The effect of tadalafil on the time to exercise-induced myocardial ischaemia in subjects with coronary artery disease

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Objective

To investigate the effect of tadalafil on the time to exercise-induced myocardial ischaemia in subjects with coronary artery disease (CAD).

Background

CAD and erectile dysfunction (ED) share similar risk factors. It is important to know the cardiovascular effects of tadalafil in patients with CAD during physical exertion that is comparable with sexual activity.

Methods

A randomized, placebo-controlled, double-blind, two-period, crossover study comparing the effects of tadalafil 10 mg and placebo on the time to exercise treadmill test (ETT)-induced myocardial ischaemia in subjects with stable CAD ($n = 23$; age range: 53–75 years, all exhibited ST-segment depression >1.5 mm at screening ETT at >5 METS). Haemodynamic responses to sublingual nitroglycerin (NTG) were assessed before and after ETT.

Results

Compared with placebo, tadalafil did not significantly affect the time to ETT-induced ischaemia (13 min/31 s vs. 13 min/36 s, respectively). Before exercise, NTG evoked decreases in sitting systolic blood pressure (SBP) that were significantly greater when subjects received tadalafil compared with placebo, and after exercise, more subjects experienced a decrease in SBP <85 mmHg in response to NTG after taking tadalafil vs. placebo. When subjects received tadalafil compared with placebo, SBP was lower at rest (-7 mmHg; -12 , -2), during ETT (-10 mmHg; -16 , -3), and after ETT (-13 mmHg; -19 , -7).

Conclusion

Tadalafil did not significantly alter the time to ETT-induced ischaemia compared with placebo in subjects with CAD. Tadalafil reduced resting and exercise SBP. Due to the potential for hypotension, the concomitant use of nitrates and tadalafil is contraindicated.

Introduction

Coronary artery disease (CAD) and erectile dysfunction (ED) often coexist and share similar risk factors, including hypertension, hyperlipidemia, diabetes mellitus, and smoking [1, 2]. The severity of CAD has been correlated with the severity of ED [3]. Because men with CAD may seek treatment for ED, it is important to thoroughly assess potential cardiac risks associated with sexual activity in this patient population [4–6]. Guidelines for men with cardiovascular disease and ED showed that the majority of patients were classified as low risk and could be encouraged to resume sexual activity and receive treatment for ED [4].

Physical exertion during sexual activity is similar in intensity to mild-to-moderate exercise as measured by increases in metabolic equivalents (MET) of energy expenditure [4]. Energy expenditure during sexual activity averages from 2 to 4 METs with an upper range of 5–6 METs (usually measured in younger patients) [4]. Based on the Framingham Heart Study data, the hourly absolute risk of myocardial infarction (MI) is low in healthy men aged 50 years, being one chance per million per hour [4, 7, 8]. In the 2 h after sexual activity this baseline hourly risk of MI was shown to be 2.5-fold greater in patients with no history of cardiovascular disease compared with 2.9-fold greater in patients with a history of MI [7]. This equates to an increase in hourly risk of only two chances per million for the 2 h after sexual activity [7]. However, in subjects who are relatively sedentary and engage in renewed sexual activity this hourly risk is probably greater [9]. Thus, as with any type of moderate physical exertion, there is a small but definite increased risk of a cardiac event for patients with cardiovascular disease who resume sexual activity [4–9].

Medications that inhibit phosphodiesterase 5 (PDE5) (e.g. sildenafil, tadalafil, vardenafil) have become the first line of therapy for most men with ED [6, 10–12]. The inhibition of PDE5 evokes dilation of the penile vasculature and increases in penile blood flow via effects on the nitric oxide-cGMP pathway [11]. Although sildenafil, tadalafil, and vardenafil also produce mild systemic vasodilation (decrease blood pressure by = 10/5 mmHg) in healthy subjects [6, 13, 14], they have been shown to be safe when administered in combination with most vasodilator medications [12, 15, 16].

