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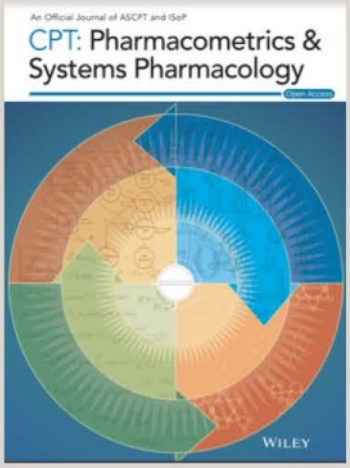

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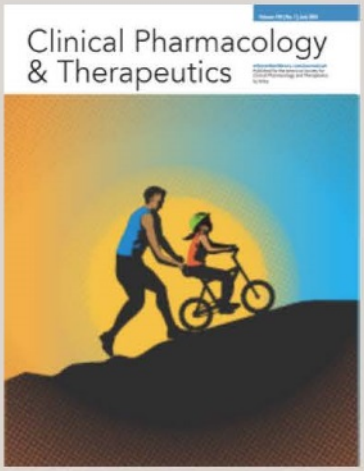

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ARTICLE

Assessment of clinical data on urocortins and their therapeutic potential in cardiovascular diseases: A systematic review and meta-analysis

Dóra K. Kovács[1] | Nelli Farkas[2] | Alexandra Soós[1] | Péter Hegyi[1,3,4] | Leonardo Kelava[1] | Szimonetta Eitmann[1] | Anna Schekk[1] | Zsolt Molnár[1] | Bálint Erőss[1] | Márta Balaskó[1]

[1]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary

[2]Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary

[3]Department of Translational Medicine, First Department of Internal Medicine, University of Pécs, Pécs, Hungary

[4]MTA-SZTE Translational Gastroenterology Research Group, University of Szeged, Szeged, Hungary

Correspondence
Márta Balaskó, Institute for Translational Medicine, Medical School, University of Pécs, 12. Szigeti str., Pécs, H-7624, Hungary.
Email: marta.balasko@aok.pte.hu

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Abstract

Heart failure (HF) and cardiovascular diseases present public health challenges. Although great progress was achieved in their treatment, there is continuous need for new therapies. Urocortins of the corticotropin neuropeptide family were reported to exert beneficial effects in animal models of HF and cardiovascular diseases. We aimed to assess the available clinical evidence on the potential role of urocortins in HF and other cardiovascular diseases. We explored MEDLINE, Embase, CENTRAL, and Scopus databases. Twenty-seven studies were included in the qualitative and 15 studies (2005 patients) in the quantitative syntheses. Available data allowed us to meta-analyze the blood pressure (BP) lowering and heart rate (HR) increasing effects of urocortin 2 in HF with reduced ejection fraction. We applied meta-regression to explore the association between left ventricular ejection fraction and serum urocortin 1 and urocortin 2 levels. Short-term urocortin 2 infusion decreased mean arterial pressure in chronic HF with reduced ejection fraction (mean difference = −9.161 mmHg, 95% confidence interval [CI] −12.661 to −5.660 mmHg, $p < 0.001$). Such infusions increased HR mildly (mean difference = 5.629 beats/min, 95% CI 1.612 to 9.646 beats/min, $p = 0.006$). Although some studies reported increased urocortin 1 and urocortin 2 levels in HF with growing severity, our meta-regressions failed to confirm associations between blood urocortin levels and left ventricular ejection fraction. Clinical evidence confirms short-term BP lowering effects of urocortin 2, whereas individual studies report additional beneficial effects. Further clinical investigations are necessary to confirm the latter and the long-term value of these peptides in cardiovascular diseases. Review protocol: CRD42020163203.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Heart failure (HF) is a cardiovascular disease of outstanding importance, in which there is an ongoing need to develop new therapies. Based on evidence from animal studies and from isolated human coronary arteries, they indicate that urocortins play

a beneficial role in cardiovascular disorders. These hormones and their receptors are produced in peripheral tissues, including blood vessels and the heart.

WHAT QUESTION DID THIS STUDY ADDRESS?

Our systematic review and meta-analysis aimed to assess the available clinical evidence with regard to the potential role of urocortins as therapeutic options in chronic HF with reduced ejection fraction (HFrEF) and other cardiovascular disorders.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Urocortin 2 has a potential to improve cardiovascular functions in HF via vasodilation-mediated suppression of the mean arterial pressure (MAP). Side-effects include mild increase in heart rate and flushing. Meta-regression did not show any association between left ventricular ejection fraction and blood levels of urocortin 1 or urocortin 2.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These findings confirm that urocortin 2 has a potential to decrease MAP in chronic HFrEF. Further studies are needed for the better understanding of the long-term cardiovascular effects and the safety of urocortin 2 infusions.

