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Analysis of integrated clinical safety data of tadalafil in patients receiving concomitant antihypertensive medications

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Abstract

This pooled safety analysis assessed the incidence of hypotension-related treatment-emergent adverse events (TEAEs) and major adverse cardiovascular events (MACEs) in patients with concomitant use of tadalafil and antihypertensive medications. Data were pooled from seventy-two Phase II–IV studies conducted on patients with a diagnosis of erectile dysfunction (ED) and/or benign prostate hyperplasia (BPH). Studies were categorized as either *All placebo-controlled studies* or *All studies*. The incidences of hypotension-related TEAEs and MACEs were analyzed by indication; by use of concomitant antihypertensive medications; and by the number of concomitant antihypertensive medications. A total of 15 030 and 22 825 patients were included in the analyses for *All placebo-controlled studies* and *All studies*, respectively. In the *All placebo-controlled studies*, the incidence of hypotension-related TEAEs and MACEs was ranging between 0.6–1.5% and 0.0–1.0%, respectively, across all indications. Tadalafil was associated with an increase in hypotension-related TEAEs only in the *ED as-needed* group not receiving any concomitant antihypertensive medications (*p-value* = .0070); no significant difference was reported between placebo and tadalafil in the groups of patients receiving ≥1 antihypertensive medication (*p*-values ≥ .7386). Similarly, no significant differences (*p-values*≥ .2238) were observed in the incidence of MACEs between tadalafil and placebo treatment groups, with or without concomitant use of antihypertensive medications, and across all indication categories. In the *All studies* group, results were similar. The pooled analysis showed no evidence that taking tadalafil alongside antihypertensive medications increases the risk of hypotension-related TEAEs or MACEs compared with antihypertensive medications alone.

KEYWORDS
anti-hypertensive medication, benign prostatic hyperplasia, concomitant therapy, erectile dysfunction, hypotension, safety, tadalafil

1 | INTRODUCTION

Erectile dysfunction (ED) affects up to 77% of men worldwide,[1,2] of which approximately 55% are in their 60s.[3] The presence of cardiovascular diseases and other risk factors (vascular inflammation, atherosclerosis, hyperlipidemia, hypertension, diabetes, smoking, and metabolic syndrome) contributes further to the development of ED.[2] It has been estimated that about 68% of men with hypertension have some degree of ED.[4] Given the high prevalence in older men of ED and cardiovascular comorbidities, the use of ED and concomitant antihypertensive medications (AHM) is often required.[1,5]

Tadalafil is a long-acting, selective inhibitor of phosphodiesterase 5 (PDE_5) used widely as first-line treatment for ED.[6] It has also demonstrated efficacy and safety in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH), with or without coexisting ED.[7] Tadalafil is marketed either as-needed or once-daily dosing for the treatment of ED, and as once-daily for the treatment of BPH and BPH with ED.[8] PDE_5 inhibitors prevent degradation and facilitate accumulation of cyclic guanosine monophosphate in the cavernosum smooth muscle, which then mediates relaxation, vasodilation, and erection.[6] PDE_5 inhibitors are considered to be generally safe when used in combination with antihypertensive drugs,[9] however, since PDE_5 enzyme is found also in systemic arterial blood vessels, the inhibition may contribute to vasodilation of the systemic vasculature.[10]

The objective of this pooled analysis of clinical studies was to assess the incidence of hypotension-related treatment-emergent adverse events (TEAEs) and major adverse cardiovascular events (MACEs) in patients who received tadalafil (Cialis®, Eli Lilly and Company) concomitantly with AHM vs those receiving AHM alone (excluding alpha-blockers). This safety evaluation is the largest performed to date on tadalafil, and the focus on placebo-controlled, randomized, double-blind clinical trials allowed for an unbiased evaluation of the drug-drug interactions of the two medications.

2 | METHODS

2.1 | Source of clinical data

As of 31 May 2018, a total of 145 completed studies were identified in the Eli Lilly's Global Integrated Database (GID). Five studies (for which databases were not available; not part of the 145 studies), 69 clinical pharmacology studies, and four studies in healthy volunteers/mild ED patients were not included in the analysis.

The safety analysis was based on 72 Phase II–IV studies including randomized double-blind (placebo- or active-controlled) and open-label trials, either with parallel or cross-over arms (up to three-way crossovers). Dosage regimens of tadalafil included as-needed, once-daily, or a mix of both; doses ranged from 2 to 100 mg; and could be either fixed or titrated. Study periods varied from a single dose up to 24 months.

In this analysis, studies were categorized as either *All placebo-controlled studies* (including participants only from placebo-controlled trials) or *All studies* (including participants from both placebo-controlled and non-placebo-controlled studies).

2.2 | Patient populations

All patients included in the analysis had a diagnosis of ED and/or BPH and received at least one dose of the investigational product (tadalafil or placebo). The patient population was determined by the inclusion/exclusion criteria of the original studies. ED studies enrolled males ≥18 years old who had a history of ED ≥3 months in duration, ranging in severity (mild, moderate, or severe) and etiologic classification (psychogenic, mixed, or organic). BPH studies enrolled males ≥45 years old having BPH-lower urinary tract symptoms for >6 months.

Included patients were categorized by indication and dose regimen as follows: *ED as-needed; ED once-daily; BPH once-daily; All ED/BPH* (combining all ED and BPH groups). Participants were also grouped by use of AHM (*With concomitant AHM* vs *Without concomitant AHM*), and by number of concomitant antihypertensive classes of medicines taken during the study period (0, 1, 2, ≥3). Patients receiving nitrates or ED therapy other than tadalafil were excluded as per original study exclusion criteria. Patients receiving alpha-blockers were also excluded from this analysis. Alpha-blockers are relegated to fourth or fifth treatment line for hypertension due to the risk of hypotensive and cardiac events,[11–14] additionally, they may have a known orthostatic hypotension effect when co-administered with PDE_5 inhibitors.[9]

2.3 | Safety endpoints

TEAEs of hypotension/increased hypotensive effect and MACEs were the safety endpoints of interest. Coding of adverse events (AEs) collected during the clinical studies was updated to MedDRA version 23.1. TEAEs were those AEs that first occurred or worsened in severity during the treatment period. TEAEs were classified as non-serious or serious adverse events (SAE) and presented by system organ class/preferred term. TEAEs of hypotension/increased hypotensive effect were identified by the following preferred terms: hypotension; orthostatic hypotension; blood pressure ambulatory decreased; blood pressure decreased; blood pressure diastolic decreased; blood pressure systolic decreased; blood pressure orthostatic decreased; blood pressure orthostatic; dizziness; dizziness exertional; dizziness postural; presyncope; and syncope. MACEs were identified by two Standard MedDRA Queries (SMQ) (broad and narrow search): myocardial infarction and ischemic central nervous system vascular conditions, and/or the following five preferred terms: death; cardiac arrest; cardiac death; sudden cardiac death; sudden death.

