Tadalafil Use in Cardiovascular Disease

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Abstract: Tadalafil is a phosphodiesterase inhibitor currently approved for use in erectile dysfunction (ED), benign prostatic hyperplasia (BPH), and pulmonary arterial hypertension (PAH). While tadalafil's benefits in ED and BPH have been well-established for years, its benefits in PAH were identified only recently in major clinical trials, resulting in the recent approval of a single-tablet, combination therapy of tadalafil with an endothelin receptor antagonist for PAH. With Tadalafil's cardiovascular benefits in ED, BPH, and PAH, clinical researchers have begun investigating whether tadalafil's use extends to other cardiovascular diseases, especially heart failure (HF), an emerging epidemic in medicine. Recent research in animal models has demonstrated a potential benefit of tadalafil use in ischemic cardiomyopathy and HF, as numerous studies in mice and sheep demonstrated improved left ventricular function and contractility, with reduced adverse remodeling and hypertrophy. A retrospective cohort study identified that tadalafil use in patients with ED and coronary artery disease was associated with a significant decrease in the incidence of HF, acute myocardial infarction, and mortality compared with sildenafil or no treatment. However, a randomized controlled trial in patients with comorbid PAH and HF with preserved ejection fraction demonstrated no significant benefit with the use of tadalafil. Unfortunately, there is limited evidence from clinical trials investigating the impact of tadalafil in patients with HF with reduced or preserved ejection fraction without comorbid PAH. Further studies are needed on this topic to better identify whether tadalafil has a role in the prevention or treatment of HF.

Key Words: tadalafil, phosphodiesterase inhibitors, heart failure

(*Cardiology in Review* 2025;XXX: 00–00)

Tadalafil is an oral phosphodiesterase type 5 (PDE5) inhibitor that was approved by the US Food and Drug Administration (FDA) in 2003 for use in erectile dysfunction (ED). Since its approval for ED, tadalafil has now become FDA-approved for use in benign prostatic hyperplasia (BPH) and pulmonary arterial hypertension (PAH). In fact, the latest development of tadalafil in PAH was seen in 2024, with the FDA approval of a single-tablet combination therapy of tadalafil and macitentan, an endothelin receptor antagonist (ERA), for adults with PAH.[1] Tadalafil's benefits in ED, BPH, and PAH have prompted many clinical researchers to investigate whether its benefits extend to other cardiovascular conditions, such as heart failure (HF).

Researchers have thoroughly studied the mechanisms of action of tadalafil in ED, BPH, and PAH to identify a theoretical benefit for its use in HF. Briefly, in ED, tadalafil works by relaxing the smooth muscle cells in the blood vessels in the penis, increasing blood flow during sexual stimulation. In BPH, tadalafil works by relaxing the bladder and periprostatic smooth muscle, improving urinary flow. In PAH, it works by relaxing the smooth muscle cells in the pulmonary vasculature.[1] The potential mechanisms by which it can provide benefit in HF are still not entirely clear, but recent research in animal models has demonstrated that tadalafil may have a possible benefit worth further investigation in humans with HF.

In this article, we will first review the current evidence regarding tadalafil's approved uses, including a stronger focus on the recent large clinical trials identifying its benefits in PAH. With this background, we will then discuss the recent research on tadalafil use in animal models of HF to understand how these studies may pave the way for the development of clinical trials investigating tadalafil's use in humans with HF. We will also review a retrospective cohort study that investigated the use of tadalafil versus sildenafil versus no treatment in patients with ED and coronary artery disease (CAD).

TADALAFIL MECHANISM OF ACTION

Tadalafil is a selective inhibitor of PDE5, an enzyme found in the smooth muscle cells of the corpus cavernosum of the penis, prostatic tissue, and pulmonary vasculature, in addition to other locations. PDE5 is responsible for breaking down cyclic guanosine monophosphate (cGMP), a second-messenger molecule produced via an intracellular cascade. This cascade begins when nitric oxide is released and activates the enzyme guanylate cyclase, which converts guanosine triphosphate to cGMP, which acts as a second messenger with multiple downstream actions. Relevant to our discussion, cGMP is responsible for the relaxation of smooth muscle cells and, therefore, causes vasodilation of blood vessels. PDE5 breaks down cGMP to help regulate vascular tone and balance between vasodilation and vasoconstriction.[2] Therefore, inhibition of PDE5 prevents the degradation of cGMP and prolongs and enhances its effects.

