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The patient with hypertrophic cardiomyopathy has a family

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FEATURED CORRESPONDENCE

Propafenone contraindicated in the elderly?

To the Editor With great interest we read the paper by Alboni *et al.*¹ The investigators studied intravenous class Ic antiarrhythmic drug (AAD) administration (propafenone and flecainide) as a predictor for adverse effects when used in a 'pill-in-the-pocket' regimen (PITP).

Alboni and colleagues suggest that intravenous administration of flecainide or propafenone for pharmacological conversion of atrial fibrillation to sinus rhythm cannot predict the occurrence of adverse effects when these agents are subsequently used in a PITP treatment modality. In fact, intravenous AAD administration was accompanied by a 6% incidence of serious adverse effects when the AAD was used as an oral compound, particularly with propafenone. The authors concluded that clinical intravenous drug testing should not be used as a safety indicator for PITP approach.

First, the pharmacological and pharmacokinetic profile of flecainide differs from propafenone, particularly with respect to the intrinsic adrenergic receptor blocking actions.²⁻³ As the authors mentioned in the discussion section, only propafenone caused serious side effects requiring hospital admission. In addition, in the majority of cases these side effects were related to bradyarrhythmic phenomena. In our opinion, this is a very important observation with clinical implications. Second, the observed bradyarrhythmic side effects of propafenone only occurred in elderly, at least one SD above the mean study population age. In this age group latent sick sinus syndrome may be present and may become manifest by using drugs with intrinsic β -blocking properties (eg, propafenone). Did the authors consider further specifying the study conclusion for octogenarians, or use 24 h Holter criteria before intravenous infusion to preselect subjects with increased risk for bradyarrhythmic complications? Third, might the simultaneous use of other cardiovascular agents like ARBs, ACE inhibitors or β -blocking agents have interfered with propafenone in causing bradyarrhythmic or hypotension-related side effects?

In our opinion, the take-home message that intravenous drug testing, in general, should not be used to predict PITP adverse effects, is not demonstrated by the current data. Rather, the current data emphasise that further investigations are necessary to specify patient selection criteria for safe PITP use with propafenone in the treatment of paroxysmal atrial fibrillation.

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Competing interests None.

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The Authors' reply We thank Drs Kirchhof, Crijns and van Gelder¹ for their interest in our paper² referring to pill-in-the-pocket treatment of recent-onset atrial fibrillation (AF). The study was interrupted on the recommendation of the data- and safety-monitoring committee because the results suggested that the intravenous administration of flecainide or propafenone does not predict the occurrence of adverse effects after a loading oral dose of these drugs. A 5% incidence of major side effects during the first out-of-hospital treatment was regarded as high, considering that such patients have haemodynamically well-tolerated episodes of AF. All the patients showing major side effects during the first loading oral dose were receiving treatment with propafenone. No patient receiving flecainide had major adverse effects; however, only 20 patients were receiving treatment with this drug. This patient population is too small to draw conclusions about whether tolerance to intravenous administration of flecainide may predict the safety of the pill-in-the-pocket treatment. We wrote² that "further data on larger population samples should be collected in order to assess the predictive ability of an intravenous testing with flecainide".

We agree with Dr Kirchhof *et al* that the bradyarrhythmias observed after a loading oral dose of propafenone may be an expression of a latent sick sinus syndrome. The four patients showing major adverse effects during the first out-of-hospital treatment were about 70 years old and this suggests that the pill-in-the-pocket treatment cannot be indicated in the elderly because in this age group latent sick sinus syndrome may be more common. However, because of the premature interruption of the study, the patient population is too small to draw any conclusion.

We carried out the study because the pill-in-the-pocket approach is underused since

the guidelines³ recommend an in-hospital loading oral dose of flecainide or propafenone as a screening for the out-of-hospital self-administration, but the doctors of the emergency rooms prefer intravenous administration, which has a more rapid action than the time-consuming oral administration. In the real world, the recording of 24 h ECG before intravenous administration of the drug is not feasible; moreover, we believe that a prolonged ECG recording during AF is not useful to identify patients with latent sick sinus syndrome. Only seven patients were treated with β blockers and none took verapamil or diltiazem. None of the four patients showing major adverse effects during the first out-of-hospital treatment took β blockers. We did not report the use of ACE inhibitors and angiotensin receptor blockers because in the first pill-in-the-pocket study⁴ no correlation between the use of these drugs and major side effects was seen.

In our opinion, present knowledge suggests that patient's tolerance for intravenous administration of propafenone does not seem to predict adverse effects during out-of-hospital self-administration of this drug. At present, a predictive ability of intravenous testing with flecainide is not yet proved.