Potentially clinically significant abnormal (PCSA) vital sign results, identified by diastolic blood pressure (DBP) and systolic blood pressure (SBP), were also evaluated. PCSA DBP reading was defined

as <45 mmHg or a maximum decrease >20 mmHg, and PCSA SBP was defined as <85 mmHg or a maximum decrease>30 mmHg from baseline.

2.4 | Statistical analysis

Data were presented for each indication-dose regimen category (*ED as-needed; ED once-daily; BPH once-daily; All ED/BPH*) by concomitant AHM status, study group (*All placebo-controlled studies*; *All studies*) and treatment received (placebo vs tadalafil; tadalafil).

Demographic and baseline characteristics were summarized in descriptive statistics only. Duration of treatment exposure was summarized descriptively as a quantitative variable and categorically for categories between ≥1 day and ≥2 years. The total exposure in person-years was also calculated.

The incidence of hypotension-related TEAEs and MACEs, respectively, was evaluated in both *All placebo-controlled studies* and *All studies* groups, and reported as the number (%) of patients with the event. The confidence interval (CI) of the incidence was calculated by Clopper-Pearson method. A comparison of the incidence between tadalafil and placebo was conducted for *All placebo-controlled studies*. A logistic regression model was used to calculate the odds ratios (OR) of tadalafil/placebo for different concomitant AHM status with 95%CIs and associated *p*-values. The model included the fixed terms of treatment group, status of concomitant AHM, and their interaction. In addition, the interaction (ratio of ORs of tadalafil/placebo) between treatment group and concomitant AHM was evaluated by exact logistic regression.

The number (%) of patients with at least one PCSA value for SBP/DBP during the post-baseline treatment period was analyzed in *All placebo-controlled studies* group.

A descriptive overview of hypotension-related TEAEs and treatment-emergent MACEs was provided for both *All placebo-controlled studies* and *All studies* groups, reporting any AEs of interest; treatment-related AEs; serious AE; AE leading to death; and AE leading to permanent study treatment discontinuation.

3 | RESULTS

3.1 | Safety data extraction and patient disposition

Safety data were extracted from 72 Phase II–IV clinical studies of tadalafil used for ED or BPH patients (Figure 1). Based on prior/concomitant medications reported in study case report forms, patients were identified as with or without concomitant AHM. A total of 15 030 and 22 825 patients were included in the analyses for *All placebo-controlled studies* and *All studies* groups, respectively. Of these, patients receiving tadalafil with concomitant AHM were 3088 and 6868, respectively (Table 1). A summary of demographic characteristics and treatment exposure is shown in Table 2. Overall, demographic features were similar between patients included in the two

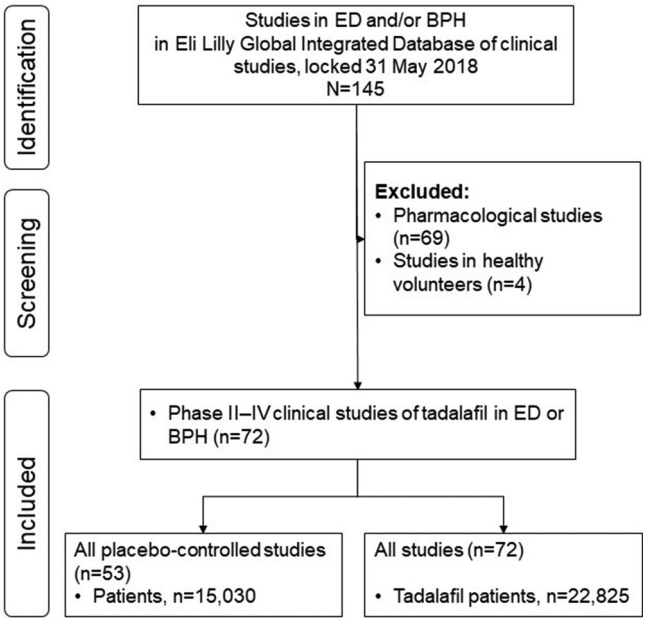

FIGURE 1 Study selection (PRISMA flowchart). Abbreviations: BPH, benign prostatic hyperplasia; ED, erectile dysfunction

study groups. Patients receiving concomitant AHM were older, with the majority being in the age group 45 to <65 years (44.9–71.5%) and had slightly higher body mass index (BMI) than those who were not receiving AHM, regardless of the study category. Overall, the incidence of cardiovascular disorders (cardiac disorder, cerebrovascular disorder, other vascular disorders) was higher in patients receiving concomitant AHM (90.7–95.3%) compared with no AHM (10.9–16.0%). Those receiving concomitant AHM had also higher incidence of severe ED (organic etiology), regardless of the study category. The number of patients not receiving concomitant AHM was two- to three-fold higher than those receiving concomitant AHM. In both study groups, most patients used only one AHM (Table 3); across the *All ED/BPH* category in the *All studies* group (n = 22 832), the percentage of those taking one concomitant antihypertensive was 16.6% (n = 3788), followed by 9.6% (n = 2194) and 3.9% (n = 884) receiving 2 or ≥3 concomitant AHM, respectively. The most frequently used AHMs were angiotensin-converting-enzyme (ACE) inhibitors in ED studies and calcium channel blockers in *BPH once-daily* category. Other commonly prescribed classes of AHM included angiotensin receptor blockers (ARB), beta-blockers, diuretics, and centrally acting sympathomimetics.

