CLINICAL STUDY

Thrombolytic therapy for patients with acute myocardial infarction
Causes increasing the probability of not receiving thrombolytic therapy

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Abstract

Intravenous thrombolysis is the most accessible and the most common form of reperfusion therapy. The aim of this study was to identify demographic, clinical and electrocardiographic factors, which based on published data and in patients included in the project Audit of diagnostic and therapeutic procedures in patients with acute myocardial infarction (AUDIT), increased the probability of not receiving thrombolytic therapy. In order to maximize the impact of thrombolytic therapy to reduce the case fatality rate associated with an acute myocardial infarction, we review, which a number of studies provide evidence on the usage of thrombolytic therapy in elder, women, patients with diabetes mellitus, bundle-branch block and after stroke. ***(Fig. 10, Ref. 52.)***
Key words: acute myocardial infarction, thrombolytic therapy, audit.

Intravenous thrombolysis is the most accessible and the most common form of reperfusion therapy. In "Thrombolysis for acute myocardial infarction (AMI) – yesterday, today, tomorrow" this is described in detail (1). Based on the most recent guidelines of American College of Cardiology and American Heart Association, thrombolysis is beneficial for patients with symptoms of AMI lasting <12 hours and with the elevation of ST segments or bundle-branch block (2). Clinical observations recognised wide inter-regional differences in the application of reperfusion therapy. In many epidemiological studies reperfusion therapy is given only to the minority of patients admitted to a hospital with AMI (3, 4). Based on the representative European survey – study ENACT (a pan-European survey of acute coronary syndromes), an average of 43 % patients with AMI receive thrombolytic therapy (TLT) (Fig. 1) (5). Based on the National Registry of Myocardial Infarction (NRMI) in the USA, which includes data from 1 514 292 patients with AMI, in the year 1990 the percentage of those who were treated with immediate TLT was 34.3 % and in the year 1999 it decreased to 20.8 %. In the USA the percentage of patients with AMI who received the reperfusion therapy (TLT or primary percutaneous coronary angioplasty — pPTCA) decreased from 36.8 % in the year 1990 to 28.1 % in 1999 (6).

The present paper focuses on patients with AMI, who did not receive TLT. We concentrate on identification of demographic, clinical and electrocardographic factors which, based on the published data and in the sample of patients included in the study Audit of diagnostic and therapeutic procedures in patients with acute myocardial infarction in prehospital and hospital phase (AUDIT), increased the probability of not receiving TLT. In comparing our findings with published data we would like to focus attention to the most vulnerable subpopulation of patients with AMI, for the use of TLT.

The project AUDIT was realized in the Slovak Republic as a prospective multicentric study during the period of 16.9.1997 to 15.9.1998. Detailed information about its realization was al-

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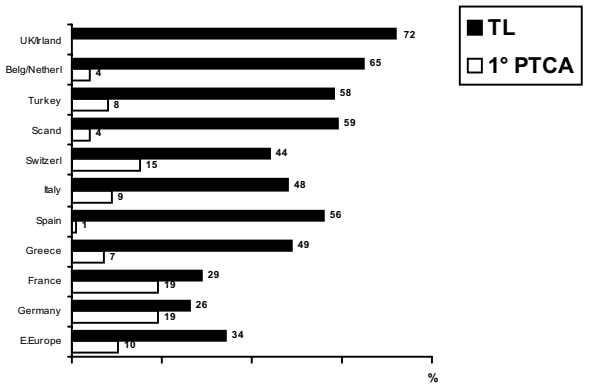

Fig. 1. Reperfusion therapy of acute myocardial infarction in Europe, adapted by (5)
1°PTCA – primary percutaneous coronary angioplasty, TL – thrombolysis