INTRODUCTION

The prevalence of heart failure (HF) and other cardiovascular diseases shows an increasing tendency worldwide.[1,2] The lifetime risk of HF at the age of 40 approaches 20% in the general population.[3] Despite the progress in the treatment options, the healthcare burden of HF and other cardiovascular diseases is increasing with population aging worldwide.[1,2] According to experts, there is an ongoing need to develop new therapies for HF and other cardiovascular diseases.[2,4] The mechanism of action of such new treatments includes enhancement of myocardial contractility or lusitropy, reduction of the vascular resistance, enhancement of angiogenesis or cell viability, to name just a few.[4]

Urocortins (Ucns) are members of the corticotropin neuropeptide family that are also produced along with their receptors in peripheral tissues.[5,6] Evidence from animal studies indicate that Ucns, especially specific agonists of corticotropin-releasing factor type 2 receptors (CRF2R), such as Ucn2 and Ucn3 play a complex beneficial role in cardiovascular disorders.[6–8] These hormones are produced in peripheral tissues, including blood vessels and the heart.[9–11] Moreover, CRF2Rs also show high levels of expression in the cardiovascular system.[10] Specific ligands of CRF2R were demonstrated to induce positive inotropic, lusitropic, and vasodilatory effects, among others.[6] The fact that CRF2R knockout mice develop hypertension suggests a role for CRF2R in the regulation of blood pressure (BP).[12,13] Another study demonstrated that specific CRF2R agonist Ucn2 decreased BP in hypertensive rats.[14]

Urocortin 2 also induced vasodilation in isolated human coronary arteries.[15] Preliminary clinical studies suggest a positive therapeutic potential of these hormones in cardiovascular diseases, based on increases in cardiac output and in left ventricular ejection fraction (LVEF).[7,8] Some studies demonstrated elevated blood levels of Ucns in cardiovascular diseases.[8] In order to decide whether Ucns could serve as therapeutic tools or as biomarkers in cardiovascular diseases and HF, further investigations are needed.

Our systematic review and meta-analysis aimed to assess the available clinical evidence with regard to the potential role of Ucns as biomarkers or therapeutic options in HF and other cardiovascular diseases. We present our work in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist.[16]

METHODS

Data collection and search strategy

Our systematic review and meta-analysis were conducted based on the Cochrane Handbook guidance[17] and reported using the PRISMA guideline.[16] The article was registered in PROSPERO on April 28, 2020 (CRD42020163203). The systematic search was carried out in four databases: MEDLINE, Embase, CENTRAL, and Scopus. The following search terms were used on May 4, 2020: (urocortin OR ucn) AND (cardi* OR heart* OR "vascular resistance" OR vasodil* OR vasoconst*). We did not use any filters. After the selection, the articles' reference lists were manually screened for other eligible publications. We also searched Google Scholar for articles citing our relevant records.

Selection and eligibility criteria

The selection of the articles was carried out by two independent authors (D.K.K. and A.S.). Following screening for

duplicates, the main part of the selection involved three stages. The first stage was screening by title, in the second stage, publications were screened for eligibility based on the abstracts, and in the third stage, selection was based on full-text evaluation. Disagreements were settled by a third party (author M.B.). Only human studies were included into this systematic review and meta-analysis. We included studies, which investigated the cardiovascular effects of Ucn1, 2, or 3, and studies which measured the blood Ucn levels in healthy volunteers or in patients with cardiovascular diseases. Exclusion criteria were: participants below the age of 18 years, pregnancy, in vitro experiments, studies with tissue samples, animal studies, articles without cardiovascular data, reviews, editorials, letters, notes, case-reports, and abstracts without proper data.

Data extraction

Two authors (D.K.K. and A.S.) extracted data from the articles, including the names of first authors, year of the publication, study design, intervention therapy, Ucn doses, durations of the interventions, epidemiology of the populations, investigated diseases, blood Ucn levels, and parameters of cardiovascular functions, such as heart rate (HR), mean arterial pressure (MAP), systolic and diastolic blood pressures (SBP and DBP), cardiac output (CO), systemic vascular resistance, etc. A third author (M.B.) resolved any disagreement. Data were extracted from figures of articles by the application of the WebPlotDigitizer online program.[18] For meta-regression analysis, we collected every study that measured Ucn levels and LVEF, as well. To carry out the meta-regression analysis, we had to convert the different values of Ucn1, N-terminal-pro-Ucn2 (NT-ProUcn2) and Ucn2 levels to the same units. Thus, we converted pg/dl, pg/ml, ng/L, ng/ml values to pmol/L units, based on the molecular weights of different Ucns.[19–21]

Risk of bias and quality assessment

Quality assessment was carried out by two investigators (authors M.B. and D.K.K.). For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool 1,[17] for nonrandomized studies the nine-star Newcastle-Ottawa Scale adapted for cross-sectional and for cohort studies[22] were applied. We also used the GRADE score to evaluate the certainty of evidence.[23,24] All disagreements were solved by consensus.

Statistical analysis

From the individual studies, we collected information about the HR and MAP at baseline and after 25 μg Ucn2 administration (via short-term infusion). There was one study where the value of change (difference between the post-treatment values of the placebo and those of the Ucn2 groups) was given.[25] From the available information, we calculated mean differences (MDs) with their 95% confidence intervals (CIs) between the control and intervention groups. We used random effect models in each of the meta-analyses calculating with the DerSimonian and Laird weighting method. Results of the meta-analyses were displayed graphically using Forest plots. Heterogeneity was tested by using the Cochrane's Q and the I^2 statistics, where $I^2 = 100\% \times (Q-df)/Q$, and represents the magnitude of the heterogeneity (moderate: 30%–60%, substantial: 50%–90%, and considerable: 75%–100%). We applied this test to assess whether the heterogeneity observed among MDs could be attributed to random chance or to other factors (e.g., body mass index [BMI], age, and sex of the participants). We considered the Q test significant if $p < 0.1$.[17] We used meta-regression models to explore the association between LVEF and serum levels of Ucn1 and Ucn2. In each case, we tested the whole model (simultaneously hypothesized that all coefficients are zero) and reported the regression coefficients, 95% CIs, standard errors, and z tests. We also calculated the explained variance of the model (R^2 analogue) and the result of the Q test to evaluate if the unexplained variance was zero. All statistical analyses were performed with Comprehensive Meta-Analysis software version 3 (Biostat Inc.) and Stata version 15.1.