3.2 | Incidence of TEAEs of hypotension/increased hypotensive effect

Across all indications in the *All placebo-controlled studies* category the incidence of TEAEs of hypotension/increased hypotensive effect ranged between 0.6% and 1.5% (Table 4). In *ED as-needed* patients, not receiving AHM, the incidence of hypotension-related TEAEs was low but significantly higher in the tadalafil group compared with the placebo group (1.5% vs 0.6%, respectively; *p*-value = .0070; Table 4).

TABLE 1 Patient disposition by concomitant use of AHM and study category

	Without concomitant AHM		With concomitant AHM		
Indication	**Placebo**	**Tadalafil**	**Placebo**	**Tadalafil**	**All[a]**
ED as-needed					
All placebo-controlled, no. = 31	1512	3290	553	1228	6499
All studies[b], no. = 50		11 980		4648	16 628
ED once-daily					
All placebo-controlled, no. = 10	673	1484	405	832	3394
All studies[b], no. = 12		2314		1355	3669
BPH once-daily					
All placebo-controlled, no. = 13	1465	2065	717	1028	5275
All studies[b], no. = 13		2195		1114	3309
All ED/BPH					
All placebo-controlled, no. = 53	3552	6839	1635	3088	15 030
All studies[b], no. = 72		15 957		6868	22 825

[a]Total number of patients in all treatment groups may not be equal to the sum of numbers in each treatment group, since patients might have taken more than one treatment in crossover studies. [b]Patients who took placebo only (without tadalafil) were not counted in this row.
Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; ED, erectile dysfunction; no., number of studies.

However, among patients in the same indication category (*ED as-needed*) but receiving AHMs (≥1), the incidence of hypotension-related TEAEs was similar in the tadalafil (1.4%) and placebo (1.4%) groups (*p*-value = 1.0000; Table 4). In all other indication categories (*ED once-daily*; *BPH once-daily*; *All ED/BPH*) no significant difference between placebo and tadalafil was reported, regardless of the use of AHM (*p*-values ≥ .0850). Among patients receiving ≥1 AHMs in the All *ED/BPH category of All placebo-controlled studies*, there was no statistically significant difference in the rate of hypotension-related TEAEs between patients receiving tadalafil vs those receiving placebo (1.2% v. 1.1%, *p*-value = .8890), and the OR for the tadalafil vs placebo group was 1.09 (95%CI: 0.60, 2.04; Table 4).

The incidence of hypotension-related TEAEs was further analyzed in patients who received 0, 1, 2, or ≥3 concomitant AHMs, as shown in Figure 2. Tadalafil was associated with an increase in TEAEs of hypotension/increased hypotensive effect only in the category of *ED as-needed* patients not receiving any concomitant AHM (OR = 2.58; 95%CI: 1.25; 5.98). No significant difference in the incidence of hypotension-related TEAEs between placebo and tadalafil was reported in the other indication categories, regardless of the use and/or the number of AHMs.

In the *All placebo-controlled studies*, no patient receiving concomitant AHM had a hypotension-related TEAE that was serious or resulted in death. Only two patients receiving concomitant AHM in the *BPH once-daily* indication group (tadalafil, n = 1; placebo, n = 1) had hypotension-related TEAEs that led to treatment discontinuation (syncope and dizziness). Data are available in the Supplementary Table 1.

In the *All studies* group, the incidence of hypotension-related TEAEs ranged between 0.0% and 2.6% (Supplementary Table 2). As with the *All placebo-controlled studies*, no patients receiving concomitant AHM with tadalafil had a hypotension/increased hypotensive effect AE that led to death. Four patients discontinued treatment due to hypotension TEAEs (receiving one concomitant AHM, n = 3; receiving two concomitant AHM, n = 1) and three patients experienced a hypotension SAE (Supplementary Table 2). All events were resolved.

3.3 | MACE

Across all indications in the *All placebo-controlled studies* category the incidence of MACEs ranged between 0.0% and 1.0% (Table 5). A comparison of MACEs incidence between tadalafil and placebo treatment groups was performed in patients who received none or ≥1 AHM concomitantly. As shown in Table 5, no significant differences (*p*-values ≥ .2238) were observed in the incidence of MACEs between tadalafil and placebo treatment groups, with or without concomitant AHM, and across all indication categories. In addition, there was no significant interaction (*p*-values ≥ .5736) on the incidence of MACEs between the study treatment (placebo or tadalafil) and the concomitant use of AHM (either 0 or ≥1). The incidence of MACEs was further analyzed in patients who received 0, 1, 2, or ≥3 concomitant AHMs (Figure 3). Across all indication categories, no significant difference was observed in the incidence of MACEs between tadalafil and placebo groups, regardless of the number of concomitant AHM.

Overall, in *All placebo-controlled studies*, the reported incidence of at least one MACE was less than 1% in patients receiving tadalafil or placebo, with or without concomitant AHM. Among patients receiving concomitant AHM (tadalafil, n = 3088; placebo, n = 1635), six patients had a fatal MACE (tadalafil, n = 4; placebo, n = 2); 13 patients had a serious MACE (tadalafil, n = 7; placebo, n = 6); and 12 patients discontinued treatment due to MACE (tadalafil, n = 8; placebo, n = 4). Data are available in the Supplementary Table 3.

Across *All studies* group, less than 0.1% (1/15957) of MACE-related deaths were reported in patients receiving tadalafil without concomitant AHM; 0.2% (6/3788) of MACE-related death were reported

TABLE 2 Demographic characteristics and treatment exposure by concomitant use of AHM and study category