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The patient with hypertrophic cardiomyopathy has a family

To the Editor We have read the paper on hypertrophic cardiomyopathy (HCM) by ten Berg *et al* with great interest.¹ As the paper

has an educational aim, we would like to address some minor misconceptions that could have major implications.

Genotyping in HCM to establish a molecular diagnosis in HCM patients can indeed probably not be used to guide prognosis or therapy. However, it has been proved to be a more cost-effective strategy than cardiac screening to identify relatives at risk.² This is mainly due to the inability of ECG and echocardiography to exclude a future risk of HCM, which is possible by genotyping, because contrary to what the authors state hypertrophy in relatives often develops after adolescence. Studies in HCM mutation carriers have shown that disease penetrance increases with age and a significant subset of carriers develops hypertrophy well into adulthood.^{3–4} Unfortunately the misconception that hypertrophy does not develop after adolescence is still around leading to inappropriate cardiac care and sometimes even sudden cardiac death, because relatives are incorrectly discharged from cardiac follow-up.

The incomplete and age-dependent disease penetrance together with the clinical heterogeneity of the disease also explain why many HCM patients do not know of any affected relatives. The latter is therefore probably not due to sporadic mutation and more complex patterns of inheritance as the authors suggest. With the current knowledge the main causal genetic defect seldom arises de novo and is usually inherited in an autosomal dominant way. Individuals without the disease-causing mutation therefore do not have an increased risk of developing HCM and carriers do. Clinical heterogeneity and disease penetrance, however, are likely to be influenced by genetic modifiers, which still need to be identified. Hopefully, future genetic research in HCM will enable us to predict the phenotype and prognosis better in the individual HCM patient or carrier of a disease-causing mutation.

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The Authors' reply We thank Christiaans and coworkers for their critical review of our paper on hypertrophic cardiomyopathy (HCM).¹ We fully agree—as is stated in our paper—that genotyping is useful to identify relatives at risk while ECG and echocardiography are often unable to exclude HCM. As we also stated, it is recommended to repeat ECG and echocardiographic evaluation every 5 years even in adults without hypertrophy because hypertrophy can develop after the end of adolescence. In our experience, however, the incidence of patients developing hypertrophy late in life is low. We appreciate the additional information that it is probably not sporadic mutations but the influence of modifier genes on the autosomal inherited trait that explains the heterogeneity of the penetrance of HCM.

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Competing interests None to declare.

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What is the best dose of aspirin in association with P2Y12 antagonists?

To the Editor In their Viewpoint article, Warner *et al*¹ hypothesised that the administration of aspirin to patients who are treated with potent antagonists of the platelet P2Y12 receptors might increase cardiovascular risk. The authors' hypothesis is based on the observation that P2Y12 antagonists inhibit the platelet production of thromboxane A2 (TxA2) (which would render the use of aspirin superfluous), and on the consideration that aspirin may cause adverse effects. It is my opinion that there is no evidence yet to suggest that aspirin is superfluous or even detrimental when administered in combination with P2Y12 antagonists. In fact, the inhibition of TxA2 production by P2Y12 antagonists in mono-

therapy is incomplete and may be insufficient to inhibit the TxA2-dependent component of thrombus formation. The clinical relevance of effective TxA2 inhibition is demonstrated by the extremely good efficacy of aspirin in patients with acute coronary syndromes,² which, in my opinion, was underestimated by Warner *et al*.¹ I think that the real question is not whether or not aspirin should be associated with P2Y12 antagonists, but rather, what is the best dose of aspirin to be used in association. We recently showed that inhibition of the platelet P2Y12 receptor potentiates the antiplatelet effect of prostacyclin and hypothesised that this effect may substantially contribute to the antithrombotic efficacy of P2Y12 antagonists.³ As aspirin, at high doses, inhibits the endothelial production of prostacyclin, it can be hypothesised that the higher the dose of aspirin used in combination with P2Y12 antagonists, the lower will be the prostacyclin-dependent antithrombotic activity of P2Y12 antagonists.³ The results of the PLATO trial, which showed that high-dose aspirin tended to be less effective than low-dose aspirin in acute coronary syndrome patients treated with the potent P2Y12 antagonist, ticagrelor,¹ are compatible with our hypothesis and with the suggestion by Warner *et al*¹ that high-dose aspirin may be more detrimental when associated with potent P2Y12 antagonists. However, the results of the CURRENT OASIS-7 trial, which showed that high-dose aspirin was more effective than low-dose aspirin in combination with high-dose clopidogrel (but not with standard dose clopidogrel), oppose it.⁴ Therefore, the issue of the best dose of aspirin to be associated with P2Y12 antagonists can only be settled by the results of properly designed experimental studies.

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