RESULTS

Results of search and selection

Our systematic search identified 4385 articles. The flow diagram describes the process of the search and selection with exclusion criteria in Figure 1. At the end of the selection process, we found 27 articles for the qualitative assessment and 15 studies with data of 2005 patients could be included in the statistical analyses.

Characteristics of the studies included

With regard to Ucn1, 12 studies measured the plasma levels in healthy volunteers[26] and in patient groups with various cardiovascular diseases, such as acute myocardial infarction (AMI; with or without controls)[27] or HF.[28–38] Seven studies reported significantly increased blood Ucn1 levels in cardiovascular diseases as compared with healthy controls (Table 1).[27,28,32,34,36–38]

Only one research team administered an infusion of this hormone to healthy volunteers and to patients with HF.[26,30] The characteristics of these studies are summarized in Table 1.

Blood Ucn2 levels were reported by 10 studies.[21,29,31,39–45] Five studies showed significantly increased blood Ucn2

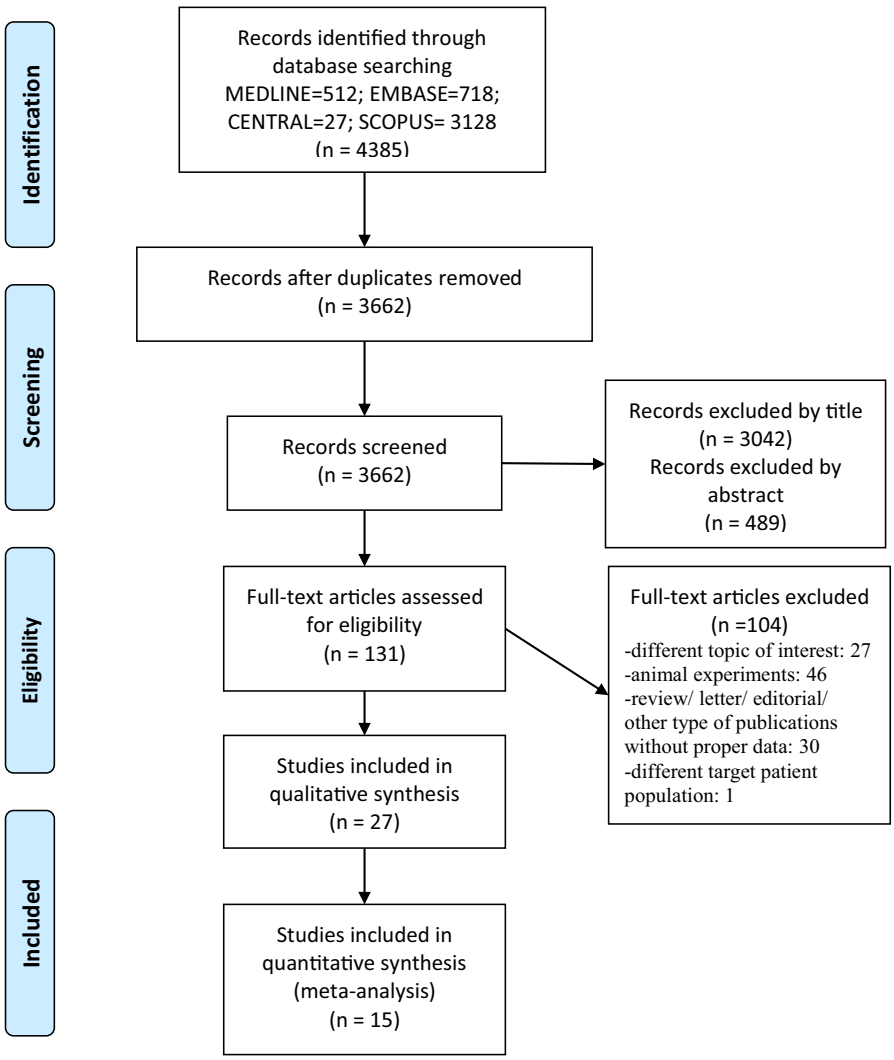

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) Flow diagram of the search and selection process. Two independent reviewers searched and reviewed papers and extracted data. Disagreements were settled by a third party

levels in cardiovascular diseases, such as coronary artery disease,[43] chronic HF,[21,44] hypertension,[39] and abdominal aortic aneurysm[41] (Table 2).

Cardiovascular effects of this hormone were tested in healthy volunteers,[25,40,46,47] in acute decompensated HF[29] and in chronic HF.[25,31,46] Their characteristics are described in Table 2.

Blood Ucn3 levels were not reported in cardiovascular patients. The blood level of the peptide of healthy volunteers was reported by one study.[11] An additional study reported Ucn3 levels in normal weight, overweight diabetic, and overweight nondiabetic patients.[48] Another study reported elevated Ucn3 levels in subjects with newly diagnosed type 2 diabetes mellitus as compared with controls.[49]

Two clinical studies administered Ucn3 infusion to healthy volunteers[25,47] and to patients with HF[25] (Table 3).

Hemodynamic effects of urocortin 1 infusion

Short-term Ucn1 infusion did not change any of the hemodynamic parameters (HR, SBP, DBP, and CO) in healthy volunteers[26] and in patients with stable congestive HF[30] (Table 1).

Hemodynamic effects of urocortin 2 infusion

In healthy volunteers, Ucn2 infusion increased CO, cardiac index, and HR and induced a decrease of DBP, MAP, and the peripheral vascular resistance (PVR)[25,40,46,47] (Table 2).

