

# Haemodynamic effects of the nitroxyl donor cimlanod (BMS-986231) in chronic heart failure: a randomized trial

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## Aims

Nitroxyl provokes vasodilatation and inotropic and lusitropic effects in animals via post-translational modification of thiols. We aimed to compare effects of the nitroxyl donor cimlanod (BMS-986231) with those of nitroglycerin (NTG) or placebo on cardiac function in patients with chronic heart failure with reduced ejection fraction (HFrEF).

## Methods and results

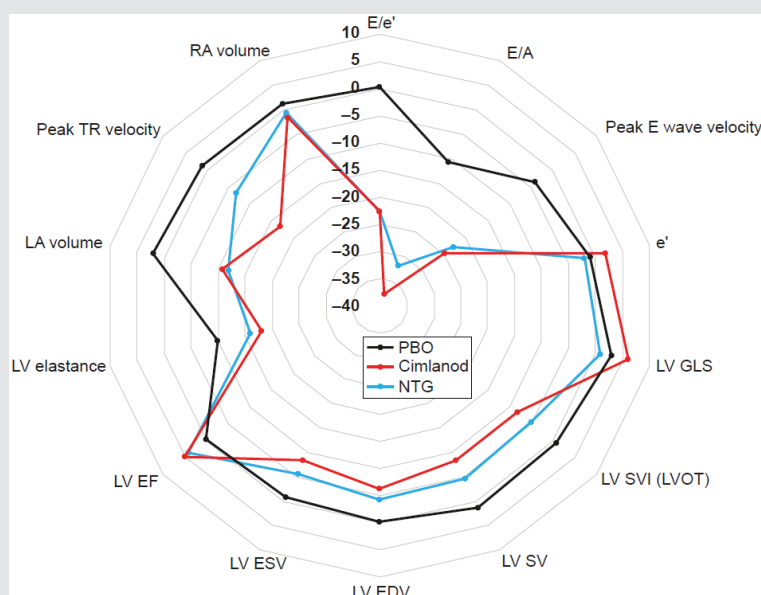
In a randomized, multicentre, double-blind, crossover trial, 45 patients with stable HFrEF were given a 5 h intravenous infusion of cimlanod, NTG, or placebo on separate days. Echocardiograms were done at the start and end of each infusion period and read in a core laboratory. The primary endpoint was stroke volume index derived from the left ventricular outflow tract at the end of each infusion period. Stroke volume index with placebo was  $30 \pm 7$  mL/m<sup>2</sup> and was lower with cimlanod ( $29 \pm 9$  mL/m<sup>2</sup>;  $P = 0.03$ ) and NTG ( $28 \pm 8$  mL/m<sup>2</sup>;  $P = 0.02$ ). Transmitral E-wave Doppler velocity on cimlanod or NTG was lower than on placebo and, consequently,  $E/e'$  ( $P = 0.006$ ) and  $E/A$  ratio ( $P = 0.003$ ) were also lower. NTG had similar effects to cimlanod on these measurements. Blood pressure reduction was similar with cimlanod and NTG and greater than with placebo.

## Conclusion

In patients with chronic HFrEF, the haemodynamic effects of cimlanod and NTG are similar. The effects of cimlanod may be explained by venodilatation and preload reduction without additional inotropic or lusitropic effects. Ongoing trials of cimlanod will further define its potential role in the treatment of heart failure.

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## Graphical Abstract



The nitroxyl donor cimlanod (BMS-986231) has similar haemodynamic effects to nitroglycerin (NTG), including venodilatation with consequent cardiac preload reduction and systemic blood pressure reduction in patients with heart failure with reduced ejection fraction. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; LA, left atrial; LV, left ventricular; LVOT, left ventricular outflow tract; PBO, placebo; RA, right atrial; SV, stroke volume; SVI, stroke volume index; TR, tricuspid regurgitation.

## Keywords

Heart failure • Nitroxyl donor • Nitrate • Echocardiography • Haemodynamics • Randomized trial

## Introduction

Although vasodilators, primarily nitrates, are often used to treat patients with acute heart failure provided they are not hypotensive,<sup>1,2</sup> there is no compelling evidence that they improve clinical outcomes.<sup>1</sup> Conventional inotropic agents are reserved principally for use in patients with low blood pressure (BP) and, despite potential short-term haemodynamic benefits, have been associated with harm.<sup>1–3</sup> These harmful effects have been attributed mainly to elevated concentrations of intracellular calcium and increases in heart rate, myocardial oxygen consumption, and both atrial and ventricular arrhythmias.<sup>1,4</sup>

