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ORIGINAL ARTICLE

The safe use of metformin in heart failure patients both with and without T2DM: A cross-sectional and longitudinal study

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Aims: This study investigated the safe use of metformin in patients with (1) type 2 diabetes mellitus (T2DM) and heart failure on metformin, and (2) heart failure without T2DM and metformin naïve.

Methods: Two prospective studies on heart failure patients were undertaken. The first was a cross-sectional study with two patient cohorts, one with T2DM on metformin (n = 44) and one without T2DM metformin naive (n = 47). The second was a 12-week interventional study of patients without T2DM (n = 27) where metformin (500 mg immediate release, twice daily) was prescribed. Plasma metformin and lactate concentrations were monitored. Individual pharmacokinetics were compared between cohorts. Univariable and multivariable analysis analysed the effects of variables on plasma lactate concentrations.

Results: Plasma metformin and lactate concentrations mostly (99.9%) remained below safety thresholds (5 mg/L and 5 mmol/L, respectively). Metformin concentration had no significant relationship with lactic acidosis safety markers. In the interventional study, New York Heart Association (NYHA) II ($P < .03$) and III ($P < .001$) grading was associated with higher plasma lactate concentrations, whereas male sex was associated with 47% higher plasma lactate concentrations ($P < .05$). The pharmacokinetics of heart failure patients with and without T2DM were similar.

Conclusions: We observed no unsafe plasma lactate concentrations in patients with heart failure treated with metformin. Metformin exposure did not influence plasma lactate concentrations, but NYHA class and sex did. The pharmacokinetics of metformin in heart failure patients are similar irrespective of T2DM. These findings may support the safe use of metformin in heart failure patients with and without T2DM.

KEYWORDS
diabetes, drug safety, heart failure, pharmacokinetics

1 | INTRODUCTION

Heart failure and type 2 diabetes mellitus (T2DM) are often comorbid chronic conditions. Metformin is one of the few antihyperglycemic (AHG) agents that does not increase the risk of hospitalization in heart failure patients (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.75-0.98).[1,2] It is therefore important to optimize the use of metformin in heart failure. Metformin has a well-described safety profile in uncomplicated T2DM patients; it does not cause hypoglycaemia and reduces glycated haemoglobin (HbA1C).[3] Metformin also has benefits beyond glycaemic control, including weight neutrality and cardiovascular protection.[4] It has been shown to reduce the risk of myocardial infarction by 39%, all-cause macrovascular disease by 30%[5] and overall all-cause mortality of heart failure patients.[6]

The cardiovascular benefits of metformin have been recognized, with metformin prescribed in approximately 20-25% of all heart failure patients with T2DM.[7] However, in Australia, according to the product information, metformin is currently contraindicated in patients with "acute or chronic disease that causes tissue hypoxia including cardiac failure".[8] These constraints are attributed to the perceived risk of lactic acidosis (lactate >5 mmol/L and arterial pH < 7.35), a rare but potentially fatal form of metabolic acidosis.[9] When lactic acidosis occurs in the setting of metformin use, it is termed metformin-associated lactic acidosis (MALA). However, usually, there are other contributing factors making causality difficult to discern. For example, T2DM itself is associated with increased plasma lactate concentrations.[10–12] Recent work suggests metformin can be given safely in T2DM populations who have been considered at risk of developing lactic acidosis, including those with chronic liver disease (CLD) and chronic kidney disease (CKD).[13–16]

Knowledge of the pharmacokinetics of metformin in heart failure patients is limited. In the absence of evidence, dosing decisions are made based on regimens commonly used in other patient populations or extrapolating findings from pharmacokinetic studies of other heart failure medications such as perindopril, carvedilol and furosemide, which show consistent reductions in drug absorption and distribution.[17–19] This change in drug disposition has been attributed to heart failure progression, specifically organ hypoperfusion, which leads to congestion that can result in injury and potential failure of target organs, including the liver, kidneys and intestines.[20] Metformin is absorbed predominately via active transport in the jejunum region of the small intestine.[21] In heart failure, intestinal congestion is common, especially in the small intestine.[20,22,23] These changes could alter the pharmacokinetics of metformin in heart failure patients, consequently necessitating dose adjustments. Due to a lack of safety data, the use of metformin in heart failure currently focuses on dosing and monitoring the patient based on renal function. A better understanding of the factors associated with lactic acidosis and the pharmacokinetics of metformin in heart failure are required to inform dosing decisions. This study therefore investigated the safety and pharmacokinetics of metformin in patients with (1) T2DM and heart failure already prescribed metformin, and (2) heart failure without T2DM and metformin naïve.

What is already known about this subject

- Metformin is contraindicated for heart failure patients in Australia due to a concern regarding lactic acidosis.
- Metformin is prescribed for patients with heart failure despite this contraindication.
- Understanding of the safety and pharmacokinetics of metformin in heart failure patients with respect to plasma metformin, lactate, bicarbonate and anion gap concentrations is lacking.

