heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75 mg dose in non-carriers; in contrast, for *CYP2C19**2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition.

Perspective

It is an established fact that those patients who have high platelet reactivity while on clopidogrel are at a higher risk of cardiovascular events including stent thrombosis. The reason for higher platelet reactivity includes importantly loss-of-function *CYP2C19* allele. This gene decides the rate of conversion of clopidogrel pro-drug to active form. Platelet function testing has raised a lot of hope that we might by tailoring the dose overcome this problem. However, major trials which involved platelet function testing and gene testing failed to show improvement in clinical end-points. The GRAVITAS trial failed to show improvement in clinical end-points. The TRIGGER-PCI was halted midway for the same reason. However, the final word whether platelet function testing is useful or not has not been said. Further trials like TARGET-PCI are likely to clarify the issue. Newer P2Y₁₂ inhibitors like prasugrel and ticagrelor by their more powerful action might make these tests redundant.

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1. Risk stratification in Brugada syndrome. Results of the PRELUDE (PRogrammed ELectrical stimulation preDICTive valuE) Registry.

Priori SG, Gasparini M, Napolitano C, et al.
J Am Coll Cardiol 2012;59:37–45.

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Study question: Would inducibility of sustained ventricular tachycardia/ventricular fibrillation (VTs/VF) by programmed electrical stimulation (PES) accurately predict arrhythmic events in asymptomatic Brugada syndrome patients?

Methods: This was a prospective Italian registry of 308 patients (80% men, median age 44 years) with a spontaneous or drug-induced type I Brugada electrocardiogram (ECG) and without history of cardiac arrest. The PES was performed at enrolment, and patients were followed up every 6 months.

Results: During a median follow-up of 34 months, 14 arrhythmic events (4.5%) occurred (13 appropriate implantable defibrillator shocks, and one resuscitated cardiac arrest). History of syncope and spontaneous type I ECG (hazard ratio [HR]: 4.20), ventricular refractory period ≤ 200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) were significant predictors

of arrhythmias. The PRELUDE was able to induce ventricular arrhythmias in 40% patients; however, arrhythmia inducibility was not a predictor of events at follow-up (9 of 14 events occurred in non-inducible patients).

Conclusion: Inducibility of VT/VF is unable to identify candidates for prophylactic implantable defibrillator therapy in Brugada syndrome patients who have not experienced arrhythmic events.

Perspective

In this PRELUDE registry, data of Brugada syndrome patients without previous arrhythmic events, rate of events during follow-up is much lower: 1.5%/year versus 4.1%/year previously reported (Brugada et al. *Circulation* 2003;108:3092–6). As is well-known, occurrence of Type I Brugada ECG pattern in combination with history of syncope was a strong predictor of arrhythmic events. New findings in this study are that a short ventricular effective refractory period ≤ 200 ms and fragmented QRS are independent risk indicators for life-threatening events. Programmed electrical stimulation, irrespective of the number of premature beats used, is not predictive of arrhythmic events.

2. Distinguishing 'benign' from 'malignant early repolarization': the value of the ST-segment morphology.

Rosso R, Glikson E, Belhassen B, et al.
Heart Rhythm 2012;9:225–9.

doi: 10.1016/S0019-4832(12)60073-X

Study question: Can the very common 'benign early repolarisation' be distinguished from the very rare but malignant form associated with idiopathic ventricular fibrillation (VF)?

Methods: This was a case control study of 45 idiopathic VF patients, 124 controls matched for age and sex, and 121 young athletes. Patients with J-point elevation on ECG were taken and their ST-segment morphology was graded as either 'horizontal' or 'scending'. ST-segment patterns were coded as 'concave/rapidly ascending' when there was ≥ 0.1 mV elevation of the ST-segment within 100 ms after the J-point or as 'horizontal/descending' when the ST-segment elevation was ≤ 0.1 mV within 100 ms after the J-point).

Results: J-waves were more prevalent among patients with idiopathic VF than among age- and sex-matched controls (42% vs 13%; $P \leq 0.001$) or among young athletes (42% vs 22%; $P \leq 0.013$). Of the 19 idiopathic VF patients with J-waves 13 (68.4%) had horizontal ST-segments; in contrast, only 4 (25%) of the 16 age-matched controls and 4 (14.3%) of the 28 young athletes with J-waves had a horizontal ST-segment.

Conclusion: The OR for having idiopathic VF for patients with J-waves was 4.0 (95% CI=2.0–7.9), but having J-waves and horizontal ST-segment has an odds ratio of 13.8 (95% CI=5.1–37.2). Despite the increased risk predicted by combination (of J-point elevation and horizontal ST-segment), using Bayes Theorem of conditional probabilities, estimated odds for developing idiopathic VF for an individual in the age

range of 35–45 years (even if he has both criteria) is only 34 in 100,000 or 0.03%.

