

Refinements and clarifications in the Modernized Oxford classification of anti-arrhythmic drugs

We are very grateful for the correspondents' constructive comments and suggestions, viewing our drug classification system¹ as a dynamic work open to amendment and development in the light of current and future advances in the underlying fundamental science and its clinical translation. Furthermore, their letter draws attention to issues we ourselves encountered when writing our article, which will likely influence future revision. First, it was difficult to do full justice to enormous number of K⁺ channel subtypes, identified and characterized since the Vaughan-Williams classification. Our article did allude to inward rectifying *I*_{K1}, and two-pore channels mediating K2P currents in the text, additional to the more familiar voltage-gated K⁺ channels. Nevertheless, we agree Table 1 or supplemental Table 3 themselves could also elaborate on these in addition to considering the small-conductance Ca²⁺-activated K⁺ channels, under Class III. Similarly, our class V cites investigational drugs related to mechanosensitive channels. Finally, we ourselves contemplated further intracellular sites targeted by inhibitors of p21-activated kinase-1 and synthesis or actions of Ca²⁺ mobilizing agents including inositol *tris*-phosphate, cyclic adenosine diphosphate ribose and nicotinic acid adenine dinucleotide phosphate for possible inclusion under class IV³,

We also faced terminological issues arising from adopting single defined 'principal' actions for each specific drug when this definition often actually originated from historic experimental or clinical use. This approach nevertheless provided simplifications valuable for constructing Table 1 and supplemental Table 2 with Table 2 summarizing their multiple actions. Flecainide and propafenone were indeed the exceptions. The cardiac literature identifies flecainide by its Na⁺ channel blocking action², but its recent application modulating ryanodine receptor activation originated from its chemical parallels with the established excitation-contraction coupling blocker tetracaine. There was also its successful recent clinical monotherapeutic application in treating catecholaminergic polymorphic ventricular tachycardia⁴. These points prompted our exceptionally including it in *both* class Ic and class IVb.

Similar terminological compromises also arose distinguishing *approved* drugs, appropriate for Table 1 and supplemental Table 2, and *investigational new drugs* for listing in supplemental Table 3. Thus, the class IIIb K_{ATP} channel openers nicorandil and pinacidil are *approved* as smooth muscle vasodilators in hypertension and angina, but likely would be regarded as *investigational agents* for anti-arrhythmic therapy⁵.

Finally, our article focussed mainly on management of, and off-target effects bearing on the problem of cardiac arrhythmias as posing difficult and important issues meriting attention in their own right. Nevertheless we are grateful for your correspondents' suggestion to extend our classification to capture clinically important multiple effects of anti-arrhythmic medication on other aspects of cardiac physiology, or function in other organ systems, whilst recognizing that this will be an enormous task. Similarly, we also would value inclusion of previously unexplored natural products including traditional Chinese anti-arrhythmic medicine, once information from well controlled clinical trials become available. We finally thank the correspondents for spotting typographical errors which we will correct to enhance the reliability and therefore usefulness of the information we have collated in the process of producing this modernized classification.

{500 words}

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