

# Overview of the cardiovascular effects of tadalafil

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Because erectile dysfunction (ED) and cardiovascular disease share a number of risk factors, it is important to understand the haemodynamic and cardiovascular effects of treatments for ED, including the phosphodiesterase (PDE) type 5 inhibitors. In healthy subjects, administration of tadalafil (a potent and selective inhibitor of PDE5 indicated for the treatment of ED) resulted in small decreases in standing blood pressure. In the general population of men with ED, the effects of tadalafil on haemodynamic parameters were similar to those observed with placebo. As with sildenafil, administration of tadalafil with any nitrate is contraindicated. Tadalafil administration was not associated with prolongation in QT interval. Safety data show that the incidence rate of myocardial infarction following treatment with tadalafil was comparable to that observed in the age-standardized male population, and incidence rates of

cardiovascular events observed in patients who were and were not treated with concomitant antihypertensive therapy were comparable. These results demonstrate that tadalafil has no clinically relevant effects on haemodynamics, although it should not be used in combination with nitrates. In addition, integrated analyses of the cardiovascular adverse events in the phase III safety database as a whole, and in patients taking concomitant antihypertensive medication, demonstrate that tadalafil is not associated with increased risk for clinically significant cardiovascular events.

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## Introduction

The aetiology of erectile dysfunction (ED) may be psychogenic, organic, or mixed, with mixed being most commonly observed<sup>[1]</sup>. It is estimated that vascular abnormalities are the primary cause of ED in approximately 40% of men aged 50 years or older<sup>[2]</sup>. Not surprisingly, ED and coronary heart disease (CHD) share numerous risk factors, such as age, hypertension, diabetes mellitus, obesity, smoking, hyperlipidaemia, and physical inactivity<sup>[3]</sup>. Additionally, it has been proposed that ED may serve as a marker for cardiovascular disease<sup>[4]</sup>. The severity of ED may serve as a useful indicator of the progression of cardiovascular disease in patients with ischaemic heart disease<sup>[5]</sup>.

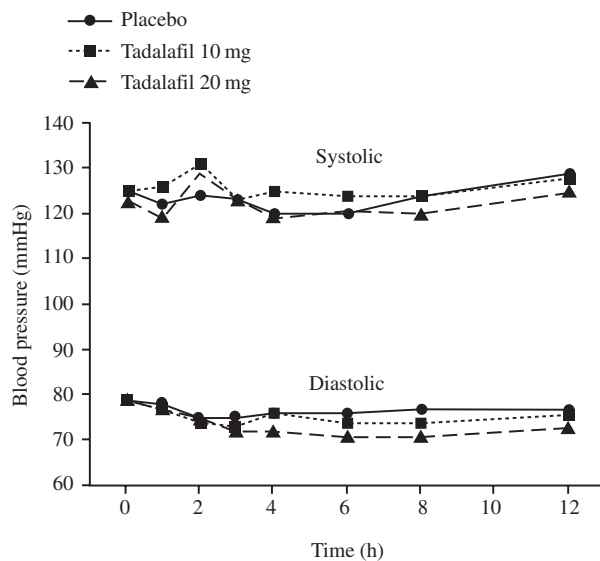
Sildenafil, the first available oral treatment for ED, effectively inhibits phosphodiesterase (PDE) type 5, thereby sustaining nitric oxide mediated smooth muscle relaxation in the corpus cavernosum of the penis. Sildenafil also acts systemically with vasodilatory properties, similar to the

effect of a modest nitrate<sup>[6]</sup>. In fact, the combination of sildenafil and nitrates is contraindicated because the synergistic potentiation of vasodilatation when these agents are combined may cause excessive reductions in blood pressure<sup>[7,8]</sup>. However, sildenafil has been demonstrated to be safe in men with hypertension<sup>[9]</sup>, in patients taking antihypertensive medication<sup>[10]</sup>, and in patients with CHD<sup>[11,12]</sup>.

Tadalafil is a potent, selective, reversible inhibitor of PDE5 that is indicated for the oral treatment of ED. As mentioned elsewhere in this supplement (see the report by F. Giuliano and L. Varanese, presented herein), the pharmacokinetic and pharmacodynamic profile of tadalafil differs markedly from that of sildenafil. Accordingly, the cardiovascular effects of tadalafil may differ from those observed for sildenafil. The present overview of the cardiovascular effects of tadalafil includes the effects of tadalafil on blood pressure and heart rate in healthy subjects and in patients with ED in placebo-controlled phase III studies. In addition, the pharmacodynamic interactions between tadalafil and nitrates in healthy subjects and in patients with chronic stable angina are described, as are the cardiovascular adverse events in patients with ED in the

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**Figure 1** Mean standing systolic and diastolic blood pressure following a single oral dose of tadalafil 10 mg, tadalafil 20 mg or placebo in healthy subjects.

placebo-controlled phase III studies and incidence rates of myocardial infarction in all patients treated with tadalafil. Finally, data are presented from analyses of the haemodynamic effects and adverse effects observed when tadalafil was administered to patients who were on concomitant antihypertensive therapy.

## Haemodynamic effects of tadalafil in healthy subjects

In a randomized, double-blind, placebo-controlled, parallel-group study, the effects of tadalafil on haemodynamics were assessed in 80 healthy subjects. Participants received a single oral dose of tadalafil 10 mg ( $n = 32$ ), tadalafil 20 mg ( $n = 33$ ) or placebo ( $n = 15$ ) once daily for 10 consecutive days. Haemodynamic evaluations, including the mean maximal change from baseline in standing and supine blood pressure and heart rate, were performed on day 1 (pre-dose and post-dose) and on day 10 (pre-dose and post-dose).

A two-sided 95% confidence interval (CI) was constructed from the comparison of tadalafil (10 mg and 20 mg) with placebo for the mean difference (tadalafil minus placebo) in the mean maximal decrease in standing systolic blood pressure (SBP). Provided this CI was entirely within  $\pm 8$  mmHg, tadalafil would be considered to be equivalent to placebo.

As demonstrated in Figure 1, tadalafil 10 mg and 20 mg resulted in a modest decrease in standing SBP and diastolic blood pressure (DBP) when compared with placebo. Based on the primary end-point (mean maximal decrease in standing SBP), the tadalafil 10 mg dose was not equivalent to placebo on either day 1 or day 10 (Table 1), although the 95% CI values were only slightly outside the limits for equivalence (0.1 mmHg and 0.2 mmHg, respectively). In fact, the mean difference in standing SBP between tadalafil 10 mg and placebo was actually +1.3 mmHg on day 1 (demonstrating that blood pressure actually decreased less with tadalafil 10 mg than with placebo), and the upper limit of the 95% CI for the mean difference between treatments was outside the limit for equivalence. Conversely, on day 10,

**Table 1** Mean maximal changes from baseline in standing and supine blood pressure and heart rate following a single oral dose of tadalafil 10 mg, tadalafil 20 mg or placebo in healthy subjects

Parameter	Day	LS mean maximal change from baseline			Mean difference (95% CI) for the maximal change from baseline		
		Placebo (n = 15)	Tadalafil		Tadalafil 10 mg vs placebo	Tadalafil 20 mg vs placebo	Tadalafil 20 mg vs Tadalafil 10 mg
			10 mg (n = 32)	20 mg (n = 33)			
Standing SBP (mmHg)	1	-13.1	-11.9	-13.4	1.3 (-5.6, 8.1)	-0.2 (-7.1, 6.6)	-1.5 (-7.0, 4.0)
	10	-13.7	-15.0	-12.8	-1.3 (-8.2, 5.6)	0.9 (-6.0, 7.8)	2.2 (-3.4, 7.8)
Standing DBP (mmHg)	1	-9.4	-12.0	-14.0	-2.6 (-5.9, 0.8)	-4.6 (-7.9, -1.2)	-2.0 (-4.7, 0.7)
	10	-10.0	-14.6	-15.1	-4.6 (-8.7, -0.5)	-5.1 (-9.2, -1.0)	-0.5 (-3.9, 2.8)
Standing heart rate (bpm)	1	19.7	18.9	19.6	-0.8 (-6.5, 5.0)	0.0 (-5.8, 5.7)	0.7 (-3.9, 5.3)
	10	19.7	17.6	19.2	-2.0 (-9.4, 5.3)	-0.4 (-7.8, 6.9)	1.6 (-4.4, 7.6)
Supine SBP (mmHg)	1	-9.2	-10.4	-10.8	-1.2 (-6.6, 4.2)	-1.6 (-6.9, 3.8)	-0.4 (-4.7, 3.9)
	10	-6.9	-11.1	-11.2	-4.2 (-9.8, 1.3)	-4.4 (-9.9, 1.2)	-0.1 (-4.7, 4.4)
Supine DBP (mmHg)	1	-9.0	-9.3	-9.8	-0.3 (-3.2, 2.6)	-0.8 (-3.7, 2.1)	-0.5 (-2.9, 1.8)
	10	-8.7	-10.5	-11.1	-1.8 (-5.6, 2.0)	-2.4 (-6.2, 1.4)	-0.6 (-3.7, 2.5)
Supine heart rate (bpm)	1	12.7	18.0	16.1	5.3 (0.9, 9.7)	3.4 (-1.0, 7.7)	-1.9 (-5.4, 1.6)
	10	15.1	18.3	20.2	3.2 (-2.1, 8.6)	5.1 (-0.2, 10.5)	1.9 (-2.5, 6.3)

A negative value indicates a decrease from baseline. CI=confidence interval; DBP=diastolic blood pressure; LS=least squares; SBP=systolic blood pressure.

the mean difference between tadalafil 10 mg and placebo was  $-1.3$  mmHg. It should be noted that the mean differences between the two treatments were small (2 mmHg or lower) and considered to be of no clinical significance. Tadalafil 20 mg was equivalent to placebo on both day 1 and day 10. The mean difference in standing SBP between tadalafil 20 mg and placebo was  $-0.2$  mmHg on day 1 and  $0.9$  mmHg on day 10. Therefore, the findings with tadalafil 10 mg were not replicated with the 20 mg dose. These results indicate that tadalafil has no clinically relevant effects on haemodynamic measurements in healthy subjects.