What this study adds

- Metformin appears to be safe to use in heart failure patients if the plasma metformin and lactate concentrations are maintained below 5 mg/L and 5 mmol/L, respectively.
- Steady-state metformin concentrations do not influence plasma lactate concentrations. However, male sex and New York Heart Association grading were significantly associated with increased plasma lactate concentrations in heart failure patients on metformin.

2 | METHODS

2.1 | Study design

Two studies in heart failure patients were undertaken in two hospitals in Sydney, Australia: a prospective, cross-sectional observational study with two cohorts (both with heart failure, one with and one without T2DM) and a prospective, interventional study (heart failure patients without T2DM) (Figure 1). Inclusion criteria for both studies were patients with all-cause heart failure, namely reduced (HFrEF) and preserved (HfpEF) ejection fractions, New York Heart Association (NYHA) grading I-III, and with an estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2. Patients were over the age of 18 years and gave written, informed consent to participate. Patients were recruited between February 2016 and December 2021 from heart failure and diabetes outpatient clinics at St Vincent's Hospital, Sydney, and Liverpool Hospital, Sydney. The screening visit for all studies was defined as the first visit of the patient in which demographic information was collected and a venous blood sample was drawn. The exit visit was defined as the week 12 study visit for the interventional study only. For all studies, plasma metformin and lactate concentrations above the safety threshold (5 mg/L and 5 mmol/L) were reported to study clinicians for safety monitoring. The study was approved on 18 February 2016 by the St Vincent's Hospital Human Research and Ethics Committee (HREC/15/SVH/43) and registered (ACTRN12617001418369).

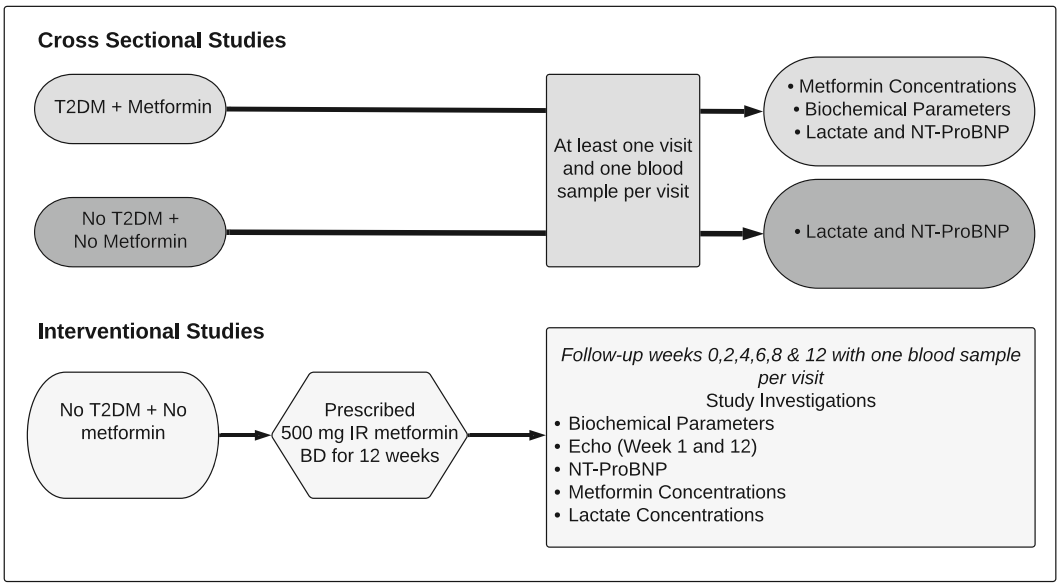

FIGURE 1 All study flow diagram for the cross-sectional and interventional study. BD, twice daily; Echo, echocardiogram; IR, immediate release; NT-ProBNP, N-terminal B-type natriuretic peptide; T2DM, type II diabetes mellitus.

2.2 | Prospective, cross-sectional studies

The prospective, cross-sectional study opportunistically recruited two cohorts of patients with heart failure, the first with T2DM already on metformin, and the second without T2DM and metformin naïve. Patients attended at least one study visit (screening) where demographics, medical history and concomitant medications were recorded (Supporting Information Table S5). At least one venous blood sample (random time) was collected to determine plasma lactate, N-terminal B-type natriuretic peptide (NT-ProBNP) concentrations and standard biochemistry (Supporting Information Table S3). The same data was collected at any unscheduled or opportunistic additional visits. For the first cohort with T2DM on metformin, metformin prescription history (dosage, time of last dose) and a venous blood sample to determine plasma metformin concentration were collected (Supporting Information Table S3).

2.3 | Prospective, interventional study

The prospective, interventional study was conducted in patients with heart failure without T2DM (to avoid potential confounding of T2DM on plasma lactate concentrations) who were metformin naïve. Eligible patients were prescribed a low dose (500 mg immediate release) formulation, twice daily for 12 weeks. Patients attended up to six study visits (weeks 0, 2, 4, 6, 8 and 12). On screening (week 0), demographics, medical history and concomitant medications were collected (Supporting Information Table S5). At each study visit venous blood samples (random time) for determination of plasma metformin, lactate and standard biochemistry parameters were collected (Supporting Information Table S4). Patients recorded their metformin dosing history in a diary and reported any adverse effects. Patients who attended at least one study visit formed the intention-to-treat (ITT) population and those who attended all study visits formed the per protocol (PP) population.