Perspective

Previous studies by Tikkanen et al. (NEJM 2009;361:2529–37) reported that location of the early repolarisation pattern in the inferior leads and amplitude of the J-point elevation ≥ 0.2 mV had adverse prognostic value. This study adds ST-segment morphology analysis to risk stratify people with J-point elevation on ECG to differentiate 'benign' from 'malignant' form of early repolarisation syndrome.

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1. Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation. The APPROPRIATE study (ACE inhibitors for potential prevention of the deleterious effects of pulmonary regurgitation in adults with repaired tetralogy of Fallot).

Babu-Narayan SV, Uebing A, Davlourous PA, et al.
Inter J Cardiol 2012;154:299–305.

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There is no consensus on optimal medical treatment and timing of pulmonary valve replacement for stable repaired tetralogy of Fallot (rTOF) patients with pulmonary regurgitation (PR) and consequent right ventricular (RV) dilatation. This randomised double-blind placebo study from United Kingdom aimed at studying the tolerability of the angiotensin-converting-enzyme (ACE) inhibitor, ramipril and its effect on cardiovascular function in rTOF patients. Clinically, stable rTOF patients with moderate/severe PR were included with 6 months follow-up. Cardiovascular magnetic resonance (CMR), echocardiography, neurohormonal analysis, and objective cardiopulmonary exercise testing were done at baseline and at follow-up.

Cardiovascular magnetic resonance-derived RV ejection fraction (EF) was considered the primary end-point. Seventy-two patients were enrolled of whom final analysis was performed on 64. Though, there was no difference in the primary end-point RV, i.e., EF, RV long-axis shortening improved significantly in the ramipril group compared to placebo (RV: 2.3 ± 3.8 vs 0.02 ± 2.7 mm; $P=0.017$) as did left ventricular (LV) long-axis shortening (1.9 ± 4.5 vs -0.2 ± 3.7 mm respectively; $P=0.030$). Other measurements did not differ in two groups. Patients on ramipril, compared to controls showed decrease in LV end-systolic volume index (-2.4 ± 5.0 vs 2.7 ± 3.6 mL/m²; $P=0.005$) and increase in LVEF (2.5 ± 5.0 vs -1.3 ± 3.5 ; $P=0.03$) in subgroup with restrictive RV physiology. Ramipril did not cause adverse events and was well-tolerated. Authors concluded that ramipril is a well-tolerated therapy, improves

biventricular function in patients with rTOF and may have a particular role in patients with restrictive RV physiology. Larger, longer term studies are needed to determine if ACE inhibitors can improve both ventricular remodelling and clinical outcomes.

Comment

Advances in diagnosis and management of congenital heart disease have resulted in an ever increasing adult cohort of rTOF patients. The PR subsequent to TOF repair though can be well-tolerated for several years, is a major cause of late morbidity in this population. Taking cues from beneficial effects of ACE inhibition in various conditions, authors undertook this randomised placebo-controlled study to look at tolerability, feasibility and efficacy of such therapy in these patients. Six months of ramipril therapy did not show improvement in RVEF. However, it was well-tolerated and did result in an increase in biventricular longitudinal systolic function. The ACE inhibition in patients with restrictive RV filling showed reduction in LVESVi and improvement in LVEF. Despite limited number of patients included, a relatively short follow-up and not so robust data to support benefit, this randomised trial has paved the path for future studies. This strategy of ACE inhibition, if found useful; can help deferring deleterious effects of PR in rTOF patients and thereby postponing pulmonary valve replacement.

2. Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicenter survey.

van Geldorp IE, Delhaas T, Gebauer RA, et al.
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Chronic right ventricular (RV) pacing is associated with deleterious effects on cardiac function. This observational multicentre study by Geldrop et al. looked at the importance of the ventricular pacing site on left ventricular (LV) function in children with isolated atrioventricular (AV) block receiving chronic ventricular pacing. Demographics, maternal autoantibody status, and echocardiographic measurements on LV end-diastolic and end-systolic dimensions and volumes at age <18 years were collected retrospectively from patients who have undergone ventricular pacing >1 year ago for isolated AV block. The LV contractility was assessed using LV Fractional Shortening (LVFS) and, if possible LV ejection fraction (LVEF) analysis. Linear regression analyses were adjusted for patient characteristics. Two-hundred and ninety-seven children from 27 centres were included, in whom pacing was applied at the RV epicardium (RVepi, $n=147$), RV endocardium (RVendo, $n=113$) or LV epicardium (LVepi, $n=37$). LVFS was significantly affected by pacing site ($P=0.001$), and not by maternal autoantibody status ($P=0.266$). The LVFS in LVepi ($39 \pm 5\%$) was significantly higher than in RVendo ($33 \pm 7\%$, $P<0.001$) and RVepi ($35 \pm 8\%$, $P=0.001$; no significant difference between