Nitroxyl (HNO) is chemically related to nitric oxide but pre-clinical models and early phase studies suggest that its mechanisms of action are markedly different.<sup>5,6</sup> HNO causes post-translational modification of thiol residues and, in particular, cardiomyocyte sarcoplasmic reticulum  $\text{Ca}^{2+}$  adenosine triphosphatase, ryanodine receptors, phospholamban, and myofilament proteins.<sup>6–9</sup> Importantly, *in vitro* studies demonstrated inotropic and lusitropic effects by increasing calcium sensitivity and calcium handling efficiency rather than by increasing intracellular calcium concentrations.<sup>10</sup> In a canine model of heart failure, HNO had

positive inotropic and lusitropic effects that were independent of beta-adrenergic signalling.<sup>11</sup> In addition to these potentially attractive myocardial effects, HNO also causes vasodilatation via soluble guanylate cyclase.<sup>12</sup> These properties suggest that HNO might be effective for the treatment of patients hospitalized for heart failure.<sup>13</sup>

The haemodynamic effects of cimlanod (BMS-986231), an HNO donor, have been investigated in patients with advanced heart failure, congestion, and a reduced left ventricular ejection fraction (LVEF).<sup>13,14</sup> In that Phase II dose escalation study, intravenous (IV) infusion of cimlanod for 6 h was well tolerated, reduced systemic arterial and intra-cardiac filling pressures, and increased cardiac index (CI), as measured by thermodilution but not by the Fick method.<sup>14</sup> Any potential effect on CI may have been secondary to vasodilator effects rather than inotropy *per se*.

We conducted the StandUP-Imaging trial (NCT03357731) to evaluate the effects of a continuous 5 h IV infusion of cimlanod on cardiac performance measured by echocardiography in patients with chronic stable heart failure with reduced ejection fraction (HFrEF). Nitroglycerin (NTG), a vasodilator without direct inotropic effects, was used as an active comparator.

## Methods

This was a multicentre, prospective, Phase II, randomized, double-blind, placebo- and active-controlled trial with a crossover design.<sup>13</sup> Continuous 5 h infusions of cimlanod were compared with infusions of NTG and with placebo in patients with chronic stable HFrEF. The study was approved by the relevant health authorities and by the Institutional Review Board of each participating site. All study participants provided written informed consent.

## Patients

We enrolled patients aged  $\geq 18$  years with a clinical diagnosis of heart failure (New York Heart Association class I to III), an echocardiographic LVEF of  $\leq 40\%$  and plasma N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)  $\geq 125$  pg/mL [or B-type natriuretic peptide (BNP)  $\geq 35$  pg/mL]. Patients were required to be in sinus rhythm, on stable therapy for heart failure [including an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor–neprilysin inhibitor (ARNi) and mineralocorticoid receptor antagonist plus beta-blockers, as tolerated], and have good quality echocardiographic images. The main exclusion criteria at screening or pre-randomization were systolic BP (SBP)  $< 110$  mmHg or heart rate  $< 50$  or  $> 90$  bpm. Patients with heart rate  $< 50$  bpm were excluded to avoid the confounding influence of bradycardia upon diastolic function and we excluded patients with heart rate  $> 90$  bpm to permit optimal Doppler analysis. Patients with paced rhythm were excluded, as were those with restrictive, obstructive, or hypertrophic cardiomyopathy, severe valvular disease, or prior aortic or mitral valve repair or replacement. Patients who had been hospitalized for heart failure in the previous month or had an acute coronary or cerebrovascular event in the previous 3 months were ineligible.

## Procedures

Participants were asked to omit their usual heart failure medications on each study day. In a crossover design, participants were exposed to each of the three interventions (cimlanod, NTG, and placebo) in random order. Randomization was via centralized electronic interactive response technology. Each treatment period included a 5 h IV infusion, followed by a washout period of 5 to 28 days. In order to maintain blinding, the infusions were administered according to a pre-specified flow rate and had similar appearance and packaging. The target doses were  $12 \mu\text{g/kg/min}$  for cimlanod and  $80 \mu\text{g/min}$  for NTG, which were attained after a short initial up-titration period (10 min at 25% of target dose followed by 10 min at 50% of target dose followed by target dose thereafter, providing BP tolerability criteria were met). BP and heart rate were recorded prior to the infusion, every 30 min for the first hour, and then hourly until the end of the infusion. They were recorded again at 1, 2, and 3.5 h after the end of the infusion. In the event of a decrease in SBP during infusions, an algorithm was used to down-titrate, interrupt, or discontinue the infusion. If a patient experienced SBP of 80 to 90 mmHg without symptoms of hypotension, the infusion rate was reduced by 50%. If SBP fell below 80 mmHg (and remained  $< 80$  mmHg following a repeated measurement within 15 min), or if the patient experienced symptoms of hypotension (regardless of BP), the infusion was interrupted for at least 1 h. It was subsequently resumed at 50% of the prior dose, provided that SBP had recovered to  $\geq 105$  mmHg and symptoms of hypotension had resolved. The infusion was permanently discontinued if study medication had

been interrupted for low BP, resumed, and an episode of hypotension (or symptoms of hypotension) re-occurred. After the 5 h infusion, patients remained in the study facility for a further 3.5 h but were discharged on the same day unless there had been prolonged or symptomatic hypotension or other events of concern, in which case patients were kept overnight.