2.4 | Assessment of heart failure severity

For all studies, at screening, heart failure severity was assessed using clinician assessment and clinical diagnostic tools. The severity of heart failure was determined by study clinicians using the NYHA grading system, 2015. Echocardiogram (echo) within 6 months of the first visit was accepted to categorise the ejection fraction (EF). Patients with an EF below 45% were classified as having reduced EF (HfrEF) and those with an EF above or equal to 45%, preserved EF (HfpEF). NT-ProBNP plasma concentration was used as a supportive indicator of heart failure severity. Estimates of renal function for all studies included the calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and creatinine clearance estimated by the Cockcroft-Gault formula using lean body weight.

2.5 | Biochemical analysis

Biochemical analyses, except for metformin, were conducted at the central pathology laboratory (SydPath, St Vincent's Hospital, Sydney) using standard methods. Plasma concentrations of metformin were determined by high-performance liquid chromatography (Shimadzu Prominence system; Shimazdu, Rydalmere, NSW, Auatralia), conducted in the Clinical Pharmacology laboratory, St Vincent's Hospital,

Sydney. A validated adapted method[24] was used (Supporting Information Text S1). The inter-day variability of low and high QC samples for plasma were 1.5% and 1.1%, respectively. Samples were assayed in duplicate.

2.6 | Statistical analyses

IBM SPSS Statistics (IBM Corp, Version 28.0, Armonk, USA) was used for all analyses on the effects of variables on plasma lactate concentrations. For the cross-sectional study, a linear regression model was used to test if any of the variables (furosemide dose, steady-state metformin concentration [$C_{av,ss}$], NT-ProBNP, age, sex, body mass index [BMI], left ventricular assist device [LVAD] status, NYHA grading, EF) predicted plasma lactate concentrations. For the prospective, interventional study, a generalized linear-mixed effects model was used with random slopes for individuals across time, with log-lactate as a response variable. Four models were used (Supporting Information Table S8). Model predictor variables were eliminated based on the largest *P* value in the multivariate-adjusted model. $C_{av,ss}$ (mg/L) and time (weeks on metformin) were included in all models. Beta coefficients were transformed to the normal scale by exponentiating the values from the log domain. Model fit was assessed by Akaike information criteria. The multiple imputation method in SPSS was used to address any missing data (Supporting Information Text S1).

All graphing and other statistical analyses were performed in Graphpad Prism (Graphpad Software Inc., version 9.3.1, San Diego, California, USA). For comparisons of pharmacokinetic parameters, nonparametric analyses were performed due to nonnormal distribution of data; Kruskal Wallis ANOVA and Dunns multiple comparison tests were performed.

We used a binomial noninferiority test of one proportion for the power calculation. A noninferiority proportion of 15% of heart failure patients with plasma lactate exceeding of 4 mmol/L in those taking metformin was judged to be the maximum clinically acceptable proportion for this trial. Assuming an actual proportion of 0.5% of patients exceeded 4 mmol/L, a target power of 90% and alpha of 0.025, a sample size of 19 was estimated (using PASS software PASS 2020, NCSS Statistical Software, version 20.0.9, Kaysville, Utah, USA).

2.7 | Pharmacokinetic analyses

A previously published two-compartment population pharmacokinetic model[25] was used to obtain pharmacokinetic parameters (empirical Bayes estimates) for each patient (method: MAXEVAL = 0, NONMEM 7.4 Icon development solutions). Body weight, height, age, sex and plasma metformin and creatinine concentrations for each patient were entered into the population model to obtain each individual's pharmacokinetic parameters. The apparent clearance of metformin (CL/F) and apparent central volume of distribution (Vc/*F*) values obtained from the cross-sectional and prospective study were compared. $C_{av,ss}$ were calculated for each participant by dividing the area under the plasma metformin concentration-time curve (derived as dose/CL/*F*) by the dosage interval in hours. Visual predictive checks were performed to evaluate the suitability of the published population pharmacokinetic model to estimate the pharmacokinetic values in our study population.

2.8 | Nomenclature of targets and ligands

Key proteins targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to Pharmacology 2019/20.

3 | RESULTS

3.1 | Cross-sectional studies

In the cross-sectional study, 99 patients with heart failure were recruited (52 with and 47 without T2DM) (Table 1). Among those with T2DM, eight patients were excluded before their first study visit (lost to follow-up), leaving an analytic sample of 44 T2DM patients.

A total of 44 patients were recruited to the heart failure and T2DM cohort, 43 patients attended one visit and one patient attended two visits. Most patients in this cohort had HFrEF (70%; Table 1) and the main cause of heart failure was ischemic heart disease (57%; Supporting Information Table S1). Aside from metformin, the main AHG medications prescribed were insulin (23%) and sodium-glucose cotransporter-2 inhibitors (19%). The heart failure medications prescribed were mainly beta-blockers (66%) followed by loop diuretics (44%) (Supporting Information Table S5).