In its treatment of ED, tadalafil effectively increases cGMP levels, causing relaxation of the smooth muscle cells in the corpus cavernosum, vasodilation of the arteries, and increased blood flow into the penile tissue to achieve erection. In addition, nitric oxide release is increased drastically during sexual stimulation, promoting downstream production of cGMP and increasing tadalafil's effectiveness in ED.[2]

Due to PDE5's presence in prostatic tissue as well, tadalafil is an effective treatment for BPH by increasing cGMP levels and inducing relaxation of the smooth muscle cells in the periprostatic tissue and detrusor muscle of the bladder. This alleviates BPH symptoms by improving urinary flow.[3]

PDE5 is also present in the pulmonary vasculature, allowing for tadalafil's use in PAH. By selective inhibition of PDE5, tadalafil increases cGMP levels in the pulmonary vasculature, causing vasodilation and reducing pulmonary arterial pressure.[1]

TADALAFIL USE IN ED

Tadalafil's use in ED is well-established from multiple major studies confirming its efficacy; this section will briefly summarize the major findings from these studies. In most studies investigating tadalafil use, an international index of erectile function was used to determine how patients perceived their success with treatment. The results of these studies showed tadalafil significantly improved erectile function, with the highest success rates seen in patients with mild

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Disclosure: The authors have no conflicts of interest to report.

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ISSN: 1061-5377/25/XXX00-0000
DOI: 10.1097/CRD.0000000000000877

to moderate ED. The medication was found to be very effective across various demographics and comorbidities such as diabetes or hypertension. In addition, these studies demonstrated that higher doses of tadalafil are more effective than lower doses. Interestingly, some studies specifically demonstrated that tadalafil has superior efficacy in patients with spinal cord injuries compared with sildenafil, another PDE5 inhibitor used as a first-line option for ED.[4]

TADALAFIL USE IN BPH

Tadalafil's benefits in BPH were identified over the years in multiple randomized controlled trials; this section will review 2 of these major studies. In 2011, an international, randomized, placebo-controlled trial in 325 patients was completed to investigate tadalafil's benefit in the treatment of lower urinary tract symptoms in patients with BPH. The study used the International Prostate Symptom Score (IPSS) to evaluate baseline symptoms and improvement in symptoms in patients on tadalafil. Objectively, the maximum urinary flow rate (Qmax) and postvoid residual volume were measured to determine any differences between the 2 groups. The study showed that tadalafil 5 mg once daily for 12 weeks resulted in a clinically meaningful and significant reduction in total IPSS at 4 weeks in men with BPH. However, there was no significant difference in the Qmax score or postvoid residual volume between the 2 groups.[5]

In 2012, another international, randomized, placebo-controlled trial in 511 patients assessed the use of tadalafil in patients with BPH versus an active control, tamsulosin, a first-line agent for BPH. This study used subjective measurements such as IPSS and BPH impact index to evaluate patients at baseline and after therapy. Objectively, the Qmax was measured for both groups. The study found that IPSS and BPH impact index significantly improved in the tadalafil and tamsulosin groups through 12 weeks versus placebo. The Qmax also increased significantly with both tadalafil and tamsulosin compared with placebo. The authors concluded that monotherapy with tadalafil or tamsulosin resulted in similar, significant improvements in symptoms and urinary flow rate versus placebo in patients with BPH with lower urinary tract symptoms. The study also reaffirmed the efficacy of tadalafil in improving ED symptoms, which tamsulosin had no effect on.[6] From this study, clinicians learned that tadalafil is a viable option for patients with BPH who may not tolerate tamsulosin therapy.