Indication	All placebo-controlled studies				All studies	
	Without concomitant AHM		With concomitant AHM		Without concomitant AHM	With concomitant AHM
ED As-Needed	**Placebo (no. = 1512)**	**Tadalafil (no. = 3290)**	**Placebo (no. = 553)**	**Tadalafil (no. = 1228)**	**Tadalafil (no. = 11 980)**	**Tadalafil (no. = 4648)**
Age (years), mean (SD)	53.32 (10.91)	52.56 (11.46)	59.60 (8.32)	59.47 (8.50)	52.39 (11.27)	59.03 (8.64)
Age group 45 to < 65 years, no. (%)	1008 (66.7)	2034 (61.8)	373 (67.5)	822 (66.9)	7536 (63.0)	3201 (68.9)
White, no. (%)	1092 (72.2)	2357 (71.6)	417 (75.4)	903 (73.5)	9108 (76.1)	3628 (78.1)
BMI (kg/m^2), mean (SD)	26.76 (3.89)	26.83 (4.11)	28.70 (4.79)	28.79 (4.54)	26.79 (4.27)	28.91 (4.51)
Exposure, patient years	354.8	764.2	130.3	288.7	4632.5	1923.9
Duration of study treatment, days						
Median	87.0	90.0	85.0	89.0	101.0	101.0
Min : Max	1 : 358	1 : 311	1 : 291	1 : 295	0 : 961	0 : 893
Comorbidities, no./No. (%)						
Cardiovascular disorder[a]	219/1512 (14.5)	412/3290 (12.5)	504/553 (91.1)	1117/1228 (91.0)	1335/11618 (11.5)	4106/4488 (91.5)
Hypertension	71/1512 (4.7)	125/3290 (3.8)	464/553 (83.9)	1054/1228 (85.8)	446/11980 (3.7)	3922/4648 (84.4)
Baseline IIEF-EF severity, severe, no./No. (%)	507/1393 (36.4)	1023/3022 (33.9)	242/525 (46.1)	493/1142 (43.2)	2580/8245 (31.3)	1303/3297 (39.5)
ED Once-Daily	**Placebo (no. = 673)**	**Tadalafil (no. = 1484)**	**Placebo (no. = 405)**	**Tadalafil (no. = 832)**	**Tadalafil (no. = 2314)**	**Tadalafil (no. = 1355)**
Age (years), mean (SD)	55.79 (10.13)	55.14 (10.32)	60.60 (8.71)	60.42 (9.10)	54.46 (10.51)	60.02 (8.96)
Age group 45 to < 65 years, no. (%)	481 (71.5)	1011 (68.1)	258 (63.7)	519 (62.4)	1575 (68.1)	879 (64.9)
White, no. (%)	586 (87.1)	1287 (86.8)	359 (88.6)	710 (85.3)	1994 (86.3)	1168 (86.3)
BMI (Kg/m^2), mean (SD)	28.02 (4.71)	27.61 (4.11)	29.95 (4.66)	29.92 (4.97)	27.61 (4.17)	29.69 (4.77)
Exposure, patient years	183.9	342.5	103.5	202.5	848.8	510.9
Duration of study treatment, days						
Median	86.0	86.0	86.0	86.0	86.0	86.0
Min : Max	2 : 358	1 : 576	5 : 291	3 : 380	1 : 1009	3 : 935
Comorbidities, no./No. (%)						
Cardiovascular disorder[a]	108/673 (16.0)	209/1484 (14.1)	386/405 (95.3)	762/832 (91.6)	312/2314 (13.5)	1258/1355 (92.8)
Hypertension	59/673 (8.8)	97/1484 (6.5)	363/405 (89.6)	724/832 (87.0)	152/2314 (6.6)	1194/1355 (88.1)
Baseline IIEF-EF severity, severe, no./No. (%)	211/668 (31.6)	401/1478 (27.1)	184/405 (45.4)	327/830 (39.4)	696/2305 (30.2)	541/1351 (40.0)
BPH once-daily	**Placebo (no. = 1465)**	**Tadalafil (no. = 2065)**	**Placebo (no. = 717)**	**Tadalafil (no. = 1028)**	**Tadalafil (no. = 2195)**	**Tadalafil (no. = 1114)**
Age (years), mean (SD)	61.07 (8.11)	61.33 (7.93)	65.54 (7.90)	65.41 (7.51)	61.44 (7.95)	65.56 (7.46)
Age group 45 to < 65 years, no. (%)	993 (67.8)	1356 (65.7)	322 (44.9)	484 (47.1)	1426 (65.0)	510 (45.8)
White, no. (%)	593 (40.5)	915 (44.3)	387 (54.0)	591 (57.5)	958 (43.6)	625 (56.1)
BMI (Kg/m^2), mean (SD)	25.86 (3.83)	25.73 (3.87)	27.59 (4.44)	27.63 (4.41)	25.67 (3.87)	27.57 (4.45)
Exposure, patient years	430.7	569.4	210.6	279.6	947.1	525.1
Duration of study treatment, days						
Median	86.0	85.0	86.0	85.0	90.0	92.5
Min : Max	1 : 252	1 : 267	7 : 274	1 : 295	1 : 541	1 : 490

(Continues)

TABLE 2 (Continued)

BPH once-daily	Placebo (no. = 1465)	Tadalafil (no. = 2065)	Placebo (no. = 717)	Tadalafil (no. = 1028)	Tadalafil (no. = 2195)	Tadalafil (no. = 1114)
Comorbidities, no./No. (%)						
Cardiovascular disorder[a]	181/1465 (12.4)	230/2065 (11.1)	650/717 (90.7)	943/1028 (91.7)	240/2195 (10.9)	1021/1114 (91.7)
Hypertension	104/1465 (7.1)	118/2065 (5.7)	628/717 (87.6)	904/1028 (87.9)	120/2195 (5.5)	978/1114 (87.8)
Baseline IIEF-EF severity, severe, no./No (%)	–	–	–	–	–	–
All ED/BPH	**Placebo (no. = 3552)**	**Tadalafil (no. = 6839)**	**Placebo (no. = 1635)**	**Tadalafil (no. = 3088)**	**Tadalafil (no. = 15 957)**	**Tadalafil (no. = 6868)**
Age (years), mean (SD)	56.88 (10.44)	55.77 (10.94)	62.50 (8.72)	61.70 (8.76)	53.90 (11.22)	60.32 (8.87)
Age group 45 to < 65 years, no. (%)	2393 (67.4)	4401 (64.4)	915 (56.0)	1825 (59.1)	10175 (63.8)	4404 (64.1)
White, no. (%)	2176 (61.3)	4559 (66.7)	1123 (68.7)	2204 (71.4)	11608 (72.8)	5210 (75.9)
BMI (Kg/m^2), mean (SD)	26.63 (4.13)	26.67 (4.10)	28.53 (4.74)	28.71 (4.70)	26.75 (4.25)	28.85 (4.63)
Exposure, patient years	903.9	1676.1	420.1	770.8	6421.7	2964.4
Duration of study treatment, days						
Median	86.0	87.0	85.0	86.0	101.0	102.0
Min : Max	1 : 358	1 : 576	1 : 291	1 : 380	0 : 1009	0 : 935
Comorbidities, no./No. (%)						
Cardiovascular disorder[a]	497/3552 (14.0)	851/6839 (12.4)	1500/1635 (91.7)	2822/3088 (91.4)	1850/15611 (11.9)	6168/6716 (91.8)
Hypertension	230/3552 (6.5)	340/6839 (5.0)	1416/1635 (86.6)	2682/3088 (86.9)	704/15957 (4.4)	5885/6868 (85.7)
Baseline IIEF-EF severity, severe, no./No. (%)	819/2767 (29.6)	1660/5610 (29.6)	524/1297 (40.4)	1016/2540 (40.0)	3371/11289 (29.9)	1958/5039 (38.9)