A total of 47 patients were recruited for the heart failure without T2DM cohort. All patients attended one study visit only. Most patients in this cohort had HFrEF (72%; Table 1) and the main cause of heart failure was idiopathic (41%). The main heart failure medications prescribed were beta-blockers (66%) and loop diuretics (66%; Supporting Information Table S5).

3.2 | Interventional study

Twenty-seven patients with heart failure and without T2DM were commenced on metformin in the prospective, interventional study. Of these, 26 (ITT population) attended at least one study visit and 22 (PP population) completed the study (18% dropout rate) (Figure 2). Reasons for dropout following the screening visit included loss due to cardiac transplant (n = 1) (Figure 2). The number of study visits attended by ITT patients at which blood was collected ranged from two to four. Reasons for exclusion of patients from the PP population included loss due to cardiac transplant (n = 2), loss to follow-up

TABLE 1 Baseline patient demographics, heart failure characteristics and biochemistry for all studies.

	Cross-sectional		Prospective, interventional
	HF, T2DM, metformin (n = 44)	HF, no T2DM, no metformin (n = 47)	HF, no T2DM (ITT), metformin (n = 26)
General patient characteristics			
Age (y)	63 ± 13	61 ± 13	61 ± 12
Weight (kg)	93 ± 17	85 ± 19	88 ± 15
BMI (kg/m^2)	31 ± 5	28 ± 5	29 ± 4
eGFR (mL/min/1.73m^2)[a]	62 (25->90)	60 (19->90)	61 (35->90)
Sex (% male)[+]	40 (93)	35 (75)	22 (81)
BMI category+ (kg/m^2)			
Underweight (<18.5)	…	2 (4)	…
Normal (18.5-24.9)	4 (9)	11 (23)	8 (29)
Overweight, not obese (25 ≥ BMI < 30)	15 (34)	28 (60)	5 (18)
Obese (BMI ≥ 30)	25 (57)	12 (25)	14 (51)
HF severity			
NYHA grading[b]			
I	1 (2)	…	2 (7)
II	23 (53)	32 (68)	8 (30)
III	20 (45)	15 (32)	17 (63)
Ejection fraction (%)[b]			
HFrEF (<45%)	31 (70)	34 (72)	17 (63)
HFpEF(>45%)	13 (30)	13 (28)	10 (37)
NT-ProBNP concentration (ng/mL)[a]	498 [30-4100]	1170 [71-11 229]	771 [153-7637]
Safety and monitoring [reference range]			
Lactate concentration (mmol/L) [0.0-5.0]	2.0 ± 0.7	1.5 ± 1.8	1.6 ± 0.7
Anion gap (mmol/L) [12.0-18.0]	18.0 ± 5.1	19.0 ± 3.0	18.3 ± 3.3
HCO_3^- (mmol/L) [22.0-32.0]	27.0 ± 4.3	25.0 ± 5.0	26.0 ± 2.5
HbA1c (%) [0.0-5.9]	7.5 ± 1.8	N/A	5.5 ± 0.4

[a]Median (range).
[b]n (%).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HCO_3^-, bicarbonate; HbA1c, glycosylated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ITT, intention-to-treat; N/A, not applicable; NT-ProBNP, N-terminal of the b-type natriuretic peptide; NYHA, New York Heart Association; T2DM, type II diabetes mellitus.

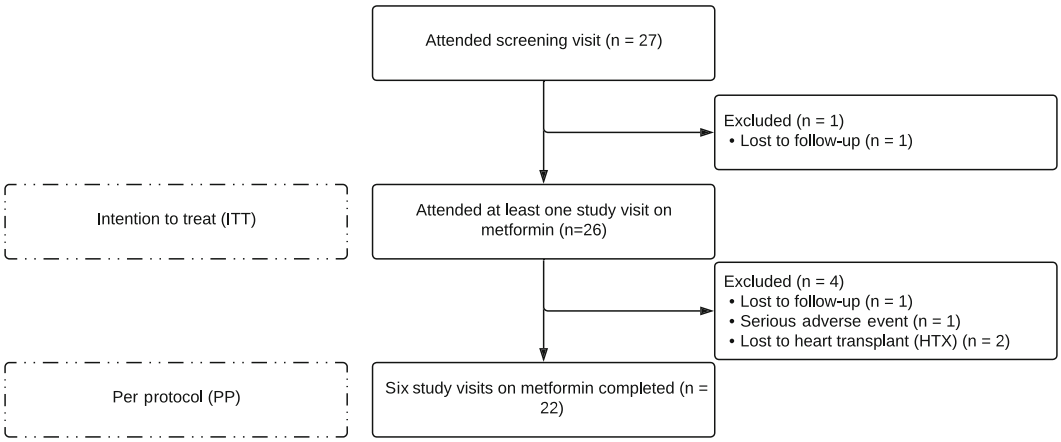

FIGURE 2 Interventional study population for patients with heart failure without type II diabetes mellitus. HTX, heart transplant.