A core laboratory performed all echocardiographic analyses blinded to infusion assignment (Brigham and Women's Hospital, Boston, MA, USA). Reproducibility data are provided in online supplementary *Methods S1*. An echocardiogram was done at screening and was submitted for review and confirmation of eligibility on the basis of LVEF and imaging quality. At least two echocardiograms were done on the first day of each period (prior to infusion and near the end of the infusion between hour 4 and hour 5). In the event of premature interruption of an infusion, an echocardiogram was done as soon as possible. A pre-specified echocardiographic protocol for image acquisition was created by the core laboratory. Recordings were optimized for endocardial border definition and echocardiographic contrast agent used when required. Sonographers at each site were trained by the core laboratory and underwent a certification process. The core laboratory worked with individual sites to identify the proper equipment settings to optimize images.

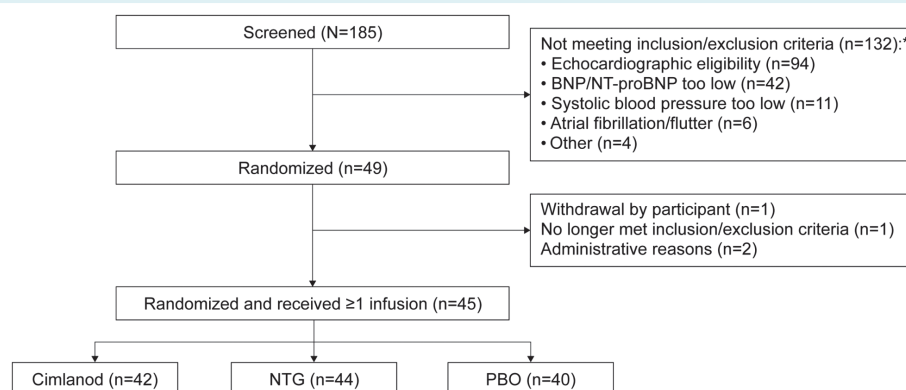
The primary outcome of interest was stroke volume index (SVI) derived from the left ventricular (LV) outflow tract velocity time integral (VTI) as measured by Doppler at the end of infusion of cimlanod compared with placebo. Secondary outcomes of interest included the effect of cimlanod compared with that of NTG or placebo on SVI and on other LV systolic and diastolic indices (LVEF, tissue Doppler, LV diastolic function, including mitral inflow velocities and other indices such as LV power index and global longitudinal strain). LV volumes, elastance, and myocardial performance (Tei) index were also measured, as were left atrial (LA) size and function and right ventricular size and function.

Safety was monitored by physical examination, standard clinical biochemistry and haematology tests, and urinalysis. Twelve-lead electrocardiograms were recorded before and after each infusion period. The occurrence of any adverse events (AEs) was recorded from the start of the infusion until 24 h after the end of the infusion. Patients were contacted by telephone on the day after each infusion to enquire about potential AEs. Serious AEs were recorded from the date of informed consent and up to 30 days after the end of the last infusion.

## Sample size calculation and statistical analyses

Sample sizes were calculated based on comparison of post-baseline SVI values, adjusting for the differences in the baseline value. Sample size calculations assumed an increase of SVI of  $4.5 \text{ mL/m}^2$  from baseline, relative to placebo, an inter-individual standard deviation of  $10 \text{ mL/m}^2$ , and intra-individual correlations for the difference between assessments of 0.7. A sample size of approximately 36 participants, with data from the treatment periods being compared, was estimated to provide 90% power, with a type I error probability of 0.05 (two-sided). The sample size was increased by 20% to compensate for the possibility of missing data due to patient withdrawal.

Comparisons between placebo and cimlanod were done using a mixed model repeated measures analysis that examined within-subject differences, controlling for treatment sequence, treatment period, and specific treatment (i.e. cimlanod, NTG, or placebo), with the difference in the treatment period baselines as co-variables. All randomized



**Figure 1** Patient disposition. BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; NTG, nitroglycerin; PBO, placebo. \* $\geq 1$  reason for screen failure possible.

patients who started study drug infusion in at least one assessment period were included in the final analysis. No adjustments were made for multiple comparisons. Statistical significance was defined by a  $P$ -value of  $<0.05$ . All data analyses were performed using SAS version 9.3 or higher (SAS Institute, Inc., Cary, NC, USA).