Short-term Ucn2 infusion decreased MAP in patients with stable HF with reduced EF (HFrEF) (MD = −9.161 mmHg, 95% CI −12.661 to −5.660 mmHg, $p < 0.001$; Figure 2). Substantial heterogeneity based on I-squared = 74.377%, $p = 0.020$ was calculated. Small-study effect could not be calculated because of the low number of available studies.

Short-term Ucn2 infusion increased the HR in patients with stable HFrEF (MD = 5.629, 95% CI 1.612 to 9.646, $p = 0.006$; Figure 3). Substantial heterogeneity based on I-squared = 72.134%, $p = 0.028$ was calculated. Small-study effect could not be calculated because of the low number of studies.

TABLE 1 Characteristics of the studies reporting data on urocortin 1

Urocortin 1									
						Outcome			
First author, publication year	Type of study	Population	Number of patients	Age (years)	Intervention	Cardiovascular effects	Urocortin levels	Unit	Significance (p)
Argan et al. 2015[28]	Abstract	HF with AF	62	68[a]			179.2 ± 165[a]	pg/dl	<0.05
		HF without AF	68	61[a]			166.5 ± 174[a]		
		control	50	57[a]			95.4 ± 135[a]		
Chan et al. 2013[29]	RCT	ADHF urocortin infusion	27	63[a]			11.2 ± 0.02[c]	pmol/L	
		ADHF control	26	68[a]					
Davis et al. 2004[26]	Randomized, crossover	Healthy	4+4	36.3[a]	50 μg Ucn1 infusion	CO, HR, SBP, DBP, unchanged	9.6 ± 0.9 ($n = 4$)[f]	pmol/L	
							9.2 ± 0.7 ($n = 4$)[f]		
Davis et al. 2005[30]	Randomized, crossover	Chronic stable HF	4+4	68.1[a]	50 μg Ucn1 infusion	CO, HR, SBP, DBP, unchanged	10.9 ± 1.1 ($n = 4$)[f]	pmol/L	
							11.1 ± 0.6 ($n = 4$)[f]		
Davis et al. 2007[31]	Dose escalation	Stable congestive HF	8	61.2[a]			10.6 [9.3, 12.2][c]	pmol/L	
							10.2 [8.9, 11.8][c]		
							9.2 [8.2, 10.5][c]		
Gruson et al. 2010[32]	Case-control	HF	42	64[a]			88 [75, 105][c]	pmol/L	<0.001
		Control	20				46 [39, 54][c]		
Gruson et al. 2011[33]	Abstract	Cardiac disease	43	67[a]			18.2[a]	pg/ml	
		Non-cardiac disease	34				17.1[a]		
Ng et al. 2004[34]	Case-control	HF	119	63[b]			43.6 [3.9, 112.5][e]	pmol/L	<0.0005
		Control	212	60.9[b]			17.3 [3.9, 68.8][e]		
Phrommintikul et al. 2010[27]	Case-control	AMI	66	62.7[a]			155.05 ± 10.42[f]	pmol/L	<0.05
		Control		63.8[a]			99.63 ± 8.19[f]		
Tang et al. 2010[35]	Prospective, cohort	HF	154	58[a]			12.2 [10.1, 15.3][d]	pmol/L	
Wright et al. 2009[36]	Case-control	HF	74	74[a]			13.6 ± 4.1[g]	pmol/L	<0.001
		Symptomatic, non-HF	225				11.1 ± 3.2[g]		
		Control	98				7.2 ± 2.9[g]		
Yildirim et al. 2017[38]	Observational	Systolic HF	86	62.5[a]			446.2 ± 145.7[g]	pg/ml	<0.001
		control	85	60.1[a]			126.6 ± 32.7[g]		
Yildirim et al. 2014[37]	Observational	Systolic HF	90	64.82[a]			391.5 [357, 482][d]	pg/ml	<0.001
		Control	90	34.83[a]			109.0 [102, 158][d]		

Note: [a] = mean, [b] = median, [c] = mean plus confidence interval, [d] = median with interquartile range, [e] = median, range, [f] = mean with standard error of mean, [g] = mean with standard deviation.

Abbreviations: ADHF, acute decompensated heart failure; AF, atrial fibrillation; AMI, acute myocardial infarct; CO, cardiac output; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; RCT, randomized controlled trial; SBP, systolic blood pressure; Ucn1, urocortin 1.

In acute decompensated HF (LVEF% <40%), Ucn2 infusion decreased SBP, DBP, and calculated total peripheral resistance without increasing the HR significantly[29] (Table 2).

Hemodynamic effects of urocortin 3 infusion

Ucn3 infusion has been shown to increase the cardiac index and the HR, and to decrease the MAP and the PVR index in patients with HF and healthy controls alike, although it failed to change stroke volume.[25] Other researchers reported that the infusion of the peptide decreased the DBP (but not the SBP) and increased the HR in healthy volunteers.[47]

Association between left ventricular ejection fraction and blood levels of urocortins

Meta-regressions did not show significant associations between the LVEF of healthy volunteers and patients with various cardiovascular diseases and their blood Ucn1 level (number of groups: 14, coefficient: 0.026, $p = 0.740$, r-square analogue: 0.00%) or blood Ucn2 level (number of groups: 12, coefficient: 0.173, $p = 0.465$, r-square analogue: −11.22%; Figures S1 and S2). The goodness of fit of the regression lines are poor in both cases. The heterogeneity of the data may stem from the varied methodology of the measurements of blood Ucn1 and Ucn2 levels and from the different patient populations (with hypertension, AMI, aneurysm of the abdominal aorta, chronic HF, etc.).