In that study, the proportion of subjects with potentially clinically significant changes in blood pressure (outliers) was also assessed. An outlier was defined as a participant who had experienced a decrease in SBP of greater than 30 mmHg from baseline or had a SBP below 85 mmHg, or a decrease in DBP of greater than 20 mmHg from baseline or had a DBP below 45 mmHg. Although no formal statistical analysis was performed, the proportions of outliers were generally similar in the tadalafil and placebo treatment groups for most of the outlier criteria. A change from baseline in standing DBP of more than 20 mmHg was observed in a greater proportion of subjects following dosing with tadalafil 10 mg and tadalafil 20 mg (approximately 27% and 20%, respectively) than with placebo (approximately 7%).

Since each blood pressure assessment in that study was obtained as a pair (supine and after standing for 2 min), it was possible to evaluate the potential for tadalafil to induce significant orthostatic blood pressure changes. There were no apparent differences between treatment groups in the mean maximal decreases in SBP when patients went from the supine to standing position. On day 1, the post-dose values were  $-12$  mmHg for the placebo group,  $-11$  mmHg for the tadalafil 10 mg group and  $-14$  mmHg for the tadalafil 20 mg group. The post-dose value after 10 days of daily dosing was  $-13$  mmHg for all three treatment groups. The proportion of subjects with orthostatic hypotension (SBP decreases  $\geq 30$  mmHg) post-dose on day 1 was 0% for placebo versus 3.1% for tadalafil 10 mg and 9.1% for tadalafil 20 mg. On Day 10, the proportion of subjects with orthostatic hypotension was 0% for placebo, 0% for tadalafil 10 mg and 3.3% for tadalafil 20 mg. Although the proportion of patients with SBP drops of 30 mmHg or more was greater in tadalafil treated patients on day 1, these findings are consistent with the pharmacology of PDE5 inhibitors (vasodilatation).

The adverse event profile did not reveal any clinical consequences of the haemodynamic effects of tadalafil in this experimental cohort. Taken together, the above findings suggest that tadalafil is a mild vasodilator, which results in a small change in blood pressure in healthy subjects.

### Placebo-controlled phase III safety database

The placebo-controlled phase III safety database consisted of six clinical trials; five were conducted in a general

population with ED and one in a population of patients with ED and diabetes. Study participants included men with a history of ED of duration at least 3 months who were 22–82 years old (mean age 58 years). Patients with different aetiologies of ED and all degrees of ED severity were enrolled. Patients were excluded from the study if they had any of the following: a history of myocardial infarction within the previous 3 months; unstable angina or angina occurring during sexual intercourse; New York Heart Association functional class II or greater heart failure during the previous 6 months; uncontrolled arrhythmias, hypotension ( $< 90/50$  mmHg) or uncontrolled hypertension; stroke within the previous 6 months; clinically significant renal disease; clinically significant hepatobiliary disease (alanine aminotransferase or aspartate aminotransferase more than three times upper limit of normal); or concomitant treatment for ED. No statistically significant differences in patient characteristics and demographics were observed between tadalafil and placebo treated patients.

### *Haemodynamic effects of tadalafil in placebo-controlled phase III studies*

In order to further delineate the haemodynamic effects of tadalafil, blood pressure and heart rate data were collected at baseline and then generally at 4-week intervals in the placebo-controlled phase III tadalafil studies. It should be noted that patients in these studies were taking tadalafil as needed. Therefore, haemodynamic measurements were not taken at specific times following dosing. However, given the 17.5 h half-life of tadalafil and a mean of two doses of tadalafil per week across all the phase 3 trials, it is likely that many patients had measurable plasma concentrations when hemodynamic measurements were made. No significant differences in mean changes from baseline to end-point for SBP, DBP and heart rate on an overall basis among the tadalafil and placebo groups were observed (Table 2). Similar results were observed for the subgroup of patients older than 65 years old. In summary, no statistically or clinically significant haemodynamic effects of tadalafil, as compared with placebo, were observed in the placebo-controlled phase III tadalafil studies.

### Tadalafil interaction with organic nitrates

Because sildenafil, another PDE5 inhibitor, is contraindicated in men taking nitrates, studies were undertaken to determine potential interactions between tadalafil and various nitrate preparations. Two studies evaluated the potential interaction of tadalafil with either a short-acting nitrate (sublingual nitroglycerin) or a long-acting nitrate (isosorbide mononitrate) in patients with chronic stable angina. A third study compared the interaction of tadalafil and sublingual nitroglycerin with that of sildenafil and sublingual nitroglycerin in healthy subjects.

**Table 2** Mean change from baseline for blood pressure and heart rate in placebo-controlled phase III tadalafil studies

Parameter	Mean change from baseline					P value
	Placebo	Tadalafil*				
		2.5 mg	5 mg	10 mg	20 mg	
SBP (mmHg)	-1.42	-4.22	-1.94	-2.83	-3.21	0.325
DBP (mmHg)	-0.64	-0.96	-0.86	-1.19	-2.60	0.322
Heart rate (bpm)	-0.86	-0.03	-2.93	-0.76	-0.49	0.300

Type III sums of squares from analysis of variance. \*Not all doses were included in all studies. DBP=diastolic blood pressure; SBP=systolic blood pressure.

### *Tadalafil and sublingual nitroglycerin in patients with stable angina*

The haemodynamic effects and potential for interaction of sublingual nitroglycerin 0.4 mg and tadalafil 5 mg and 10 mg were examined in patients with chronic stable angina in a double-blind, placebo-controlled, three-way, crossover study. On day 1, patients were administered sublingual nitroglycerin 2 h after tadalafil (or placebo) administration, and blood pressure and heart rate were measured repeatedly for 4 h following administration of sublingual nitroglycerin. On day 2 of each treatment period, they received a repeat nitroglycerin dose 26 h after tadalafil (or placebo) administration in order to evaluate the potential for any residual interaction with tadalafil.

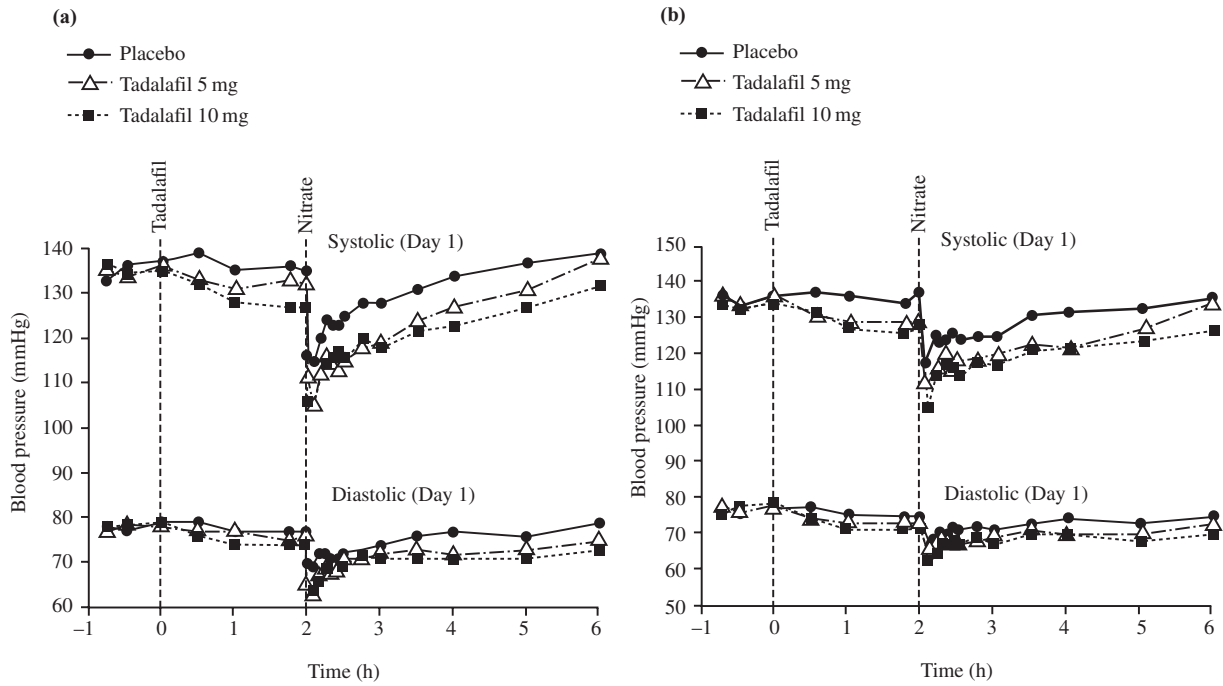
Fifty of the 51 randomized patients completed all three treatment periods. No serious hypotensive adverse events and no discontinuations due to hypotension were observed. A non-inferiority analysis was used to assess whether tadalafil augments the hypotensive response that occurs after nitroglycerin administration relative to placebo. A one-sided 95% CI was constructed from the comparison of tadalafil with placebo for the mean difference (tadalafil minus placebo) in the maximal decrease in standing SBP. Provided this CI was entirely above -8 mmHg, then tadalafil would be considered to be non-inferior to placebo. In addition to mean changes in blood pressure, the proportion of patients with potentially clinically significant changes in blood pressure (outliers) was also evaluated. An outlier was defined as a patient who experienced a decrease in SBP of greater than 30 mmHg from baseline or had a SBP below 85 mmHg, or a decrease in DBP of more than 20 mmHg from baseline or had a DBP below 45 mmHg. Finally, the proportion of hypotensive adverse events was compared among the three treatment periods.