## Results

### Enrolment of participants

Between December 2017 and March 2019, patients were randomized at nine sites in the United Kingdom, Netherlands, United States of America, and Japan. Overall, 45 participants were randomized and received at least one infusion and were included in the final analysis on an intention-to-treat basis (Figure 1). Thirty-nine participants completed all three infusions.

### Baseline characteristics

Of the 45 participants, 37 (82%) were men and the mean age was  $64 \pm 12$  years. Most (89%) were white and 71% had ischaemic heart disease (Table 1). Median (interquartile range) NT-proBNP and BNP levels were 505 (325–1111) pg/mL and 177 (136–325) pg/mL, respectively (Table 1). The main baseline medications are outlined in Table 1.

### Echocardiographic measurements

Mean baseline SVI derived from the LV outflow tract VTI was low at the beginning of all infusion periods. At the end of the infusion of cimlanod, SVI was significantly lower than it was at the end of placebo infusion (SVI with cimlanod:  $29 \pm 9$  mL/m<sup>2</sup> vs. SVI with placebo:  $30 \pm 7$  mL/m<sup>2</sup>;  $P = 0.027$ ). SVI was also lower at the end of NTG infusion than it was at the end of placebo (SVI with NTG:  $28 \pm 7$  mL/m<sup>2</sup>;  $P = 0.017$  vs. SVI with placebo) (Table 2). The effects of cimlanod and NTG on SVI were similar ( $P = 0.8$ ) (Table 2 and Figure 2).

At the end of NTG infusion, LV end-diastolic and end-systolic volumes were lower than with placebo and LVEF was statistically

higher, although the effect was modest. Similar trends were seen with cimlanod, although only LV end-systolic volume was significantly different from placebo. The effects of NTG and cimlanod, including upon mean LV global longitudinal strain, cardiac power index, LV Tei index, LV end-systolic elastance (Ees) and arterial elastance (Ea) were similar (Table 2).

Peak early transmitral velocity (E wave) was similarly reduced by cimlanod and NTG compared with placebo ( $P = 0.008$  and  $P = 0.014$  for cimlanod and NTG vs. placebo, respectively). There were no significant differences in peak active transmitral velocity (A wave) or lateral early diastolic myocardial velocity ( $e'$ ). Therefore, although E/A and E/ $e'$  ratios were lower at the end of both cimlanod and NTG infusions compared with placebo, these differences were driven primarily by changes in E wave velocity and not by other markers of diastolic performance. When compared with placebo, LA volume was reduced by cimlanod ( $P = 0.002$  vs. placebo) and NTG ( $P < 0.001$  vs. placebo). The effects of cimlanod and NTG upon LA volume were similar ( $P = 0.73$  for cimlanod vs. NTG) (Table 2).

Echocardiographic contrast agent was used in four patients.

### Blood pressure and heart rate effects

Overall mean SBP decreased during all infusions: it dropped by  $5 \pm 13$  mmHg during placebo, by  $19 \pm 15$  mmHg during cimlanod ( $P < 0.0001$  vs. placebo), and by  $15 \pm 18$  mmHg during NTG ( $P = 0.0024$  vs. placebo) (Figure 3A). Recovery of SBP after the end of the infusion was similar for cimlanod and NTG. The pattern of change for diastolic BP was similar for cimlanod and NTG (Figure 3B). Although there was a small reduction in mean heart rate during all infusion periods, this was not statistically significant compared with baseline or across groups. Mean heart rate reduction was  $1 \pm 11$  bpm during placebo,  $2 \pm 8$  bpm during cimlanod, and  $1 \pm 8$  bpm during NTG (Figure 3C).

### Safety

During placebo infusion, no patient met the pre-specified BP criteria for dose reduction, interruption, or cessation. During cimlanod,

**Table 1** Patient baseline characteristics

Patients, <i>n</i>	45
Age, years	64 ± 12
Male sex	37 (82)
Race	
White	40 (89)
Black or African American	1 (2)
Asian	3 (7)
Other	1 (2)
Heart failure aetiology	
Ischaemic	32 (71)
Non-ischaemic	10 (22)
Unknown	3 (7)
BMI, kg/m <sup>2</sup>	27 ± 5
Heart rate, bpm	66 ± 11
SBP, mmHg	129 ± 15
DBP, mmHg	74 ± 11
LVEF, %	30 ± 7
Natriuretic peptides, pg/mL	
NT-proBNP	505 [325–1111]
BNP	177 [136–325]
eGFR, mL/min/1.73 m <sup>2</sup>	62.3 ± 14.7
Medication	
Beta-blocker	43 (96)
Angiotensin-converting enzyme inhibitor	28 (62)
Angiotensin receptor blocker	5 (11)
Angiotensin receptor–neprilysin inhibitor	8 (18)
Mineralocorticoid receptor antagonist	11 (24)
Loop diuretic	26 (58)

Data are presented as mean ± standard deviation, *n* (%), or median [interquartile range]. Due to rounding, percentage values may not total 100%.