Risk of bias assessment and quality of evidence

Our analysis revealed various sources of risk of bias in the included six randomized and 21 nonrandomized studies. The results of the risk of bias assessments are shown in Table S1 in the Supplementary information online. Even randomized studies failed to report their randomization protocol in some cases. We also found some potential bias based on the lack of blinding of participants and/or of researchers. Allocation concealment was broken in one of the randomized studies, in which accidentally biologically inactive Ucn2 was administered and thus the infusion needed to be repeated with the appropriate product.[46] Some bias was assumed in association with incomplete outcome data, selective reporting, or the small number of participants indicated within the category of "other bias." The 21 nonrandomized studies were evaluated by the modified or original Newcastle-Ottawa Scale. They received four to eight points. The risk of bias of these studies showed an even distribution ranging from high to low.

The overall evidence level of the analyzed data, based on our GRADE score, was very low for all four outcomes. We included mostly nonrandomized interventional and observational studies. All of our analyses showed substantial heterogeneity. Study populations of the meta-regressions varied from healthy volunteers to groups of patients with acute or chronic HF, hypertension, aortic aneurysm, metabolic syndrome, and diabetes mellitus. Results also showed wide CIs. Therefore, we needed to downgrade the level of our evidence (Table S2).

DISCUSSION

In our systematic review and meta-analysis, we assessed the available clinical evidence with regard to the potential therapeutic role of Ucns in various cardiovascular diseases and the association between their plasma level and LVEF.

A large body of evidence from animal studies indicated that Ucns, especially agonists of CRF2R, play a predominantly beneficial role in cardiovascular disorders. These hormones are produced in a wide variety of peripheral tissues, including blood vessels and the heart.[6–8] High levels of expression of CRF2R were also detected in these peripheral tissues. Activation of CRF2R was shown to affect myocardial and vascular functions, including vasodilatory, positive inotropic, and lusitropic effects. BP of CRF2R knockout mice was found to be higher, suggesting a potential role of these receptors in the regulation of BP.[13] Another research group found that Ucn2, a specific CRF2R agonist, decreased BP without increasing the HR in hypertensive rats.[14] Previous reviews unequivocally suggested positive therapeutic potential of these hormones in cardiovascular diseases.[6–8] They emphasized the need for appropriate clinical studies, and they saw great potential in manipulating the bioactivity and/or signal transduction of Ucns for therapeutic purposes.

Concerning the therapeutic potential of Ucns, we searched for studies that tested the effects of these hormones in cardiovascular diseases.

With regard to Ucn2, the available clinical data allowed us to perform meta-analyses on the effects of short-term infusions (at a dose around 25 μg) only in patients with chronic HFrEF. These infusions significantly decreased MAP and mildly increased HR compared to placebo. It appears that the decrease in MAP was a result of a reduction of peripheral vascular resistance. Within 40–60 min following the infusions, all cardiovascular parameters returned to baseline values. The BP lowering effects of Ucn2 may be beneficial for patients with HF, because it indicates a decrease of the afterload.[50] The Ucn2 infusion-induced rise in HR would, on the other hand, increase the oxygen consumption of the myocardium and reduce the diastolic time. Clinical studies and patient registry analysis demonstrated that lower HR or additional reduction of HR improved the mortality rates in HF.[51,52] In our analysis, the rise in HR due to the Ucn2 infusion was fortunately minimal.

TABLE 2 Characteristics of the studies reporting data on urocortin 2

Urocortin 2									
						Outcome			
First author, publication year	Type of study	Population	Number of patients	Age (years)	Intervention	Cardiovascular effects	Urocortin levels	Unit	Significance (p)
Aslan et al. 2020[39]	Observational	HT	86	66[b]			5.17 [1.26, 11.68][d]	ng/ml	<0.0005
		non-HT	53	62[b]			0.79 [0.07, 4.1][d]		
Chan et al. 2013[29]	RCT	ADHF urocortin infusion	27	63[a]	400 μg Ucn2 infusion	CO ↑; SBP ↓, DBP ↓, CTPR ↓; HR unchanged	0.438 ± 0.01[c]	ng/ml	
		ADHF control	26	68[a]	Placebo				
Chan et al. 2015[46]	Controlled crossover	Stable heart failure	4	58[a]	25 μg Ucn2 infusion	MAP ↓, CTPR ↓; CO, HR unchanged			
		Healthy	8	48[a]		CO ↓, HR ↓; MAP ↓, CTPR ↓			
Davis et al. 2007[31]	Dose escalation	Stable, congestive heart failure	8	61.2[a]	25 μg, 100 μg Ucn2 infusion	CO ↑, HR ↑, cardiac work ↑; SBP ↓, DBP ↓, MAP ↓, SVR ↓	230 [40, 420][c]*	pg/ml	
Davis et al. 2007[40]	Dose escalation, controlled	Healthy	8	41.1[a]	25 μg, 100 μg Ucn2 infusion	CO ↑, HR ↑, pulse pressure ↑; SBP ↓, DBP ↓, MAP ↓, SVR ↓	0.09 [0.05, 0.17][c]*	ng/ml	
Emeto et al. 2014[41]	Observational	AAA	67	72[b]			2.2 [1.14, 4.55][d]	ng/ml	0.001
		PAD but no AAA	67	72[b]			1.11 [0.76, 2.55][d]		
Liew et al. 2016[21]	Observational	HFrEF	134	59[a]			117 [98, 141][i]	ng/l	0.0007
		HFpEF	121	70[a]			119 [93, 136][i]		0.0376
		Control	160	58[a]			112 [86, 132][i]		
Pintalho et al. 2018[42]	Abstract	Acute HF	80	76.5[b]			2.3 [1.73, 0.97][d]	ng/ml	
Stirrat et al. 2016[25]	Randomized, controlled, crossover	Chronic heart failure	9	58[b]	36, 108, 360 pmol/min Ucn2 infusion[j]	CI ↑; MAP ↓, PVRI ↓; HR, SV unchanged			
		Healthy	7	58[b]		HR ↑; MAP ↓, PVRI↓; CI, SV unchanged			
Topal et al. 2012[43]	Observational	Moderate to severe systolic dysfunction	27	69[b]			8.9 [4.2, 16.6][h]	pg/ml	0.003
		Mild to moderate	29	64[b]			12.7 [4.9, 18.6][h]		
		Without	30	58[b]			11 [4.1, 17.7][h]		
Tsuda et al. 2017[44]	Observational	HF	52	57.4[a]			1755 [1166, 3130][d]	pg/ml	<0.01
		Control	260	57.6[a]			235 [54, 647][d]	pg/ml	