Figures 2 and 3 depict the standing and sitting SBP and DBP versus time for sublingual nitroglycerin coadministered with placebo and tadalafil on days 1 and 2. The mean maximal decrease in standing SBP was 36 mmHg for the tadalafil 5 mg treatment period and 28 mmHg during the placebo treatment period (Table 3). Based on the primary end-point (mean maximal decrease in standing SBP), non-inferiority could not be concluded when comparing tadalafil

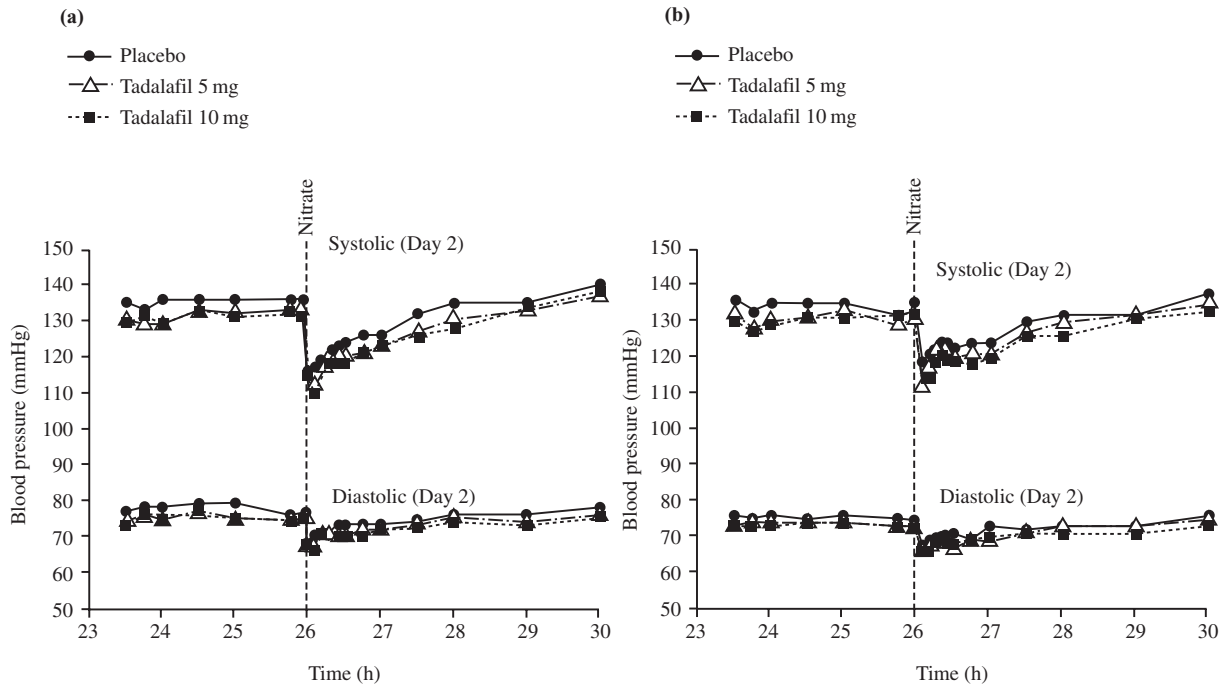
5 mg with placebo on day 1 because the lower limit of the 95% CI for tadalafil 5 mg was -12 mmHg (could not cross -8 mmHg to succeed in the non-inferiority analysis). However, the tadalafil 10 mg treatment was non-inferior to placebo based on the primary end-point. The mean maximal decrease in standing SBP for tadalafil 10 mg was 31 mmHg (compared with 28 mmHg for placebo); the lower limit of the 95% CI for tadalafil 10 mg was -6 mmHg, which was above the predefined lower limit of -8 mmHg. Both tadalafil 5 mg and 10 mg were non-inferior to placebo when the primary analysis was repeated on data collected on day 2. On day 2, the mean maximal decrease in standing SBP was 28 mmHg for placebo, 29 mmHg for tadalafil 5 mg and 28 mmHg for tadalafil 10 mg (Table 3). Similarly, both tadalafil 5 mg and tadalafil 10 mg were non-inferior to placebo with respect to maximal decreases in standing DBP on day 1 and in sitting SBP and DBP on day 2. Thus, based on the primary end-point, tadalafil was non-inferior to placebo on both days 1 and 2, with the exception of standing SBP during the tadalafil 5 mg treatment period on day 1.

Outliers were evaluated using the criteria already outlined. Each patient's lowest SBP and DBP (sitting and standing) during the 4-h observation period were used to determine whether a patient met outlier criteria, as were each patient's maximal decrease from baseline in SBP and DBP (sitting and standing). The proportions of patients meeting the outlier criteria were compared between tadalafil 5 mg and placebo, as well as between tadalafil 10 mg and placebo on days 1 and 2. On day 1, the incidence of outliers was significantly greater for tadalafil 5 mg and 10 mg than for placebo for both standing and sitting SBP below 85 mmHg and for a decrease in standing DBP of more than 20 mmHg from baseline (Table 4). No significant differences were observed between treatment groups for the other outlier criteria.

No statistically significant differences in the frequency of outliers between the two tadalafil treatment periods and the placebo treatment period were observed on day 2. Therefore, the outlier data from day 2 demonstrate that the incidence of outliers in the two tadalafil treatment periods decreased as compared with day 1. However, it is not possible to conclude definitively that tadalafil has no effect on blood pressure reductions induced by sublingual nitroglycerin administration on day 2.



**Figure 2** Mean standing systolic and diastolic blood pressure following sublingual nitroglycerin 0.4 mg administered with single oral doses of tadalafil 5 mg, tadalafil 10 mg or placebo on day 1 in the (a) standing and (b) sitting positions.



**Figure 3** Mean standing systolic and diastolic blood pressure following sublingual nitroglycerin 0.4 mg administered alone on day 2 in the (a) standing and (b) sitting positions.

**Table 3** Maximal hypotensive effect of a single dose of sublingual nitroglycerin 0.4 mg administered after a single oral dose of tadalafil 5 mg, tadalafil 10 mg or placebo

Parameter	Day	LS mean maximum change from pre-nitrate baseline		
		Placebo + nitrate 0.4 mg (n = 51)	Tadalafil 5 mg + nitrate 0.4 mg (n = 51)	Tadalafil 10 mg + nitrate 0.4 mg (n = 51)
Standing SBP (mmHg)	1	-28	-36*	-31
	2	-28	-29	-28
Standing DBP (mmHg)	1	-13	-18	-17
	2	-14	-13	-14
Standing heart rate (bpm)	1	+17	+18	+16
	2	+15	+16	+17
Sitting SBP (mmHg)	1	-24	-28	-28
	2	-23	-25	-25
Sitting DBP (mmHg)	1	-12	-14	-15
	2	-13	-12	-13
Sitting heart rate (bpm)	1	+15	+13	+13
	2	+10	+13	+12

\*Failed non-inferiority analysis because the lower limit of the 95% confidence interval of the difference between tadalafil 5 mg and placebo was greater than the pre-defined limit of -8 mmHg. DBP=diastolic blood pressure; LS=least squares; SBP=systolic blood pressure.

