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.
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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