(Continues)

TABLE 2 (Continued)

Urocortin 2								
					Outcome			
First author, publication year	Type of study	Population	Number of patients	Age (years)	Intervention	Cardiovascular effects	Urocortin levels	Unit	Significance (p)
Venkatasubramanian et al. 2013[47]	Randomized, crossover	Healthy	18	23[a]	120 pmol/min Ucn2 infusion	FBF ↑; HR, SBP, DBP unchanged			
Walczewska et al. 2019[45]	Observational	ACEI treated HT	52	58[b]			10.93 [4.17, 16.46][i]	ng/ml	
		ARB treated HT	13				5.56 [1.76, 10.42]		

Note: [a] = mean, [b] = median, [c] = mean plus confidence interval, [c]* = geometric mean plus confidence interval, [d] = median with interquartile range, [h] = median, min, max, [i] = median, 25, and 75 percentiles; [j] = these incremental doses were given to each patient within the same session.

Abbreviations: AAA, abdominal aortic aneurysm; ACEI, angiotensin-converting-enzyme inhibitors; ADHF, acute decompensated heart failure; ARB, angiotensin II receptor blockers; CI,cardiac index; CO, cardiac output; CTPR, calculated total peripheral resistance; DBP, diastolic blood pressure; FBF, forearm blood flow; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HT, hypertensive; MAP, mean arterial pressure; PAD, peripheral artery disease; PAH, pulmonary arterial hypertension; PVRI, pulmonary vascular resistance index; RCT, randomized controlled trial; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; Ucn2, urocortin 2.

Although individual studies reported decreases of SBP and DBP[29,31,47] or total peripheral resistance,[25,29,31,40,46] an increase in CO, cardiac index,[25,29,31,40,46] or forearm blood flow,[47] we could not meta-analyze these important cardiovascular parameters because of the lack of appropriate amount of data (Table 2). Urocortin 2 infusions did not induce rises in blood cortisol, plasma creatinine, N-terminal-pro brain natriuretic peptide, plasma renin, angiotensin II, and aldosterone.[29,31,40] Thus, these infusions did not induce activation of the hypothalamo-pituitary-adrenal cortical (HPA) axis, or a reduction of renal blood flow, or an abnormal stretch of the ventricles, or other cardiovascular adaptive responses that would indicate hypotension of a dangerous extent.

Because of the lack of a sufficient number of available studies, we could not meta-analyze the data on the effects of Ucn1 or Ucn3 in HFrEF (Tables 1 and 3). The available studies have shown that Ucn1 infusion failed to change cardiovascular parameters, but it increased the activity of the HPA axis, as shown by the increase in blood cortisol.[26,30] Concerning Ucn3, the infusion of this hormone has been reported to elicit strong vasodilatory effects in patients with HFrEF but not in healthy volunteers.[25]

With regard to side effects, no adverse events were detected during Ucn1 infusions either in healthy volunteers or in patients with HF.[26,30] On the other hand, the Ucn2 and Ucn3 infusions induced a number of adverse symptoms. Flushing due to vasodilation developed in the majority of the participants.[25,29,31,40,46,47] In some cases, the infusion had to be stopped due to hypotension or syncope.[25] Some patients complained about increased HR sensation.[40,47] Rarely, asymptomatic nonsustained ventricular tachycardia developed.[29] In acute decompensated HF, Ucn2 infusion-induced hypotension was associated with transiently reduced urine volume and creatinine clearance.[29]

Sporadic, rare adverse events detected on the day of the Ucn2 or Ucn3 infusions also included mild and transient hypokalemia with postprandial hyperinsulinemia, dizziness, hyponatremia, headache, anorexia, or hyperamylasemia.[25,29,31,40,46,47] Thus, contraindications to Ucn2 infusions would include hypotensive states, tachycardias, or renal failure.

With regard to the blood levels of Ucns in cardiovascular diseases, we found numerous clinical studies that confirmed increased blood levels of Ucn1 and Ucn2 in a wide variety of cardiovascular diseases from hypertension to chronic HF, or from atrial fibrillation to aortic aneurysm[21,27,28,32,34,36–39,41,43,44] (Tables 1 and 2).

