diffusion-weighted MRI, demonstrated that the incidence of new ischaemic lesions was 87% in the filter group versus 45% in balloon group. Clinically, although only one patient had a minor stroke in the filter group versus none in balloon group, it may not be practical to use a MO.MA device in every case. The study establishes the logic behind it.

3. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification.

Lancellotti P, Magne J, Donal E, et al.
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Objective: This study examined the clinical course of patients with asymptomatic severe aortic stenosis (AS) according to the new proposed aortic valve stenosis (AVS) grading classification.

Background: The management of patients with asymptomatic severe AS remains controversial. Moreover, under the same denomination of severe AS, several entities might be identified according to transvalvular flow rates and pressure gradients, resulting in four flow-gradient patterns.

Methods: Transthoracic echocardiography and measurement of B-type natriuretic peptide (BNP) level from venous blood sample were performed in 150 consecutive patients with asymptomatic severe AS and normal exercise test. Patients were classified in four groups, depending on left ventricular (LV) flow state (normal flow [NF] vs low flow [LF]: 35 mL/m²) and pressure gradient levels (low gradient [LG] vs high gradient [HG]: 40 mmHg).

Results: Patients with NF/LG had significantly lower BNP than those with LF/HG and LF/LG. The mean follow-up was 27–12 months. At 2 years, cardiac event-free survival was 83–6%, 44–6%, 30–12%, and 27–13% in NF/LG, NF/HG, LF/HG, and LF/LG groups, respectively ($P=0.0001$). On multivariable analysis, LF/LG (hazard ratio [HR]: 5.26, 95% confidence interval [CI]: 2.04–14.3, $P=0.045$) and LF/HG (HR: 2.38, 95% CI: 1.02–5.55, $P=0.001$) were identified as strong independent determinants of poor prognosis as compared with NF/HG. By limiting the multivariable analysis to patients with LF, LF/LG was an independent predictor of markedly reduced cardiac event-free survival when compared with LF/HG (HR: 5.4, 95% CI: 1.03–28.6, $P=0.046$).

Conclusion: The use of the new proposed AS grading classification integrating valve area and flow-gradient patterns allows a better characterisation of the clinical outcome of patients with asymptomatic severe AS.

Perspective

This is a very elegantly done study involving asymptomatic patients with severe AS with ejection fraction (EF) >55%. The study goes on to prove that all these patients are not to be clubbed as one. The group which had LF and LG had the worst outcome and also the highest BNP levels (the so-called paradoxical LF/LG group with normal EF). The group which had

HF and LG had the best outcome with lowest BNP levels. The other two groups with HGs had intermediate outcome. The study highlights the importance of taking all the parameters together including flow, gradient, and natriuretic peptide levels. The EF is just one of the many parameters of LV function that should be taken into consideration while determining the prognosis and further treatment.

4. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease.

Mega JL, Sabatine MS.
JAMA 2011;306:2221–8.

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Context: Variants in the *CYP2C19* gene influence the pharmacologic and clinical response to the standard 75 mg daily maintenance dose of the antiplatelet drug clopidogrel.

Objective: To test whether higher doses (up to 300 mg daily) improve the response to clopidogrel in the setting of loss-of-function *CYP2C19* genotypes.

Design, setting, and patients: ELEVATE-TIMI 56 was a multi-centre, randomised, double-blind trial that enrolled and genotyped 333 patients with cardiovascular disease (CVD) across 32 sites from October 2010 to September 2011.

Interventions: Maintenance doses of clopidogrel for four treatment periods, each lasting approximately 14 days, based on genotype. In total, 247 non-carriers of a *CYP2C19**2 loss-of-function allele were to receive 75 mg and 150 mg daily of clopidogrel (two periods each), whereas 86 carriers (80 heterozygotes, six homozygotes) were to receive 75 mg, 150 mg, 225 mg, and 300 mg daily.

Main outcome measures: Platelet function test results (VASodilator-Stimulated Phosphoprotein [VASP] phosphorylation and verify now P2Y₁₂ assays) and adverse events.

Results: With 75 mg daily, *CYP2C19**2 heterozygotes had significantly higher on-treatment platelet reactivity than did non-carriers (VASP platelet reactivity index [PRI]: mean, 70.0%; 95% CI, 66–74.0%, vs 57.5%; 95% CI, 55.1–59.9%, and verify now P2Y₁₂ reaction units [PRU]: mean, 225.6; 95% CI, 207.7–243.4, vs 163.6; 95% CI, 154.4–173.9; $P<0.001$ for both comparisons). Among *CYP2C19**2 heterozygotes, doses up to 300 mg daily significantly reduced platelet reactivity, with VASP PRI decreasing to 48.9% (95% CI, 44.6–53.2%) and PRU to 127.5 (95% CI, 109.9–145.2) ($P<0.001$ for trend across doses for both). Whereas 52% of *CYP2C19**2 heterozygotes were non-responders (≥ 230 PRU) with 75 mg of clopidogrel, only 10% were non-responders with 225 mg or 300 mg ($P<0.001$ for both). Clopidogrel, 225 mg daily, reduced platelet reactivity in *CYP2C19**2 heterozygotes to levels achieved with standard clopidogrel, 75 mg, in non-carriers (mean ratios of platelet reactivity, VASP PRI, 0.92; 90% CI, 0.85–0.99, and PRU, 0.94; 90% CI, 0.84–1.04). In *CYP2C19**2 homozygotes, even with 300 mg daily of clopidogrel, mean VASP PRI was 68.3% (95% CI, 44.9–91.6%) and mean PRU, 287 (95% CI, 170.2–403.8).

Conclusion: Among patients with stable CVD, tripling the maintenance dose of clopidogrel to 225 mg daily in *CYP2C19**2

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.
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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.

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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