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COMMENTARY

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Tadalafil in patients on antihypertensive medications: Does safety remain an issue?

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The paper by Kloner and associates published in this issue of the Journal handles an exciting topic in the hypertension community; the safety of tadalafil in patients with erectile dysfunction (ED) and/or benign prostatic hyperplasia (BPH) concerning major adverse cardiovascular events (MACE) and hypotension-related treatment-emergent adverse events (TEAE).[1] This pooled analysis of 22 825 patients from 72 Phase II-IV studies on patients with ED and BPH demonstrated the considerable safety of tadalafil in all of the subgroups examined, with the exception of the as-needed indication in ED patients without concomitant antihypertensive medication intake.[1]

The worldwide burden of ED is believed to be high owing to the increased life expectancy.[2] However, it cannot be estimated appropriately due to the differences in the sensitivity of screening methods applied across the studies. Other than its detrimental role in the quality of life of male individuals, ED is widely regarded as a risk factor associated with cardiovascular morbidity and mortality.[2] At the same time, ED frequently coexists with BPH and is also linked to incident dementia.[2] ED shares common pathophysiologic mechanisms (low-grade inflammation, oxidative stress, endothelial dysfunction, thrombosis-fibrinolysis imbalance) and risk factors (age, arterial hypertension, diabetes mellitus, smoking, hypercholesterolemia, obesity) with cardiovascular diseases (Figure 1).[3] Moreover, the prominent prevalence of arterial hypertension in aging populations dictates its treatment with agents also involved in the induction of ED, including b-blockers, thiazide diuretics, and aldosterone antagonists.[4] Consequently, the development of ED may have important implications in nonadherence to antihypertensive medications as a method of improving the sexual life,[5] leading to adverse cardiovascular outcomes and impaired quality of life.[6]

According to recent guidelines, phosphodiesterase type 5 (PDE5) inhibitors are the cornerstone of ED treatment.[7] These drugs inhibit the breakdown of cyclic guanosine monophosphate, thus improving penile blood flow. Meta-analytic evidence has established their efficacy in ameliorating ED.[8] However, within-class differences may be present, with sildenafil, the first developed PDE5 inhibitor, displaying the highest potency at the cost of increased adverse events.[9,10] On the other hand, tadalafil is another first-line, selective PDE5 inhibitor used to treat ED, BPH, and pulmonary hypertension since 2003, with a long duration of action, whose efficacy and tolerability are also well-documented (Figure 1).[9,10] A higher patient preference for tadalafil compared to sildenafil has been noted, especially in younger individuals.[11] However, no head-to-head randomized trials exist and such observations should be cautiously interpreted. Other PDE5 inhibitors (avanafil, lodenafil, mirodenafil) appear to be less effective or safe than sildenafil and Tadalafil.[12]

PDE5 inhibitors and tadalafil, in particular, have been considered a generally safe treatment approach.[13] The pooled safety analysis by Kloner and associates provides the necessary validation based on adequate sample size, taking into account both randomized and non-randomized studies.[1] Although tadalafil led to a mild and transient decrease in blood pressure (BP) owing to its vasodilating properties, it did not result in a higher incidence of hypotension-related TEAE or MACE, irrespective of study design, indication, and the use and the quantity of antihypertensive medications (Figure 1). Importantly, hypotension-related TEAE in patients receiving concomitant antihypertensive medication did not result in deaths both in the placebo-controlled and all studies analyses. However, an interesting observation of this present analysis was the significantly higher rates of