[a]Included any of cardiac disorder, cerebrovascular disorder, and other vascular disorder.
Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; ED, erectile dysfunction; IIEF-EF; International Index of Erectile Function – Erectile Function; SD, standard deviation.

in those receiving tadalafil and one AHM; and no MACE-related deaths were reported in those with ≥2 concomitant AHM (Supplementary Table 4). Moreover, among patients receiving concomitant AHM (tadalafil, n = 6868), 34 patients experienced serious MACEs, and 27 patients discontinued the study treatment due to MACEs.

3.4 | Patients with abnormal blood pressure readings

The incidence of PCSA BP readings across *All placebo-controlled ED and BPH studies* is shown in the Supplementary Table 5. Overall, the use or number of concomitant AHM with tadalafil had no marked effect on the incidence of PCSA BP readings. In patients receiving ≥3 AHM, the tadalafil group had numerically higher incidences of PCSA DBP (tadalafil, 4.2% [15/356]; placebo, 2.8% [5/177]) and SBP (tadalafil, 5.3% [19/356]; placebo, 1.7% [3/177]) readings compared with those in the placebo group. However, these differences were within data variability since a similar incidence was observed in patients receiving placebo and 2 AHM (PCSA DBP, 4.2% [22/518; PCSA SBP, 5.2% [27/518]). Of note, none of the patients receiving tadalafil or placebo with ≥1 concomitant AHM had DBP <45 mmHg or SBP <85 mmHg. The vast majority of PCSA BP events were asymptomatic. Among those with PCSA SBP/DBP, only four patients (three in tadalafil with zero concomitant AHM and one in placebo with three concomitant AHMs) reported hypotension-related TEAEs and no one reported MACEs within 3 days of the BP reading.

4 | DISCUSSION

Patients receiving tadalafil for ED or BPH are often older and may suffer from cardiovascular comorbidities. Taken alone, tadalafil may induce hypotension-related TEAEs in a small proportion of patients, as would be expected with a vasodilator. This pooled analysis closely examined hypotension-related TEAEs and MACEs in patients receiving tadalafil with or without concomitant AHM to determine whether these effects can be attributed to tadalafil, and if their frequency is affected by concomitant AHM. The analysis of safety data extracted from 72 Phase II–IV studies revealed no significant differences in the

TABLE 3 Concomitant AHM by indication and study category

Indication, no. (%)	Placebo-controlled studies		All studies
ED As-Needed	**Placebo (no. = 2065)**	**Tadalafil (no. = 4518)**	**Tadalafil (no. = 16628)**
Number of antihypertensives			
0	1512 (73.2)	3290 (72.8)	11980 (72.0)
1	322 (15.6)	716 (15.8)	2614 (15.7)
2	175 (8.5)	391 (8.7)	1451 (8.7)
≥3	56 (2.7)	121 (2.7)	583 (3.5)
ED Once-Daily	**Placebo (no. = 1078)**	**Tadalafil (no. = 2316)**	**Tadalafil (no. = 3669)**
Number of antihypertensives			
0	673 (62.4)	1484 (64.1)	2314 (63.1)
1	220 (20.4)	419 (18.1)	694 (18.9)
2	131 (12.2)	294 (12.7)	476 (13.0)
≥3	54 (5.0)	119 (5.1)	185 (5.0)
BPH once-daily	**Placebo (no. = 2182)**	**Tadalafil (no. = 3093)**	**Tadalafil (no. = 3309)**
Number of antihypertensives			
0	1465 (67.1)	2065 (66.8)	2195 (66.3)
1	409 (18.7)	583 (18.8)	619 (18.7)
2	237 (10.9)	322 (10.4)	351 (10.6)
≥3	71 (3.3)	123 (4.0)	144 (4.4)
All ED/BPH	**Placebo (no. = 5187)**	**Tadalafil (no. = 9927)**	**Tadalafil (no. = 22 832)**
Number of antihypertensives			
0	3552 (68.5)	6839 (68.9)	15 957 (69.9)
1	924 (17.8)	1718 (17.3)	3788 (16.6)
2	532 (10.3)	1007 (10.1)	2194 (9.6)
≥3	179 (3.5)	363 (3.7)	884 (3.9)

Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; ED, erectile dysfunction.

incidence of hypotension-related TEAEs or MACEs in patients taking tadalafil with concomitant AHM vs those receiving AHM alone. The results showed a similar trend when only placebo-controlled studies were included in the analysis, and when the studies were analyzed by indication and tadalafil dosing schedule (once-daily or as-needed). An increase in hypotension-related TEAEs was observed only in the subgroup of *ED as-needed* patients receiving tadalafil without any concomitant AHM compared with placebo, but no significant difference was reported between placebo and tadalafil in the other treatment categories regardless of AHM use. PCSA DBP and/or SBP were reported in a small proportion of patients across placebo-controlled studies. However, since the majority of patients were asymptomatic, the clinical relevance of acute hypotension is unclear.