BMI, body mass index; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; SBP, systolic blood pressure.

the infusion was discontinued because of hypotension in two participants, while another four (10%) required protocol-mandated dose reduction as a result of low BP but went on to complete the total 5 h infusion period at 50% of target dose. One patient who experienced hypotension was on chronic treatment with sacubitril/valsartan (although, per protocol, this had been omitted on the morning of the study). One patient discontinued NTG because of chest pain and hypotension and, similar to cimlanod, four patients (9%) required a BP-related dose reduction but went on to complete the 5 h infusion period at 50% of target dose.

There was no incidence of arrhythmia during placebo or cimlanod infusion. During NTG, one patient had very brief (eight beats) non-sustained ventricular tachycardia, and another had brief, self-terminating supraventricular tachycardia.

Most AEs were mild or moderate in severity and were reported in eight participants (20%) receiving placebo, 15 participants (36%) receiving cimlanod and 15 participants (34%) receiving NTG. The most common AE reported with cimlanod was headache (*n* = 10, 24%; all graded 'mild'). Mild or moderate headache was reported by seven participants (16%) during NTG and by

two patients (5%) during placebo. There were two serious AEs. One participant reported abdominal discomfort during placebo infusion and had acutely deranged liver function tests. Further investigation confirmed acute cholecystitis. Another participant had marked hypotension and bradycardia (vasovagal pre-syncope) during infusion of NTG. He was admitted to hospital overnight for observation and made an uncomplicated recovery.

## Discussion

We have demonstrated that cimlanod, a novel HNO donor, has haemodynamic effects similar to those of NTG in ambulatory patients with chronic stable HFrEF. We did not demonstrate an inotropic effect of cimlanod. Although cimlanod improved echocardiographic markers of diastolic function, this appeared to reflect venodilatation and preload reduction rather than a direct lusitropic effect.

Almost all patients in the trial were on an ACEi/ARB/ARNI and a beta-blocker, although only a minority were treated with a mineralocorticoid receptor antagonist. Patients had well controlled symptoms and many did not require diuretic therapy. Natriuretic peptides were only modestly elevated, and patients were excluded if they had had a recent decompensation of heart failure. Furthermore, patients with an SBP <110 mmHg were excluded. Consequently, the participants in the trial reflect patients with ambulatory heart failure without substantial volume overload. This is in contrast to the patients included in an earlier study examining dose-ranging effects of IV cimlanod in patients with advanced heart failure and elevated pulmonary capillary wedge pressure ( $\geq 20$  mmHg).<sup>14</sup> In those patients, cimlanod evoked dose-dependent reductions in cardiac filling pressures and an increase in CI assessed by thermodilution, but not when assessed by the Fick method. Heart rate was unaffected by cimlanod in that study and therefore any increase in CI must have been due to an increase in stroke volume, caused by a reduction in afterload, improved myocardial contractility, or both.<sup>14</sup>

In the current study, cimlanod led to a small but significant reduction in SVI when compared with placebo. This effect on SVI, the primary outcome measure, was similar to that of NTG and contrasts with the earlier study described above. The reduction in SVI in our study most likely reflects a reduction in preload (as a result of venous dilatation) in patients who already had relatively low filling pressures. This effect might be different in patients with more severe heart failure and high LV end-diastolic pressures.<sup>15</sup> In such patients, CI might increase when afterload is reduced despite a reduction in intra-cardiac filling pressure.<sup>15</sup> Indeed, in an historical invasive haemodynamic study of patients after myocardial infarction, IV NTG was associated with a rise in cardiac output in patients with high LV filling pressures, while in those with normal LV filling pressures NTG caused cardiac output to fall.<sup>16</sup> Cimlanod and NTG reduced LV volumes, which can be attributed to altered loading conditions and accounts for the small increase in LVEF with NTG. Importantly, the effects of cimlanod on sensitive measures of systolic function including LV global longitudinal strain, cardiac power index and LV Tei index



**Table 2** Echocardiographic measurements before and at the end of 5 h of infusion of placebo, nitroglycerin, or cimlanod