(n = 1) and suspected unexpected serious adverse reaction (n = 1). For the ITT and PP subgroups, most patients had HFrEF (63%; Table 1) and the main cause of heart failure was idiopathic (41%; Supporting Information Table S1). Baseline heart failure medications prescribed included loop diuretics (82%) and beta-blockers (78%; Supporting Information Table S5).

3.3 | Metformin concentrations and pharmacokinetics in heart failure patients

For both the cross-sectional and interventional study the majority (68% and 97%, respectively) of patient plasma samples were collected within 10 h of dosing metformin (Table 2 and Supporting Information Figure S5). Plasma metformin concentrations remained below 5 mg/L in both studies, except for one patient in the cross-sectional study who had a single elevated concentration (5.92 mg/L). As patient renal function improved, plasma metformin concentrations (Supporting Information Figure S4) and $C_{av,ss}$ (Supporting Information Figure S6) decreased and apparent metformin clearance (CL_F) increased (Supporting Information Figure S6). The plasma metformin concentration data from both studies fit the two-compartment population pharmacokinetic model well (Supporting Information Figure S2). The metformin pharmacokinetic parameters were similar for the patients in the interventional and cross-sectional studies (Table 2).

3.4 | Metabolic effects of metformin use in heart failure patients with and without T2DM

$C_{av,ss}$ was not associated with any of the safety markers in heart failure patients irrespective of T2DM comorbidity (Supporting Information Figure S1).

3.4.1 | Cross-sectional study

Plasma lactate concentrations remained below 5 mmol/L for all patients except for one in the heart failure without T2DM cross-sectional cohort (Supporting Information Table S9 and Figure 3). Serum bicarbonate concentrations were mostly within the reference range, whereas most (52-66%) patients had elevated anion gap (Table S9 and Figure 3).

3.4.2 | Interventional study

Plasma lactate, serum bicarbonate and anion gap concentrations remained unchanged after initiation of metformin (Supporting Information Table S8 and Figure 3). Half (50%) of the anion gap concentrations were above the reference range upper limit but there was no trend discernible (Supporting Information Table S9 and Figure 3).

3.5 | Factors associated with plasma lactate concentrations in patients with heart failure on metformin

For the interventional study, univariable analysis revealed that BMI, EF, NT-ProBNP concentrations, LVAD status, sex and NYHA grading contributed to interpatient variability in plasma lactate concentrations in a linear mixed model (Supporting Information Table S8). Following multivariable analysis (Supporting Information Table S8), sex and NYHA grading (Table 3) remained significant ($P < .05$).

Male sex was associated with 44% higher plasma lactate concentrations compared to females (Table 3 and Figure 4). Increasing NYHA grades were associated with higher plasma lactate concentrations

TABLE 2 Estimated pharmacokinetic values (median and ranges) for metformin and renal function for patients in the cross-sectional and interventional studies.

	Cross-sectional heart failure with T2DM (n = 44)	Interventional heart failure no T2DM (n = 26)	*P* value
CL/F[a] (mL/min)	40 (16-109)	34 (11-75)	>0.99
CLcr (mL/min)	57 (25-127)	60 (30-138)	>0.99
Vd (L)	335 (81-724)	284 (80-742)	0.06
$T_{1/2}$ (h)	9.3 (2.6-18.6)	7.9 (2.4-17.4)	0.22
$C_{av,ss}$ (mg/L)	1.0 (0.4-2.5)	1.3 (0.6-4.0)	0.10
AUC (mg*h/L)	34.6 (6.2-100.6)	30.4 (13.4-79.7)	0.68
Total daily metformin dose (mg/day)[b]	IR: 1000 (500-3000) XR: 2000 (500-2000)	IR: 1000 (N/A)	...
Time after last dose (hours)	5 (1-29)	3 (1-15)	...

[a]CLCR, calculated using Cockcroft-Gault equation with lean body weight.
[b]Mode (range).
Abbreviations: AUC, area under the plasma metformin concentration-time curve; $C_{av,ss}$, average steady state metformin concentrations; CLcr, creatinine clearance; CL/F, apparent metformin clearance; IR, immediate release; N/A, not applicable; T2DM, type II diabetes mellitus; $T_{1/2}$, half-life; Vd, volume of distribution; XR, extended release.

