92%) in HF patients. It is not possible to establish whether changes in liver and/or renal function might have influenced the results as the relevant information was not provided in this study [87]. By contrast, no significant alterations in the pharmacokinetics of fosinopril and irbesartan were observed in HF [77, 88].

Non-cardiovascular drugs

Five drugs (theophylline, conivaptan, tolvaptan, dabigatran and darbopoetin) were investigated in 10 studies (Table 6). Studies of theophylline pharmacokinetics consistently showed a significant reduction (between −25% and −69%) in clearance in HF patients [47, 48, 68, 78–80]. Two studies also reported a significantly longer (between +84% and +267%) elimination half-life of the drug in HF [68, 79]. By contrast, the volume of distribution was similar to that of controls [47, 68, 79]. Theophylline undergoes significant metabolism in the liver and only a minimal fraction of the unchanged drug is eliminated in the urine (Table S1). Notably, significant liver and renal dysfunction were reported in only one study investigating theophylline pharmacokinetics [48]. A significant reduction in the volume of distribution

(between −40% and −49%) and clearance (between −42% and −55%) of tolvaptan, primarily metabolized by CYP3A4 in the liver (Table S1), were observed in HF patients when compared to controls. The presence of significant liver dysfunction might have at least partly contributed to the alterations in clearance reported in this study [94]. A mild, albeit statistically significant, reduction in clearance (−7%), and a mild increase in the area under the curve (+7%), were observed with dabigatran, a drug that is primarily eliminated in unchanged form in the urine (Table S1), in HF patients. Notably, significant renal dysfunction was reported in these patients [95]. By contrast, the pharmacokinetics of conivaptan and darbopoetin were not significantly affected by HF [89, 90].

Discussion

This review identified studies that investigated pharmacokinetic parameters of currently marketed cardiovascular and selected non-cardiovascular drugs in patients with HF and in control groups. The most studied, and consistently reported, HF-related pharmacokinetic changes involved a limited number of drugs and parameters, i.e. higher steady state concentrations and reduced clearance of the sympathomimetics adrenaline, noradrenaline and isoprenaline [70–72], longer elimination half-life and greater area under the curve of prazosin [41, 57], reduced volume of distribution and clearance of quinidine [45, 65, 76], and reduced clearance of theophylline [47, 48, 68, 78–80]. However, the potential translation of these findings into the contemporary management of HF is partly limited by the specific settings in which these drugs are administered and the current recommendations of professional guidelines. For example, the use of intravenous sympathomimetics is restricted to critically ill patients. Even in the presence of reduced clearance and increased plasma concentrations in HF patients, the infusion rate of sympathomimetics is typically adjusted according to haemodynamic responses, rather than pharmacokinetic parameters [99]. The alpha-1 adrenergic blocker prazosin and the antiarrhythmic quinidine are not commonly prescribed and/or contraindicated in HF [1, 100]. Furthermore, the use of theophylline is largely confined to patients with severe COPD or asthma and those experiencing disease exacerbations [101].

Despite the gastrointestinal tract alterations observed in experimental and human HF, only nine of the identified studies investigated bioavailability. Notably, none of these studies reported significant differences in bioavailability between HF patients and controls [51, 52, 56, 58, 65, 73, 77, 88, 90]. Therefore, the practice of administering several drugs, e.g. digoxin and loop diuretics, intravenously in patients with acute decompensated or end-stage HF with concomitant portal venous congestion and gut wall oedema is not supported by any evidence of a reduced bioavailability in this setting. This review also identified a significant knowledge gap regarding potential HF-related pharmacokinetic changes of several widely prescribed cardiovascular and non-cardiovascular drugs, particularly the aldosterone antagonists spironolactone and eplerenone, the antiarrhythmics

amiodarone, flecainide, verapamil, diltiazem, and sotalol, statins, warfarin and the new oral anticoagulants, antiplatelet drugs and anti-diabetic drugs.