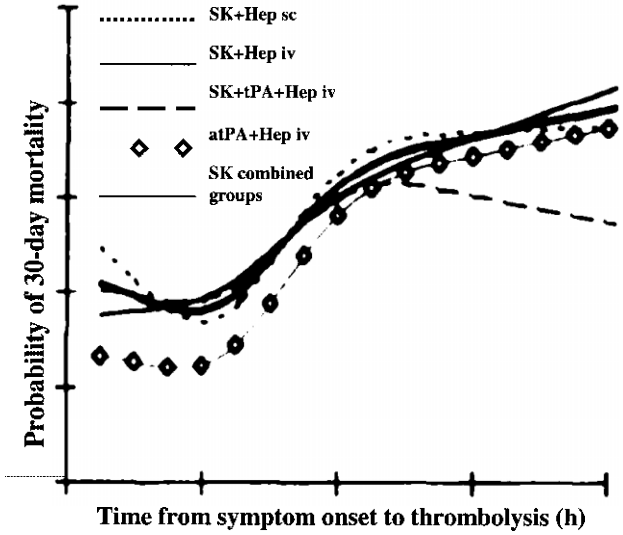

Fig. 2. Probability of 30-day mortality as a function of time from symptom onset to thrombolytic treatment of acute myocardial infarction, adapted by (8)
TL – thrombolysis, SK – streptokinase; Hep – heparin; tPA – tissue-type plasminogen activator; atPA – accelerated t-PA

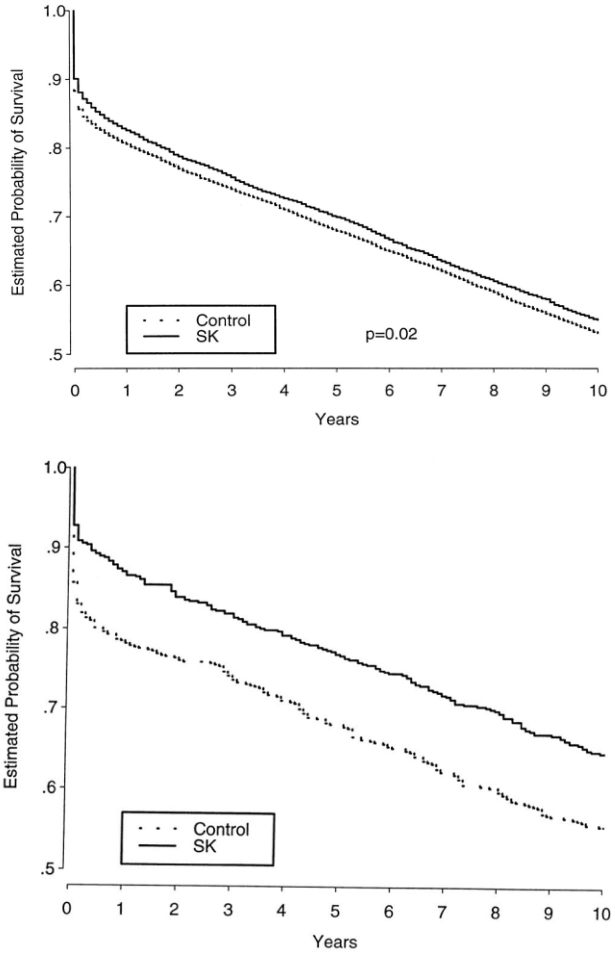

Fig. 3. 10-year survival of patients with acute myocardial infarction treated with thrombolysis – streptokinase and without this treatment, adapted by (9)
top – patients admitted to coronary care unit within 12 hours from onset of myocardial infarction symptoms; bottom – patients admitted to coronary care unit within 1hour from onset of myocardial infarction symptoms, SK – streptokinase

ready published (7). 3 123 patients were included, admitted within 96 hours from symptom onset with the diagnosis or suspicion of AMI and discharged with diagnosis of AMI.

The most important determinant of the thrombolytic treatment efficacy, independent on the type of fibrinolytic drug, is the *time delay* of its administration (Fig. 2) (8). Late arrival of the patient with AMI into the hospital decreases the probability of administering the reperfusion therapy, decreases its effectiveness and therefore the probability of the patients survival. Many observations and analysis of national registries recognised that the risk of not receiving TLT is greater in older patients and in females. Furthermore, TLT is usually not given to patients with co-morbidity, which influences the manifestation of AMI (diabetes mellitus), its diagnosis (previous myocardial infarction, bundle-branch block) or to patients who have a greater risk of serious haemorrhagic complications (high blood pressure, diabetes – diabetic retinopathy). *Contraindications* of TLT deserve an "evidence based medicine" reconsideration.