TADALAFIL IN PAH

The use of tadalafil in PAH was initially investigated in a large clinical trial called the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST)-1 trial. It was a multicenter, randomized, dose-ranging, placebo-controlled trial with 405 patients with PAH. The primary end point was the change from baseline to week 16 in the 6-minute walk distance (6MWD). The study results showed that tadalafil significantly improved the mean placebo-corrected 6MWD in a dose-dependent manner, with the 40-mg dose meeting the prespecified level of statistical significance ($P < 0.01$). Overall, the mean placebo-corrected treatment effect was 33 meters. In addition, the results showed that the time to clinical worsening was significantly increased in the tadalafil group ($P = 0.041$), potentially representing a slower disease progression.[7] The study also demonstrated that the cardiopulmonary hemodynamics available from 93 patients were improved compared with baseline in patients on tadalafil 20 and 40 mg. The mean pulmonary arterial pressure decreased by 8.5 mm Hg ($P < 0.001$) in the 20-mg group and 4.3 mm Hg ($P = 0.01$) in the 40-mg group. The pulmonary vascular resistance decreased by 254 dyne·s·cm^{-5} ($P = 0.001$) in the 20-mg group and by 209 dyne·s·cm^{-5} ($P = 0.039$) in the 40-mg group. A statistically significant improvement in cardiac index of 0.6 L/min/m^2 was also seen in the tadalafil 40-mg group ($P = 0.028$). A significant improvement in quality of life, measured with validated questionnaires, was also seen in patients taking tadalafil 40 mg.[7,8]

A follow-up investigation, the PHIRST-2 trial, a double-blinded, 52-week uncontrolled extension study, enrolled patients who either completed PHIRST-1 or patients who had discontinued PHIRST-1 while taking a placebo. The goal of this study was to evaluate the durability of efficacy and long-term safety of tadalafil. Patients who were stable on tadalafil from the PHIRST-1 trial were continued on the regimen for 52 more weeks. All other patients enrolled were started on tadalafil 40 mg daily for 52 weeks. The 6MWD was used to address the durability of efficacy, comparing the results across the PHIRST-1 and PHIRST-2 studies. The results showed that in patients receiving either tadalafil 20 or 40 mg, the improvements in 6MWD in the 16-week PHIRST-1 study were sustained for up to 52 additional weeks of treatment. However, it is important to note that in these patients on tadalafil 20 or 40 mg, the 6MWD did not continue improving in the PHIRST-2 study; rather, the benefits from the PHIRST-1 trial were simply sustained for an additional 52 weeks in the PHIRST-2 study. In patients who received a placebo, tadalafil 2.5 mg, or tadalafil 10 mg in PHIRST-1, they had lower 6MWDs throughout PHIRST-2 than patients randomized to tadalafil 20 mg or tadalafil 40 mg in PHIRST-2. The authors state that this may indicate that a delay in the initiation of tadalafil may result in less effective long-term efficacy.[9]

In 2014, 2 post hoc analyses of the PHIRST studies were completed. The first analysis investigated the safety and efficacy differences in patients under the age of 65 years versus those of ≥65 years of age at the time of the PHIRST-1 trial. The results showed that at the conclusion of the 16-week PHIRST-1 trial, patients under 65 years of age demonstrated a significantly improved 6MWD, while patients ≥65 years of age had a nonsignificant increase in 6MWD. However, at the conclusion of the 52-week PHIRST-2 trial, the 6MWD was significantly increased in both age groups.[10]

The second post hoc analysis evaluated factors that increase the likelihood of achieving a clinically relevant response (ie, obtaining a minimally important difference in 6MWD or in the quality-of-life questionnaire scores) in the PHIRST-1 study. The analysis found that patient factors of younger age, male sex, and a lower baseline 6MWD were associated with a stronger likelihood of achieving a clinically relevant response. Of note, if the patient developed PAH due to a connective tissue disorder, there was a lower likelihood of achieving a clinically relevant response with tadalafil. The increased likelihood of response in men compared with women was considered a novel finding in this analysis, potentially representing pathophysiologic differences between the sexes.[11]