**Table 4** Number of subjects with clinically significant blood pressure effects after a single dose of sublingual nitroglycerin 0.4 mg administered following a single dose of tadalafil 5 mg, tadalafil 10 mg or placebo on day 1 and alone on day 2

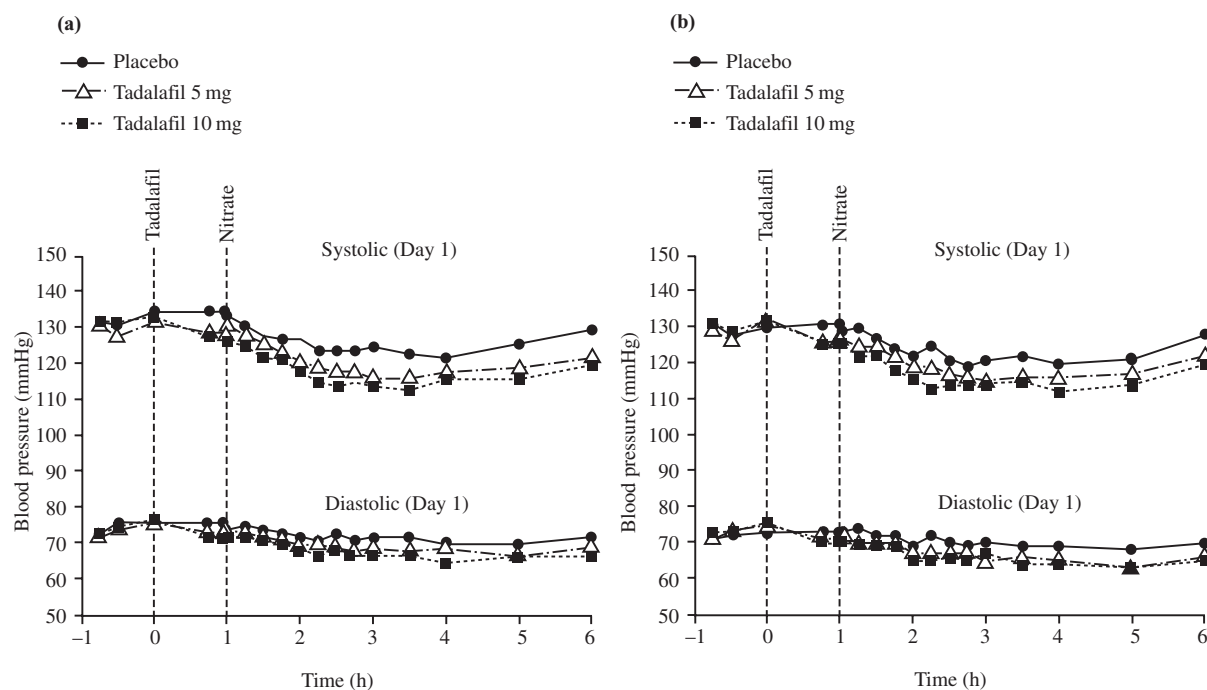
Criteria	Day	Placebo + nitrate 0.4 mg (n = 51)	Tadalafil 5 mg + nitrate 0.4 mg (n = 50)	Tadalafil 10 mg + nitrate 0.4 mg (n = 50)
Standing SBP <85 mmHg	1	1 (2%)	13‡ (26%)	11† (22%)
	2	3 (6%)	6 (12%)	5 (10%)
Standing DBP <45 mmHg	1	2 (4%)	6 (12%)	5 (10%)
	2	2 (4%)	1 (2%)	4 (8%)
Sitting SBP <85 mmHg	1	0 (0%)	6* (12%)	10† (20%)
	2	2 (4%)	1 (2%)	3 (6%)
Sitting DBP <45 mmHg	1	1 (2%)	1 (2%)	5 (10%)
	2	2 (4%)	0 (0%)	1 (2%)
Change from baseline in standing SBP >30 mmHg	1	19 (37%)	26 (52%)	24 (48%)
	2	19 (37%)	21 (42%)	20 (40%)
Change from baseline in standing DBP >20 mmHg	1	4 (8%)	19‡ (38%)	15† (30%)
	2	11 (22%)	9 (18%)	7 (14%)
Change from baseline in sitting SBP >30 mmHg	1	18 (35%)	24 (48%)	20 (40%)
	2	11 (22%)	17 (34%)	16 (32%)
Change from baseline in sitting DBP >20 mmHg	1	5 (10%)	11 (22%)	8 (16%)
	2	6 (12%)	5 (10%)	9 (18%)

P values computed using a two-sided McNemar's test. \* $P \leq 0.05$ , † $P \leq 0.01$  and ‡ $P \leq 0.001$  vs placebo. DBP=diastolic blood pressure; SBP=systolic blood pressure.

In summary, compared with placebo, tadalafil was associated with minimal to small effects on mean blood pressure decreases induced by sublingual nitroglycerin. However, the frequency of outliers was higher during the tadalafil treatment periods, indicating that tadalafil augments the decrease in blood pressure induced by nitrates in a subset of patients. The number of outliers during tadalafil treatment periods decreased from day 1 to day 2. However, it is not possible to conclude definitively that tadalafil had no residual effect on decreases in sitting or standing blood pressure induced by sublingual nitroglycerin administered 26 h after tadalafil administration.

#### *Tadalafil and isosorbide mononitrate in patients with stable angina*

A second study examined the haemodynamic effects of the long-acting nitrate oral isosorbide mononitrate (30 or 60 mg) administered 1 h after tadalafil in patients with chronic stable angina. The study was a double-blind, placebo-controlled, three-way, crossover study that examined the potential for interaction with both tadalafil 5 mg and 10 mg. Patients were also evaluated on day 2 of each treatment period, at which time they received a



**Figure 4** Mean standing systolic and diastolic blood pressure following administration of the long-acting oral nitrate isosorbide mononitrate (30 or 60 mg) administered with single oral doses of tadalafil 5 mg, tadalafil 10 mg or placebo on day 1 in the (a) standing and (b) sitting positions.

subsequent dose of isosorbide mononitrate approximately 24 h after the first dose of isosorbide mononitrate (25 h after the tadalafil dose) in order to evaluate the potential for any residual interaction with tadalafil.

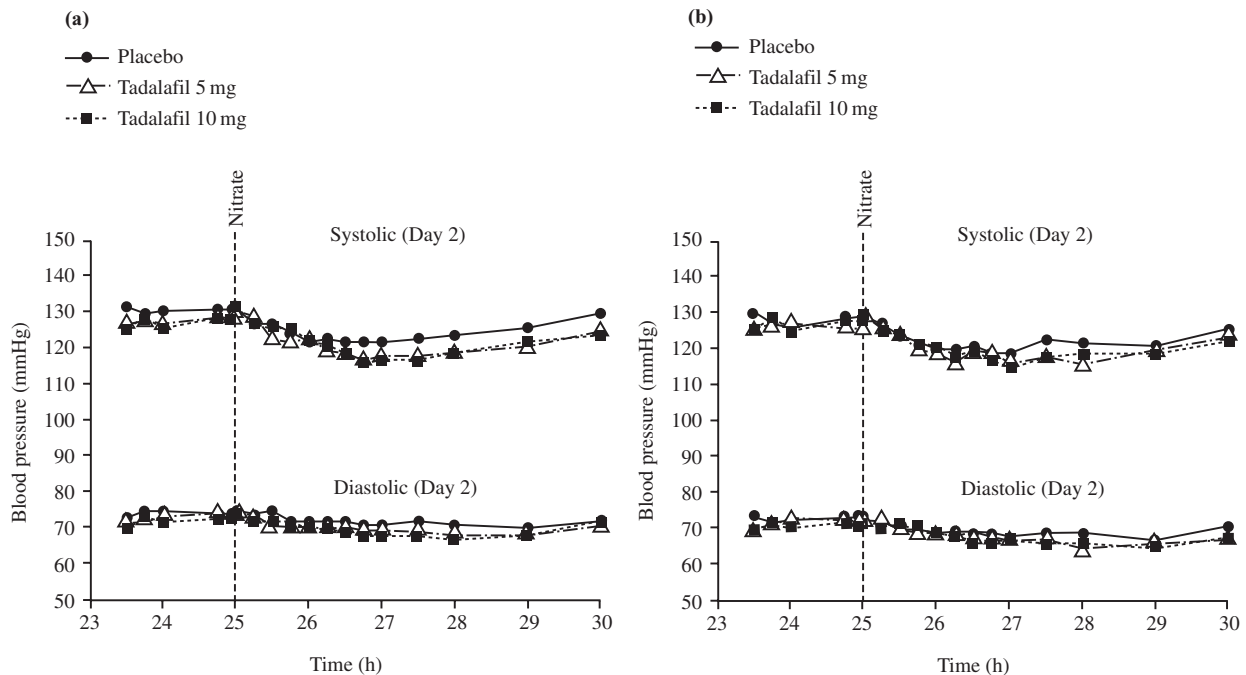
A total of 44 of the 45 randomized patients completed all three treatment periods. No serious hypotensive adverse events and no study discontinuations due to hypotension were observed. Analyses of both the primary end-point and of outliers were performed using the same procedures as described for the previous nitrate study. Figures 4 and 5 depict the standing and sitting SBP and DBP versus time for oral isosorbide mononitrate (30 or 60 mg) coadministered with placebo and tadalafil on days 1 and 2. Based on the primary end-point (mean maximal decrease in standing SBP), both doses of tadalafil were non-inferior to placebo on Day 1. The mean maximal decrease in standing SBP was 23 mmHg for the placebo treatment period as compared with 23 mmHg for the tadalafil 5 mg treatment period and 26 mmHg for the tadalafil 10 mg treatment period (Table 5). Both tadalafil 5 mg and 10 mg dose strengths were also non-inferior to placebo when the primary analysis was repeated on day 2 data (following the second dose of isosorbide mononitrate). On day 2, the mean maximal decreases in standing SBP were 20 mmHg for placebo, 23 mmHg for tadalafil 5 mg and 21 mmHg for tadalafil 10 mg (Table 5). In addition, both tadalafil 5 mg and tadalafil 10 mg were non-inferior to placebo with respect to maximal decreases in standing DBP on day 1 and in sitting SBP and DBP on day 2.