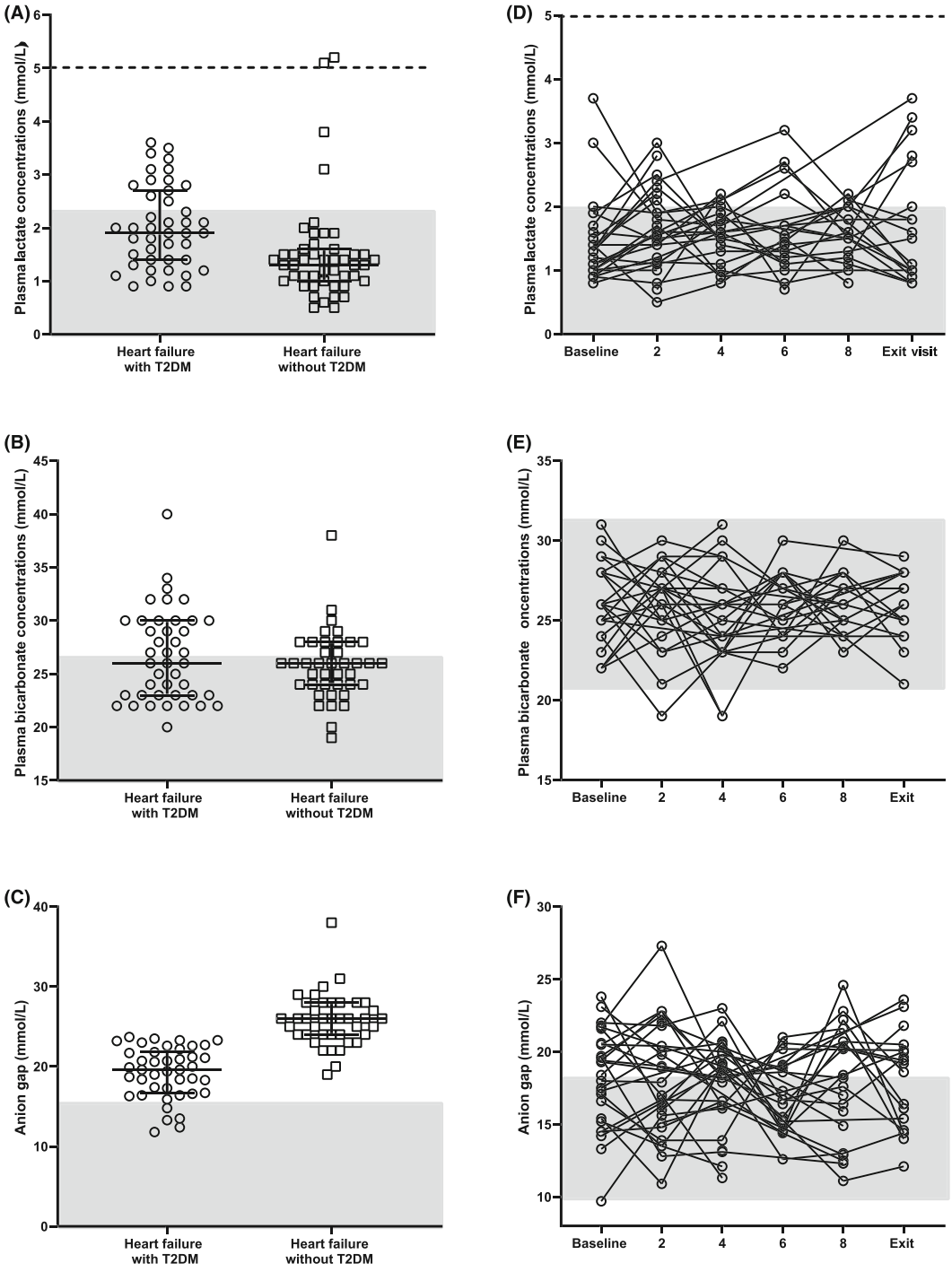

FIGURE 3 Plasma safety marker results for patients at all study visits in the cross-sectional studies: (A) plasma lactate concentrations; (B) plasma bicarbonate concentrations; (C) anion gap concentrations and the intention-to-treat interventional study population (all data points included); (D) plasma lactate concentrations; (E) plasma bicarbonate concentrations; (F) anion gap concentrations. Error bars represent median and interquartile range. Shaded areas are the reference ranges reported by Sydpath. The dashed line in (A) and (D) represents the safety threshold for plasma lactate concentrations for the studies for the monitoring of potential lactic acidosis. T2DM, type II diabetes mellitus.

(Table 3). The average plasma lactate concentrations increased by 28% from NYHA I to NYHA II and 14% from NYHA II to NYHA III (Figure 4). Importantly, neither metformin exposure alone (beta coefficient [*B*] = 1.04, *P* = .54) nor metformin exposure over time (*B* = 0.96, *P* = .06) significantly influenced plasma lactate concentrations. In the cross-sectional study, none of the evaluated factors were associated with plasma lactate concentrations (Supporting Information Table S7).

TABLE 3 Generalized linear mixed effects model final multivariable (adjusted) factors influencing plasma lactate concentrations in heart failure patients without T2DM on metformin.

	Multivariable adjusted (final model) AIC = 121.88	
Predictor variables	***B* (95% CI)**	***P* value**
$C_{av,ss}$ (mg/L)	1.04 (0.92 to 1.16)	0.54
Sex		
Female	0.73 (0.57 to 0.95)	0.02
Male	…	…
NYHA grading		
I	…	
II	1.32 (1.01 to 1.73)	0.04
III	1.46 (1.13 to 1.90)	0.004
Time since baseline (weeks)	1.07 (1.01 to 1.14)	0.03
$C_{av,ss}$ × time	0.96 (0.92 to 1.00)	0.06

Abbreviations: AIC, Akaike information criteria; *B*, beta coefficient; $C_{av,ss}$, steady-state plasma metformin concentration; CI, confidence interval; NYHA, New York Heart Association; T2DM, type II diabetes mellitus.