	Placebo		NTG		P-value vs. placebo	Cimlanod		P-value vs. placebo	P-value vs. NTG
	Pre-infusion	Post-infusion	Pre-infusion	Post-infusion		Pre-infusion	Post-infusion		
SVI, mL/m <sup>2</sup>	29 ± 7	30 ± 7	29 ± 7	28 ± 7	<b>0.017</b>	30 ± 9	29 ± 9	<b>0.027</b>	0.846
SV, mL	57 ± 16	58 ± 14	57 ± 14	55 ± 15	<b>0.036</b>	59 ± 17	57 ± 17	<b>0.045</b>	0.837
LVEDV, mL	160 ± 52	160 ± 54	163 ± 51	155 ± 50	<b>0.009</b>	165 ± 54	155 ± 45	0.065	0.914
LVESV, mL	111 ± 43	110 ± 42	112 ± 41	105 ± 41	<b>0.006</b>	114 ± 45	106 ± 39	<b>0.046</b>	0.918
LVEF, %	32 ± 7	32 ± 7	32 ± 7	34 ± 7	<b>0.039</b>	32 ± 8	33 ± 8	0.177	0.839
Mean LV GLS, %	-11.6 ± 3.1	-12.0 ± 2.9	-11.5 ± 3.2	-11.4 ± 3.1	<b>0.006</b>	-11.3 ± 3.3	-11.9 ± 3.5	0.705	0.105
Cardiac power index, W/m <sup>2</sup>	0.40 ± 0.11	0.41 ± 0.14	0.38 ± 0.08	0.35 ± 0.09	0.063	0.44 ± 0.17	0.34 ± 0.10	<b>0.007</b>	0.103
LV Tei index	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.3	0.7 ± 0.2	<b>0.009</b>	0.7 ± 0.3	0.8 ± 0.4	<b>0.012</b>	0.6
LV Ees, mmHg/mL	3.5 ± 1.4	3.2 ± 1.0	3.3 ± 1.3	2.8 ± 1.0	<b>0.033</b>	3.3 ± 1.3	2.6 ± 1.1	0.174	0.342
Ea, mmHg/mL	2.2 ± 0.7	2.0 ± 0.5	2.2 ± 0.7	1.9 ± 0.5	0.364	2.1 ± 0.7	1.9 ± 0.6	0.685	0.711
Ea/Ees	0.69 ± 0.23	0.69 ± 0.4	0.76 ± 0.36	0.76 ± 0.30	<b>0.044</b>	0.76 ± 0.45	0.90 ± 0.43	0.075	0.981
Peak E wave velocity, cm/s	63 ± 24	59 ± 17	67 ± 25	54 ± 23	<b>0.014</b>	66 ± 23	53 ± 19	<b>0.008</b>	0.753
Peak A wave velocity, cm/s	72 ± 21	77 ± 24	75 ± 21	76 ± 19	0.687	74 ± 22	75 ± 20	0.876	0.798
E/A ratio	0.9 ± 0.5	0.8 ± 0.3	0.9 ± 0.5	0.7 ± 0.3	<b>0.005</b>	1.0 ± 0.5	0.7 ± 0.3	<b>0.003</b>	0.904
Lateral e', cm/s	7.3 ± 2.5	7.2 ± 2.5	7.3 ± 2.5	7.2 ± 2.1	0.231	7.5 ± 2.6	8.1 ± 2.3	0.994	0.073
E/e' ratio	9.2 ± 4.2	9.4 ± 4.1	10.0 ± 4.5	7.8 ± 2.7	<b>0.016</b>	9.8 ± 4.2	7.0 ± 2.5	<b>0.006</b>	0.503
LA volume, mL	57.7 ± 15.0	58.8 ± 17.0	61.8 ± 16.8	54.3 ± 18.0	<b>&lt;0.001</b>	62.0 ± 17.0	55.3 ± 18.7	<b>0.002</b>	0.73
RA volume, mL	15.5 ± 3.6	15.6 ± 4.1	15.4 ± 3.7	14.8 ± 2.9	0.639	14.8 ± 2.6	14.8 ± 2.9	0.759	<b>0.009</b>
Peak TR velocity, cm/s	240 ± 67	261 ± 31	251 ± 74	232 ± 49	0.098	248 ± 60	235 ± 32	NA	0.556
TAPSE, cm	1.7 ± 0.3	1.8 ± 0.4	1.6 ± 0.3	1.6 ± 0.3	0.092	1.7 ± 0.4	1.6 ± 0.4	<b>0.042</b>	0.879
RV EDA, cm <sup>2</sup>	20.8 ± 6.0	20.4 ± 5.4	20.2 ± 5.9	20.1 ± 7.2	0.693	19.4 ± 5.1	19.7 ± 4.4	0.983	0.426
RV ESA, cm <sup>2</sup>	11.7 ± 11.4	11.4 ± 3.3	11.1 ± 4.5	11.3 ± 4.4	0.146	11.4 ± 3.4	11.2 ± 3.2	0.894	0.399
RV FAC, %	44.0 ± 7.0	43.9 ± 6.8	45.3 ± 8.3	44.7 ± 7.0	0.919	41.3 ± 5.9	43.3 ± 6.9	0.466	0.751

