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LETTER TO THE EDITOR

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Thrombolysis in cardiac arrest: Initial enthusiasm tempered

We read with great interest the comprehensive review advocating thrombolysis during cardiopulmonary resuscitation conducted by Professor Mysiak and co-workers [1]. However, we feel obliged to mention that an important contribution in this field was made last year.

At the World Congress of Cardiology 2006 in Barcelona, the eagerly awaited results of the Thrombolysis in Cardiac Arrest (TROICA) trial were reported [2]. This prospective, randomized, double-blind, placebo-controlled study was set up to determine whether thrombolysis benefits in the cardiac arrest scenario extend beyond the approved indications such as ST-elevation myocardial infarction and massive pulmonary embolism. One thousand and fifty patients with a witnessed cardiac arrest of presumed cardiac origin were randomized out of hospital to receive either a weight-adjusted dose of tenecteplase or placebo after the first dose of a vasopressor. Patients were enrolled in the trial if they were at least 18 years of age and either if basic life support had been started within 10 min of onset and had been performed up to 10 min or if advanced life support had been started within 10 min of onset of cardiac arrest. The investigated drug or placebo was given by paramedics at the same time as cardiopulmonary resuscitation. The primary endpoint of the study was the 30-day survival rate, and the co-primary endpoint was hospital admission. Secondary endpoints were the return of spontaneous circulation, survival after 24 hours and survival until hospital discharge. Safety endpoints included major bleeding complications and symptomatic intracranial haemorrhage [3].

As indicated in Table 1, tenecteplase failed to improve survival in cardiac arrest patients. Nevertheless, despite the lack of difference in any of the efficacy endpoints, thrombolysis administration was safe, and no significant increase in rates of symptomatic intracranial haemorrhage or major bleeding between the two groups were observed.

The negative result of the trial does not necessarily mean that thrombolysis is ineffective as an adjunctive approach to cardiopulmonary resuscitation. Contrary to the TROICA investigators, Li et al. [4], in a recent meta-analysis including 926 patients from eight studies, concluded that thrombolytic agents, when given during cardiopulmonary resuscitation, significantly improved the rate of return of spontaneous circulation, 24-hour survival, survival to discharge and long-term neurological function. Despite these facts, thrombolysis recipients were at an increased risk of severe bleeding.

Similarly to the TROICA findings, in a post hoc analysis of the large randomized trial comparing vasopressin with epinephrine in out-of-hospital cardiac arrest, the use of thrombolysis did not confer any advantage in terms of hospital admission and discharge rates after adjustment for confounding variables [5]. Of note, a significantly higher crude rate of hospital admission (45.5% *vs*. 32.7%, $p = 0.01$) and a trend towards higher crude hospital discharge rate (14.1% *vs*. 9.5%, $p = 0.14$) were noticed in the thrombolysis arm. These differences may reflect the worse baseline characteristics (older age, smaller proportion of patients diagnosed with myocardial infarction or pulmonary embolism, lower occurrence

Table 1. Results of the TROICA trial.

Endpoint	Tenecteplase [%]	Placebo [%]	p
30-day survival	18.2	20.2	0.512
Hospital admission	59.0	59.5	0.931
Return of spontaneous circulation	59.6	59.2	0.977
24-hour survival	35.4	37.9	0.511
30-day survival or hospital discharge	18.8	21.0	0.481
Symptomatic intracranial haemorrhage	1.0	0.0	0.133
Major bleedings	8.9	7.4	0.528

of witnessed cardiac arrest, lower presentation with ventricular fibrillation as initial rhythm, longer estimated interval between the collapse and the beginning of basic or advanced life support) of the placebo group. Thrombolytic agents in this study were given at the discretion of the emergency physician. Furthermore, as reported by Mysiak at al., no evidence of a beneficial effect of tissue plasminogen activator was observed in the challenging population of patients with cardiac arrest and pulseless electrical activity of unknown or presumed cardiovascular cause unresponsive to initial therapy [6]. In the study, 233 subjects were randomly assigned to receive a thrombolytic agent or placebo intravenously in a double-blind fashion. One patient in the tissue plasminogen activator group survived until hospital discharge, as compared with none in the placebo group ($p = 0.99$). The proportion of patients with return of spontaneous circulation was 21.4% in the tissue plasminogen activator group and 23.3% in the placebo group ($p = 0.85$).

It should be also emphasised that most studies suggesting advantageous effects of thrombolytics in cardiac arrest possess major limitations (non-randomized character, retrospective or observational design, small sample size) [7–9]. Other potential explanations for the unexpected negligible effect of thrombolysis in cardiac arrest include inappropriate timing and dosing regimen, possible negative interactions (vasopressors, acidosis, etc.), the need for additional antithrombotic therapy and insufficiency of blow flow to bring the thrombolytic agent to the thrombus in patients with prolonged cardiac arrest. Moreover, patients with a quick return of spontaneous circulation, a group with much more favourable prognosis, were excluded from the TROICA study [3]. On the other hand, the choice of tenecteplase, a potent, fibrin-specific, single bolus-dosing drug with excellent pharmacokinetic profile, seems to be optimal in the resuscitation setting [10].

Finally, the obtained evidence does not support unrestricted use of thrombolysis in victims of non-traumatic cardiac arrest. A subanalysis of the TROICA trial would be helpful to identify subjects who benefited from tenecteplase. Additionally, the application of simple score systems assessing the risk of pulmonary embolism and myocardial infarction might enhance the selection process.

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Marek Koziński and Jacek Kubica
Department of Cardiology and Internal Diseases,
Collegium Medicum,
Nicolaus Copernicus University,
Bydgoszcz, Poland