

Do not consider amiodarone, give it!

Comment on antiarrhythmic drugs for shock-refractory ventricular fibrillation or pulseless ventricular tachycardia

To the Editor Cardiac arrest is an event of such speed and intensity that predetermined management guided by algorithms is likely needed to provide a meaningful chance of survival. Current European and North American guidelines call for immediate and effective cardiopulmonary resuscitation (CPR) and rapid delivery of defibrillation for shockable rhythms (ie, ventricular fibrillation [VF], pulseless ventricular tachycardia [pVT]).^{1,2} Definitive airway management follows closely. The use of drugs in cardiac arrest, however, remains controversial.

Epinephrine remains recommended, while vasopressin has been removed from the guidelines as single vasoactive therapy in cardiac arrest. The use of antiarrhythmic drugs (ie, amiodarone or lidocaine) for VF/pVT is recommended in European guidelines, and North American guidelines suggest these medications be considered under such circumstances when defibrillation and epinephrine have not restored spontaneous circulation.^{1,2} However, the evidence to support these recommendations is of low to very-low quality with an overall lack of information on long-term patient important outcomes.³ Recently, the results of a study by the Resuscitation Outcomes Consortium of amiodarone versus lidocaine versus placebo in patients with out-of-hospital shock-refractory VF or pVT cardiac arrest have provided some new insights into this clinical question.⁴

In this study, adults with nontraumatic, shock-refractory, out-of-hospital VF and pVT were randomized to receive amiodarone, lidocaine, or placebo. By way of cointervention, approximately 25% to 30% of patients in each group received intravenous bicarbonate, and between 5% and 10% received procainamide before hospital admission. Approximately 75% of patients admitted to the hospital were treated with targeted temperature management and approximately 55% of them had coronary angiography in the first 24 hours. In this study population, between 20% and 25% of all such patients were discharged from the hospital, with between 16.6% and 18.8% having favorable neurological outcome. There was no

significant difference between the 3 study groups in the primary outcome at discharge from the hospital, or the secondary outcome of favourable neurologic status at discharge.

The authors of the study concluded that “Overall, neither amiodarone nor lidocaine resulted in a significantly higher rate of survival or favorable neurologic outcome than the rate with placebo among patients with out-of-hospital cardiac arrest due to initial shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.”⁴ However, this statement may be misleading. Here the devil is, as usual, in the details.

First, the overall lack of statistical significance brings an issue of clinical interpretation of that very concept. The 3.2% absolute difference in survival to discharge between amiodarone and placebo (and 2.6% between lidocaine and placebo) is nonsignificant (P values of 0.08 and 0.16, respectively). However, if this is a real difference, it is very likely of clinical importance. Similarly, a 2.2% absolute difference in favorable neurological outcome in favor of amiodarone versus placebo (nonsignificant) was observed. In this sense, lack of proof of a significant difference should not be interpreted as proof of a lack of such difference. Of note, looking at the absolute numbers, the improvement in survival rate was accompanied by a nonsignificant 1% absolute increase in survival of people with severe or very severe neurological disability.

Second and more importantly, there was a difference in survival among the predefined subgroup of those who suffered witnessed cardiac arrest (and, presumably, received faster intervention): the survival rate was higher with amiodarone (27.7%) or lidocaine (27.8%) than with placebo (22.7%). The absolute risk difference (this time statistically significant) is likely larger than, for example, any medication intervention used in the short to medium term in acute coronary syndrome, or for several years in hypertension or hyperlipidemia. This difference was yet larger if the arrest was witnessed by emergency services personnel: survival to discharge was 38.6% among amiodarone-treated patients versus 23.3%

for the lidocaine group and 16.7% for the placebo group (with few patients in those categories, the results were significant only for the amiodarone versus placebo groups). Of note, no differences were observed if the arrest was unwitnessed, or if the bystander witnessing the event did not initiate CPR.

Admittedly, all of these considerations rely on small numbers of patients in particular categories, combining the limitations of subgroup analyses and imprecision. However, it also seems clear that in no group of patients did administration of active drug result in worsening of patient-important outcomes (survival to discharge or survival with favorable neurological outcome). Similarly, amiodarone was not inferior to lidocaine in any of the analyses.

We conclude, while admitting uncertainty, that if resuscitation is attempted in shockable out-of-hospital cardiac arrest, the use of amiodarone (and, if not available, lidocaine) should follow, especially in patients with witnessed arrest. It appears that if used in the early period of electrical or hemodynamic instability, it may well be beneficial and is almost certainly not detrimental. If administered late, during profound metabolic derangements, it likely makes no difference. The significant increase in temporary pacing in the amiodarone group (4.9% in the amiodarone group versus 3.2% in the lidocaine group and 2.7% in the placebo group), together with a possibly increased number of patients surviving with poor neurological outcome, is, in our mind, outweighed by an increased likelihood of survival to hospital discharge with a favorable neurologic outcome. Such conclusion is most certain in the scenario of an arrest witnessed by emergency medical services personnel, and likely with a bystander witnessing it. Admitting the low quality of evidence, one may wonder about earlier administration of antiarrhythmic therapy than guidelines currently suggest (ie, after 2–3 shocks).

In summary, contrary to the apparent conclusion of the paper's authors, we believe this study strengthens the case for amiodarone (and, if not available, lidocaine), especially in patients with witnessed arrest.

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