Hypertension and ED are both caused by endothelial dysfunction and/or dysregulation of the vascular and the autonomic nervous system. Hypertension is the most common comorbidity associated with ED,[15] and ED is a well-known adverse effect of some AHM,[16,17,18] such as thiazide diuretics, and β-blockers. A medical outpatient clinic study reported that ED was a common issue among middle-age men after initiating AHM, resulting in low treatment adherence.[19] Similarly, sexually-related side effects prompted discontinuation of treatment in 8.3% of participants in a long-term study of AHM AE.[20] Nevertheless, it should be noted that a study on intensive control of BP suggested that antihypertensive treatment has a small clinical impact on ED.[21] Noteworthy, recent evidence has shown that patients receiving PDE_5 inhibitors are more likely to initiate an antihypertensive regime and more willing to adhere to the treatment.[22,23]

Concomitant use of ED and antihypertensive medications is engrained in clinical practice guidelines, increasing the complexity of prescribing decisions for patient having or developing ED. The 2017 High Blood Pressure Clinical Practice Guideline does not state any specific therapeutic recommendations related to ED, but does recommend the use of thiazide diuretics for first-line therapy and resistant hypertension treatment, despite ED side effect.[24] A specific therapy for ED

TABLE 4 Comparison of TEAEs in patients with and without concomitant AHM across placebo-controlled studies

	Number of concomitant AHM			
	0		≥1	
Indication	Placebo	Tadalafil	Placebo	Tadalafil
ED as-needed				
Number of patients	1512	3290	553	1228
Patients with any hypotension TEAE	9 (0.6%)	50 (1.5%)	8 (1.4%)	17 (1.4%)
95%CI of TEAE proportion[a]	(0.3%, 1.1%)	(1.1%, 2.0%)	(0.6%, 2.8%)	(0.8%, 2.2%)
OR with 95%CI (Tadalafil/Placebo)[b]		2.58 (1.25, 5.98)		0.96 (0.39, 2.58)
p-value (Tadalafil vs Placebo)[b]		**.0070**		**1.0000**
Ratio of ORs with 95%CI[b]				0.38 (0.11, 1.32)
p-value (Tadalafil and AHM interaction)[b]				**.1406**
ED once-daily				
Number of patients	673	1484	405	832
Patients with any hypotension TEAE	7 (1.0%)	12 (0.8%)	5 (1.2%)	10 (1.2%)
95%CI of TEAE proportion[a]	(0.4%, 2.1%)	(0.4%, 1.4%)	(0.4%, 2.9%)	(0.6%, 2.2%)
OR with 95%CI (Tadalafil/Placebo)[b]		0.78 (0.28, 2.34)		0.97 (0.30, 3.65)
p-value (Tadalafil vs Placebo)[b]		**.7551**		**1.0000**
Ratio of ORs with 95%CI[b]				1.25 (0.24, 6.77)
p-value (Tadalafil and AHM interaction)[b]				**1.0000**
BPH once-daily				
Number of patients	1465	2065	717	1028
Patients with any hypotension TEAE	14 (1.0%)	20 (1.0%)	5 (0.7%)	10 (1.0%)
95%CI of TEAE proportion[a]	(0.5%, 1.6%)	(0.6%, 1.5%)	(0.2%, 1.6%)	(0.5%, 1.8%)
OR with 95%CI (Tadalafil/Placebo)[b]		1.01 (0.49, 2.18)		1.40 (0.43, 5.24)
p-value (Tadalafil vs Placebo)[b]		**1.0000**		**.7386**
Ratio of ORs with 95%CI[b]				1.37 (0.33, 6.33)
p-value (Tadalafil and AHM interaction)[b]				**.8694**
All ED/BPH				
Number of patients	3552	6839	1635	3088
Patients with any hypotension TEAE	29 (0.8%)	82 (1.2%)	18 (1.1%)	37 (1.2%)
95%CI of TEAE proportion[a]	(0.5%, 1.2%)	(1.0%, 1.5%)	(0.7%, 1.7%)	(0.8%, 1.6%)
OR with 95%CI (Tadalafil/Placebo)[b]		1.47 (0.95, 2.34)		1.09 (0.60, 2.04)
p-value (Tadalafil vs Placebo)[b]		**.0850**		**.8890**
Ratio of OR with 95%CI[b]				0.74 (0.35, 1.61)
p-value (Tadalafil and AHM interaction)[b]				**0.5100**

[a]The 95%CI for the response rate was calculated using Clopper Pearson exact method.

[b]*P*-value, OR, and 95%CI were calculated using exact logistic regression. TEAEs of hypotension/increased hypotensive effect included hypotension, orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, blood pressure orthostatic decreased, blood pressure orthostatic, dizziness, dizziness exertional, dizziness postural, presyncope, and syncope.

Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; CI, confidence interval; ED, erectile dysfunction; OR, odds ratio; TEAE, treatment-emergent adverse event.

is required in most patients, however there is still a lack of communication on this matter both in the medical literature and the clinical guidelines. One of the recommendations of the Princeton Consensus Conferences on Sexual Dysfunction and Cardiac Risk was that patients whose BP is well controlled with ≥1 AHM may safely receive approved medical therapies for sexual dysfunction,[25,26] as treatment with beta-blockers and thiazide diuretics was recognized as predisposing men to ED.[26]

This analysis presents safety data from over six-thousands patients receiving tadalafil with AHM, and complements a number of other published studies on the cardiovascular safety of tadalafil. Tadalafil has been associated with mild and transient decreases in BP due to