While these previous studies provided evidence regarding the use of tadalafil as monotherapy in PAH, there was a need for further investigation regarding the use of tadalafil in a combination therapy for PAH. A post hoc analysis of the PHIRST-1 study investigated the effect of tadalafil on bosentan, an ERA, background therapy in the treatment of PAH. The analysis showed that only patients who were treatment-naive to bosentan therapy (ie, never received bosentan therapy) and received tadalafil 40 mg had a significant improvement in 6MWD in the PHIRST-1 trial. There was no significant improvement when tadalafil was added to background bosentan therapy in patients. The authors concluded that a potentially critical reason for the lack of additional benefit seen with bosentan background therapy was the small sample size of the analysis. However, the authors also identified a biochemical mechanism, which may be responsible for the lack of benefit with this combination therapy, as bosentan is known to induce the CYP3A4 enzyme, which is responsible for breaking down tadalafil. Therefore, bosentan may indirectly cause increased breakdown of tadalafil, resulting in reduced serum concentrations of tadalafil and decreased benefit in the background bosentan

patients started on tadalafil.[12] Nevertheless, there was a clear need for subsequent randomized controlled trials for further evaluation of the potential benefits of tadalafil in combination therapy in patients with PAH.

A randomized, double-blind, placebo-controlled study evaluated the benefits of adding tadalafil in 124 stable patients who had previously received ambrisentan, an ERA, for 4 months. Patients were randomized to receive either a placebo or tadalafil 40 mg daily for 16 weeks in addition to ambrisentan therapy. The results showed that the tadalafil/ambrisentan group had a significant increase in the 6MWD from baseline to weeks 8, 12, and 16 and compared with placebo. However, the authors concluded that the data and small study size are insufficient to prove the additional therapeutic benefits of tadalafil add-on therapy. In addition, the authors mention that ambrisentan should theoretically be considered a stronger combination option with tadalafil as opposed to bosentan since ambrisentan does not induce CYP3A4 and should not affect tadalafil serum concentrations and therapeutic efficacy.[13]

In 2015, the Ambrisentan and Tadalafil in Patients With Pulmonary Arterial Hypertension trial in *The New England Journal of Medicine* investigated the effect of initial combination therapy with ambrisentan and tadalafil on long-term outcomes in 500 patients with PAH. Patients with World Health Organization (WHO) class II or class III symptoms of PAH who had not previously received treatment were randomized to receive initial combination therapy with ambrisentan 10 mg/tadalafil 40 mg, ambrisentan 10 mg/placebo, or tadalafil 40 mg/placebo. The primary end point was the time to the first event of clinical failure, which was defined as the first occurrence of a composite end point of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. The results showed a significant difference in the primary end point for the tadalafil/ambrisentan combination therapy group compared with the pooled monotherapy groups ($P < 0.001$). In addition, the results showed a significant improvement in the 6MWD (median change from baseline, 48.98 versus 23.8 m; $P < 0.001$) and a significant satisfactory clinical response ($P = 0.03$; defined as an increase of 10% from baseline in the 6MWD, with a reduction in symptoms to, or maintenance of, WHO functional class I or II and no events of worsening clinical condition before or at the week 24 visit) in the tadalafil/ambrisentan group. The authors concluded that in patients with PAH who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil results in a significantly lower risk of clinical failure events than the risk with ambrisentan or tadalafil monotherapy. However, it is important to note that the combination therapy group had more frequent adverse effects of peripheral edema, headache, nasal congestion, and anemia compared with monotherapy.[14] Nevertheless, the benefits of combination therapy in this patient population are still believed to outweigh the risks associated with treatment.

In 2024, another multicenter, randomized, double-blind, controlled trial investigated the potential benefit of using a combination therapy of macitentan, an ERA, and tadalafil in patients with PAH. The study used a fixed-dose combination of macitentan and tadalafil in a once-daily, single-tablet formulation to simplify treatment. The patients were either treatment-naive, on prior ERA monotherapy, or tadalafil monotherapy. Patients were randomly placed into macitentan/tadalafil combination therapy, macitentan monotherapy, or tadalafil 40-mg monotherapy. The primary end point was the change in PVR. The results showed that the tadalafil/macitentan combination group had a significant PVR reduction versus macitentan (29%; $P < 0.0001$) and versus tadalafil (28%; $P < 0.0001$). Adverse effects of anemia, hypotension, and edema were more frequent in the combination therapy group.[15] The authors concluded that the tadalafil/macitentan combination therapy significantly improved PVR versus monotherapies in patients with PAH, with a safety and tolerability profile consistent with the monotherapy groups.