Data are presented as mean ± standard deviation. Statistically significant P-values are indicated in bold.

e', lateral early diastolic myocardial velocity; Ea, arterial elastance; EDA, end-diastolic area; Ees, end-systolic elastance; ESA, end-systolic area; FAC, fractional area change; GLS, global longitudinal strain; LA, left atrium; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NA, not assessed (because of a low number of measures); NTG, nitroglycerin; RA, right atrium; RV, right ventricle; SV, stroke volume; SVI, stroke volume index derived from the left ventricular outflow tract area; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

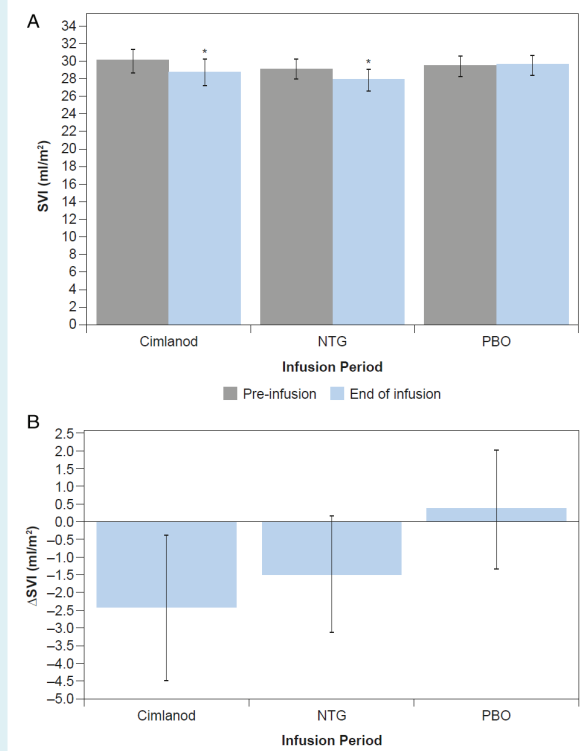
were similar to those of NTG and did not suggest an inotropic effect. LV Ees and Ea were also similar at the end of NTG and cimlanod, as was Ea/Ees, a marker of ventriculo-arterial coupling efficiency.<sup>17</sup> Two of the most striking effects of cimlanod were reductions in LA volume and E wave velocity. These changes were also evoked by NTG and are consistent with preload reduction.<sup>18</sup> The effects on E wave velocity account for the observed reductions in E/e' and E/A ratios. Neither e' velocity nor A wave velocity was altered by either cimlanod or NTG and, as such, these apparently beneficial effects on diastolic indices reflect reductions in cardiac preload and filling pressures rather than direct lusitropy.

The effects of cimlanod on heart rate and BP were not the primary focus of the current study. Defining the BP effects of cimlanod in patients with heart failure-related hospitalization is the aim of the StandUP-AHF trial.<sup>13</sup> However, in the current study, cimlanod had broadly similar effects on BP and heart rate as NTG, although the onset of the BP-lowering effect appeared to be slightly delayed compared with NTG. It is notable that, despite the fall in BP and SVI during cimlanod and NTG, there was no appreciable reflex tachycardia. The reduction in SVI associated with cimlanod and NTG was small and we believe that the hypotensive effect of these agents primarily reflects arterial vasodilatation although a smaller contribution from reduced cardiac output cannot be fully excluded. Although patients did not take their

usual medications on the morning of the study infusion, a residual effect of beta-blockers may account for the absence of a rise in heart rate.

Infusion visits were separated by at least 5 days and, given the short half-lives of NTG and cimlanod, no carry-over effect of these agents upon haemodynamics would be expected. We minimized the potential for changes in baseline haemodynamics over time by including patients with stable heart failure symptoms who had had no change in heart failure medications (nor of their dosage) within the 2 weeks prior to enrolment.