Concerning Ucn1, most studies confirmed higher hormone levels in HF or AMI[27,28,32,34,36–38] as compared with controls. However, Ucn1 levels did not always correlate with the severity of the disease.[33,34] Our meta-regression also failed to confirm any correlation between serum Ucn1 and LVEF (Figure S1), although several individual

TABLE 3 Characteristics of the studies reporting data on urocortin 3

Urocortin 3									
						Outcome			
First author, publication year	Type of study	Population	Number of patients	Age (years)	Intervention	Cardiovascular effects	Urocortin levels	Unit	Significance (p)
Alarslan et al. 2019[49]	Case-control	nT2DM	80	50[a]			115.64 ± 39.26[e]	pg/ml	<0.001
		Control	80	51[a]			86.16 ± 22.81[e]		
Kavalakatt et al. 2019[48]	Case-control	Overweight diabetic	98	52[a]			9.03 [0.77–104.92][c]	ng/ml	Overweight diabetic and nondiabetic: <0.01
		Overweight nondiabetic	107	42[a]			6.27 [0.64–77.04][c]		
		Normal weight	37	40[a]			11.99 [0.78–86.07][c]		Normal-weight and overweight non- diabetic: <0.001
Stirrat et al. 2016[25]	Randomized, crossover	HF	9	58[b]	360, 1200, 3600 pmol/min Ucn 3 infusion[f]	CI ↑, HR ↑; MAP ↓, PVRI ↓; SV unchanged			
		Healthy	7	58[b]		CI ↑, HR ↑; MAP ↓, PVRI ↓; SV unchanged			
Takahashi et al. 2003[11]	Observational	Healthy	5				51.8 ± 16[d]	pmol/l	
Venkatasubramanian et al. 2013[47]	Randomized, crossover	Healthy	18	23[a]	1.2 to 36 nmol/min Ucn3 infusion	HR ↑, FBF ↑; DBP ↓; SBP unchanged			

Note: [a] = mean, [b] = median, [c] = mean plus confidence interval, [d] = mean with standard error of mean, [e] = mean with standard deviation, [f] = These incremental doses were given to each patient within the same session.

Abbreviations: CI, cardiac index; DBP, diastolic blood pressure; FBF, forearm blood flow; HF, heart failure; HR, heart rate; MAP, mean arterial pressure; PVRI, pulmonary vascular resistance index; SBP, systolic blood pressure; SV, stroke volume; nT2DM, newly diagnosed type 2 diabetes mellitus; Ucn3, urocortin 3.

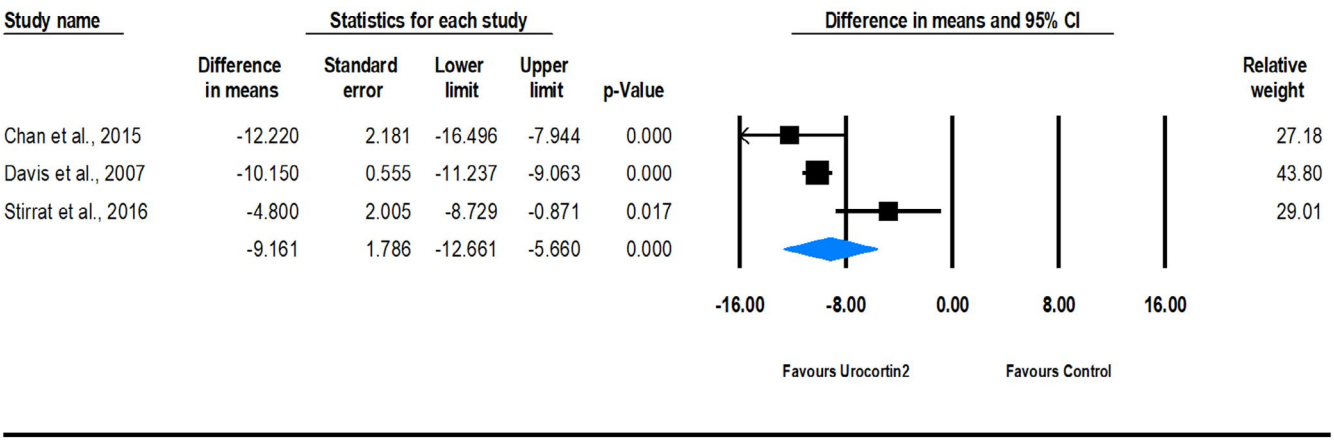

FIGURE 2 Hemodynamic effects of urocortin 2 infusion: change in mean arterial pressure (MAP) [mmHg] following urocortin 2 (Ucn2) versus placebo infusion. Squares show the mean difference (MD) of mean arterial pressure (MAP) [mmHg] after urocortin 2 (Ucn2) infusion versus placebo infusion. The black center area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall MD with its corresponding 95% CI

