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TIME-DEPENDENT FACTORS OF EFFECTIVENESS AND TOLERABILITY OF STATINS: SCIENTIFIC AND PRACTICAL ASPECTS

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SUMMARY

The article considers modern approaches to analyzing the effectiveness of interventions in relation to time, that is, the length of the period after the beginning of their application. The role of the analysis of the Kaplan-Meier curves for the evaluation of the effects of compared interventions depending on the time is discussed. Various options of the relative layout of the Kaplan-Meier curves in the course of the study are examined. The results of a recent analysis of the duration of the period between the onset of statin use and the development of clinical benefits of therapy are presented. In particular, the possibility of using the TTB indicator of intervention and TTH indicator, caused by the intervention, is discussed in making a clinical decision about the validity of the choice of a particular treatment method, in particular the indicator of number of patients who need to be treated with a particular drug. Opinions that emphasize the importance of evaluating the effectiveness of interventions with absolute rather than relative risk of adverse clinical outcomes are mentioned. Clinical situations in which the duration of the TTB is of particular importance, in particular, in patients with a very high risk of developing complications of cardiovascular diseases (for example, after an acute coronary syndrome) and in patients who in most cases have limited life expectancy are considered. The role of atorvastatin in clinical situations is emphasized, in which the earlier achievement of the clinical advantages of lipid-lowering therapy is important. Data on the role of statins, in particular atorvastatin, are given in the early stages after the development of acute coronary syndrome.

Key words: *time factors, Kaplan-Meier curves, atorvastatin, cardiovascular diseases.*

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Analysis of the Kaplan-Meier curves as an approach to assessing the effectiveness of therapy

Modern effective clinical practice largely depends not only on the clinical experience of the physician, but also on the skills of searching and evaluating the evidence-based information that allows to choose the optimal treatment strategy. Such tactics can be determined only in the course of large and well-planned randomized clinical trials (RCTS). Analysis of the survival curves constructed using the Kaplan-Meier method has become one of the main approaches to assessing the incidence of adverse outcomes in modern clinical trials.

There may be several variants of the "behavior" of such curves [1]. Such curves may not diverge throughout the study period (Figure 1A), indicating that there is no difference between the efficacy and / or safety of the interventions compared. Such curves may diverge, which will indicate a difference between the groups for effectiveness and / or safety. Moreover, in such cases there may be several options. After an early discrepancy, such curves may continue to diverge (Figure 1B) or may go in parallel (Figure 1C). If the intervention is accompanied by an increased risk of developing adverse outcomes at an earlier stage after the intervention (for example, an increased risk of stroke in the early period after coronary bypass surgery), then in the future, after the early divergence of the curves, they will converge. Such situation can be also with the advantages of intervention, which eventually loses (Figure 1D). For example, when very serious patients are included in the study at some stage of the observation, this convergence of the survival curves becomes almost inevitable [2].

Recall that in 1958 Edward Kaplan and Paul Meyer published an article [3], which considered the approach to the analysis of incomplete observations. Subsequently, the Kaplan-Meier curves and the calculation of survival data became the standard approach to assessing differences in the duration of the period before

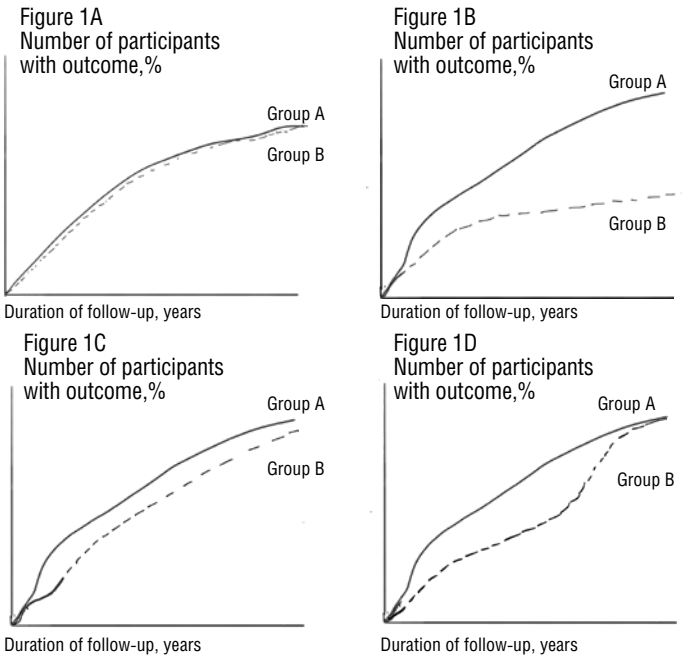

Figure 1. Embodiments mutual arrangement Kaplan-Meier curves in the course of clinical studies

the development of a certain clinical outcome (times-to-event), especially in cases where not all participants in the study continue to be observed until the end of the study. Survival curves do not evaluate actuarial survival (the incidence of fatal outcome in general), but reflect the length of the period before the development of any clinical outcome studied (not only death from all or certain causes, but also outcomes such as, for example, myocardial infarction or stroke).

When analyzing the Kaplan-Meier curves, the moment when the curves begin to diverge is of special interest. It is believed that the duration of the period from the beginning of the observation to this point corresponds to the duration of the period before the development of the benefits of the intervention being studied in comparison with the control. In the literature published in English, such a term is referred to as "time to benefit" (TTB). More precisely, the term duration of the period before the development of benefits is understood as the duration of the period until the advantages of the intervention studied are revealed in comparison with the control [4]. Similarly, for the time from which the harmful effects of the intervention studied begin to be detected compared to the control, it is called the time to harm (TTH), in the intervention group compared to the control [4].