Our study is the first to examine the effect of tadalafil, a selective inhibitor of PDE5 with a half-life of 17.5 h, on the time to exercise treadmill test (ETT)-induced myocardial ischaemia in subjects with stable CAD. A secondary aim of this study was to characterize the

haemodynamic responses to sublingual nitroglycerin (NTG) administered before and immediately after ETT when subjects received tadalafil vs. placebo. Although it is now well recognized that nitrate use is contraindicated with medications that inhibit PDE5, this secondary aim was designed to examine the response to NTG plus tadalafil compared with NTG plus placebo during ETT-induced myocardial ischaemia.

Methods

This study was approved by Institutional Review Boards and subjects gave informed written consent. The study was conducted in accordance with the declaration of Helsinki and guidelines for Good Clinical Practice. The study was completed at two sites: Ninewells Hospital, Dundee, UK and Maastricht Hospital, Maastricht, The Netherlands.

The primary objective was to test the hypothesis that tadalafil 10 mg compared with placebo did not affect the time to ETT-induced myocardial ischaemia in subjects with stable CAD.

The secondary objective was to test the hypothesis that the mean maximum NTG-induced decrease in sitting SBP during ETT-induced ischaemia was similar after subjects received tadalafil 10 mg compared with placebo.

This was a randomized, placebo-controlled, double-blind, two-period crossover study in 23 subjects (=18 years of age) with stable CAD; defined as having a diagnosis of CAD with at least one episode of angina requiring NTG in the preceding 3 months. Subjects continued on their usual medication apart from withholding nitroglycerin or long acting nitrates for the 24 h prior to each study visit. Long acting nitrates were withheld for only 24 h due to potential safety concerns related to withholding for longer time periods.

Exclusion criteria included: SBP >170 or <90 mmHg, DBP >115 or <60 mmHg, percutaneous coronary intervention within 14 days of the study, uncomplicated myocardial infarction within 30 days of the study, coronary artery bypass grafting within 60 days of the study, supraventricular arrhythmia with an uncontrolled ventricular response, significant atrio- or intraventricular conduction defect, history of sustained ventricular tachycardia, presence of a pacemaker or internal cardioverter-defibrillator, unstable angina, congestive heart failure (New York Heart Association Class II or above), history of alcohol or substance abuse within 6 months of the study, and history of ED or female sexual arousal disorder for which the subject sought treatment within 6 months of the study. Also excluded were subjects with a haemoglobin concentration

<10 g dL⁻¹ or creatinine clearance <50 mL min⁻¹, subjects taking digoxin, and subjects incapable of discontinuing long acting nitrate use for 24 h or short acting nitrate use prior to the start of each study day.

The study required two visits during the screening phase and two visits during the treatment phase.

Visit 1: Clinical laboratory tests, medical history and physical exam were completed.

Visit 2: With subjects seated, sublingual nitroglycerin (NTG; 0.4 mg, spray) was administered. Sitting BP and heart rate (HR) were measured (Dinamap Pro100; General Electric, USA) before (every 30 s for 2 min) and for 1 h after NTG dosing (every 30 s for 5 min, then every 5 min for 25 min, then every 15 min for 30 min). After administration of NTG, BP and HR were monitored until the values returned to within 10% of baseline or until subjects were deemed clinically stable after = 1 h of monitoring.

Approximately 1.5 h after receiving NTG, the ETT was begun using the modified Bruce protocol [17]. The subjects were exercised until exhaustion, until the investigator believed it was unsafe to continue, or if SBP decreased by 20% from pre-exercise baseline. A 12-lead ECG was recorded continuously and BP was measured (sphygmomanometer) at 3-min intervals during the ETT. The time to ischaemia or total exercise time was recorded. Subjects were considered eligible for randomization to the treatment phase if they had a positive screening ETT defined as >1.5 mm ST depression in at least two contiguous leads or >1.5 mm ST depression in a continuous ECG recording with symptoms of cardiac ischaemia but were excluded if these signs of ischaemia were evident before 5 METs.

The timings of tadalafil and NTG dosing shown in Figure 1 were followed at Visits 3 and 4 of the treatment phase. With subjects seated, NTG (0.4 mg, spray) was

administered ~1.5 h before and immediately after ETT (BP and HR were measured for ≥ 1 h after each dose of NTG as described for Visit 2).

All treatment-emergent adverse events were recorded throughout the study.