Overall, the incidence of outliers was generally low among all three treatment periods on both days 1 and 2 (Table 6). On day 1, the only statistically significant difference between tadalafil and placebo treatment periods was observed for standing SBP below 85 mmHg for the tadalafil 10 mg treatment period. On day 2 no statistically significant differences between placebo and tadalafil treatment periods were noted.

In summary, compared with placebo, tadalafil had minimal effects on mean changes in blood pressure induced by the long-acting nitrate isosorbide mononitrate. The frequency of outliers was somewhat higher in the tadalafil treatment groups, indicating that tadalafil might augment the decrease in blood pressure induced by isosorbide mononitrate in a subset of patients. However, in contrast to sublingual nitroglycerin, the between-group differences were small and, like with sublingual nitroglycerin, these differences were even less pronounced on day 2.

#### *Tadalafil and sublingual nitroglycerin in healthy subjects: a comparison with sildenafil*

A third double-blind, placebo-controlled, three-way, crossover study examined the haemodynamic effects of sublingual nitroglycerin 0.4 mg administered after tadalafil 10 mg, sildenafil citrate 50 mg and placebo in healthy men and women aged 55 years and older. In order to maximize



**Figure 5** Mean standing systolic and diastolic blood pressure following administration of the long-acting oral nitrate isosorbide mononitrate (30 or 60 mg) administered alone on day 2 in the (a) standing and (b) sitting positions.

**Table 5** Maximal hypotensive effect of a single oral dose of isosorbide mononitrate administered after a single oral dose of tadalafil 5 mg, tadalafil 10 mg or placebo

Parameter	Day	LS mean maximum change from pre-nitrate baseline		
		Placebo + isosorbide mononitrate (n = 45)	Tadalafil 5 mg + isosorbide mononitrate (n = 45)	Tadalafil 10 mg + isosorbide mononitrate (n = 45)
Standing SBP (mmHg)	1	-23	-23	-26
	2	-20	-23	-21
Standing DBP (mmHg)	1	-13	-11	-12
	2	-9	-12	-11
Standing heart rate (bpm)	1	+12	+9	+11
	2	+9	+11	+10
Sitting SBP (mmHg)	1	-21	-21	-24
	2	-20	-20	-21
Sitting DBP (mmHg)	1	-11	-12	-12
	2	-12	-13	-12
Sitting heart rate (bpm)	1	+12	+9	+10
	2	+10	+10	+10

Tadalafil 5 mg and tadalafil 10 mg were non-inferior to placebo for all haemodynamic parameters. DBP=diastolic blood pressure; SBP=systolic blood pressure.

detection of the interaction, nitroglycerin was administered at the expected time of maximum concentration for both tadalafil and sildenafil (2 h and 1 h, respectively). The individuals were also re-evaluated on day 2 of each treatment period, at which time they received a repeat nitroglycerin dose approximately 24 h after the first nitroglycerin dose (26 h after the tadalafil dose and 25 h

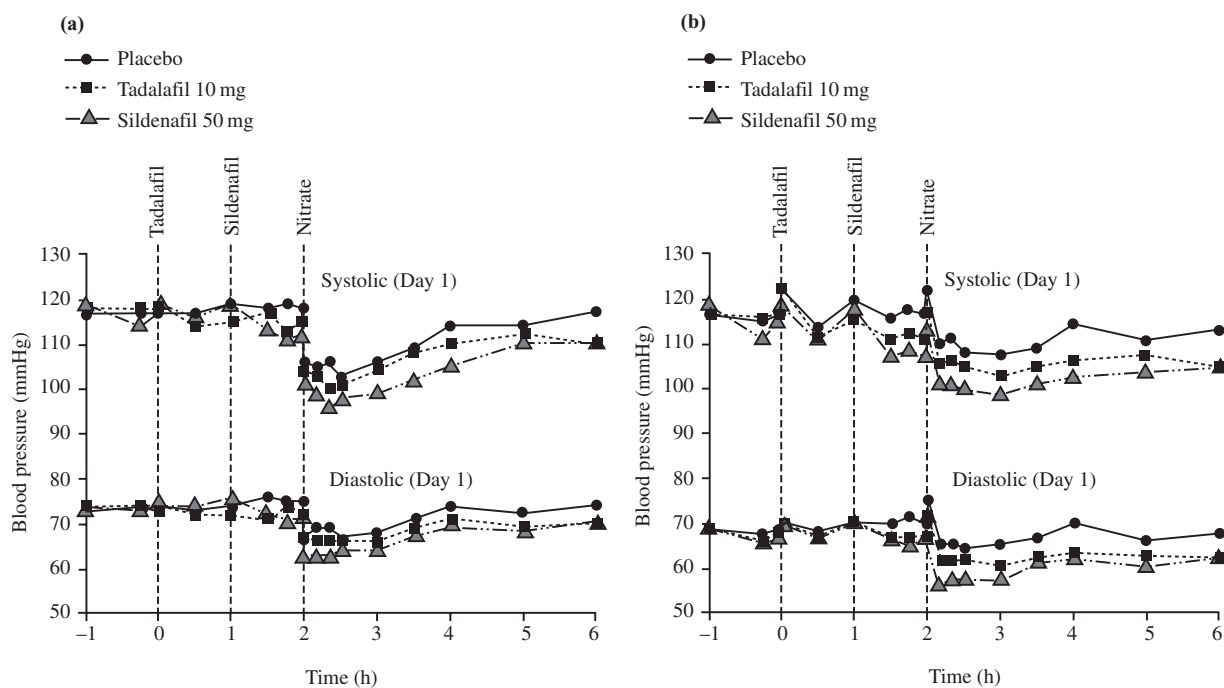
after the sildenafil dose) in order to evaluate the potential for any residual interaction with tadalafil or the active metabolites of sildenafil.

In that study, 48 of the 52 randomized subjects completed all three treatment periods of the crossover. No serious hypotensive adverse events and no discontinuations resulting from hypotension were observed. Figures 6 and 7 depict the

**Table 6** Number of subjects with clinically significant blood pressure effects after a single oral dose of isosorbide mononitrate administered following a single dose of tadalafil 5 mg, tadalafil 10 mg or placebo on day 1 and alone on day 2

Criteria	Day	Placebo + isosorbide mononitrate (n = 45)	Tadalafil 5 mg + isosorbide mononitrate (n = 45)	Tadalafil 10 mg + isosorbide mononitrate (n = 44)
Standing SBP <85 mmHg	1	0 (0%)	0 (0%)	6* (14%)
	2	0 (0%)	2 (4%)	2 (5%)
Standing DBP <45 mmHg	1	1 (2%)	2 (4%)	2 (5%)
	2	0 (0%)	2 (4%)	3 (7%)
Sitting SBP <85 mmHg	1	1 (2%)	0 (0%)	5 (11%)
	2	3 (7%)	1 (2%)	2 (5%)
Sitting DBP <45 mmHg	1	1 (2%)	1 (2%)	3 (7%)
	2	1 (2%)	3 (7%)	3 (7%)
Change from baseline in standing SBP >30 mmHg	1	12 (27%)	10 (22%)	13 (30%)
	2	5 (11%)	10 (22%)	9 (21%)
Change from baseline in standing DBP >20 mmHg	1	7 (16%)	5 (11%)	5 (11%)
	2	3 (7%)	8 (18%)	2 (5%)
Change from baseline in sitting SBP >30 mmHg	1	8 (18%)	7 (16%)	10 (23%)
	2	9 (20%)	7 (16%)	9 (21%)
Change from baseline in sitting DBP >20 mmHg	1	5 (11%)	5 (11%)	6 (14%)
	2	5 (11%)	7 (16%)	5 (11%)