The contrasting results reported in studies investigating digoxin [37, 49, 69, 81, 91, 92], bumetanide [51, 53], furosemide [38, 52, 53], lidocaine [42, 43, 60], mexiletine [61, 86] and procainamide [44, 62–64, 75] might be, at least partly, due to differences in study design and/or participant clinical and demographic characteristics. The available knowledge regarding the pharmacokinetics in HF of other drugs, such as enoximone [50], levosimendan [73], hydroflumethiazide [39], metolazone [40], carvedilol [82], metoprolol [83], nifedipine [54], bosentan [93], hydralazine [55], nicorandil [84], cibenzoline [58], disopyramide [59], ibutilide [85], enalapril [66], fosinopril [77], irbesartan [88], lisinopril [67], perindopril [87], conivaptan [89], tolvaptan [94], dabigatran [95] and darbopoetin [90] is based on results from single studies. However, the data on enoximone, reduced clearance and increased half-life in HF, require further confirmation because of the lack of statistical analyses and the relatively small study population, seven patients with HF and only two controls [50]. Similarly, the study investigating metolazone was conducted in three HF patients and three controls, the population pharmacokinetic study of metoprolol included only five patients with HF, and the study on enalapril did not report statistical analyses [40, 66, 83]. In the studies investigating hydroflumethiazide, carvedilol, lisinopril and perindopril, there was a marked age difference, not accounted for in statistical analysis, between HF patients and controls [39, 67, 82, 87]. Furthermore, a significant number of these studies did not provide information regarding the NYHA functional class [40, 54, 59, 67, 82, 89], age [40, 50, 54, 83, 84, 89, 90, 93, 95], sex [50, 54, 59, 67, 83, 89, 93–95] or presence of significant renal or hepatic impairment [39, 40, 50, 54, 84, 87, 90, 95]. Therefore, it is not possible to clearly establish whether the findings from these studies are directly relevant to the management of HF patients with specific clinical and demographic characteristics.

Several other issues might affect the interpretation of the results of the studies identified in this review. First, no sample size calculation for specific pharmacokinetic parameters was performed, with the exception of two studies [85, 88]. This increases the risk of underpowered studies and, consequently, a type 2 error [102]. Second, there is uncertainty regarding the contributing role of various degrees of renal and hepatic impairment, singly or combined, on the pharmacokinetics of specific drugs in HF. Third, participants had different severity of HF, according to the NYHA functional classification. However, no specific analysis was conducted, barring three studies [48, 94, 95], on the possible effects of severe *vs*. mild HF on pharmacokinetics. Fourth, the potential effect of polymorphisms of transporters and/or metabolizing enzymes on pharmacokinetics was not considered, except for studies on metoprolol and bosentan [83, 93]. Fifth, the potential confounding effect of concomitant drug treatment either on the drugs tested or on organ function, particularly the kidney, was not investigated.

The aforementioned issues, whilst limiting the interpretation of the available evidence, offer several opportunities for more rigorously investigating pharmacokinetic changes in patients with HF in future studies. In such studies, an *a priori* sample size calculation should be based on specific pharmacokinetic parameters, serving as primary end-points. A comprehensive assessment of the severity of HF, based on functional as well as haemodynamic measures, and the presence and severity of concomitant kidney and/or hepatic impairment, should be performed to investigate independent associations between these parameters and pharmacokinetic end-points. The use of physiologically based pharmacokinetic drug-disease models that incorporate information on pathophysiological changes in liver and renal function might be useful in this context. In a recent study, the reduced hepatic and renal blood flows, typically observed in HF [103], were incorporated in two models, one based on human liver and intestinal microsome clearances and the other on the clearance by specific cytochrome P450 enzymes, to predict the pharmacokinetics of carvedilol in HF. The increased severity of HF was strongly associated with a reduction in the hepatic clearance of carvedilol. Furthermore, the incorporation of hepatic and renal blood flow parameters improved the prediction of the area under the curve of carvedilol in some, but not all, HF study groups [104]. Pending further research using this approach, analyses of HF-related pharmacokinetic changes should also take into account the role of specific polymorphisms and the treatment with concomitant drugs [105]. Furthermore, it is now established that a significant proportion of HF patients are frail [106]. As there is evidence that frailty *per se* might affect pharmacokinetics, this factor should be accounted for in future studies in HF [107, 108]. The proposed strategies might allow the identification of those pharmacokinetic changes that are biologically and clinically relevant for the safe and effective management of this complex patient population.

In conclusion, the significant between-study variability in clinical and demographic characteristics, the identified issues with study design, the contrasting results of studies investigating similar drugs, and the paucity of pharmacokinetic data with newer drugs prevent, at this stage, the provision of robust evidence-based recommendations to predict the influence of HF on pharmacokinetics. The proposed suggestions for future clinical studies, together with the development and refinement of physiologically based pharmacokinetic drug-disease HF models, will likely enhance the safe and effective use of several cardiovascular and non-cardiovascular drugs in this patient group.