The addition of NTG as an active control arm is a major strength of the study. The dose of NTG was chosen to produce an equivalent reduction in pulmonary capillary wedge pressure to the 12 µg/kg/min dose of cimlanod. Given the remarkable similarity of the observed haemodynamic effects of NTG and cimlanod, it seems that we chose an appropriate active comparator dose. Furthermore, we have provided comprehensive data pertaining to the haemodynamic effects of NTG which, although in routine clinical use, has no compelling evidence demonstrating that it improves clinical outcomes. Continuous IV infusion of cimlanod for 5 h was well tolerated and had a safety profile similar to that of NTG when administered to subjects with chronic heart failure and impaired systolic function. No new safety concerns were identified. However, it is notable that almost one quarter of

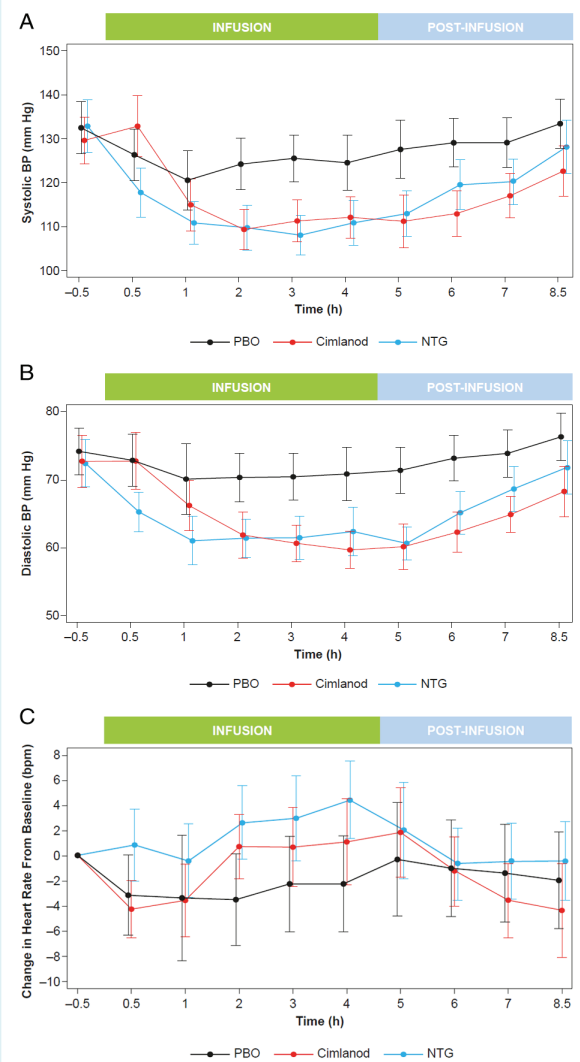


**Figure 2** Stroke volume index (SVI) derived from the left ventricular outflow tract area. (A) Absolute SVI (pre-infusion vs. post-infusion). (B) Change in SVI vs. baseline in the presence of placebo (PBO), nitroglycerin (NTG), or cimlanod. Data are presented as mean  $\pm$  standard error of the mean. \* $P < 0.05$  vs. placebo at end of infusion.

patients receiving cimlanod experienced headache, albeit of mild severity.

## Limitations

We assume that the preload reduction induced by cimlanod is mediated by venodilatation. However, cimlanod might reduce congestion by increasing diuresis or diuretic sensitivity, which would differentiate it from NTG. While there is currently no evidence to support or refute this hypothesis and it was not addressed in the current study, this is the focus of the ongoing StandUP-Kidney study.<sup>13</sup> Secondly, while we administered infusions over 5 h to achieve steady-state drug bioavailability, this period is shorter than that often used for NTG in clinical practice. NTG-mediated vasomotor effects are associated with tachyphylaxis<sup>19</sup> and, although there are data to suggest that this may not be an issue with HNO donors,<sup>20,21</sup> infusions in the current study were not of sufficient duration to address this question. The StandUP-AHF trial randomized patients to 48 h IV infusion of cimlanod or placebo<sup>13</sup> and should provide some insight to this question, albeit without direct comparison to NTG. Invasive assessment using conductance catheters to create pressure–volume loops may provide greater accuracy in the assessment of cardiac haemodynamics. However,



**Figure 3** Mean ( $\pm$  95% confidence interval) change in blood pressure (BP) and heart rate during and after study infusions. (A) Mean systolic BP at baseline, during, and after study infusions. (B) Mean ( $\pm$  95% confidence interval) diastolic BP at baseline, during, and after study infusions. (C) Mean ( $\pm$  95% confidence interval) change in heart rate during and after study infusions. NTG, nitroglycerin; PBO, placebo.

we wished to avoid an invasive approach, and ensured an appropriate sample size was recruited to allow robust comparisons to be made with echocardiographic assessment of SVI as the primary outcome of interest.

## Conclusion

In patients with chronic stable HFrEF, infusion of cimlanod, a novel HNO donor, causes venous and arterial vasodilatation but does not appear to exert inotropic or direct lusitropic effects. The haemodynamic profile is similar to that of NTG.

## Supplementary Information

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

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### Data-sharing statement

The Bristol-Myers Squibb policy on data sharing can be found at: <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>

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