Time delay. In 1998, results of the 10 year survival of patients with AMI treated with streptokinase, in two large studies – GISSI (9) a ISIS 2 were published (10). The influence of an intravenous infusion of 1.5 mil. units streptokinase to prolong the life of those who had an AMI lasted even 10 years after the randomization into these "mega trials" (9, 10). As seen on the Figure 3, there is a significant trend to better survival of those treated in the first hours of AMI, which lasts even 10 years later. It is the best proof of the relationship of efficacy of TLT and its delay. It documents that the first hour of AMI is the "golden hour" of fibrinolytic effectiveness. Postponement of TLT does not only

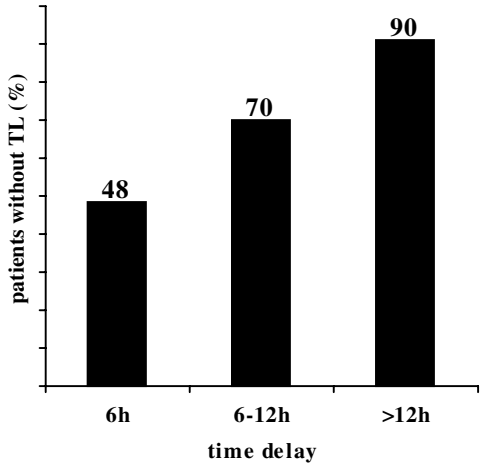

Fig. 4. Relation between percentage of patients without thrombolysis and time from myocardial infarction symptoms onset to hospital admission in the study AUDIT

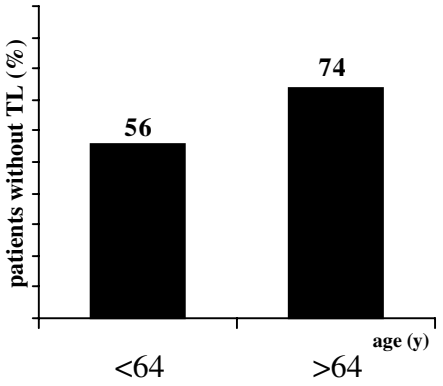

Fig. 5. Relation between percentage of patients with acute myocardial infarction without thrombolysis and their age in the study AUDIT

decrease its effectiveness but also the percentage of the patients who receive this treatment. Danchin et al studied 2 563 patients admitted to intensive care units in France. He documented that patients with AMI admitted within 6 hours received reperfusion therapy in 62 %, from 6–12 h in 33 % and 17 % of patients admitted after 12 h (11). The strong relation between the longer time delay and increasing number of patients without TLT was also found in the study AUDIT (Fig. 4**).** The number of patients with AMI, who did not receive TLT was 48.5 % of patients admitted within 6 hours, 70.1 % of patients admitted within 6 to 12 hours and 90.8 % of patients admitted after more than 12 hours after symptom onset (12).

Age. The risk of death for AMI rises dramatically with the advancing age of the patient (13, 14). Trials about the effectiveness of TLT, which include a large sample of older patients, found out positive effect of thrombolysis on short term mortality (15, 16). The proportional decrease of case fatality rates in patients with AMI due to TLT is significantly higher in younger patients.

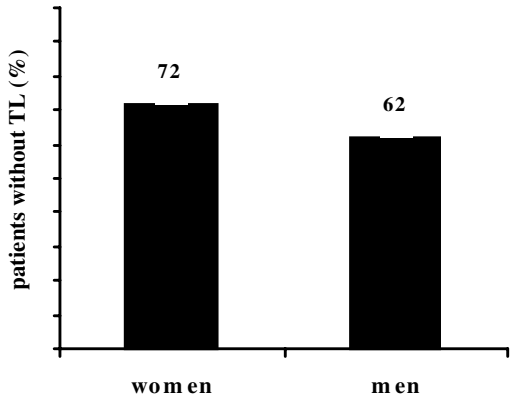

Fig. 6. Relation between percentage of patients with acute myocardial infarction without thrombolysis and their sex in the study AUDIT