Competing Interests

There are no competing interests to declare.

References

1 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, *et al*. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the Management of Heart Failure: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136: e137–61.

2 Curtis LH, Whellan DJ, Hammill BG, Hernandez AF, Anstrom KJ, Shea AM, et al. Incidence and prevalence of heart failure in elderly persons, 1994–2003. Arch Intern Med 2008; 168: 418–24.

3 de Giuli F, Khaw KT, Cowie MR, Sutton GC, Ferrari R, Poole-Wilson PA. Incidence and outcome of persons with a clinical diagnosis of heart failure in a general practice population of 696 884 in the United Kingdom. Eur J Heart Fail 2005; 7: 295–302.

4 Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002; 347: 1397–402.

5 van der Wal HH, van Deursen VM, van der Meer P, Voors AA. Comorbidities in heart failure. Handb Exp Pharmacol 2017; 243: 35–66.

6 Sharma A, Zhao X, Hammill BG, Hernandez AF, Fonarow GC, Felker GM, et al. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: insights from the Get With The Guidelines-Heart Failure Registry. Circ Heart Fail 2018; 11: e004646.

7 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 128: 1810–52.

8 Mangoni AA. Cardiovascular drug therapy in elderly patients: specific age-related pharmacokinetic, pharmacodynamic and therapeutic considerations. Drugs Aging 2005; 22: 913–41.

9 Reeve E, Wiese MD, Mangoni AA. Alterations in drug disposition in older adults. Expert Opin Drug Metab Toxicol 2015; 11: 491–508.

10 Benowitz NL, Meister W. Pharmacokinetics in patients with cardiac failure. Clin Pharmacokinet 1976; 1: 389–405.

11 Shammas FV, Dickstein K. Clinical pharmacokinetics in heart failure: an updated review. Clin Pharmacokinet 1988; 15: 94–113.

12 Sokol SI, Cheng A, Frishman WH, Kaza CS. Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure. J Clin Pharmacol 2000; 40: 11–30.

13 Ogawa R, Stachnik JM, Echizen H. Clinical pharmacokinetics of drugs in patients with heart failure: an update (part 1, drugs administered intravenously). Clin Pharmacokinet 2013; 52: 169–85.

14 Ogawa R, Stachnik JM, Echizen H. Clinical pharmacokinetics of drugs in patients with heart failure: an update (part 2, drugs administered orally). Clin Pharmacokinet 2014; 53: 1083–114.

15 Lainscak M, Vitale C, Seferovic P, Spoletini I, Cvan Trobec K, Rosano GM. Pharmacokinetics and pharmacodynamics of cardiovascular drugs in chronic heart failure. Int J Cardiol 2016; 224: 191–8.

16 Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol 2007; 50: 1561–9.

17 Jacob N, Jacobs JP, Kumagai K, Ha CWY, Kanazawa Y, Lagishetty V, et al. Inflammation-independent TL1A-mediated intestinal fibrosis is dependent on the gut microbiome. Mucosal Immunol 2018; 11: 1466–76.

18 Pasini E, Aquilani R, Testa C, Baiardi P, Angioletti S, Boschi F, et al. Pathogenic gut flora in patients with chronic heart failure. JACC Heart Fail 2016; 4: 220–7.

19 Addisu A, Gower WR Jr, Serrano M, Villarreal D, Dietz JR. Heart failure mice exhibit decreased gastric emptying and intestinal absorption. Exp Biol Med (Maywood) 2011; 236: 1454–60.

20 Allen LA, Felker GM, Pocock S, McMurray JJ, Pfeffer MA, Swedberg K, et al. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Eur J Heart Fail 2009; 11: 170–7.

21 Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail 2011; 17: 451–8.

22 Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. Circulation 2016; 133: 1696–703.

23 Henrion J, Descamps O, Luwaert R, Schapira M, Parfonry A, Heller F. Hypoxic hepatitis in patients with cardiac failure: incidence in a coronary care unit and measurement of hepatic blood flow. J Hepatol 1994; 21: 696–703.

24 Carubelli V, Lombardi C, Gorga E, Ravera A, Metra M, Mentz RJ. Cardiorenal interactions. Heart Fail Clin 2016; 12: 335–47.