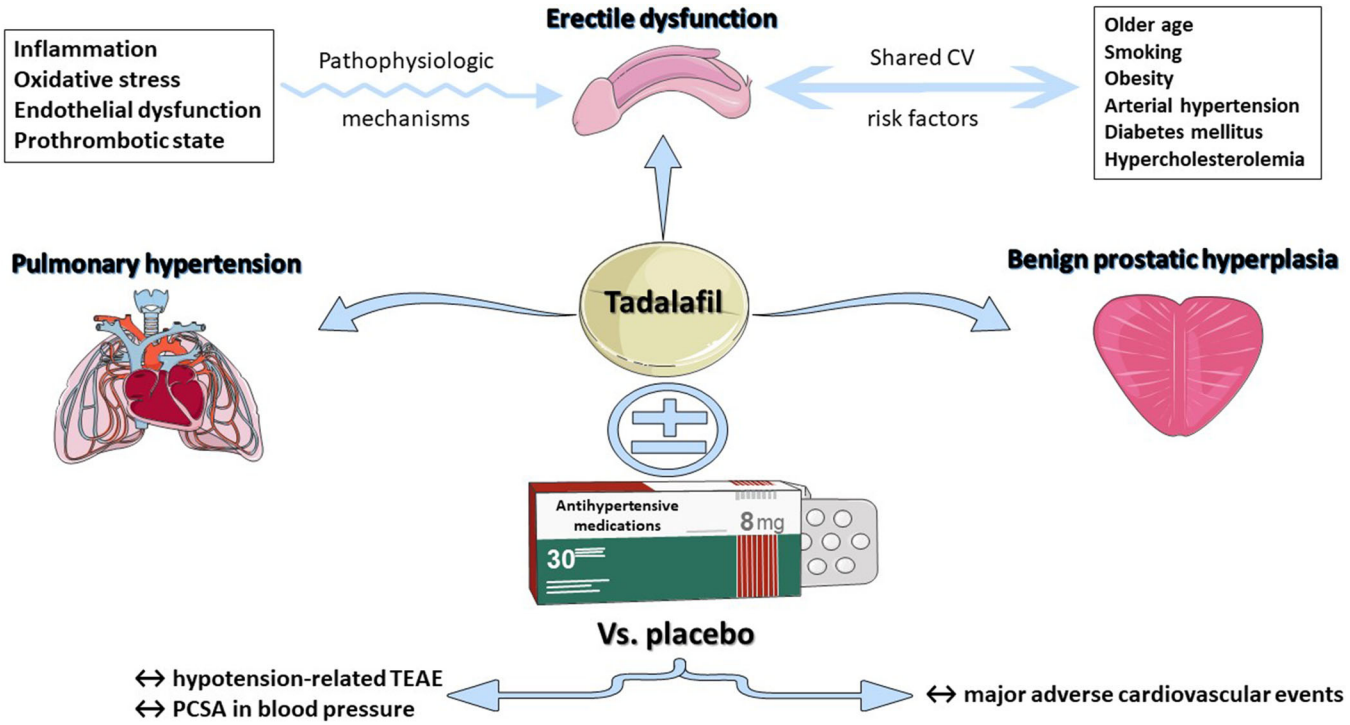

FIGURE 1 The therapeutic efficacy and safety of Tadalafil. Abbreviations: CV, cardiovascular; TEAE, treatment-emergent adverse events; PCSA, potentially clinically relevant abnormalities; MACE, major adverse cardiovascular events. ↔ denotes no significant differences

hypotension-related TEAE in the group of the ED as-needed patients who were not on antihypertensives. Although this finding was not associated with excess MACE, it merits further validation and investigation regarding its clinical significance.

Another interesting point analyzed in the study of Kloner and associates was the prevalence of potentially clinically significant abnormalities (PCSA) in BP. According to the results, only eight patients in the tadalafil arm of all placebo-controlled studies had systolic BP readings below 85 mmHg and none had diastolic BP below 45 mmHg. As expected, the use of an increasing number of antihypertensive medications resulted in a numerically higher prevalence of PCSA in BP, which was not statistically significantly different than placebo. The BP-lowering effect of tadalafil was also examined in all the prespecified disease and dosing regimens groups. Patients with ED or BPH who were not on antihypertensive medications experienced significantly higher reductions in systolic and diastolic BP regardless of dosing regimen compared to placebo. When the interaction between the use of antihypertensive medications and the treatment with tadalafil was examined, no significant differences in BP reduction were noted between tadalafil and placebo. The magnitude of blood pressure-lowering was less than 1.5 mmHg, much lower than those reported previously by Patterson and associates in treated hypertensive patients receiving additional tadalafil.[14] Therefore, the use of tadalafil on coexisting arterial hypertension and ED/BPH may not lead to a clinically relevant added reduction in blood pressure.

The concomitant use of PDE5 inhibitors with alpha-blockers is an additional concern not touched upon in this analysis. Although alpha-blockers are not among the main antihypertensive medications, their use increases in patients with BPH and ED. Several recent meta-analyses have been conducted to test the efficacy and safety of the alpha-blocker-PDE5 inhibitor combination. Although this drug combination provides a higher and marginally higher efficacy in BPH- and ED-related symptoms compared to monotherapy, it is associated with a greater burden of adverse events.[15,16] Interestingly, in the meta-analysis of Zhou and associates, which assessed the efficacy and safety of tadalafil and tamsulosin compared to tadalafil monotherapy, the latter arm was associated with a higher number of adverse events.[17] However, it should be noted that none of these studies assessed hypotension-related TEAE. Previous studies have shown minor, insignificant BP reductions with the combination of tadalafil-alpha blocker,[18,19] indicating the safety of this combination in this aspect.

In conclusion, tadalafil's use is essential in managing ED and BPH, which are increasingly frequent entities. The results of this integrated pooled safety analysis provide the rationale for tadalafil's seamless use without worrying about excess hypotension-related TEAE and MACE even in patients with concomitant use of antihypertensive medications. The PCSA in BP and the noticed BP reductions were similar between tadalafil and placebo. Further research may be warranted to assess the excess hypotension-related TEAE in patients using tadalafil as-needed.

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CONFLICT OF INTEREST

The authors have no competing interests.

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