In March 2024, the FDA-approved OPSYNVI, a single-tablet combination of tadalafil/macitentan, for the chronic treatment of adults with PAH (WHO group I and WHO functional classes II and III). This medication can be used as the initial treatment in patients with PAH who are treatment-naive or who are already on an ERA or PDE5 inhibitor.[16]

TADALAFIL USE IN HF

With tadalafil's proven benefits in multiple cardiovascular conditions, clinical researchers have sought to investigate whether tadalafil has any role in the treatment of HF. Current guideline-directed medical therapy for HF with reduced ejection fraction (EF) includes angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor, β-blockers, mineralocorticoid-receptor antagonists, and sodium-glucose cotransporter-2 inhibitors. There is active research in this area to identify more medications that can provide additional mortality benefits in this patient population.

The potential for tadalafil use in HF stems from previous animal studies showing that PDE5 inhibitors (eg, tadalafil and sildenafil) have protective effects in various animal models of cardiomyopathy. One of these early studies demonstrated that prophylactic administration of tadalafil delayed the onset of dystrophic cardiomyopathy in rats with Duchenne muscular dystrophy. However, it is still unclear whether tadalafil may have a similar benefit in humans with Duchenne muscular dystrophy, as this topic has not yet been investigated in a clinical trial.[17]

In 2019, researchers used a sheep model of advanced HF to evaluate any potential benefit from tadalafil use. The results showed that tadalafil treatment improved contractile function, restored the heart's response to catecholamines, and normalized brain natriuretic peptide mRNA levels, a marker of HF. From this study, the authors concluded that because tadalafil improves the indices of cardiac contractility and restores catecholamine responsiveness in this animal model of HF, it is worth further investigation in humans with HF.[18]

In 2021, researchers studied another animal model of ischemic cardiomyopathy in mice. Adult male mice underwent myocardial infarction (MI) by left coronary artery ligation and were then treated daily with either tadalafil or volume-matched 10% dimethyl sulfoxide (DMSO). The results showed that the tadalafil group had a significant reduction in infarct size, measured by 2,3,5-triphenyltetrazolium chloride staining, 24 hours after coronary artery ligation compared with the DMSO group. In addition, the tadalafil group had a smaller fibrotic area, assessed by Masson trichrome staining, compared with the DMSO group. The tadalafil group also had decreased apoptosis measured by Terminal Deoxynucleotidyl Transferase dUTP Nick-End Labeling assay compared with DMSO at 28 days post-MI. Finally, the tadalafil mice had reduced cardiac hypertrophy and pulmonary edema following infarction. The authors state that these parameters reflect diminished left ventricular (LV) adverse remodeling and preserved fractional shortening, which is an estimate of EF that is calculated by measuring the percentage change in LV diameter during systole, with tadalafil at 7 and 28 days post-infarction. Therefore, the authors concluded that tadalafil attenuates ischemic cardiomyopathy in mice and preserves LV function.[19]

In 2022, a study investigated the effects of tadalafil treatment in rats with HF. HF induction was completed by an aortocaval fistula, resulting in increased LV mass, increased LV end-diastolic volume, increased LV end-systolic volume, and a reduced EF. Tadalafil treatment in these HF rats resulted in decreased hypertrophy and

improvement of LV function.[20] These numerous animal studies on tadalafil's efficacy in HF reinforced the need for investigation of tadalafil in humans with HF.

A recent 2024 study, the Phosphodiesterase-5 Inhibition in Patients With Heart Failure With Preserved Ejection Fraction and Combined Post- and Pre-Capillary Pulmonary Hypertension trial, assessed the efficacy and safety of tadalafil in patients with HF with preserved EF (HFpEF) and combined postcapillary and precapillary PAH. While tadalafil has been FDA-approved for use in PAH, its benefit has not been well-studied in those with comorbid PAH and HF. Patients were randomized to receive either a target dose of tadalafil 40 mg or placebo. The primary end point in the study was the time to first composite event of adjudicated HF hospitalization or all-cause death. Unfortunately, the study was terminated prematurely due to an issue with the study's medication supply. The results obtained showed no significant difference in the primary end point between the 2 groups. In addition, the authors identified a possible signal of higher all-cause mortality in the tadalafil group. The authors concluded that this trial did not support tadalafil use in patients with HFpEF and combined postcapillary and precapillary PAH.[21] While this study showed no benefit in patients with comorbid HFpEF and PAH, further investigation is still needed to investigate tadalafil's effect in patients with HF with reduced EF or HFpEF without PAH.