25 Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol 2016; 12: 610–23.

26 Lawson CA, Testani JM, Mamas M, Damman K, Jones PW, Teece L, et al. Chronic kidney disease, worsening renal function and outcomes in a heart failure community setting: a UK national study. Int J Cardiol 2018; 267: 120–7.

27 Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. Eur J Clin Invest 2012; 42: 153–63.

28 Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JP. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. Mod Pathol 2015; 28: 932–43.

29 Macolic V, Vrhovac B. Pharmacokinetics and interactions of digoxin, theophylline and furosemide in diseases with edema. Int J Clin Pharmacol Ther Toxicol 1993; 31: 6–11.

30 Vrhovac B, Sarapa N, Bakran I, Huic M, Macolic-Sarinic V, Francetic I, et al. Pharmacokinetic changes in patients with oedema. Clin Pharmacokinet 1995; 28: 405–18.

31 Saitoh M, Ishida J, Doehner W, von Haehling S, Anker MS, Coats AJS, et al. Sarcopenia, cachexia, and muscle performance in heart failure: review update 2016. Int J Cardiol 2017; 238: 5–11.

32 Trobec K, Kerec Kos M, von Haehling S, Springer J, Anker SD, Lainscak M. Pharmacokinetics of drugs in cachectic patients: a systematic review. PLoS One 2013; 8: e79603.

33 Buckingham R. Martindale: the complete drug reference 2018. Available at http://www.medicinescomplete.com.salus.idm.oclc.org/ (last accessed 1 July 2018).

34 Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res 2018; 46: D1074–82.

35 Brunton LL, Chabner BA, Knollmann BC. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th edn. New York: McGraw-Hill, 2011.

36 Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995; 12: 413–20.

37 Korhonen UR, Jounela AJ, Pakarinen AJ, Pentikainen PJ, Takkunen JT. Pharmacokinetics of digoxin in patients with acute myocardial infarction. Am J Cardiol 1979; 44: 1190–4.

38 Andreasen F, Mikkelsen E. Distribution, elimination and effect of furosemide in normal subjects and in patients with heart failure. Eur J Clin Pharmacol 1977; 12: 15–22.

39 Brors O, Jacobsen S, Arnesen E. Pharmacokinetics of a single oral dose of hydroflumethiazide in health and in cardiac failure. Eur J Clin Pharmacol 1978; 14: 29–37.

40 Tilstone WJ, Dargie H, Dargie EN, Morgan HG, Kennedy AC. Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. Clin Pharmacol Ther 1974; 16: 322–9.

41 Jaillon P, Rubin P, Yee YG, Ball R, Kates R, Harrison D, et al. Influence of congestive heart failure on prazosin kinetics. Clin Pharmacol Ther 1979; 25: 790–4.

42 Thomson PD, Melmon KL, Richardson JA, Cohn K, Steinbrunn W, Cudihee R, et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. Ann Intern Med 1973; 78: 499–508.

43 Prescott LF, Adjepon-Yamoah KK, Talbot RG. Impaired lignocaine metabolism in patients with myocardial infarction and cardiac failure. Br Med J 1976; 1: 939–41.

44 du Souich P, Erill S. Metabolism of procainamide in patients with chronic heart failure, chronic respiratory failure and chronic renal failure. Eur J Clin Pharmacol 1978; 14: 21–7.

45 Crouthamel WG. The effect of congestive heart failure on quinidine pharmacokinetics. Am Heart J 1975; 90: 335–9.

46 Kessler KM, Lowenthal DT, Warner H, Gibson T, Briggs W, Reidenberg MM. Quinidine elimination in patients with congestive heart failure or poor renal function. N Engl J Med 1974; 290: 706–9.

47 Powell JR, Vozeh S, Hopewell P, Costello J, Sheiner LB, Riegelman S. Theophylline disposition in acutely ill hospitalized patients. The effect of smoking, heart failure, severe airway obstruction, and pneumonia. Am Rev Respir Dis 1978; 118: 229–38.

48 Jusko WJ, Gardner MJ, Mangione A, Schentag JJ, Koup JR, Vance JW. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. J Pharm Sci 1979; 68: 1358–66.

49 Naafs MA, van der Hoek C, van Duin S, Koorevaar G, Schopman W, Silberbusch J. Decreased renal clearance of digoxin in chronic congestive heart failure. Eur J Clin Pharmacol 1985; 28: 249–52.