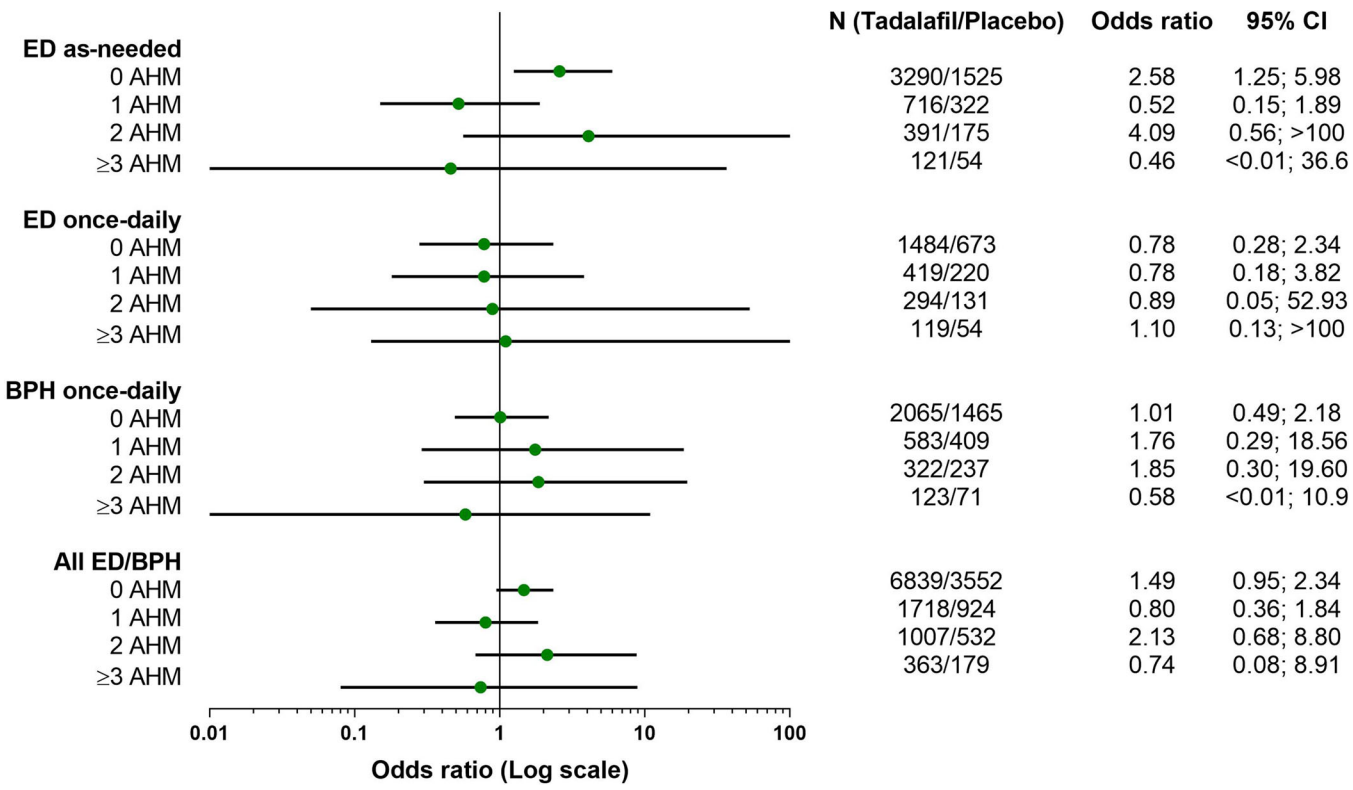

FIGURE 2 Comparison of TEAEs of hypotension/increased hypotensive effect between placebo and tadalafil treatment groups by number of concomitant AHM in ED and BPH placebo-controlled studies. Odds ratio and 95%CI were calculated using exact logistic regression. Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; CI, confidence interval; ED, erectile dysfunction

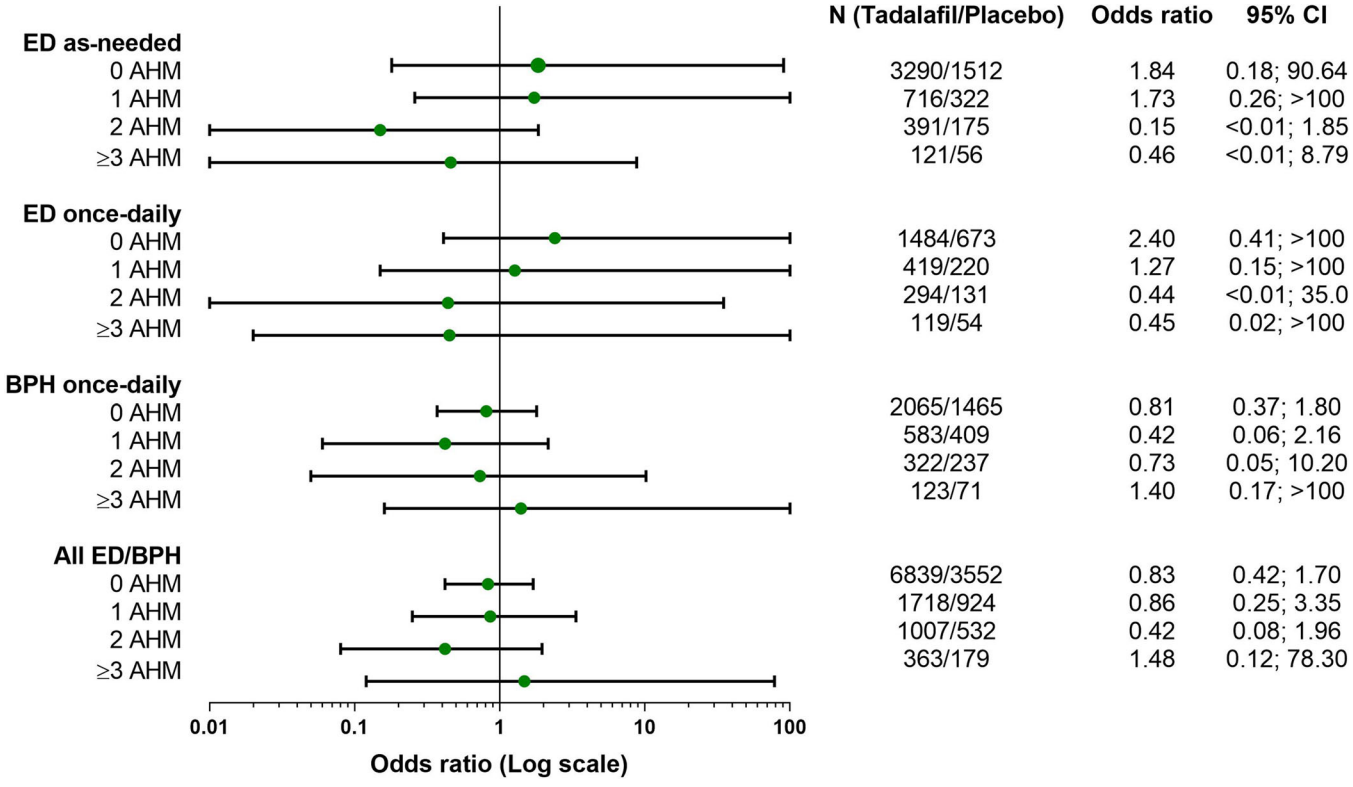

FIGURE 3 Odds ratio of incidences of treatment emergent MACEs between placebo and tadalafil groups by number of concomitant AHM in ED and BPH placebo-controlled studies. Odds ratio and 95%CI were calculated using exact logistic regression. Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; ED, erectile dysfunction; MACE, major adverse cardiovascular event