The treatment randomization (Eli Lilly and Company, Indianapolis, IN) was stratified to ensure that half the subjects received tadalafil first (the two possible study drug sequences were tadalafil/placebo or placebo/tadalafil). Numbered kits containing single doses of tadalafil 10 mg and placebo (identically appearing tablets) were allocated to the study sites. All personnel directly involved in the study were blinded to treatment.

For sample size calculations, it was assumed that a mean reduction in the time to ETT-induced ischaemia of 1.5 min or greater (tadalafil compared with placebo), would constitute inferiority. It was also assumed that there would be no reduction in the time to ETT-induced ischaemia with tadalafil compared with placebo, and that the standard deviation (within subject) of the difference between time to ischaemia after receiving placebo compared with tadalafil would be 2.25 min. With these assumptions, 22 subjects were required to give the study at least 90% power to reject the null hypothesis that tadalafil was inferior to placebo using a 95% one-sided confidence interval (CI).

The times to ETT-induced ischaemia were analysed with a mixed effects model analysis of variance (ANOVA). If a subject attained a total exercise time prior to demonstrating ECG evidence of ischaemia, the total exercise time was used in place of time to ischaemia. The mean difference in time to ETT-induced ischaemia (tadalafil minus placebo) and the residual variance from the ANOVA was used to construct a one-sided 95% CI for the difference. Tadalafil was considered noninferior

Figure 1

Protocol followed during treatment phase Visits 3 and 4; NTG = sublingual nitroglycerin

**Treatment phase protocol
visits 3 and 4**

to placebo if the 95% CI for the difference (tadalafil minus placebo) did not include -60 s.

The mean maximum NTG-induced decrease in sitting SBP Post-exercise (secondary study endpoint) was analysed using a one-sided 95% CI constructed for the mean difference (tadalafil minus placebo). If the 95% CI was above -8 mmHg, tadalafil was concluded to be noninferior to placebo.

Mean maximal NTG-induced changes in pre-exercise SBP and pre- and Post-exercise DBP and HR after treatment with tadalafil and placebo were analysed using ANOVA and by calculating least squares mean values, mean differences [tadalafil minus placebo], and 95% CIs for the mean differences. Mean differences were considered significant if the 95% CIs did not contain zero. Additionally, the number of subjects experiencing potentially clinically important decreases in BP (i.e. BP 'outliers') in response to NTG pre- and Post-exercise was analysed. These BP 'outliers' were defined as SBP <85 mmHg, DBP <45 mmHg, a decrease in sitting SBP >30 mmHg, and a decrease in sitting DBP >20 mmHg. A Fisher's exact test was used to compare tadalafil with placebo for the BP 'outlier' data.

The SBP and DBP measurements recorded before, during, and after ETT were analysed by calculating mean values, mean differences (tadalafil minus placebo) and the 95% CI for the mean differences. Mean differences were considered significant if the 95% CIs did not contain zero.

Results

Thirty-nine subjects were screened at the Dundee study site in the UK and eight subjects were screened at the Maastricht study site in the Netherlands. Twenty-four subjects were randomized to the treatment phase and 23 subjects completed the study. A single subject was withdrawn after Visit 3 due to a protocol violation.

Table 1 shows the demographics of the 23 subjects who completed the study. During Screening Visit 2, the mean time to ETT-induced myocardial ischaemia for the 23 subjects who completed the study was 13 min 9 s $\pm$ 2 min 7 s (range = 9.0 min 0 s to 16 min 21 s), which is equivalent to 8 METs.

Five of the study population were female. The mean exercise time for the female subjects was shorter than the mean for the males (11 min 31 s vs. 14 min 6 s). Six of the subjects were on long acting nitrates and a review of their data did not reveal a significant trend in haemodynamic variables. However, they tended to have shorter exercise times than subjects not on long acting nitrates.