50 Lima JJ, Leier CV, Holtz L, Sterechele J, Shields BJ, MacKichan JJ. Oral enoximone pharmacokinetics in patients with congestive heart failure. J Clin Pharmacol 1987; 27: 654–60.

51 Cook JA, Smith DE, Cornish LA, Tankanow RM, Nicklas JM, Hyneck ML. Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with congestive heart failure. Clin Pharmacol Ther 1988; 44: 487–500.

52 Brater DC, Seiwell R, Anderson S, Burdette A, Dehmer GJ, Chennavasin P. Absorption and disposition of furosemide in congestive heart failure. Kidney Int 1982; 22: 171–6.

53 Brater DC, Day B, Burdette A, Anderson S. Bumetanide and furosemide in heart failure. Kidney Int 1984; 26: 183–9.

54 Chen DG, Feng QP, Wang ZQ, Chen K. Pharmacodynamics and pharmacokinetics of nifedipine in patients with congestive heart failure. Zhongguo Yao Li Xue Bao 1989; 10: 233–8.

55 Hanson A, Johansson BW, Wernersson B, Wahlander LA. Pharmacokinetics of oral hydralazine in chronic heart failure. Eur J Clin Pharmacol 1983; 25: 467–73.

56 Fung HL, Ruggirello D, Stone JA, Parker JO. Effects of disease, route of administration, cigarette smoking, food intake on the pharmacokinetics and circulatory effects of isosorbide dinitrate. Z Kardiol 1983; 72 (Suppl. 3): 5–10.

57 Baughman RA Jr, Arnold S, Benet LZ, Lin ET, Chatterjee K, Williams RL. Altered prazosin pharmacokinetics in congestive heart failure. Eur J Clin Pharmacol 1980; 17: 425–8.

58 Massarella JW, Silvestri T, DeGrazia F, Miwa B, Keefe D. Effect of congestive heart failure on the pharmacokinetics of cibenzoline. J Clin Pharmacol 1987; 27: 187–92.

59 Bonde J, Angelo HR, Bodtker S, Svendsen TL, Kampmann JP. Kinetics of disopyramide after intravenous infusion to patients with myocardial infarction and heart failure. Acta Pharmacol Toxicol (Copenh) 1985; 56: 278–82.

60 Cusson J, Nattel S, Matthews C, Talajic M, Lawand S. Age-dependent lidocaine disposition in patients with acute myocardial infarction. Clin Pharmacol Ther 1985; 37: 381–6.

61 Vozeh S, Katz G, Steiner V, Follath F. Population pharmacokinetic parameters in patients treated with oral mexiletine. Eur J Clin Pharmacol 1982; 23: 445–51.

62 Kessler KM, Kayden DS, Estes DM, Koslovskis PL, Sequeira R, Trohman RG, et al. Procainamide pharmacokinetics in patients with acute myocardial infarction or congestive heart failure. J Am Coll Cardiol 1986; 7: 1131–9.

63 Grasela TH, Sheiner LB. Population pharmacokinetics of procainamide from routine clinical data. Clin Pharmacokinet 1984; 9: 545–54.

64 Bauer LA, Black D, Gensler A, Sprinkle J. Influence of age, renal function and heart failure on procainamide clearance and n-acetylprocainamide serum concentrations. Int J Clin Pharmacol Ther Toxicol 1989; 27: 213–6.

65 Ueda CT, Dzindzio BS. Bioavailability of quinidine in congestive heart failure. Br J Clin Pharmacol 1981; 11: 571–7.

66 Schwartz JB, Taylor A, Abernethy D, O'Meara M, Farmer J, Young J, et al. Pharmacokinetics and pharmacodynamics of enalapril in patients with congestive heart failure and patients with hypertension. J Cardiovasc Pharmacol 1985; 7: 767–76.

67 Gautam PC, Vargas E, Lye M. Pharmacokinetics of lisinopril (MK521) in healthy young and elderly subjects and in elderly patients with cardiac failure. J Pharm Pharmacol 1987; 39: 929–31.

68 Kuntz HD, Straub H, May B. Theophylline elimination in congestive heart failure. Klin Wochenschr 1983; 61: 1105–6.

69 Yukawa E, Honda T, Ohdo S, Higuchi S, Aoyama T. Population-based investigation of relative clearance of digoxin in Japanese patients by multiple trough screen analysis: an update. J Clin Pharmacol 1997; 37: 92–100.