3.6 | Tolerability and adverse effects

In the interventional study, metformin was mostly well-tolerated. The most common adverse effects reported were gastrointestinal (GIT)-related (33%), including nausea (22%) and diarrhoea (7%) (Supporting Information Table S6), with symptoms resolving over the course of the study. Only one patient had ongoing GIT symptoms and subsequently dropped out of the study in week 6. Additional adverse effects were cardiac decompensation (11%) or heart transplant (11%). One patient experienced sudden cardiac death after 8 weeks of metformin therapy. No relationship was found between $C_{av,ss}$ and adverse events.

4 | DISCUSSION

This study provides insight into the safety and pharmacokinetics of metformin in a small population of heart failure patients with and without T2DM. Overall, metformin pharmacokinetics were similar in heart failure patients with (cross-sectional study) or without (interventional study) T2DM, and metformin exposure ($C_{av,ss}$) did not contribute to variability in plasma lactate concentrations. In the interventional study, plasma metformin and lactate concentrations remained below the accepted safety thresholds in all patients when using a low dose (500-mg IR) of metformin. In addition, increased severity of heart failure (based on NYHA grading) and male sex were associated with increased plasma lactate concentrations.

Despite metformin being available since 1957, the therapeutic range of plasma metformin concentrations for efficacy or toxicity remain unclear. However, plasma metformin concentrations above 5 mg/L are a commonly reported feature in people with

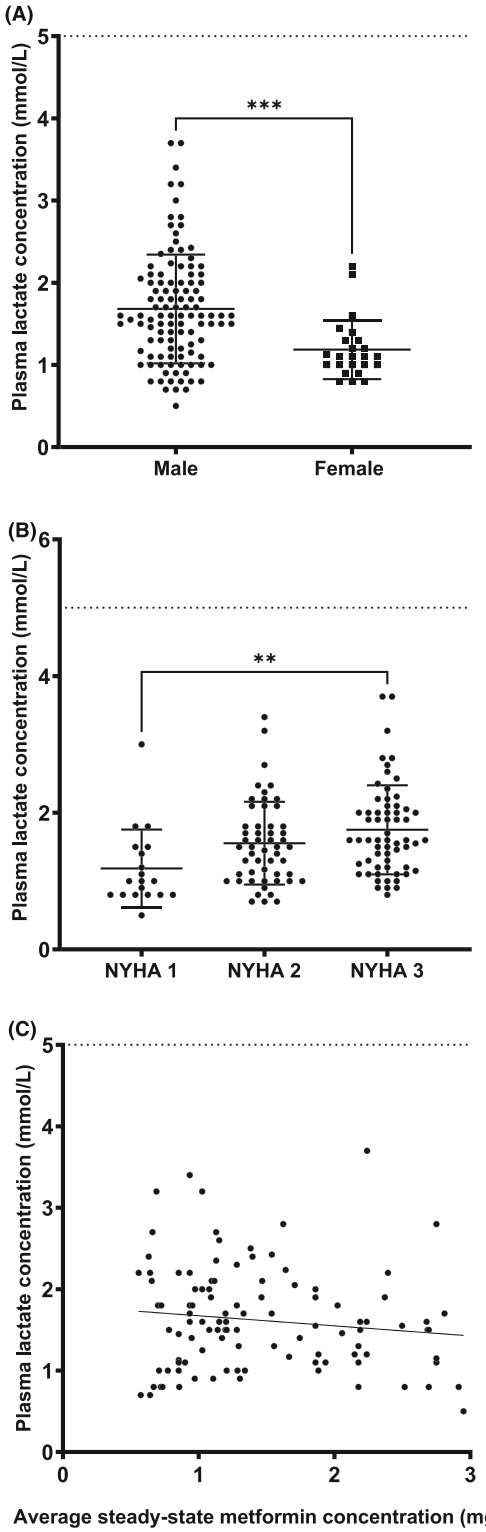

FIGURE 4 Factors influencing plasma lactate concentrations in patients from the interventional study with heart failure without type II diabetes mellitus on metformin. Significant fixed effects in the final generalized linear-mixed effects model. Plasma lactate concentrations were significantly higher in those who were (A) male and (B) with increasing New York Heart Association (NYHA) grading. No significant relationship was found between plasma lactate concentrations and average steady-state metformin concentrations ($C_{av,ss}$) (C). ** $P < .05$ and ***$P < .01$.