The time to ETT-induced myocardial ischaemia when subjects received tadalafil 10 mg was similar to that

Table 1
Patient demographics

	Total (n = 23)
Age (years; mean $\pm$ SD)	63 $\pm$ 6.4
Age range (years)	53–75
Gender; n (%)	
Male	18 (78%)
Female	5 (22%)
Body mass index (kg m ⁻² ; mean $\pm$ SD)	27.7 $\pm$ 3.4
Race	
Caucasian	22 (96%)
Asian	1 (4%)
Smoking status (yes; n [%])	4 (17%)
Alcohol consumption (yes; n [%])	18 (78%)
Cardiovascular medications; n	
Nitroglycerin	20
Aspirin	19
Beta-blocker	18
Statin	12
Calcium channel blocker	7
Isosorbide mononitrate or dinitrate	6
Angiotensin converting enzyme inhibitor	2
Clopidogrel	2
Bezafibrate	2
Alpha-blocker	1

Alcohol consumption ranged from occasional to 18 units/week (1 unit = 284 mL beer, 125 mL wine or 25 mL spirits).

measured after placebo (Primary Endpoint, Table 2). The effect of tadalafil was noninferior to placebo with the 95% CI for the mean least squares difference (tadalafil minus placebo) being -14 s which did not exceed the predefined limit of -60 s.

Three subjects did not demonstrate ECG evidence of ETT-induced ischaemia after administration of either tadalafil 10 mg or placebo during Visits 3 and 4, and one subject did not demonstrate ECG evidence of ETT-induced ischaemia after placebo, but did after tadalafil 10 mg. For these subjects, the total exercise time was used in the analyses, in place of the time to ischaemia.

At rest, the sitting SBP and DBP were significantly lower ~ 1.5 h after subjects received tadalafil compared with placebo (Figure 2, Table 3). At all time points after administering the pre-ETT dose of NTG (Figure 3), the mean SBP and DBP were lower when subjects received tadalafil compared with placebo, and the mean maximal NTG-induced decreases in SBP and DBP were significantly greater when subjects received tadalafil compared with placebo (Table 4). There was no significant differ-

Table 2

Summary of time to ischaemia/total exercise time after tadalafil 10 mg and placebo

	Placebo	Tadalafil 10mg	Mean difference*	Lower 95% CI
Mean time to ischaemia†	13:31 ± 2:08	13:36 ± 1:59	3 s	-14 s‡
Minimum time to ischaemia	9:12	9:19		
Maximum time to ischaemia	17:15	16:36		

*Mean difference = tadalafil 10 mg minus placebo; †times represent time to ischaemia or total exercise time in minutes : seconds (least squares mean ± SD; n = 23); ‡tadalafil was noninferior to placebo (lower 95% CI for the mean difference was -14 s which did not exceed the a priori limit of -60 s).

Table 3

Comparison of systolic and diastolic blood pressure (BP) before, during and after exercise treadmill testing (ETT) – effects of tadalafil 10 mg compared with placebo

	Pre- Placebo or Tadalafil Baseline		Post-dosing with placebo or tadalafil 10 mg								Immediately post-exercise	
	P	Tad	P	Tad	P	Tad	P	Tad	P	Tad	P	Tad
Systolic BP	136	137	133	126	141	132	143	137	149	143	163	150
Mean difference	1		-7*		-10*		-6		-7*		-13*	
(95% CI)	(-3, 5)		(-12, -2)		(-16, -3)		(-11, 0)		(-13, -1)		(-19, -7)	
	P	Tad	P	Tad	P	Tad	P	Tad	P	Tad	P	Tad
Diastolic BP	75	75	74	70	76	76	78	76	79	78	76	74
Mean difference	0		-4*		0.3		-2		-1		-2	
(95% CI)	(-2, 2)		(-7, -2)		(-2, 3)		(-6, 1)		(-4, 3)		(-6, 2)	

Values for placebo (P) and tadalafil (Tad) are means (n = 22–23); 95% confidence interval (CI) is for the mean difference; *mean difference (tadalafil minus placebo) significant (CI did not contain zero); baseline, pre-exercise, and post-exercise BPs measured in the sitting position; BPs during ETT measured in the standing position.

ence in the mean maximal change in HR (tadalafil minus placebo) after the pre-exercise dose of NTG (Table 4).

Table 3 shows that during exercise, the mean standing SBP was lower when subjects received tadalafil compared with placebo at 3, 6, and 9 min of ETT. At the 3 and 9 min time points during ETT, the mean differences (tadalafil minus placebo) in SBP were significant (95% CIs did not contain zero).