70 Kaye DM, Lefkovits J, Cox H, Lambert G, Jennings G, Turner A, *et al*. Regional epinephrine kinetics in human heart failure: evidence for extra-adrenal, nonneural release. Am J Physiol 1995; 269: H182–8.

71 Stylos L, Parilak L, Green MH, Leuenberger U, Zelis R. Compartmental analysis of norepinephrine kinetics in congestive heart failure. Am J Cardiol 1995; 75: 299–301.

72 Leuenberger U, Kenney G, Davis D, Clemson B, Zelis R. Comparison of norepinephrine and isoproterenol clearance in congestive heart failure. Am J Physiol 1992; 263: H56–60.

73 Sandell EP, Hayha M, Antila S, Heikkinen P, Ottoila P, Lehtonen LA, *et al*. Pharmacokinetics of levosimendan in healthy volunteers and patients with congestive heart failure. J Cardiovasc Pharmacol 1995; 26 (Suppl. 1): S57–62.

74 Meissner A, Petersenn S, Heidemann HT, Osterkamp U, Simon R, Schulte HM. Pharmacokinetics of oral isosorbide-5-mononitrate in patients with ischemic heart failure. Klin Wochenschr 1991; 69: 213–9.

75 Tisdale JE, Rudis MI, Padhi ID, Borzak S, Svensson CK, Webb CR, *et al*. Disposition of procainamide in patients with chronic congestive heart failure receiving medical therapy. J Clin Pharmacol 1996; 36: 35–41.

76 Fattinger K, Vozeh S, Ha HR, Borner M, Follath F. Population pharmacokinetics of quinidine. Br J Clin Pharmacol 1991; 31: 279–86.

77 Kostis JB, Garland WT, Delaney C, Norton J, Liao WC. Fosinopril: pharmacokinetics and pharmacodynamics in congestive heart failure. Clin Pharmacol Ther 1995; 58: 660–5.

78 Otero MJ, Buelga DS, Vazquez MA, Barrueco M, Dominguez-Gil A. Application of population pharmacokinetics to the optimization of theophylline therapy. J Clin Pharm Ther 1996; 21: 113–25.

79 Cuzzolin L, Schinella M, Tellini U, Pezzoli L, Lippi U, Benoni G. The effect of sex and cardiac failure on the pharmacokinetics of a slow-release theophylline formulation in the elderly. Pharmacol Res 1990; 22 (Suppl. 1): 137–8.

80 Ueno K, Miyai K, Koyama M, Seki T, Kawaguchi Y, Horiuchi Y. Effect of congestive heart failure on theophylline disposition. Clin Pharm 1990; 9: 936–7.

81 Yukawa E, Suematu F, Yukawa M, Minemoto M, Ohdo S, Higuchi S, *et al*. Population pharmacokinetics of digoxin in Japanese patients: a 2-compartment pharmacokinetic model. Clin Pharmacokinet 2001; 40: 773–81.

82 Laer S, Mir TS, Behn F, Eiselt M, Scholz H, Venzke A, *et al*. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. Am Heart J 2002; 143: 916–22.

83 Taguchi M, Nozawa T, Mizumaki K, Inoue H, Tahara K, Takesono C, *et al*. Nonlinear mixed effects model analysis of the pharmacokinetics of metoprolol in routinely treated Japanese patients. Biol Pharm Bull 2004; 27: 1642–8.

84 Iida S, Kinoshita H, Holford NH. Population pharmacokinetic and pharmacodynamic modelling of the effects of nicorandil in the treatment of acute heart failure. Br J Clin Pharmacol 2008; 66: 352–65.

85 Tisdale JE, Overholser BR, Sowinski KM, Wroblewski HA, Amankwa K, Borzak S, *et al*. Pharmacokinetics of ibutilide in patients with heart failure due to left ventricular systolic dysfunction. Pharmacotherapy 2008; 28: 1461–70.

86 Kobayashi M, Fukumoto K, Ueno K. Effect of congestive heart failure on mexiletine pharmacokinetics in a Japanese population. Biol Pharm Bull 2006; 29: 2267–9.

87 Bellissant E, Giudicelli JF. Pharmacokinetic-pharmacodynamic model for perindoprilat regional haemodynamic effects in healthy volunteers and in congestive heart failure patients. Br J Clin Pharmacol 2001; 52: 25–33.