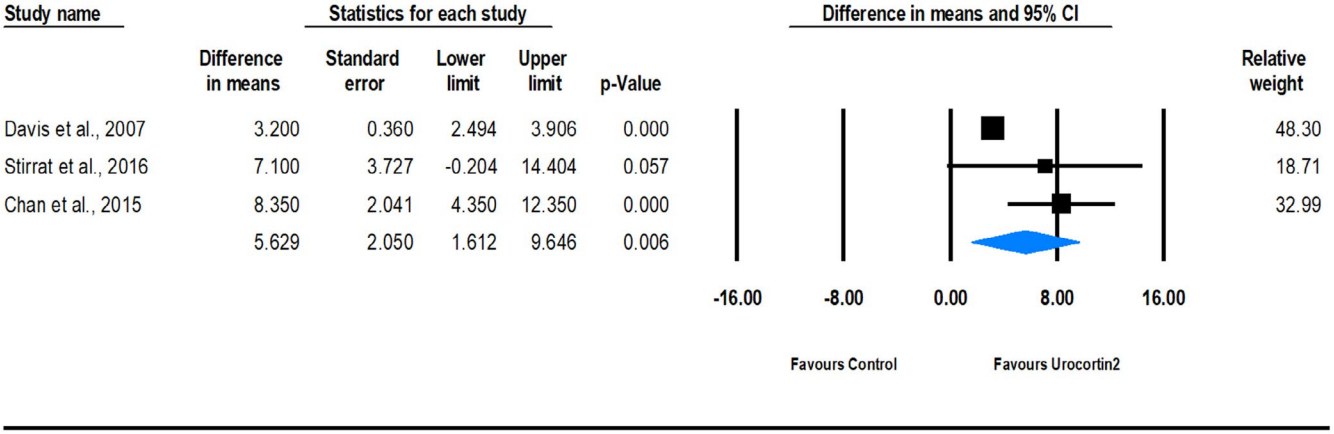

FIGURE 3 Hemodynamic effects of urocortin 2 infusion: change in heart rate (HR) [beats/min] following urocortin 2 (Ucn2) versus placebo infusion. Squares show the mean difference (MD) of heart rate (HR) [beats/min] after urocortin 2 (Ucn2) infusion versus placebo infusion. The black center area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall MD with its corresponding 95% CI

studies demonstrated correlations between Ucn1 levels and the New York Heart Association (NYHA) stage of the HF.[36–38]

Urocortin 2 levels were also higher in chronic HF,[44] in hypertension,[39] in coronary artery disease,[43] or in patients with aneurysm of the abdominal aorta.[41] One study found higher NT-ProUcn2 level in patients with HF with more severe disease.[21] However, certain studies found a lack of association between Ucn2 and LVEF.[29,43] It is interesting that treatment modalities in hypertension also appeared to influence Ucn2 levels. Walczewska and coworkers found higher Ucn2 levels in angiotensin convertase enzyme inhibitor-treated patients as compared with the angiotensin receptor blocker-treated group.[45] In addition, adrenergic alpha-blockers seemed to decrease Ucn2 levels.[45]

With regard to Ucn2, once again, meta-regression failed to confirm the hypothesized correlation between increasing blood Ucn2 levels and decreasing LVEF values (Figure S2).

In case of Ucn3, higher hormone levels were demonstrated for a number of pathological conditions, such as metabolic syndrome, diabetes mellitus type 2, polycystic ovary syndrome (PCOS), or obesity, but not for HF or for other cardiovascular diseases.[48,49,53]

Because all Ucn levels were determined by ELISA techniques, gross differences in measurement could not contribute

to the substantial heterogeneity of our results. Other factors, such as BMI, age, and sex, may have contributed to the heterogeneity of these findings.[21,39,42,43]

Interestingly, we did not find remarkable differences among Ucn types and in their association with specific cardiovascular diseases. Moreover, blood Ucn levels appear to increase in a number of other general systemic challenges, including metabolic syndrome,[49] PCOS,[53,54] or type 2 diabetes mellitus.[48,49] Thus, increases in Ucn levels may not even be specific for cardiovascular disorders or HF.

In the future, regression analyses will be worthwhile if enough data pairs from large patient registries for cardiovascular parameters in well-defined cardiovascular disorders will become available.

Various limitations have to be considered with regard to the present systematic review. Due to the lack of classical RCTs, we had to analyze observational, nonrandomized interventional studies or randomized crossover studies. Moreover, the small study populations also limit the generalizability of our results. With regard to Ucn2 infusions, the dose of 100 µg was the most effective in increasing the CO and in decreasing the total peripheral resistance in healthy volunteers and cardiac patients.[31,40] Unfortunately, there was no sufficient clinical data with this dose for proper meta-analysis. Thus, we had to analyze data with the dose of 25 µg. Some results had to be extracted from graphs. The risk of bias of the individual studies ranged from moderate to low, however, the certainty of evidence according to GRADE was very low for all outcomes.

The usefulness of vasodilatory agents in HF have also been questioned by recent clinical trials.[55] For example, vasodilatory agent serelaxin, and the decreased BP failed to improve the 180-day mortality in acute HF in a recent large multicentric RCT.[55]

In order to decide whether Ucns could serve as biomarkers to cardiovascular diseases, measurement of Ucn levels would have to be included in prospective, large patient registries. With regard to the therapeutic use of Ucn2 in HF and other cardiovascular diseases, RCTs also measuring changes in cardiovascular mortality or in parameters (e.g., NT-ProBNP, LVEF, and CO) could provide decisive evidence. Future studies could investigate the potential contribution of Ucn2 to the treatment of hypertension of patients with HF or to the acute intervention of hypertensive crises in such patients.

CONCLUSION

Results of our meta-analysis and systematic review confirm the suggestions of animal studies and in vitro tests, according to which Ucn2 has a potential to improve cardiovascular functions in HF. Further clinical studies are needed for the better understanding of the long-term cardiovascular effects and the safety of Ucn2 infusions. With regard to blood Ucn levels as potential biomarkers of cardiovascular diseases, we did not find any association between LVEF and Ucn1 or Ucn2 levels. Large prospective cardiovascular patient registries also measuring Ucn levels in acute and chronic cardiovascular conditions could help us understand the cause of the elevated Ucn levels and their prospective value.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. P.H., M.B., and D.K.K. designed the research. D.K.K., M.B., and A.Sch. performed the research. A.S. and N.F. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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