Although the absolute sitting SBP was substantially higher immediately Post-exercise compared with pre-exercise when subjects received either tadalafil or placebo (Figure 3, Table 3), the SBP post-exercise remained significantly lower when subjects received tadalafil compared with placebo (150 vs. 163 mmHg,

respectively; Table 3). Additionally, for 1 h after receiving the post-ETT dose of NTG (Figure 4), the mean SBP and DBP were lower when subjects received tadalafil compared with placebo.

Post-exercise, the mean maximal NTG-induced decrease in sitting SBP (Secondary Endpoint) was similar when subjects received tadalafil (-55 mmHg) compared with placebo (-56 mmHg) (Table 4). Tadalafil was noninferior to placebo with respect to the mean difference (tadalafil minus placebo) in the NTG-induced decrease in sitting SBP after ETT (the lower 95% CI of -6 mmHg was above the a priori value of -8 mmHg). The NTG-induced changes in sitting DBP and HR after exercise were also similar when subjects received

Figure 2

Pre-exercise: Sitting systolic and diastolic blood pressure before and after administration of sublingual nitroglycerin 0.4 mg. Tadalafil 10 mg or placebo was administered ~1.5 h before giving the dose of nitroglycerin. Data points represent the mean ($n = 23$). ●, placebo; ■, tadalafil 10 mg

Figure 3

Post-exercise: Sitting systolic and diastolic blood pressure in response to a dose of sublingual nitroglycerin 0.4 mg administered immediately Post-exercise. Tadalafil 10 mg or placebo was administered ~2.5 h before beginning the exercise treadmill test. Data points represent the mean ($n = 23$). ●, placebo; ■, tadalafil 10 mg

Table 4

Mean maximum changes in sitting systolic blood pressure (BP), diastolic BP, and heart rate in response to sublingual nitroglycerin (NTG) – pre-exercise and immediately post-exercise

Criteria	Pre-exercise			Post-exercise		
	NTG plus placebo	NTG plus tadalafil 10mg	Mean difference (95% CI)	NTG plus placebo	NTG plus tadalafil 10mg	Mean difference (95% CI)
Maximum decrease systolic BP (mmHg)	–25	–34	–9* (–14, –4)	–56	–55	1 (–6, 7)
Maximum decrease diastolic BP (mmHg)	–12	–17	–5* (–7, –3)	–15	–19	–4 (–9, 0)
Maximum change in heart rate (bpm)	8	7	–2 (–5, 2)	–4	–2	2 (–2, 6)

Values ($n = 23$) are least squares means; *mean difference (tadalafil minus placebo) significant (CI did not contain zero); CI = confidence interval; bpm = beats per minute.

Table 5

Number (%) of subjects experiencing clinically important decreases in sitting systolic and diastolic blood pressure (BP) in response to sublingual nitroglycerin (NTG)

Criteria	Pre-exercise		Post-exercise	
	NTG plus placebo	NTG plus tadalafil 10mg	NTG plus placebo	NTG plus tadalafil 10mg
Systolic BP <85 mmHg	0	3 (13%)	1 (4%)	7 (30%)*
Diastolic BP <45 mmHg	0	2 (9%)	0	1 (4%)
Decrease in systolic BP >30 mmHg	3 (13%)	3 (13%)	23 (100%)	21 (91%)
Decrease in diastolic BP >20 mmHg	0	2 (9%)	5 (22%)	8 (35%)

*Tadalafil significantly different than placebo ($P = 0.024$; Fisher's exact test); $n = 23$.

tadalafil compared with placebo (CIs for the mean differences did not contain zero [post hoc analyses]).

Before ETT, the number of subjects with sitting SBP <85 mmHg, DBP <45 mmHg, and a decrease in DBP >20 mmHg occurring in response to NTG was slightly higher when subjects received tadalafil compared with placebo (Table 5; differences not significant).