88 Kostis JB, Vachharajani NN, Hadjilambris OW, Kollia GD, Palmisano M, Marino MR. The pharmacokinetics and pharmacodynamics of irbesartan in heart failure. J Clin Pharmacol 2001; 41: 935–42.

89 Mao ZL, Stalker D, Keirns J. Pharmacokinetics of conivaptan hydrochloride, a vasopressin V(1A)/V(2)-receptor antagonist, in patients with euvolemic or hypervolemic hyponatremia and with or without congestive heart failure from a prospective, 4-day open-label study. Clin Ther 2009; 31: 1542–50.

90 Cleland JG, Sullivan JT, Ball S, Horowitz JD, Agoram B, Rosser D, *et al*. Once-monthly administration of darbepoetin alfa for the treatment of patients with chronic heart failure and anemia: a pharmacokinetic and pharmacodynamic investigation. J Cardiovasc Pharmacol 2005; 46: 155–61.

91 Yukawa M, Yukawa E, Suematsu F, Takiguchi T, Ikeda H, Aki H, *et al*. Determination of digoxin clearance in Japanese elderly patients for optimization of drug therapy: a population pharmacokinetics analysis using nonlinear mixed-effects modelling. Drugs Aging 2011; 28: 831–41.

92 Chen R, Zou SL, Wang ML, Jiang Y, Xue H, Qian CY, *et al*. Population pharmacokinetics of digoxin in elderly patients. Eur J Drug Metab Pharmacokinet 2013; 38: 115–21.

93 Taguchi M, Ichida F, Hirono K, Miyawaki T, Yoshimura N, Nakamura T, *et al*. Pharmacokinetics of bosentan in routinely treated Japanese pediatric patients with pulmonary arterial hypertension. Drug Metab Pharmacokinet 2011; 26: 280–7.

94 Van Wart SA, Shoaf SE, Mallikaarjun S, Mager DE. Population pharmacokinetics of tolvaptan in healthy subjects and patients with hyponatremia secondary to congestive heart failure or hepatic cirrhosis. Biopharm Drug Dispos 2013; 34: 336–47.

95 Liesenfeld KH, Lehr T, Dansirikul C, Reilly PA, Connolly SJ, Ezekowitz MD, *et al*. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemost 2011; 9: 2168–75.

96 Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet 2007; 46: 535–52.

97 Jaillon P. Clinical pharmacokinetics of prazosin. Clin Pharmacokinet 1980; 5: 365–76.

98 Reidenberg MM, James M, Dring LG. The rate of procaine hydrolysis in serum of normal subjects and diseased patients. Clin Pharmacol Ther 1972; 13: 279–84.

99 Annane D, Ouanes-Besbes L, de Backer D, Du B, Gordon AC, Hernandez G, *et al*. A global perspective on vasoactive agents in shock. Intensive Care Med 2018; 44: 833–46.

100 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al*. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891–975.

101 Barnes PJ. Theophylline. Am J Respir Crit Care Med 2013; 188: 901–6.

102 Stolley PD, Strom BL. Sample size calculations for clinical pharmacology studies. Clin Pharmacol Ther 1986; 39: 489–90.

103 Leithe ME, Margorien RD, Hermiller JB, Unverferth DV, Leier CV. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. Circulation 1984; 69: 57–64.

104 Rasool MF, Khalil F, Laer S. A physiologically based pharmacokinetic drug-disease model to predict carvedilol exposure in adult and paediatric heart failure patients by incorporating pathophysiological changes in hepatic and renal blood flows. Clin Pharmacokinet 2015; 54: 943–62.

105 Talameh JA, Lanfear DE. Pharmacogenetics in chronic heart failure: new developments and current challenges. Curr Heart Fail Rep 2012; 9: 23–32.

106 Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: a systematic review and meta-analysis. Int J Cardiol 2017; 236: 283–9.

107 Wynne HA, Yelland C, Cope LH, Boddy A, Woodhouse KW, Bateman DN. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. Age Ageing 1993; 22: 354–9.

108 Johnston C, Hilmer SN, McLachlan AJ, Matthews ST, Carroll PR, Kirkpatrick CM. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J Clin Pharmacol 2014; 70: 549–55.

Supporting Information

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

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Table S1 Physicochemical and pharmacokinetic characteristics of the identified cardiovascular and non-cardiovascular drugs