MALA.[9,26–28] Most studies have found that dosing metformin based on renal function, even in those with multiple comorbidities, including CKD and CLD, is reasonably safe.[13,14,16] Consistent with this, when metformin was dosed appropriately, we found that plasma metformin concentrations across all cohorts remained below 5 mg/L. The exception was one patient (83-year-old female) in the cross-sectional study, who had a plasma metformin concentration of 5.92 mg/L. This patient had an EF of 56% (HFpEF), NYHA III grading, CKD stage 3a (eGFR = 55 mL/min/1.73m^2), and stable glucose control (HbA1C = 8.0%) on metformin (2000 mg extended release once daily). According to the product information, the daily dose of metformin prescribed for this patient was 500 mg higher than recommended based on her renal function.[8,16,25,29] This likely contributed to the elevated plasma metformin concentration. Overall, the pharmacokinetic parameters of metformin were similar for all heart failure patients, irrespective of T2DM comorbidity. This suggests that current dosing approaches used in T2DM patients, based predominantly on renal function, may also be safe for heart failure patients.

In both studies, the plasma lactate concentrations remained below 5 mmol/L for patients receiving metformin. The threshold for lactic acidosis is plasma lactate concentrations above 5 mmol/L, in association with pH <7.35.[9] In general, serum bicarbonate concentrations were mostly within the normal reference range. Less than 10% of all bicarbonate concentrations were above (>32 mmol/L) or below (<22 mmol/L) the reference range. Acid-base and electrolyte disturbances are commonly reported in heart failure patients, and attributed to activation of neurohumoral mechanisms or adverse effects of heart failure medications, especially diuretics.[30–32] Consistent with this, the anion gaps for most patients, both baseline and additional study visit, were elevated above the upper limit reference range of 18 mmol/L. Almost all patients in this study were on diuretics, therefore commenting on the relationship between diuretics and anion gap was not possible.

In the interventional study, elevated plasma lactate concentrations were associated with NYHA grading. Similarly, in the cross-sectional study, plasma lactate concentrations tended to increase with a higher NYHA grading (Supporting Information Figure S3). Few studies document the association of NYHA gradings with lactate concentrations.[33–37] Compared to healthy subjects, heart failure patients (NYHA II and III) had higher resting serum lactate concentrations.[33] Additionally, a recent heart failure biomarkers study found that salivary lactate concentrations increased as NYHA grading increased.[37] Previous studies suggest that increased lactate concentrations observed in heart failure patients on metformin are most likely related to exacerbation of their disease rather than metformin itself.[38–41] Consistent with this, in the present study, increased symptomatic severity of heart failure (NYHA grading), but not metformin exposure, contributed to increased plasma lactate concentrations in heart failure patients.

In the interventional study, male sex was associated with higher plasma lactate concentrations. The effect of sex on plasma lactate concentrations in the context of heart failure is not well studied. Increased plasma lactate concentrations are significantly associated with poorer heart failure prognosis.[42] Interestingly, women with heart failure have a favourable age-adjusted survival rate compared to men, despite presenting with greater disease severity.[43] This improved survival is thought to be attributed to cardiac and metabolic factors, treatments received and hormonal influences.[43–45] Evidence suggests that stressed female hearts, even in the context of heart failure, maintain energy metabolism more efficiently,[46–48] and this may contribute to the lower lactate concentrations in females compared to males. Finally, consistent with observations in patients with CLD and T2DM[13] metformin exposure did not influence plasma lactate concentrations. However, patients with higher $C_{av,ss}$ tended to show a decrease in plasma lactate concentrations over time, relative to people with lower $C_{av,ss}$ ($B = -0.04$, $P = .06$). A larger, controlled prospective study may provide further insight into this finding in terms of causal inference. Again, this suggests that when dosed according to renal function, metformin is not associated with an increased risk of lactic acidosis in heart failure patients.

4.1 | Limitations

A limitation of this study is that very unwell heart failure patients (NYHA IV) could not be included. Many patients with severe heart failure have T2DM and are prescribed metformin. Given the association found in this study between increasing plasma lactate concentrations and NYHA grading, it would be beneficial to include this patient cohort in future studies. Additionally, the NYHA grading is a subjective measure determined by the clinician. This study did not include an NYHA grading questionnaire, which could have provided some validation of clinician derived NYHA status. While adequate for this study, a larger sample size may have allowed for clarification of the influence of factors such as NYHA grading, sex and the effect of metformin concentrations over time.

5 | CONCLUSIONS

Metformin is the first-line pharmacotherapy for T2DM. Although considered relatively safe, there are still concerns about the risk of lactic acidosis in heart failure patients. In many countries, metformin use remains contraindicated in heart failure patients according to official product information. However, prescribers are using metformin in these patients with limited guidance on safe use and management. This study demonstrates that clinically reasonable doses of metformin are associated with safe concentrations of plasma lactate and metformin in patients with heart failure, with and without T2DM. Additionally, the pharmacokinetics in patients with heart failure, with and without T2DM, are similar, potentially limiting the need for additional metformin dose adjustments in this cohort. These findings may support the safe use of metformin in heart failure patients with and without T2DM.

AUTHOR CONTRIBUTIONS

R.O.D., S.L.S. and S.K. conceived the original concept. G.C., S.L.S., J.E.C., R.O.D., S.L.S., S.K., J.R.G., P.M. and R.O.D. designed the experiment. S.K. assisted with pharmacokinetic analysis. G.C. carried out the experiment. G.C. and N.O. analysed the data. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST STATEMENT

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

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

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