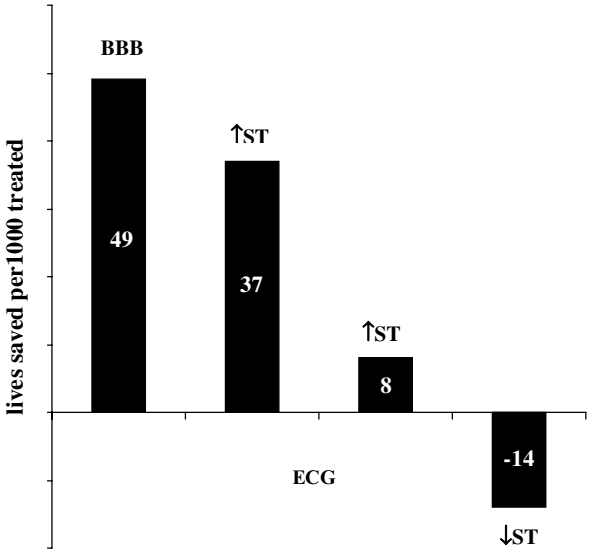

Fig. 7. Effect of thrombolytic therapy on mortality of patients with acute myocardial infarction according to admission electrocardiogram, adapted by (17)
patients with BBB - bundle branch block, ↑STant – anterior ST-segment elevation, ↑ST inf – inferior ST-segment elevation, ↓ST – ST-segment depresion

However, older patients have a higher absolute risk of death for AMI. A group of experts for the Fibrinolytic Therapy Trialist's in a generally known analysis of large studies about the effectiveness of TLT, demonstrated that the absolute decrease of deaths (lives saved per 1000 treated) was the same in younger and in older patients (17). Therefore, it is important to point out that *age should not be an important factor in deciding whether or not TLT should be administrated to patients with AMI* (18). However, many clinical trials showed a direct correlation between increasing age and the increasing number of patients with AMI without TLT (19). Gurwitz et al analysed a group of 350 755 patients with AMI included in NRMI in the United States during the years 1990–1994. They concluded that the percentage of

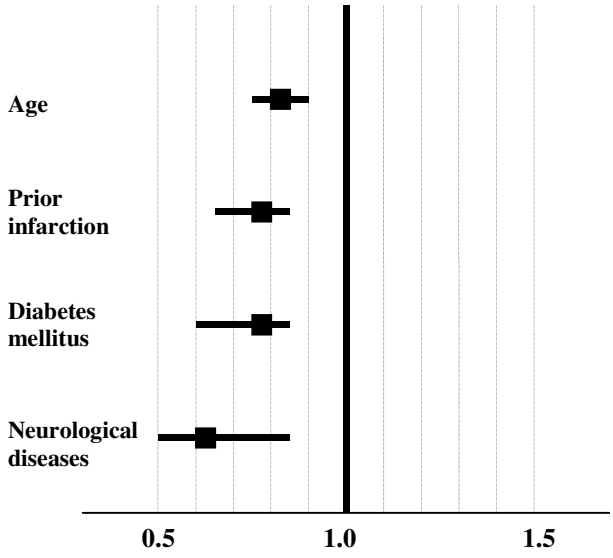

Fig. 8. Odds ratio in a multiple logistic regression model for predicting the use of thrombolysis in the SAVE Trial (Survival and Ventricular Enlargement Study), adapted by (40)

patients treated with thrombolysis had an inverse relationship with the age of the patients. However, in the group of patients younger than 55 years approximately 51 % of them received TLT, in the age group of 65 to 74 years it decreased to 33 % and in the age category of 75 to 84 it decreased to 19 % (20). As the results of the project AUDIT showed, the number of patients without TLT in the Slovak Republic is significantly higher in patients older than 64 years (73.7 %) compared to patients younger than 64 years (55.8 %) (Fig. 5) (12). One of the explanations is that older patients do not fulfill the accepted indications for thrombolysis administration. This assumption was also proved in Gurwitz's study. It showed that older patients had a longer time delay and fulfilled the electrocardiographic criteria for administration of reperfusion therapy less often (20). The Bronx Aging study, a prospective community study, showed that more than 40 % of patients with myocardial infarction older than 75 years were without symptoms (21). However, Gurwitz et al (20) and Ellerbeck et al (22), after the analysis of 16 124 hospitalizations, observed that TLT is "underused" for older patients even if they satisfied indication criteria without contraindications. The explanation for the underutilization of TLT for older patients without any contraindications is the fear of iatrogenic intracranial haemorrhage. Risk of intracranial haemorrhage increases with age of the patient (23). The proportion of patients with intracranial haemorrhage in the GUSTO-1 study was 0.42 % in the age group younger than 75 years in comparison to 1.23 % in patients older than 75 years treated with streptokinase. In patients treated with tissue activator of plasminogen the proportions of intracranial heamorrhage were 0.52 % vs 2.08 %, respectively (24).

