VIEWPOINT

Are we underestimating the full potential of early thrombolytic treatment in patients with acute myocardial infarction?

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Use of the Boersma curve in order to describe the beneficial effect of thrombolytic treatment at different treatment delays seems questionable, because the curve may underestimate the favourable prognostic effects of early thrombolysis in patients with acute myocardial infarction

In a meta-analysis from 1996 Boersma and colleagues investigated the effect of thrombolysis versus placebo in patients with acute myocardial infarction.¹ An inverse relationship between the number of lives saved per 1000 patients treated with thrombolytic therapy (Y) and treatment delay (x) was presented. The relationship was given by the equation:

$$Y = 19.4 - 0.6x + 29.3x^{-1} \text{ (fig 1)}$$

The major effect of thrombolysis was seen among patients treated within one hour, supporting the concept of the “golden hour”.

Recently Julian and Norris used the publication by Boersma and colleagues in order to calculate the beneficial effect of thrombolysis at different treatment delays, and they stated that: “The number of patients saved by successful resuscitation is higher than the number of patients saved by fibrinolytic treatment”.² The European Society of Cardiology and The International Guidelines 2000 Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, among others, has also used Boersma’s publication in order to describe the prognostic benefit of thrombolytic treatment at different treatment delays.^{3,4} Boersma’s “Reappraisal of the golden hour” is thus widely accepted, and has so far been indisputable.

However, to the best of our knowledge, the formula by Boersma and colleagues leads to a misinterpretation of the real effect of thrombolysis at different treatment delays. Boersma and colleagues’ results are based on the reviewing of 22 trials in which patients were randomised to either thrombolysis or placebo treatment. The mortality data in nine of these trials were sufficiently detailed as to be stratified according to different intervals of delay from symptom onset (n = 48 154).^{5–13} This allowed the authors to perform the described regression analysis. However, when studying these trials it is evident that information on treatment delay was not available

in six of the trials, including more than 85% of the patients used in Boersma’s regression analysis. Instead these trials presented mortality data according to different intervals of “time from pain to study randomisation” and “time from pain to admission”, respectively. This seems to be so for the ISIS-2, GISSI-I, AIMS, EMERAS and LATE trials, as well as a trial described by Simoons and colleagues (table 1).^{5–10} As evident from the GUSTO-I trial, substantial time elapses from time of study randomisation until thrombolytic treatment is initiated, averaging 45–50 minutes, and time delay from admission to initiation of thrombolytic treatment is even longer.^{14,15}

In a recent trial investigating the effect of thrombolysis versus primary percutaneous coronary intervention (primary PCI), in patients with acute ST elevation myocardial infarction, the median door-to-needle-time in patients randomised to thrombolysis was 55 minutes (www.danami-2.dk). Consequently, we believe that the x axis of the Boersma curve should have been designated “pain-to-randomisation delay” or “pain-to-admission delay” instead of “treatment delay”. Alternatively, the curve should be right shifted at least 45–60 minutes (fig 1, modified Boersma curves).

The trials in Boersma’s meta-analysis were designed to compare the effects of thrombolysis and placebo treatment on survival, but they were not designed to study differences in survival stratified according to observed treatment delays. So far, the beneficial effect obtained by a reduction in treatment delays has only been appropriately studied in randomised trials comparing pre-hospital

Figure 1 Number of extra lives saved per 1000 patients treated with thrombolysis at different treatment delays.

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Table 1 Trials included in Boersma's regression analysis

Trial/author	n	Intervals of symptom delay presented (hours)	Patients having acute ST elevation myocardial infarction or BBB-AMI (%)
ISIS-2 ⁵	17187	Pain-to-randomisation time: 0-1, 2, 3, 4, 0-4, 5-12, 12-24	56
Simoons <i>et al</i> ⁶	533	Pain-to-admission time: 1.5 (median)	100
GISSI ⁷	11712	Pain-to-randomisation time: <1, ≤3, >3-6, >6-9, >9-12	89
AIMS ⁸	1004	Pain-to-randomisation time: 0-4, 4-6	100
EMERAS ⁹	4534	Pain-to-presentation time: 0-6, 7-12, 13-24	81
LATE ¹⁰	5711	Pain-to-randomisation time: ≤12, >12 hours	55
ISAM ¹¹	1741	Pain-to-treatment time: ≤3, >3 hours	NA
ASSET ¹²	5011	Pain-to-treatment time: ≤3, 3-5 hours	<72*
Werf <i>et al</i> ¹³	721	Pain-to-treatment time: 2.8 (median)	100

*72% of patients were considered to have acute myocardial infarction. The proportion having acute ST elevation myocardial infarction not stated.

BBB-AMI, acute myocardial infarction with signs of newly developed bundle branch block.

initiated thrombolytic treatment with in-hospital initiated thrombolytic treatment, as also noted by a task force report from the European Society of Cardiology.³ In year 2000 Morrison and colleagues did a meta-analysis including six such trials (n = 6434).¹⁶ In the latter study, prehospital initiated thrombolytic treatment was associated with a reduction in treatment delay from 162 to 104 minutes, and resulted in 16 extra lives saved per 1000 patients treated. Boersma and colleagues and the EMIP investigators have performed similar meta-analyses, and reported that prehospital initiated thrombolytic treatment could save 21 and 15 extra lives per 1000 treated, respectively.^{1, 17} A reduction in treatment delay from 162 to 104 minutes estimates seven extra lives saved per 1000 patients treated using the original Boersma equation (table 2). Using the equations corresponding to modified Boersma curves, right shifted 45 and 60 minutes, a similar reduction in treatment delay would estimate 15 and 26 extra lives saved per 1000 treated, respectively (table 2) (fig 1). Indeed, a simple right shift of the Boersma curve is not mathematically optimal, since the estimated number of saved lives would be infinite if treatment was initiated instantaneously. The modified curves must intercept the y axis at the estimated number of lives saved if all patients with acute myocardial infarction were treated instantaneously. It is impossible to estimate this number because treatment delays can never be reduced to zero minutes.

Using the Boersma curve in order to describe the beneficial effect of thrombolytic treatment at different treatment delays seems questionable, because the curve may underestimate the favourable prognostic effects of early thrombolysis in patients with acute myocardial infarction. Therefore, we hypothesise that the beneficial effect of thrombolysis at different treatment delays are underestimated by the Boersma equation, and that the famous "golden hour" of thrombolysis in patients with acute myocardial infarction in fact may be "two golden hours".

Table 2 Estimated number of extra lives saved when 1000 patients with acute ST elevation myocardial infarction or acute myocardial infarction with signs of newly developed bundle branch block have treatment delays (pain-to-thrombolysis time) reduced from 160 to 104 minutes*

The original Boersma curve ¹	Estimated from:		Trials in which patients were randomised to pre-hospital versus in-hospital treatment. ^{1, 16, 17}
	A modified Boersma curve (right shifted 45 minutes)	A modified Boersma curve (right shifted 60 minutes)	
7	15	26	15-21

*Reduction in treatment delay in the meta-analysis by Morrison *et al*.¹⁶

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