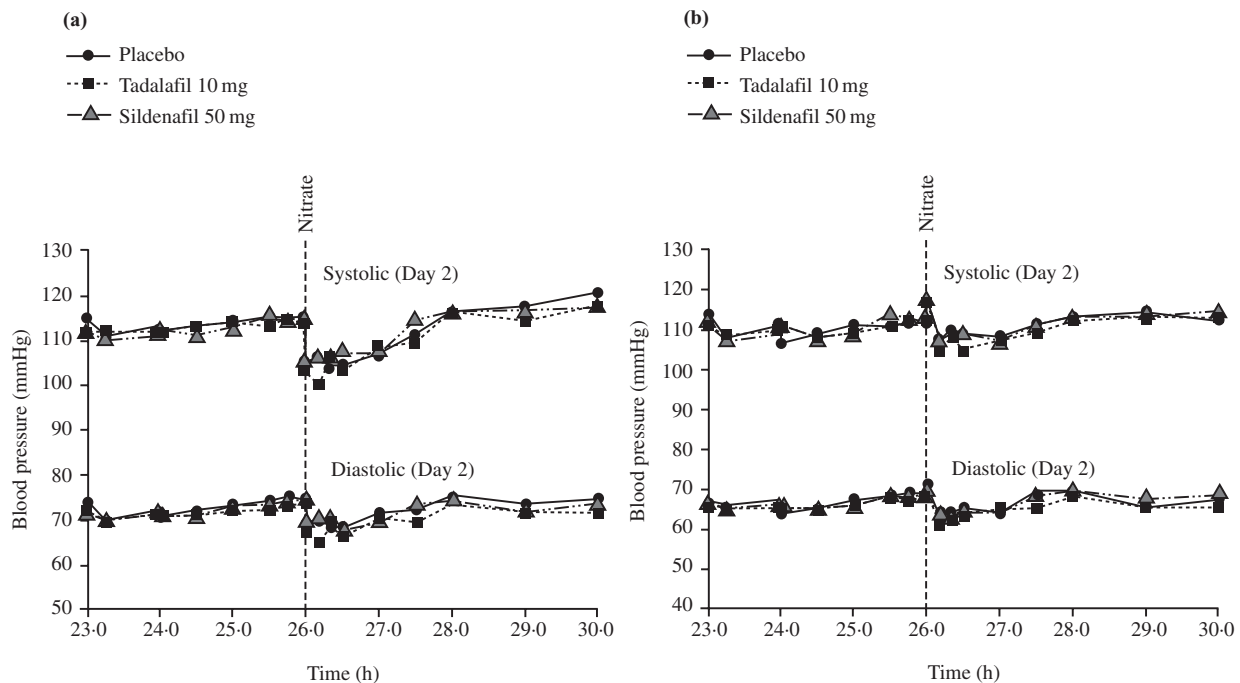
P values computed using a two-sided McNemar's test. \*P < 0.05 vs placebo. DBP=diastolic blood pressure; SBP=systolic blood pressure.



**Figure 6** Mean standing systolic and diastolic blood pressure following sublingual nitroglycerin 0.4 mg administered with single oral doses of tadalafil 10 mg, sildenafil 50 mg or placebo on day 1 in the (a) standing and (b) supine positions.

standing and supine SBP and DBP versus time for sublingual nitroglycerin coadministered with placebo, tadalafil and sildenafil on days 1 and 2. Based on the primary end-point (mean maximal decrease in standing SBP), sildenafil 50 mg was not significantly different from tadalafil 10 mg (Table 7).

A non-inferiority analysis was used to address the secondary objectives of whether tadalafil and sildenafil augment the hypotensive response after administration of nitroglycerin relative to placebo. If the lower limit of the 95% CI was entirely above the  $-8$  mmHg, then the treatments would be considered to be non-inferior to



**Figure 7** Mean standing systolic and diastolic blood pressure following sublingual nitroglycerin 0.4 mg administered alone on day 2 in the (a) standing and (b) supine positions.

**Table 7** Maximal hypotensive effect following sublingual nitroglycerin 0.4 mg administered following a single dose of tadalafil 10 mg, sildenafil 50 mg or placebo

Parameter	Day	LS mean maximum change from pre-nitrate baseline		
		Placebo + nitrate 0.4 mg (n = 49)	Tadalafil 10 mg + nitrate 0.4 mg (n = 49)	Sildenafil 50 mg + nitrate 0.4 mg (n = 49)
Standing SBP (mmHg)	1	-25	-25	-29*
	2	-19	-21	-19
Standing DBP (mmHg)	1	-14	-13	-15
	2	-10	-13	-12
Standing heart rate (bpm)	1	+17	+18	+16
	2	+16	+20	+20
Supine SBP (mmHg)	1	-15	-18	-19
	2	-10	-10	-13
Supine DBP (mmHg)	1	-10	-9	-13
	2	-8	-10	-7
Supine heart rate (bpm)	1	+10	+9	+9
	2	+10	+9	+8

\*Failed non-inferiority analysis because the lower limit of the 95% confidence interval of the difference between sildenafil 50 mg and placebo was greater than the pre-defined limit of -8 mmHg. DBP=diastolic blood pressure; LS=least squares; SBP=systolic blood pressure.

placebo. Tadalafil was non-inferior to placebo; the mean maximal decrease in standing SBP was 25 mmHg for tadalafil and 25 mmHg for placebo, and lower limit of the 95% CI for this comparison was -5 mmHg (Table 7). In contrast, sildenafil failed the non-inferiority analysis when compared with placebo. The mean maximal decrease in standing SBP was 29 mmHg for sildenafil compared with 25 mmHg for placebo. In this case, the lower limit of the

95% CI for the comparison was -9 mmHg. Both tadalafil 10 mg and sildenafil 50 mg were non-inferior to placebo with respect to maximal decreases in standing DBP on day 1 and in supine SBP and DBP on day 2.

In addition to mean changes in blood pressure, the frequency of subjects having potentially clinically significant changes in blood pressure (outliers) was also evaluated using the set of criteria outlined previously. The

**Table 8** Number of subjects with clinically significant blood pressure effects after sublingual nitroglycerin 0.4 mg administered following single doses of tadalafil 10 mg, sildenafil 50 mg or placebo on day 1 and alone on day 2

Criteria	Day	Placebo (n = 50)	Tadalafil 10 mg (n = 49)	Sildenafil 50 mg (n = 50)
Standing SBP <85 mmHg	1	12 (24%)	23* (47%)	23* (46%)
	2	9 (18%)	15 (31%)	10 (20%)
Standing DBP <45 mmHg	1	4 (8%)	5 (10%)	4 (8%)
	2	1 (2%)	1 (2%)	0 (0%)
Supine SBP <85 mmHg	1	3 (6%)	9 (18%)	18* (36%)
	2	5 (10%)	4 (8%)	4 (8%)
Supine DBP <45 mmHg	1	0 (0%)	2 (4%)	6* (12%)
	2	0 (0%)	2 (4%)	1 (2%)
Change from baseline in standing SBP >30 mmHg	1	10 (20%)	15 (31%)	18 (36%)
	2	6 (12%)	10† (20%)	2 (4%)
Change from baseline in standing DBP >20 mmHg	1	12 (24%)	13 (27%)	15 (30%)
	2	3 (6%)	6 (12%)	3 (6%)
Change from baseline in supine SBP >30 mmHg	1	3 (6%)	2 (4%)	8† (16%)
	2	0 (0%)	0 (0%)	0 (0%)
Change from baseline in supine DBP >20 mmHg	1	3 (6%)	3 (6%)	8 (16%)
	2	2 (4%)	3 (6%)	1 (2%)

*P* values computed using a two-sided McNemar's test. \**P* < 0.05 vs placebo; †*P* < 0.05 vs other active treatment (i.e. tadalafil or sildenafil). DBP=diastolic blood pressure; SBP=systolic blood pressure.

frequency of outliers on day 1 was higher for both tadalafil and sildenafil than for placebo, indicating that both PDE5 inhibitors augmented the decrease in blood pressure induced by nitrates in at least a subset of subjects (Table 8). Specifically, both the tadalafil and sildenafil treatment groups contained a significantly greater proportion of subjects meeting the standing SBP below 85 mmHg criterion on day 1 as compared with placebo. In addition, the number of subjects with supine SBP below 85 mmHg and supine DBP below 45 mmHg during the sildenafil treatment period was significantly greater when compared with the placebo treatment period. On day 1, a significantly greater proportion of subjects had a supine DBP decrease greater than 30 mmHg during sildenafil treatment when compared with tadalafil treatment.