Sex. Based on the published data, clinical trials, and national registries, women received reperfusion therapy significantly less often than men (25, 26). The same was observed in the Slovak Republic. 71.5 % of women included in the AUDIT study did not receive TLT in comparison to 61.8 % men (Fig. 6) (12). Women with acute coronary syndromes tend to be older than men, and they have higher rates of associated diabetes and hypertension (27, 28, 29). Data from the GUSTO IIb study also showed the above. A total of 12 142 patients were enrolled in the trial, 3 662 women. Overall, the women were older than men and were more likely to have hypertension, diabetes, and elevated total cholesterol, and a history of angina, congestive heart failure and cerebrovascular disease (27). Hochman et al showed that significantly fewer women than men with acute coronary syndromes presented with ST elevations (27.2 % vs 37.0 %). This correlated with the results of the coronary angiography, often showing partial (no severe) occlusion of coronary artery (27). Trials that examined TLT in patients who had acute infarction with ST elevation consistently enrolled a smaller percentage of women than did trials that included patients with other acute ischemic syndromes (28). The TIMI III investigators cautioned, however, that the sex ratios in clinical trials may be biased, with women more often excluded because of ineligibility for TLT (29).

Many trials showed that women with AMI have worse short- and long-term prognosis (30). Vaccarino et al, by examining 384 878 patients with AMI from the NRMI 2, found that younger women have high short-term mortality. Among patients less than 50 years of age, the mortality rate for women was more than twice that for the men (31). On the contrarery, other studies with similar subgroups did not prove the female sex to be an independent predictor of higher risk of death after myocardial infarction (32).

Bundle-branch block (BBB). Bundle-branch block is considered an important predictor of poor outcome in patients with AMI (33). The Fibrinolytic therapy Trialist• Collaborative Group noted a combined prevalence of 4 % for BBB (type unspecified) at presentation in the pooled data on patients suspected of having AMI from three randomized trials of TLT (17). Compared with patients with no BBB, patients with right or left BBB were more likely to be older, more often female; and to have a history of infarction, angina, congestive heart failure, CABG, stroke, diabetes mellitus, and hypertension (33). Right BBB remained a stronger predictor of death and is probably an independent marker of a larger, anterior infarction (33). Because of its dual blood supply, the right bundle brunch be more resistant to ischemia; thus, the development of right BBB complicating AMI may indicate a more extensive myocardial infarction (36, 36). It is alarming that the patients with AMI with BBB receive TLT only "exceptionally." The TLT is significantly "underused" in patients with AIM and left or right BBB (33, 34, 35, 38). Shlipak et al analysed a group of 29 585 patients with AMI and left BBB included in NRMI 2 study in the United States; only 8.4 % of the patients received the reperfusion therapy, and only 17 % of patients eligible for this treatment (35). The AUDIT project showed, even on an incomparable smaller group in Slovak Republic, that patients with AMI and the BBB receive TLT rarely. Up to 81.2 % of patients with AMI and left BBB did not receive thrombolysis (12).

Based on the date from NRMI2 unadjusted in-hospital mortality rates were almost twice as high for patients with left or

