Comment on "Bedaquiline-related QTc Prolongation in Multidrug Resistant Tuberculosis Patients: A Prospective Study"

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Dear Sir,

We read with considerable interest the article titled "Bedaquiline-related QTc Prolongation in Multidrug Resistant Tuberculosis Patients: A Prospective Study."[1] The authors should be commended for addressing an important safety concern regarding the use of bedaquiline in patients with multidrug-resistant tuberculosis (MDR-TB). Cardiac safety, particularly QT interval prolongation, remains a key issue during treatment with newer antitubercular agents, and studies focusing on this aspect are highly valuable. However, we would like to share a few observations regarding the findings reported.

In the present study, the authors reported an overall prevalence of QTc prolongation of 37.25%, with 13.7% of patients developing significant QTc prolongation. These rates appear somewhat higher than those reported in earlier studies.

For instance, Khan et al. conducted a large prospective cohort study involving MDR/rifampicin-resistant tuberculosis (RR-TB) patients from 16 countries who were treated with regimens containing bedaquiline and/or delamanid between April 2015 and September 2018.[2] The study evaluated the occurrence of clinically relevant QT prolongation (grade III or higher) or serious adverse events associated with QT changes. Among the 2,553 patients included in the study, 59% received bedaquiline and/or delamanid for more than 6 months. QT prolongation was observed in 579 patients (20.9%); however, most of these cases (95.5%) were mild, corresponding to grade I or grade II prolongation. Clinically significant QT prolongation was noted in only 64 patients (2.5%), while more severe prolongation occurred in 12 patients (0.5%). Notably, the majority of clinically relevant QT prolongation events were reported within the first 6 months of therapy.

Similarly, studies conducted in India have indicated that moderate to severe QT prolongation most commonly occurs around the third month of treatment. When compared with these findings, the overall incidence reported in the current study appears relatively higher (37.25% vs 20.9%).

The cardiac safety profile of bedaquiline has also been reviewed extensively by Gavras and Schluger.[3] Their analysis included studies evaluating bedaquiline both as monotherapy and in combination regimens. When administered alone in doses ranging from 100 to 400 mg per day, no QTcF increases >60 ms were observed, and QTcF values exceeding 500 ms were not reported.[4]

In recent years, bedaquiline has frequently been used together with delamanid in the management of drug-resistant tuberculosis. A multicountry cohort study conducted across 14 countries involving 472 patients assessed the safety of this combination therapy.[5] QTcF prolongation was observed in only seven patients (1.5%). Among them, two patients had QTcF values exceeding 500 ms without symptoms, while four experienced QT intervals >500 ms accompanied by clinical symptoms. These findings further support the generally acceptable cardiac safety profile of this combination regimen.

We concur with the authors that careful cardiac monitoring is essential when prescribing bedaquiline-containing regimens, particularly during the early months of treatment. Continued surveillance and larger prospective studies would be valuable in further clarifying the true magnitude of QT prolongation risk associated with these therapies.

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Reflections on Prosthetic Valve Thrombosis: Prevention and Evolving Therapeutic Strategies

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Dear Editor,

The recent article by Machigar et al., "Prosthetic Valve Thrombosis: Fibrinolysis, Surgery, or Percutaneous Manipulation?" offers an insightful and practical review of therapeutic strategies for prosthetic valve thrombosis (PVT).[1] The authors should be commended for addressing a complex and often life-threatening condition that continues to challenge clinicians worldwide. Beyond the valuable discussion on fibrinolysis, surgery, and emerging percutaneous options, this topic also invites reflection on the upstream and preventive aspects that remain pivotal in reducing the global burden of PVT.

Prevention of Rheumatic Fever and Rheumatic Heart Disease

In many low- and middle-income countries, rheumatic heart disease (RHD) remains the leading indication for valve replacement. This epidemiological reality underscores that the ultimate solution to the PVT burden lies not only in technological or procedural advances but also in the primary and secondary prevention of rheumatic fever. Sustained public health programs providing benzathine penicillin prophylaxis, early diagnosis of streptococcal pharyngitis, and community awareness can drastically reduce new cases of RHD and, consequently, the number of young patients who require mechanical prostheses. This preventive perspective—briefly alluded to in the authors' work—deserves renewed emphasis as the most cost-effective strategy for reducing PVT incidence globally.

Adequate Anticoagulation: The First Barrier against PVT

Once a prosthetic valve is implanted, anticoagulation management becomes the cornerstone of secondary prevention. Subtherapeutic international normalized ratio (INR) values remain the single most frequent and modifiable cause of prosthetic thrombosis. The article rightly highlights this issue, yet it cannot be overstated that maintaining an optimal time in therapeutic range (TTR) above 65–70% substantially decreases thrombotic and embolic events. In practice, patient education, systematic INR monitoring, and, where feasible, self-testing or community-based anticoagulation clinics should be implemented.[2] The inappropriate off-label use of direct oral anticoagulants in mechanical valve recipients must also be discouraged, as previous trials have demonstrated increased thrombotic complications in this context.

The Expanding Role of Thrombolysis and the "Ultraslow Low-dose" Paradigm

Machigar et al. present a balanced view of fibrinolysis as an established alternative to surgery for PVT, particularly in resource-limited settings. Over the past decade, the evolution of ultraslow low-dose alteplase regimens has markedly transformed the safety profile of thrombolytic therapy. Protocols involving infusions of 25 mg of alteplase administered over 24 hours (and repeated if necessary) have achieved thrombus resolution rates exceeding 85–90%, with major bleeding rates below 5%. These results compare favorably with both conventional fibrinolysis and emergency surgery. The physiological rationale—gradual thrombus dissolution minimizing sudden embolization—has been validated in multiple observational series and supported by current guideline recommendations for selected patients.