TABLE 5 Comparison of MACEs in patients with and without concomitant AHM across studies

	Number of concomitant AHM			
	0		≥1	
Indication	Placebo	Tadalafil	Placebo	Tadalafil
ED as-needed				
Number of patients	1512	3290	553	1228
Patients with at least one MACE	1 (< 0.1%)	4 (0.1%)	4 (0.7%)	4 (0.3%)
95%CI of TEAE proportion[a]	(0.0%, 0.4%)	(0.0%, 0.3%)	(0.2%, 1.8%)	(0.1%, 0.8%)
OR with 95%CI (Tadalafil/Placebo)[b]		1.84 (0.18, 90.64)		0.45 (0.08, 2.42)
p-value (Tadalafil vs Placebo)[b]		**.9956**		**.4263**
Ratio of ORs with 95%CI[b]				0.27 (0.00, 4.71)
p-value (Tadalafil and AHM interaction)[b]				**.6163**
ED once-daily				
Number of patients	673	1484	405	832
Patients with at least one MACE	0	4 (0.3%)	1 (0.2%)	4 (0.5%)
95%CI of TEAE proportion[a]	(0.0%, 0.5%)	(0.1%, 0.7%)	(0.0%, 1.4%)	(0.1%, 1.2%)
OR with 95%CI (Tadalafil/Placebo)[b]		2.40 (0.41, > 99.99)		1.95 (0.19, 96.35)
p-value (Tadalafil vs Placebo)[b]		**.2238**		**.9448**
Ratio of ORs with 95%CI[b]				1.35 (0.00, 25.56)
p-value (Tadalafil and AHM interaction)[b]				**.5736**
BPH once-daily				
Number of patients	1465	2065	717	1028
Patients with at least one MACE	14 (1.0%)	16 (0.8%)	7 (1.0%)	7 (0.7%)
95%CI of TEAE proportion[a]	(0.5%, 1.6%)	(0.4%, 1.3%)	(0.4%, 2.0%)	(0.3%, 1.4%)
OR with 95%CI (Tadalafil/Placebo)[b]		0.81 (0.37, 1.80)		0.70 (0.21, 2.33)
p-value (Tadalafil vs Placebo)[b]		**.6902**		**.6750**
Ratio of ORs with 95%CI[b]				0.86 (0.20, 3.72)
p-value (Tadalafil and AHM interaction)[b]				**1.0000**
All ED/BPH				
Number of patients	3552	6839	1635	3088
Patients with at least one MACE	15 (0.4%)	24 (0.4%)	11 (0.7%)	15 (0.5%)
95%CI of TEAE proportion[a]	(0.2%, 0.7%)	(0.2%, 0.5%)	(0.3%, 1.2%)	(0.3%, 0.8%)
OR with 95%CI (Tadalafil/Placebo)[b]		0.83 (0.42, 1.70)		0.72 (0.31, 1.74)
p-value (Tadalafil vs Placebo)[b]		**.6821**		**.5276**
Ratio of ORs with 95%CI[b]				0.87 (0.28, 2.71)
p-value (Tadalafil and AHM interaction)[b]				**.9857**

[a]The 95%CI for the response rate was calculated using Clopper Pearson exact method.

[b]*P*-value, OR and 95%CI were calculated using exact logistic regression. MACE were identified using five preferred terms (death, cardiac arrest, cardiac death, sudden cardiac death, and sudden death) and two standardized Medical Dictionary for Regulatory Activities queries (myocardial infarction and ischemic central nervous system vascular conditions).

Abbreviations: AHM, antihypertensive medication; BPH, benign prostatic hyperplasia; CI, confidence interval; ED, erectile dysfunction; MACE, major adverse cardiovascular event; OR, odds ratio; TEAE, treatment-emergent adverse event.

its vasodilator properties in both non-hypertensive and hypertensive individuals compared with placebo which, however, were considered not clinically meaningful.[27] Patterson and associates studied the effect of 20 mg of tadalafil vs placebo on mean 26-hour ambulatory SBP and DBP in patients with underlying hypertension. Tadalafil reduced mean ambulatory SBP by 4.8 mmHg and mean DBP by 2.9 mmHg, but these small reductions were generally well tolerated.[28] This significant decrease may be a potential advantage of tadalafil use, in that it could lower BP in patients with ED. An additional analysis of the current study data suggests that, when compared to placebo with no concomitant use of AHM, tadalafil provides small nominally significant drops (*p*-value < .05) in BP of less than 1.5 mmHg and often less than 1.0 mmHg.

In most of the analyses of tadalafil plus AHM, the addition of tadalafil was not associated with significant drops in blood pressure when compared to placebo plus AHM (Supplementary Tables 6–9).

A retrospective analysis of 36 clinical trials evaluating serious cardiovascular TEAEs of tadalafil found that there was no significant difference in the incidence rates of AEs between patients receiving tadalafil or placebo.[29] The long-term safety and tolerability of tadalafil (5, 10, or 20 mg) was assessed in a multicenter, open-label study over a period of 24-month in men suffering from ED. Although SAEs occurred in 8.6% of patients, none was considered treatment-related. Additionally, no clinically significant laboratory findings or changes in vital signs were attributable to tadalafil.[30]

A limitation of this safety analysis was that data were pooled from multiple trials without accounting for cross-study differences (duration and study size). Additionally, the concomitant use of AHM was a post-baseline variable and the smaller sample size of patients receiving AHM compared to those without AHM might have increased variability. Nevertheless, sensitivity analyses found that almost all patients (~ 99%) remained in the same group (*With concomitant AHM* or *Without concomitant AHM*) throughout the study, and results were consistent with those presented here (details in the Supplementary material). Of note, the incidences of hypotension-related TEAEs and MACEs were similar numerically between tadalafil and placebo groups in patients with AHM, and hence a larger sample size as same as that in the group without AHM would still have limited power to detect the differences as observed.

In conclusion, it is important that physicians and patients are aware of the safety of treating ED while on AHM, because restoring normal sexual function may help prevent low adherence in the use of AHM. This analysis showed no evidence that tadalafil, when given concomitantly with one or more AHM (excluding alpha-blockers or nitrates), caused an increase in hypotension-related TEAE or MACEs compared with placebo despite small additional falls in BP that may occur.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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