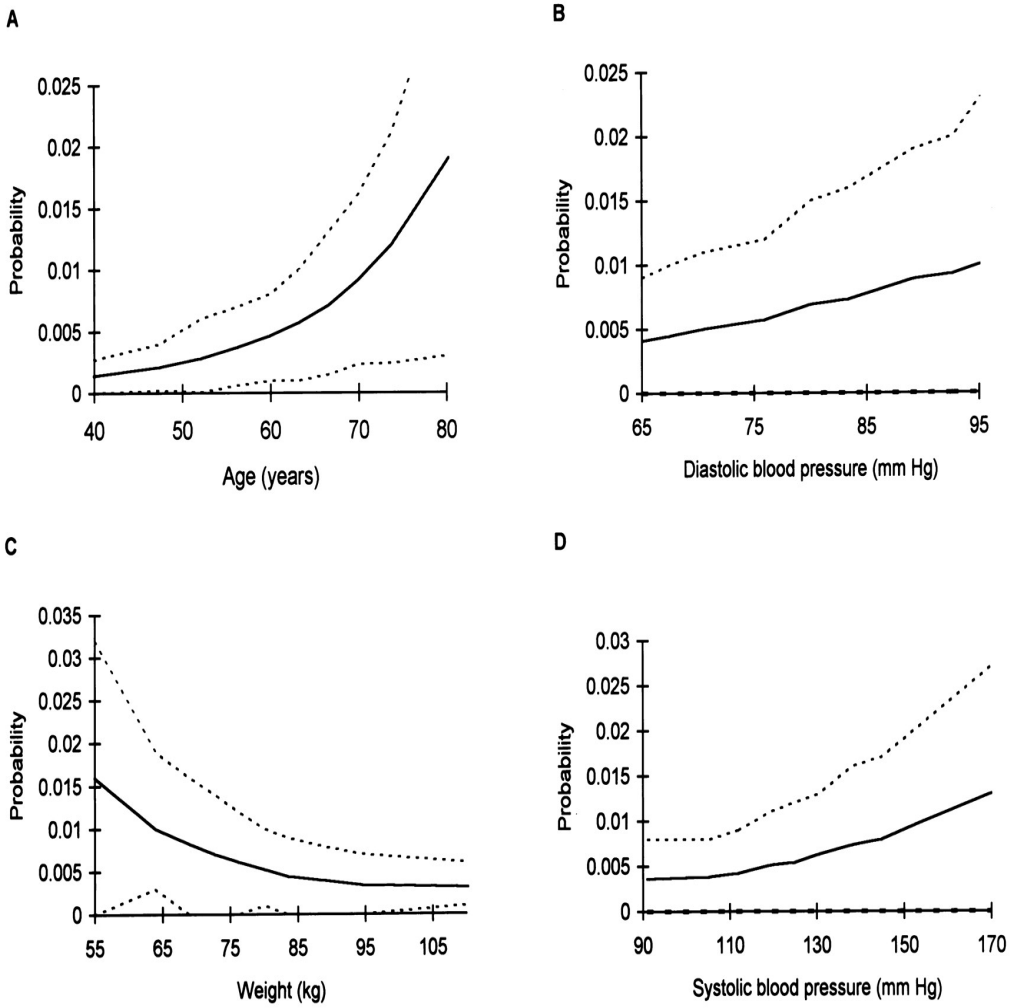

Fig. 9. Graphs show relations between age (A), diastolic blood pressure (B), weight (C), and systolic blood pressure (D) and the risk of intracranial hemorrhage, after adjustment for ther patients characteristics, adapted by (46)

right BBB (22.6 % and 23.0, respectively) as for patients with no BBB (13.1 %) (34). According to meta-analyses performed by the Fibrinolytic Therapy Trialists collaborative group, patients who present with a BBB experience a 25 % relative reduction in 30-day mortality when treated with TLT. This relative reduction in mortality translates into a saving of 49 lives per 1000 patients treated (17). The substantial undertreatment of high-risk patients with BBB strongly supports the most recent American College of Cardiology/American Heart Association Task Force recommendations: that reperfusion therapy (TLT or primary PTCA) be initiated immediately in patients with ischemic chest pain suggestive of AMI and BBB at presentation (2).

A history of previous myocardial infarction leads to a diagnostic uncertainty, to a prolongation of door to needle time and then to an underutilisation of reperfusion therapy. These were well documented in many studies, including the NRMI in the United States and also in the AUDIT project in Slovak Republic (12, 34).

Diabetes mellitus. In a major international trial involving more than 40 000 patients designed to evaluate four fibrinolytic strategies for the treatment of AMI, the 30-day mortality was 6.2 % among patients without diabetes and 10.5 % among patients with diabetes. Indeed, by pooling the data from several large fibrinolytic trials with a total of more than 80 000 patients, the one-months mortality was increased by 1.7 times among diabetics. By the end of the first year, the relative risk for mortality for a patient with diabetes has risen from 1.4 to 1.6 times (39). Thrombolytic therapy has undoubtely improved outcome of patients after AMI. Thrombolysis saved 37 lives per 1 000 patients with diabetes at 35 days, campared with 15 per 1 000 patients without diabetes (17). Thus, the absolute benefit is more than doubled for thrombolysis among diabetics. Despite its tremendous benefit, diabetics were less likely

