relate their observation that Holter abnormalities typically precede structural findings on imaging. In our clinical practice, and borne out by the data from our study, pediatric patients rarely fulfill the major criterion for arrhythmias. Arrhythmias as a minor criterion were more prevalent but did not distinguish between the different diagnostic certainty groups.

Dr. te Riele and colleagues highlight that at the time of data collection, only 49 of 142 patients had undergone genetic testing. Despite the undisputed value of genetic testing both within and outside of the Task Force Criteria, important limitations of genetic testing must be recognized: up to 50% of ARVC patients are gene-elusive, and 30% to 40% of gene-positive patients remain nonpenetrant well into adulthood (5). Thus, at present, the presence of an ARVC mutation cannot provide an alternate standard for the presence of ARVC disease.

Once again, we would like to thank Dr. te Riele and colleagues for their critical review of our work and for highlighting important areas for future research. In a disease that contributes significantly to pediatric and young adult sudden death, and which, once established in the adult, is likely difficult to reverse, improvements in pediatric diagnosis will be paramount.

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Management of Patients With Prosthetic Valve Thrombosis After Failed Thrombolytic Therapy

We would like to comment on the recent article by Karthikeyan et al. (1), which reports the outcome of oral anticoagulation in patients followed-up after failure or partial response to thrombolytic therapy (TT) for prosthetic valve thrombosis (PVT). Although we appreciate the authors’ work because they specify important data regarding the follow-up of PVT patients after TT for the first time, there remain some major drawbacks to be addressed.

The statement that about one-third of the patients treated with TT do not have successful restoration of valve function is not comparable with the most recent evidence reporting success rates of >85% in patients with PVT (2–5). Moreover, they argue that surgery is more effective than TT, which contradicts the data reported in the most recent meta-analysis by Castilho et al. (5). Clinicians should be cautious of overemphasizing the efficacy of surgery over TT for PVT, unless the results of randomized and controlled trials are available. We are currently conducting a randomized controlled trial (NCT02243839), a head-to-head comparison of outcomes of TT and surgery, which we feel will provide invaluable data in this regard.

Complete normalization of valve leaflet motion on fluoroscopy and valve gradients on echocardiography may not be a sure sign of complete normalization of valve function. Such patients may still have a significant but “Doppler silent” thrombus burden requiring further treatment with TT, because the risk of reobstruction or embolism continues. As the authors report, reduction in valve gradients may not be associated with the occurrence of adverse outcomes. The use of serial transesophageal echocardiography (TEE) is indispensable for quantitative visualization of thrombus burden in patients with PVT. Hence, TEE should play a central role in every step of management in patients with PVT, including the initial diagnosis, guidance of therapy, evaluation of the outcome, and identification of patients who are at high risk of adverse events.

In the current study, the authors report 31 eligible patients of 122 patients undergoing TT. This means a 74.6% TT success rate at most, which is relatively low compared with current evidence (2–5). This may be caused by the type of TT agents or protocols used in the current study. We have
previously reported that repeated doses of low-dose (25 mg) and slow infusion (6 h) alteplase under the guidance of serial TEE was superior to faster infusion and/or higher dose protocols or streptokinase (2). This protocol provided favorable results even in pregnant patients with PVT (3). In addition, we have very recently reported that ultra-slow (25 h) infusion of low-dose (25 mg) alteplase without bolus appears to be associated with quite low complications and mortality for PVT patients without compromising post-thrombolytic success, except for those with New York Heart Association functional class IV. The TT success rate was 90% in this study (4).

We agree with the authors that the rate of adverse events is high in PVT patients followed with oral anticoagulation after failed TT. Although the improvement of New York Heart Association functional class at least 1 step was associated with lower major complication rates, the number of patients is too small to draw a conclusion that reoperation may be delayed in these patients. We believe that reserving oral anticoagulation only for those with nonobstructive left-sided PVT who are not candidates for TT or residual small thrombi after TT may be a more plausible strategy. We are currently conducting a randomized controlled trial comparing the efficacy and safety outcomes of 3 different treatment strategies, including intensified warfarin only, warfarin plus 100 mg acetylsalicylic acid, and warfarin plus 300 mg acetylsalicylic acid (NCT02240953), which we believe will clarify the uncertainty in the management of patients with nonobstructive PVT.

Consequently, PVT patients with spontaneous normalization of valve gradients may still be at risk of adverse events due to residual thrombus burden, which only may be assessed by serial TEE. Hence, referral to surgery should not be delayed with the expectation of spontaneous valve opening in such patients.

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