An overview of the outlier data from day 2 indicates that the number of outliers in both the tadalafil and sildenafil treatment groups decreased as compared with day 1 (Table 8). The only statistically significant difference between treatment periods on day 2 was for the change from baseline in standing SBP of greater than 30 mmHg. A significantly greater proportion of subjects met this criterion during the tadalafil treatment period as compared with the sildenafil treatment period. However, this was not significantly different when comparing tadalafil with placebo, and the number of outliers was no different than with placebo on day 1. Despite the modest additive effect on mean maximal changes in blood pressure, the frequency of outliers was more common with both tadalafil and sildenafil than with placebo on day 1, indicating that in a subset of patients both agents augment the decrease in blood pressure induced by nitrates. Additionally, it cannot be definitively concluded that there is no augmentation of the hypotensive effect of nitrates 26 h following administration of tadalafil. However, there was no evidence to suggest an excess of outliers (vs placebo) when subjects were assessed in the

supine position following nitrate administration 26 h after tadalafil administration.

## Effects of tadalafil on QT interval

Drugs that prolong cardiac repolarization have been associated with torsades de pointes, which is usually observed in the setting of a prolonged QT interval. In recent years, several commonly used drugs have been removed from the market as a result of their association with prolonged QT intervals and torsades de pointes. Accordingly, all drugs in development must undergo an extensive evaluation to assess potential effects on the QT interval.

The potential effects of tadalafil on cardiac electrophysiology have been extensively examined in normal pharmacology (phase I) studies at doses up to 25 times the highest planned market dose and in randomised (phase II and III) clinical efficacy and safety trials with repeated dosing up to 5 times the highest planned market dose in men with erectile dysfunction. Extensive analyses of QT interval, which is reflective of ventricular depolarization and repolarization, from phase I, phase II and phase III studies demonstrate that tadalafil had no effect on QT interval (data not shown).

## Cardiovascular adverse events

### Cardiovascular disorders at baseline

Patients were excluded from the placebo-controlled phase III studies only if they had an underlying cardiovascular disorder

**Table 9** Frequency of underlying ischaemic cardiac disease in patients in tadalafil placebo-controlled phase III studies

	Placebo (n = 379)		All tadalafil (n = 949)		Total (n = 1328)	
	n	%	n	%	n	%
Patients with ischaemic cardiac disease*	42	11.1	89	9.4	131	9.9
Ischaemic cardiac disease by historical diagnosis or pre-existing condition	26	6.9	67	7.1	93	7.0
Electrocardiographic evidence of myocardial infarct	19	5.0	39	4.1	58	4.4
Coronary bypass or coronary angioplasty	1	0.3	14	1.5	15	1.1

\*The numbers shown on this row are patients with underlying ischaemic cardiac disease. If a single patient had more than one factor by which ischaemic cardiac disease was diagnosed, then that patient was still counted as only one patient in this row. Thus, the number of patients per event, when added, will not equal the total number of patients.

**Table 10** Frequency of underlying conditions that constitute coronary risk factors in the tadalafil placebo-controlled phase III studies

	Placebo (n = 379)		All tadalafil (n = 949)		Total (n = 1328)	
	n	%	n	%	n	%
Patients with $\geq 1$ condition*	232	61.2	550	58.0	782	58.9
Diabetes mellitus	141	37.2	310	32.7	451	34.0
Hypertension	115	30.3	289	30.5	404	30.4
Hyperlipidaemia	81	21.3	192	20.2	273	20.6

\*The numbers shown on this row are patients with underlying conditions that constitute coronary risk factors. If a single patient had more than one condition that constituted a coronary risk factor, then that patient was still counted as only one patient in this row. Thus, the number of patients for a condition that constitutes a coronary risk factor specified, when added, will not equal the total number of patients.

that was sufficiently severe or unstable to constitute a contraindication to sexual intercourse. Upon entry into these studies, 291 of 1328 (21.9%) patients had an underlying cardiovascular disorder (including cerebrovascular and peripheral vascular disorders and excluding hypertension).

Before randomisation, 131 of 1328 (9.9%) patients had evidence of ischaemic cardiac disease, based either on past medical history or electrocardiographic evidence (Table 9). The prevalence was similar between tadalafil-treated and placebo-treated patients (9.4% vs 11.1%, respectively).

The frequency of common risk factors for CHD, including diabetes mellitus, hypertension and hyperlipidaemia, was also investigated in the placebo-controlled phase III studies. Overall, 782 of 1328 (58.9%) patients had at least one of these cardiovascular risk factors at baseline (Table 10). As the data indicate, 34.0% of patients had diabetes mellitus, 30.4% had hypertension and 20.6% were reported as having hyperlipidaemia. Thus, a significant proportion of the phase III patient population had underlying risk factors for CHD.

### Cardiovascular adverse events

Overall, the incidence of cardiovascular adverse events was low. Compared with placebo, tadalafil (2.5–20 mg) was not

associated with a significant increase in any treatment-emergent cardiovascular adverse event (Table 11). Subgroup analyses of the incidence of adverse events in patients younger than 65 years and those aged 65 years or older also revealed no significant age-related safety findings.

### Myocardial infarction and cardiac mortality

The overall safety database for tadalafil encompasses more than 4000 participants from over 60 clinical studies, including more than 1000 subjects in clinical pharmacology studies and more than 2700 patients in phase II, phase III and open-label studies. Across all studies, there were six reports of myocardial infarction in tadalafil treated patients. The incidence rate was 0.39 per 100 patient-years in tadalafil treated patients as compared with 1.1 per 100 patient-years in patients who received placebo (Table 12). The incidence rate of myocardial infarction in tadalafil treated patients was lower than the rate reported for a similar age-standardized British male population (0.6/100 patient-years) as well as a British male population with more than 10,000 patient-years on sildenafil (0.57/100 patient-years)<sup>[13]</sup>.

Of the six deaths for tadalafil treated patients, three were assessed as cardiac deaths. Two of the cardiac-related

**Table 11 Cardiovascular treatment-emergent adverse events in all randomized patients in phase III studies**

Event classification	Tadalafil												P value*	
	Placebo (n = 379)		2.5 mg (n = 74)		5 mg (n = 151)		10 mg (n = 394)		20 mg (n = 330)		All doses (n = 949)			
	n	%	n	%	n	%	n	%	n	%	n	%	CMH	Fisher's
Vasodilatation (flushing)	6	1.58	1	1.35	4	2.65	13	3.30	17	5.15	35	3.69	0.286	0.089
Dizziness	7	1.85	2	2.70	4	2.65	8	2.03	9	2.73	23	2.42	0.903	0.873
Hypertension	6	1.58	0	0	2	1.32	4	1.02	4	1.21	10	1.05	0.833	0.912
Arrhythmia	0	0	2	2.70	0	0	0	0	2	0.61	4	0.42		
Palpitation	1	0.26	0	0	0	0	2	0.51	2	0.61	4	0.42	0.631	0.946
Arteriosclerosis	0	0	0	0	0	0	0	0	2	0.61	2	0.21		
Tachycardia	0	0	0	0	0	0	0	0	2	0.61	2	0.21		
Angina pectoris	0	0	0	0	0	0	0	0	1	0.30	1	0.11		
AV block	0	0	0	0	0	0	1	0.25	0	0	1	0.11		
BBB	0	0	0	0	0	0	1	0.25	0	0	1	0.11		
Cardiomegaly	0	0	0	0	0	0	0	0	1	0.30	1	0.11		
CV disorder	0	0	0	0	0	0	1	0.25	0	0	1	0.11		
Myocardial infarction	2	0.53	0	0	0	0	0	0	1	0.30	1	0.11		
Syncope	2	0.53	0	0	0	0	0	0	1	0.30	1	0.11		
Thrombosis	0	0	0	0	1	0.66	0	0	0	0	1	0.11		
Arterial anomaly	1	0.26	0	0	0	0	0	0	0	0	0	0		
Heart failure	1	0.26	0	0	0	0	0	0	0	0	0	0		
Hypotension	1	0.26	0	0	0	0	0	0	0	0	0	0		
Postural hypotension	1	0.26	0	0	0	0	0	0	0	0	0	0		
Ventricular extrasystoles	1	0.26	0	0	0	0	0	0	0	0	0	0		

AV=atrioventricular; BBB=bundle branch block; CMH=Cochran–Mantel–Haenszel general association test; CV=cardiovascular; myocardial infarction=myocardial infarction. \*Blank cells indicate that the number of events were too small to perform statistical analyses.

**Table 12 Incidence of myocardial infarction across tadalafil studies**

	Age-standardized male population*	Placebo	Tadalafil double-blind studies†	Tadalafil open-label long-term safety studies	All tadalafil studies
Total number of patients	–	>1200	>2500	1376	>4000
Total patient exposure as patient-years	–	184.9	384.4	1 155	1539.4
Rate of myocardial infarctions per 100 patient-years‡	0.6	1.1	0.28	0.43	0.39

\*Reference data from men in England <75 years old<sup>[13]</sup>. †Patient-years are slightly underestimated for tadalafil treated patients because information was not available for all patients; hence the rates are actually slightly lower than shown. ‡One patient who was randomized to tadalafil but did not take any study drug and had a myocardial infarction is not shown here.

deaths resulted from definite or suspected myocardial infarction, which both occurred in patients with multiple cardiovascular risk factors. The third cardiac-related death was believed to have resulted from cardiac arrhythmia, which was probably the result of the patient's underlying cardiopulmonary disease. All deaths were judged by the investigator as unrelated to tadalafil treatment. Based on the number of patients who received tadalafil and the total number of patient-years of exposure (1539.4 total patient-years), the cardiac mortality in tadalafil treated patients was less than 2.0 per 1000 patient-years. This rate is again similar to the cardiac mortality rates reported in an age-standardized general population of British men (2.6/1000 patient-years)<sup>[13]</sup>.