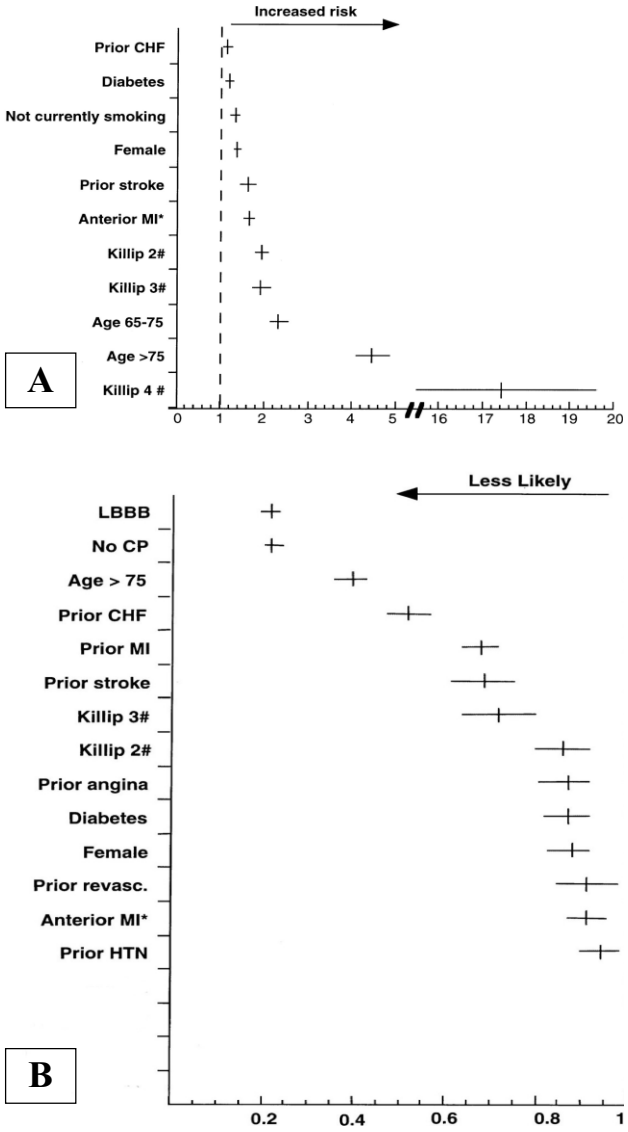

Fig. 10. Multivariate adjusted odds ratios for in-hospital mortality of patients with acute myocardial infarction (A) and multivariate adjusted odds ratios for use of reperfusion therapy in patients with acute myocardial infarction (B); adapted by (34)
CHF – congestive heart failure, AMI – acute myocardial infarction, LBBB – left bundle branch block

to receive TLT, as shown in the Survival and Ventricular Enlargement (SAVE) study (Fig. 8) (40). Among various epidemiological parameters studied, the presence of diabetes emerged as an independent variable for not using TLT. Importantly, these findings extend beyond the context af a clinical trial. In a recent report from a large national AMI registry (272 651 patients with AMI), using univariate analysis, the odds for patients with diabetes mellitus to receive reperfusion therapy was almost half non-diabetics. The presence of diabetes mellitus remaned as an independent predictor for a lower likelihood for reperfusion therapy in a multivariate statistical model (34). This unfavorable trend was also observed in a nationwide French survey (37 % diabetics vs 46 % non-diabetics patients receiving reperfusion therapy, respectively) (41)), the United Kingdom (37 % diabetics vs 54 % non-diabetics patients receiving reperfusion therapy, respectively) (42), and in the Slovak Republic (28.3 % diabetics vs 37.2 % non-diabetics patients receiving reperfusion therapy, respectively) (2). However, as with several of these clinical studies, the reasons for this finding are largely unknown and probably can be attributed to numerous factors, such as atypical or late presentation and undue concern regarding the adverse effects of thrombolysis. Diabetic patients have an impaired sensation of pain due to diabetic neuropathy. Oral hypoglycemic agents are known to cause repolarization abnormalities on the resting electrocardiogram. In particular, some animal studies suggest that the amplitude of ST-segment elevation and T-wave peaking may be reduced with these medications and, therefore, lower the sensitivity of the electrocardiogram in identifying patients with AMI (43).