Importantly, this approach extends the therapeutic spectrum even to cases of left-sided mechanical valve obstruction with moderate hemodynamic compromise, in which surgery is either unavailable or carries prohibitive risk. The data emerging from Asian and Latin American centers, where such protocols originated, demonstrate that when meticulous monitoring is ensured, ultraslow thrombolysis represents an effective, reproducible, and safe strategy that aligns with the resource realities of many institutions.[3]

Surgery: Still Indispensable but Logistically Challenging

While fibrinolysis is gaining ground, surgery remains irreplaceable for certain clinical scenarios—patients with cardiogenic shock, large mobile thrombi, pannus formation, or failed thrombolysis.[4] Nevertheless, as Machigar et al. point out, the practical availability of emergency valve surgery is often restricted to tertiary centers. Reported operative mortality for urgent valve replacement ranges from 10 to 30%, especially when cardiogenic shock or severe pulmonary hypertension coexists. In contrast, when properly selected, fibrinolysis can achieve comparable survival with shorter hospital stays and lower cost. The challenge for clinicians, therefore, lies in a multidisciplinary, case-based decision that balances hemodynamic stability, thrombus morphology, and institutional capabilities.

Percutaneous Manipulation: Promise and Peril

The authors' mention of percutaneous mechanical interventions for prosthetic valve obstruction is particularly timely. Catheter-based disruption or balloon manipulation has been reported in small series, sometimes aided by cerebral protection devices to mitigate embolic risk. While such techniques may offer a lifesaving option in extreme scenarios—such as failed thrombolysis where surgery is not immediately feasible—the current evidence remains limited to case reports. The inherent risk of prosthesis damage or systemic embolization restricts these interventions to highly experienced centers. Nonetheless, their inclusion reflects an encouraging spirit of innovation, bridging interventional cardiology and cardiac surgery in a collaborative continuum.

A Hierarchical and Integrated Approach

The synthesis provided by Machigar et al. reinforces that the management of PVT should follow a hierarchical and integrated model, beginning with the prevention of RHD to reduce the need for prosthetic valve replacement, followed by meticulous anticoagulation to prevent thrombus formation. In hemodynamically stable patients, ultraslow low-dose fibrinolysis should be considered the first-line therapy, whereas surgical intervention remains essential for unstable or refractory cases. Finally, percutaneous manipulation may represent an investigational, last-resort strategy in highly selected contexts. Within this framework, therapeutic choice should be guided by echocardiographic findings, thrombus burden, and institutional readiness, under the coordination of a multidisciplinary "heart valve team" that includes cardiologists, cardiac surgeons, and imaging specialists.

Looking Ahead

The future of PVT management will likely involve hybrid strategies combining pharmacologic and interventional methods, enhanced imaging modalities for real-time assessment of thrombus resolution, and more refined risk stratification tools to predict response to fibrinolysis vs surgery. Equally important is global collaboration to improve access to INR monitoring, antibiotic prophylaxis for rheumatic fever, and registry-based data that capture the real-world performance of emerging therapies.

In summary, Machigar et al. contribute meaningfully to the ongoing dialogue on PVT by juxtaposing established and emerging treatment modalities. Their work implicitly reminds us that the most effective way to confront prosthetic thrombosis is not solely through procedural innovation but through comprehensive prevention—from rheumatic fever control to sustained anticoagulation vigilance. The integration of these preventive strategies with evolving therapeutic techniques defines the next frontier in reducing morbidity and mortality from PVT.

Authors' Contributions

Fidel Manuel Caceres-Loriga and Humberto Morais conceptualized and drafted the letter; both authors reviewed and approved the final version.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

None declared.

Funding

Not applicable.

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Most Important Barrier to Research Publication is Lack of Incentives and Motivation

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Dear Sir,

We read the important correspondence "Why Medical Doctors Hesitate to Write for Scientific Journals?"[1] with interest and feel that it could have been better if the authors had included the important factor of lack of incentives and motivation among Indian doctors to publish research papers or contribute to journals. There is a paucity of studies exploring the barriers and challenges faced by doctors in publishing their research papers, and whatever research has been done explores the barriers among those doctors who are already publishing their research.[2] The authors have rightly included time constraints, the complexity of the publishing process, lack of formal training in research and writing, fear of rejection and criticism, challenges in finding relevant research opportunities, and funding issues as the barriers to research publication.[1] But we feel that the authors should have included lack of motivation and lack of incentives as the most important barriers because if doctors are motivated enough and academic, promotional, and economic incentives are offered, most of the doctors will overcome the above-mentioned barriers and will publish their research. Most of the doctors today are products of commercial medical institutions charging obnoxiously high medical education fees, influenced by commercial considerations rather than academic or research considerations, and they work in profit-oriented corporate or private healthcare with little motivation for research publications. Therefore, we feel that unless there is a focus on research starting from undergraduate students, and unless various types of incentives are initiated for all doctors, both in medical colleges and in private practice, motivating them to initiate research and then publish, nothing much is going to change. The barriers to publishing papers enumerated by the authors are no doubt important, but they are secondary to lack of motivation and incentives. India needs a revolutionary change in medical education and research to encourage research publications on par with Western or Chinese research publications.

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