While there currently is limited evidence available from clinical trials regarding tadalafil use in humans with HF, a retrospective, propensity-matched cohort study was completed to identify if tadalafil use in patients with ED and CAD is associated with differences in the incidence of HF, acute MI, or mortality. The study used the TriNetX Research Network to identify patients with International Classification of Diseases-10th Revision codes for CAD and ED but not PAH from January 2011 to December 2016. The patients were subdivided and analyzed according to known prescriptions for tadalafil, sildenafil, or no treatment for their ED. The outcomes of interest were 5-year rates of HF, acute MI, and mortality. Propensity matching was completed using baseline comorbidities of hypertension, ischemic heart disease, cerebral infarction, diabetes, and hyperlipidemia. The total patient count was 41,287 male patients, with 6751 on tadalafil, 12,214 on sildenafil, and 22,321 with no treatment. The results showed that the tadalafil and sildenafil groups were associated with a significant decrease in the incidence of HF, acute MI, and overall mortality compared with no treatment with PDE5 inhibitors. In a comparison between tadalafil and sildenafil, tadalafil was associated with a significant reduction in the incidence of HF, acute MI, and mortality versus sildenafil. The authors concluded that tadalafil use was associated with a significant reduction in the incidence of HF, MI, and mortality compared with sildenafil and no treatment, suggesting a meaningful clinical difference in drug choice between tadalafil and sildenafil for men suffering from ED and CAD, given that tadalafil may potentially provide further cardiovascular benefits.[22] Nevertheless, the results of this study warrant further investigation in a randomized clinical trial to better identify tadalafil's role in the prevention or treatment of HF.

TADALAFIL SIDE EFFECT PROFILE

Tadalafil is generally a well-tolerated medication, but it does have some very common side effects that patients should be notified about. The most reported side effect of tadalafil is a headache, most likely due to its vasodilatory effect on the cerebral vasculature. These headaches are generally transient but can range anywhere from mild to severe. Another common side effect of tadalafil is dyspepsia, characterized by indigestion and abdominal discomfort, most likely due to tadalafil's relaxation of the gastrointestinal smooth muscle. In patients with existing gastroesophageal reflux disease, tadalafil can cause worsening of acid reflux symptoms. Tadalafil can also cause muscle and back pain/discomfort, with an unclear mechanism potentially related to the relaxation of smooth muscle tissue in these parts of the body.[1]

Other side effects of tadalafil include hypotension, nasal congestion, flushing, nausea, and dizziness. An uncommon side effect of tadalafil can be blurry vision or alteration in color vision. In rare cases, tadalafil can cause nonarteritis anterior ischemic optic neuropathy that leads to sudden vision loss and permanent blindness in one or both eyes. Another uncommon side effect includes a sudden decrease or loss of hearing, with the potential for permanent hearing loss. One of the most severe side effects of tadalafil is priapism, a prolonged, painful erection lasting >4 hours, which occurs via the same mechanism by which tadalafil treats ED in this patient population. Priapism is a side effect that must be warned against and requires immediate medical attention to prevent permanent injury to the penile tissue. Other uncommon side effects of tadalafil include the development of a rash, urticaria, or swelling of the lips, tongue, or throat after the use of the medication.[1]

CONCLUSIONS

Tadalafil is approved for use in ED, BPH, and PAH based on proven efficacy in large randomized controlled trials. However, its cardiovascular benefits may potentially extend beyond these conditions. Research in HF animal models has demonstrated that tadalafil use results in improved LV function and contractility with reduced negative remodeling and hypertrophy. A retrospective cohort study identified that tadalafil use in patients with ED and CAD was associated with a significant reduction in the incidence of HF, acute MI, and mortality compared with sildenafil and no treatment. Unfortunately, because there are limited clinical trial data on tadalafil's impact on HF, further studies are needed on this topic to better identify whether tadalafil has a role in the prevention or treatment of HF.

ACKNOWLEDGMENTS

M.K. would like to thank Dr William H. Frishman and the Department of Medicine at New York Medical College for supporting this project.

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