After ETT, the number of subjects who experienced a sitting SBP <85 mmHg in response to NTG was significantly greater when subjects received tadalafil compared with placebo (Table 5). Additionally, although not statistically significant, more subjects experienced a DBP <45 mmHg and a decrease in DBP >20 mmHg in

response to NTG after tadalafil compared with placebo (Table 5). Although these potentially clinically important decreases in BP occurred, the number of clinical symptoms related to hypotension was low as reflected in the reported treatment emergent cardiovascular adverse events when subjects received NTG plus tadalafil (hypotension [3], palpitation [1], vasodilation [1], dizziness [1]) or NTG plus placebo (three total = dizziness [1], angina pectoris [1], peripheral vascular disorder [1]).

No subject experienced a decrease in SBP of $\geq 20\%$ from baseline during ETT. When subjects received tadalafil 10 mg and NTG, the treatment-emergent adverse

events that occurred in more than one subject were headache ($n = 4$), hypotension ($n = 3$), and pain ($n = 2$). When subjects received placebo and NTG, no treatment-emergent adverse events occurred in more than one subject. Overall the incidence of treatment-emergent adverse events was low when subjects received tadalafil plus NTG or placebo plus NTG, and no serious or severe adverse events were reported.

Discussion

In this study of tadalafil in subjects with coronary artery disease, the 10 mg dose was well tolerated and did not affect the time to exercise-induced myocardial ischaemia compared with placebo at exercise levels comparable to those experienced during sexual activity. Tadalafil significantly lowered resting SBP and DBP at 1.5 h after dosing, and the SBP remained lower during and after exercise compared with placebo. Before exercise, NTG evoked mean maximal decreases in SBP and DBP that were significantly greater after subjects received tadalafil compared with placebo, and after exercise, the number of subjects experiencing potentially clinically important NTG-evoked decreases in sitting SBP was greater when subjects received tadalafil compared with placebo. These data show that tadalafil does not affect the time to exercise-induced ischaemia in subjects with CAD, that tadalafil reduces SBP at rest and during exercise in subjects with CAD, and that tadalafil should not be used in combination with nitroglycerin due to the potential for substantial hypotension in some subjects. The maximum licensed dose of tadalafil is 20 mg and we cannot extrapolate the findings in this study to the 20 mg dose. There is, however, evidence to suggest that at the 20 mg dose tadalafil has no adverse effects on myocardial blood flow in subjects with stable CAD and that tadalafil may actually improve myocardial blood flow during periods of increased workload in normal and poorly perfused myocardium [18].

In studies of vardenafil 10 mg and sildenafil 100 mg using a standard Bruce protocol the time to ETT-induced myocardial ischaemia in patients with CAD were much shorter (mean placebo exercise times of 7 min 10 s and 6 min 30 s, respectively) compared with those reported in our study of tadalafil [19, 20]. Despite these apparent differences in times to ETT-induced ischaemia, the actual average final workload achieved in all studies was similar (~ 8 METs). Importantly workload equivalence (heart rate, rate pressure product and oxygen consumption) for matched stage between full and modified ETT protocols has been demonstrated elsewhere [21]. Subjects likely to have severe coronary vessel disease with ischaemia before 5 METs were

excluded from our study, which is similar to studies with sildenafil and vardenafil where signs and symptoms for inclusion to the study had to occur after 3 min (5 METs). Importantly, 8 METs exceeds the upper limit for energy expenditure during sexual activity [4]. Additionally, in our study, ECG evidence of myocardial ischaemia was defined as a ≥ 1.5 mm ST-segment depression, unlike the 1.0 mm used in other studies. Studies on sildenafil in ischaemic heart disease subjects using 50 and 100 mg doses demonstrated no adverse effect on exercise duration or extent of ischaemia as assessed by exercise echocardiography [22] and a slight improvement in total exercise duration and times to onset of angina and limiting angina [20], and did not increase the incidence of ventricular arrhythmias during ETT in men with ED and cardiovascular disease [23]. Vardenafil 10 mg in subjects with ischaemic heart disease was found not to alter exercise treadmill time or time to first awareness of angina, but significantly prolonged time to ischaemic threshold [19]. Taken together, these data suggest that in subjects with cardiovascular disease, the inhibition of PDE5 has little effect on exercise duration, on exercise-induced ST-segment depression, or on the incidence of ventricular arrhythmias occurring during exercise.