These findings indicate that the morbidity and mortality rates from serious cardiovascular adverse events in tadalafil trials were no greater than those reported for the general population of men with ED.

### Antihypertensive use in placebo-controlled phase III studies

Patients receiving concomitant antihypertensive therapy were included in the placebo-controlled phase III trials. Patients with uncontrolled hypertension (SBP >170 mmHg or DBP >100 mmHg) and malignant hypertension were excluded.

**Table 13** Concomitant use of single or multiple classes of antihypertensive agents in tadalafil placebo-controlled phase III studies

Antihypertensive classes used	All tadalafil (n = 272)		Placebo (n = 105)		Total (n = 377)	
	n	%	n	%	n	%
One class	145	53.3	60	57.4	205	54.4
Two classes	87	32.0	32	30.5	119	31.6
Three or more classes	40	14.7	13	12.4	53	14.1

**Table 14** Mean changes from baseline in blood pressure in all randomized patients taking one antihypertensive and two or more antihypertensive drugs in phase III studies

	Tadalafil	Placebo	P value
One antihypertensive (n = 140 and 59, respectively)			
Mean baseline SBP (mmHg)	142.75	142.12	
Mean change in SBP (mmHg)	-5.71	-3.41	0.338
Mean baseline DBP (mmHg)	83.02	85.07	
Mean change in DBP (mmHg)	-2.18	-2.08	0.521
Two or more antihypertensives (n = 126 and 44, respectively)			
Mean baseline SBP (mmHg)	139.60	136.57	
Mean change in SBP (mmHg)	-2.62	0.89	0.251
Mean baseline DBP (mmHg)	83.48	81.64	
Mean change in DBP (mmHg)	-2.65	-2.18	0.819

DBP=diastolic blood pressure; SBP=systolic blood pressure.

### Concomitant use of antihypertensive agents

A total of 272 (28.7%) of 949 tadalafil treated patients and 105 (27.7%) of 379 placebo treated patients were on concomitant antihypertensive therapy (Table 13). Among these 377 patients on antihypertensive therapy, the most commonly used classes were angiotensin-converting enzyme inhibitors (56.5%), calcium channel blockers (35.8%), thiazide diuretics and related agents (24.9%), beta-blockers (14.1%), angiotensin II receptor blockers (13.5%), alpha-blockers (6.1%) and loop diuretics (3.7%).

The mean change in SBP in patients taking one antihypertensive agent was slightly greater, although not statistically significant, for the tadalafil treatment group than for placebo (-5.71 vs -3.41 mmHg, respectively;  $P = 0.338$ ; Table 14). Additionally, no difference was observed between tadalafil and placebo treatment in the mean change in DBP in patients taking one antihypertensive ( $P = 0.521$ ). Similarly, the mean change in SBP and DBP in patients taking two or more antihypertensive agents was not significantly different between the tadalafil treatment group and the placebo treatment group ( $P = 0.251$  and  $P = 0.819$ , respectively; Table 14).

### Blood pressure changes and multiple antihypertensive agents

The frequency of potentially clinically significant changes in blood pressure in patients taking two or more antihypertensive

agents was low in both the tadalafil and placebo treatment groups. The percentages of patients with a decrease in SBP of greater than 30 mmHg from baseline were similar between the tadalafil and the placebo treatment groups (6.35% vs 4.55%). The percentage of patients with a decrease in DBP of more than 20 mmHg from baseline was lower in the tadalafil group (1.59%) than in the placebo group (6.82%).

In summary, the phase III data suggest that tadalafil administered concomitantly with two or more antihypertensive agents does not increase the occurrence of potentially clinically significant changes in blood pressure.

### Cardiovascular adverse events and antihypertensive therapy

In tadalafil treated patients, the incidence rates for treatment-emergent cardiovascular adverse events were comparable between patients who did and those who did not receive concomitant antihypertensive therapy, with the exception of events recorded as hypertension (Table 15). Among patients receiving tadalafil, hypertension occurred in 3.7% of those who received antihypertensive therapy versus 0% of those who did not receive antihypertensive therapy. Hypertension rates were comparable between tadalafil treated patients (3.7%) and placebo treated patients (4.8%) among all study patients who received concomitant antihypertensive therapy. The hypertension rates reflect the fact that, in this population, episodes of hypertension would be expected to occur periodically despite treatment.

**Table 15 Incidence of cardiovascular adverse events in patients on concomitant antihypertensives in tadalafil placebo-controlled phase III studies**

Event classification	Tadalafil With antihypertensive?				Placebo With antihypertensive?			
	No (n = 677)		Yes (n = 272)		No (n = 274)		Yes (n = 105)	
	n	%	n	%	N	%	n	%
Angina pectoris	0		1	0.4	0		0	
Arrhythmia	3	0.4	1	0.4	0		0	
Arterial anomaly	0		0		1	0.4	0	
Arteriosclerosis	1	0.2	1	0.4	0		0	
AV block	0		1	0.4	0		0	
BBB	0		1	0.4	0		0	
Cardiomegaly	0		1	0.4	0		0	
CV disorder	1	0.2	0		0		0	
Dizziness	18	2.7	5	1.8	3	1.1	4	3.8
Heart failure	0		0		0		1	1.0
Haemorrhage	1	0.2	0		1	0.4	0	
Hypertension	0		10	3.7	1	0.4	5	4.8
Hypotension	0		0		0		1	1.0
Myocardial infarction	1	0.2	0		0		2	1.9
Palpitation	2	0.3	2	0.7	1	0.4	0	
Postural hypotension	0		0		1	0.4	0	
Syncope	1	0.2	0		0		2	1.9
Tachycardia	2	0.3	0		0		0	
Thrombosis	0		1	0.4	0		0	
Flushing (vasodilatation)	23	3.4	12	4.4	6	2.2	0	
Ventricular extrasystoles	0		0		1	0.4	0	

AV=atrioventricular; BBB=bundle branch block; CV=cardiovascular.

Overall, most cardiovascular events were infrequent (<1% of patients). Flushing, a clinical consequence of vasodilatation, was more common in the tadalafil treated patients who were on concomitant antihypertensive agents than in placebo treated patients on antihypertensive therapy. However, the incidence of flushing was similar for tadalafil treated patients on antihypertensive therapy (4.4%) and tadalafil treated patients who were not on antihypertensive therapy (3.4%). Hence, coadministration of antihypertensives and tadalafil did not increase the incidence of flushing when compared with tadalafil administration alone. In addition, dizziness occurred in a similar proportion of patients who received both tadalafil and an antihypertensive agent (1.8%) and patients who received tadalafil alone (2.7%).

Most importantly, no reports of hypotension or postural hypotension were reported in any tadalafil treated patient versus one report of each in the placebo treated patients. Syncope was reported in two patients (1.9%) who received placebo and concomitant antihypertensive therapy, but this was not reported in any patient who received tadalafil and concomitant antihypertensive therapy.

Although the numbers of adverse events were too small for a statistical analysis of adverse events by the number of antihypertensives used, there was no indication that concomitant administration of tadalafil and antihypertensive agents resulted in an increased incidence of any cardiovascular adverse event.

In summary, in the placebo controlled phase III studies of tadalafil, there was a sizable proportion of patients treated with antihypertensive agents, alone and in combination. In those studies, tadalafil was not associated with an increase in cardiovascular adverse events or an increase in the incidence of potentially clinically significant changes in blood pressure in patients taking antihypertensive agents when compared with those patients not taking antihypertensive agents.

## Conclusion

Tadalafil is a mild vasodilator that resulted in mild decreases in blood pressure in healthy subjects. However, there was no increase in the incidence of adverse events related to decreases in blood pressure, indicating that the modest decrease in blood pressure following tadalafil administration in this cohort is not clinically relevant. Nitrate interaction studies demonstrate that, despite the modest additive effect of tadalafil on the nitrate induced decrease in mean blood pressure, there was an increase in the frequency of potentially significant blood pressure changes. Therefore, as with sildenafil, tadalafil should not be used in combination with nitrates. In addition, extensive analyses demonstrate that tadalafil had no effect on the QT interval. Analyses of the overall safety database for tadalafil

indicate that morbidity and mortality rates from serious cardiovascular adverse events in tadalafil trials were no greater than those reported for the general population of men with ED. Finally, integrated analyses of the phase III safety database indicate that tadalafil was not associated with an increase in cardiovascular adverse events or an increase in the incidence of potentially clinically significant changes in blood pressure in patients taking anti-hypertensive agents.

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