The fear of increased occurrence of side effects and life-threatening complications from the fibrinolytis was shown to be unjustified. In the GUSTO-1, there was only a marginal increase in moderate bleeding complications (13 % vs 11 %) without an increased risk in major bleeding rates. More importantly, the risk of intracranial hemorrhage was similar between patients with and without diabetes (0.6 % vs 0.7 %) (39). Furthermore, intraocular hemorrhage did not occur in any of the 6 011 diabetic patients (44). Hence, administration of fibrinolytic agents is not associated with increased complications. With regard to the high mortality in diabetic patients with AMI thrombolysis should be given to all diabetics who satisfy the necessary criteria.

Contraindications. Thrombolytic therapy in patients with AIM is contraindicated when the risk of serious adverse events, including death, is greater than the expected benefit of survival in these patients. Based on the published data from the national registries and from the clinical studies the occurrence of contraindications for TLT in patients with AMI is variable. Barron et al demonstrated that 3 % of 272 651 patients with AMI included in the NRMI 2 had contraindications for TLT (34). In the TRAndolapril Cardiac Evaluation study population, 6 676 consecutive patients with AMI in Denmark, thrombolysis was contraindicated in 16 % (45). An identical prevalence (16 %) of TLT contraindications was found in patients included in AUDIT project (12).

The most feared complications of thrombolysis for acute myocardial infarction are massive bleeding and stroke due to intracranial haemorrhage, because of the resulting high mortality and disability. In GUSTO-1 trial, out of 41021 patients with AMI treated with TLT, the occurrence of all strokes was 1.19 % (0.46 % due to intracranial haemorrhage) of those treated by streptokinase (and subcutanal heparin) and 1.55 % (0.70 % due to intracranial haemorrhage) of patients treated with tissue plasminogen activator. Stroke subtype affected prognosis: 60 % of patients with intracranial haemorrhage died (it is consistent with the experience in other large thrombolytic trials) and 25 % were disabled (46). The majority of intracranial haemorrhages occured within 24 hours of initiation of treatment. Most nonhemorrhagic events occurred more

than 48 hours after treatment began. Advenced age, lower weight, prior cerebrovascular disease or hypertension, systolic and diastolic blood pressure, and randomization to tissue plasminogen activator, were by multivariable analysis of GUSTO-1 trial significant predictors of intracranial hemorrhage after TLT (Fig. 9) (46, 47, 48).

Ottesen et al (45) looked at the rationale for the contraindications for TLT, which were based on controversial evidence, empiricism, rational considerations and experiences. They analysed 223 patients with AMI with at least one of the accepted contraindications who recived thrombolytic therapy. It was interesting to see that TLT in patients with a history of prior stroke was not associated with a higher occurrence of strokes during hospitalizations (45). Similarly Tanne et al found a group of patients included in the Israeli Thrombolytic National Survey that TLT could be beneficial in selected patients with AMI and a prior cerebrovascular event (49). Mortality among patients with AMI who do not receive TLT is twice as high as it is among patients treated with TLT (35-day mortality 18.2 % vs 9.6 %) (17, 50, 51). Recently published data about the positive effect of thrombolytic therapy on survival of the patients with AMI who had at least one contraindication (prior stroke) opened up the question to reconsider the contraindications. A randomized study of TLT among patients with some of the current contraindications is expected, in particular, in patients with a risk of stroke based on events some time in the past (45).

Thrombolytic therapy of acute myocardial infarction has been one of the most potent treatments ever developed for a condition that kills more patients worldwide than any other (52). Based on national- and multinational registries of AMI, TLT is most available, economic and most used reperfusion therapy for patients with AMI. The availability of TLT, easy technical application and price favor this therapy over primary PTCA for patients with AMI without any contraindications. Interest for TLT is not obsolete. Data from many thousands of patients show a realistic picture of the effectiveness and safeness of TLT. The statistical analysis showed characteristics of people with AMI with a high risk of death as characteristics increasing the probability of not applying TLT as well (Fig. 10) (34). These demographic, clinical and electrocardiographic variables were, as shown the AUDIT project, associated with a risk of not applying TLT also in the Slovak Republic (12). In an effort to maximize the use of the thrombolytic therapy potential to improve survival of patients with AMI we tried to make an overview of many large studies, what should provide a judgement on the doubts from TLT in older people, women, diabetics, patients with bundle-branch block and prior stroke.

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