The inhibition of PDE5 evokes mild systemic vasodilation by increasing intracellular concentrations of cGMP in vascular smooth muscle [11]. Because organic nitrates also increase the intracellular concentration of cGMP, the concomitant administration of a PDE5 inhibitor with a nitric oxide donor can evoke potentially clinically important hypotension. Tadalafil augmented the decrease in blood pressure compared with placebo, when NTG was given both before and after exercise. Due to this potential for marked hypotension [6, 24, 25], nitrates should be withheld for a minimum of 24 h after a dose of sildenafil [6], and for tadalafil, it is recommended that nitrates be withheld for at least 48 h after dosing [24, 26].

There is concern that renewed sexual activity may provoke cardiovascular events in high-risk patients [4, 5]. One of the mechanisms is through increased cardiac afterload brought about by increases in SBP during sexual activity. Although not an a priori endpoint of our study, we showed that tadalafil decreased resting SBP and attenuated the exercise-induced increase in SBP in subjects with CAD. The blood pressure lowering effects of tadalafil in subjects with CAD are similar to those reported in studies with sildenafil [22, 23] and vardenafil [19], however, the changes may be more relevant when one considers the comparatively long half-life of tadalafil (i.e. half-life of tadalafil = 17.5 h, half life of sildenafil and vardenafil = ~ 4 h) and that we used the lower

licensed dose of tadalafil. The effects of tadalafil on SBP may be important; exercise SBP is arguably a more potent risk factor for stroke, cardiovascular death, and survival after myocardial infarction [27–29], and a high exercise SBP may be a marker of underlying endothelial dysfunction [29, 30].

Various other cardiovascular effects of PDE5 inhibition have been demonstrated in patients with CAD. Sildenafil was shown to dilate epicardial coronary arteries and inhibit platelet aggregation [31], and tadalafil was shown to have no significant effect on myocardial blood flow as measured by positron emission tomography [18]. Furthermore, retrospective analyses of data from clinical trials enrolling patients with ED from the general population, showed that the incidence of cardiovascular adverse events, including myocardial infarction, was not increased in patients taking tadalafil or sildenafil compared with placebo [32, 33]. Most of these controlled clinical trials, however, excluded high-risk patients including those with a history of recent myocardial infarction or coronary artery bypass grafting (within 90 days of the study), uncontrolled hypertension, and congestive heart failure (Class II or above – NYHA classification).

Because there is a small but definite cardiac risk associated with sexual activity, physicians should consider the cardiovascular status of their patients before recommending a return to sexual activity and before prescribing medications that inhibit PDE5 to their patients with ED. The AHA/ACC consensus document on the use of sildenafil in patients with cardiovascular disease [6] and the Princeton consensus panel document on the management of sexual dysfunction in patients with cardiovascular disease [4] can both be used as guides for evaluating and providing treatment options for patients with ED and cardiovascular disease.

The frequency of treatment-emergent adverse events in this study, including cardiovascular-related adverse events, was low when subjects with CAD received either tadalafil or placebo (with or without NTG). Tadalafil was safe and well tolerated when administered prior to physical activity in these subjects with CAD.

Conclusions

This is the first study to investigate the effects of tadalafil on cardiovascular responses to ETT in subjects with stable CAD. The study demonstrated, that in subjects with stable CAD, tadalafil 10 mg did not significantly affect the time to exercise-induced myocardial ischaemia compared with placebo. Tadalafil 10 mg, however, did lower SBP before, during, and after exercise. Due to the potential for clinically important

hypotension, tadalafil should not be used in combination with organic nitrates.

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(1) An oral presentation at the AHA meeting in Chicago 2002: Patterson D, McDonald TM, Effron MB, Emmick JT, Mitchell M, Bedding A, Kloner RA. Tadalafil does not affect time to ischaemia during exercise stress testing in patients with coronary artery disease. Circulation 106(19):330, 2002.

(2) A poster presentation at the ISSIR Montreal 2002: Patterson D, McDonald TM, Effron MB, Emmick JT, Mitchell M, Bedding A, Kloner RA. Tadalafil does not affect time to ischaemia during exercise stress testing in patients with coronary artery disease. Int J Impot Res. 2002; 14(suppl 3):S102.

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