Experts identify three reasons why the assessment of such time-scores (TTB and / or TTH) can be useful [5]. First, such indicators

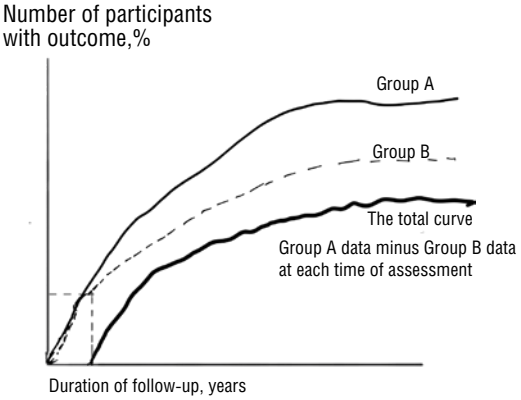

Figure 2. An example of constructing a summary curve for determining the moment of the beginning of the interference effect (by subtraction from the data of the comparison group for the intervention group)

can provide information on the most likely mechanisms of action of a particular treatment method. For example, if the use of a hypolipidemic drug used to lower the concentration of low-density lipoprotein (LDL) cholesterol (CS) leads to a reduction in the risk of cardiovascular disease complications before a statistically significant decrease in LDL cholesterol levels is detected, it can be assumed that the mechanism of action of the drug is due not only to a decrease in the level lipids in the blood, but also by other so-called pleiotropic effects [6].

Secondly, the PPRP indicator can be an important reference point in deciding the validity and timing of the termination of the clinical trial in connection with the impossibility of identifying differences between the effectiveness of the interventions being compared [7]. It should be noted that during implementation of three large randomized clinical trials for comparative evaluation of lipid-lowering drugs compared with placebo (pravastatin 40 mg in the study CARE Cholesterol and Recurrent Events [8]; gemfibrozil 1200 mg per day in the VA-HIT study - Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial [9] and the HOPE-3 study – Heart Outcomes Prevention Evaluation 3 [10]) Kaplan-Meier curves reflecting survival without the studied clinical outcomes did not diverge within 2-3 years, but on the whole, in the course of further observation, statistically significant positive effects of taking such lipid-lowering drugs were compared with placebo. So, sometimes it takes patience to wait for the clinical effect of the tested drug.

Thirdly, it is believed that the TTB and / or TTH and their ratio can be taken into account when deciding on the use of certain interventions in elderly patients who have many concomitant diseases and limited life expectancy [4]. In such cases, treatment will be useless if the TTB will exceed the estimated life expectancy of the patient. For example, the prevention of the development of cardiovascular complications by taking aspirin begins within the first 5 years after the and persists throughout the period of therapy [11]. At the same time, the prevention of the development of cancer of the rectum and large intestine is achieved 5-10 years after the start of the daily drug intake, but, given the long latency period, it may take 10-20 years to identify the benefits. In such cases, in elderly patients with a relatively small expected life expectancy, the benefits of taking aspirin may be inadequate due to large TTB. At the same time, TTH due to an increased risk of bleeding may be small. It was suggested to use TTB to determine the priorities for prescribing drug therapy in elderly patients with a large number of concomitant diseases, which often have polypharmacotherapy [12-14].

The indicator of the duration of the period before the development of advantages in the structure of approaches to assessing the effectiveness of interventions

Modern methodological approaches to assessing the effects of therapy have become widely used since the 60s of the twentieth century. Statistical methods were improved and adopted that allowed to identify the advantages and / or disadvantages of the use of drugs for the treatment and prevention of CVD that were established during the implementation of large randomized clinical trials. Standard approaches to confirming the benefits of using certain interventions have become relative risk reduction and statistical significance [15]. Later, when analyzing the data obtained in controlled drug studies, data on the observed effect proportion also began to be included, that is, the first indication of absolute risk reduction, rather than a relative risk reduction, and it is also recommended to calculate the indicator of the number of patients who need to be treated with

certain drugs for a certain period to prevent 1 adverse outcome. In the literature published in English, such indicator is called NNT ("number needed to treat"). The indicator of the number of patients who need to be treated with certain drugs for a certain period to prevent 1 adverse outcome reciprocally reflects a decrease in absolute risk [16]. The indicator of the number of patients who need to be treated with certain drugs for a certain period to prevent 1 adverse outcome should be indicated for a specific period, but focus on the severity of the effect, rather than on the length of the period during which such an effect was. TTB is associated with the indicator of the number of patients who need to be treated with certain drugs for a certain period to prevent 1 adverse outcome, but more reflect the likelihood of achieving established, statistically and clinically significant positive (or negative) effects over a period that can be correlated with the remaining life expectancy of the patient.

Obviously, the TTB indicator can be significant in assessing the effectiveness of intervention in patients in 2 groups: 1) in persons with a very high risk of CVD complications due to atherosclerosis, including patients with acute coronary syndrome (ACS) and/or those with a 10-year calculated risk of developing a myocardial infarction or stroke of more than 20%; 2) in very elderly people, who have a limited life expectancy.

For very elderly people, the need to evaluate the TTB index relates to cases of statin administration for primary prevention, since for the purpose of secondary prevention, statins are used regardless of age and expected life expectancy. Given the conflicting views on the use of statins in such situation, let us dwell a little more on the problem of using statins in people of this age category for the purpose of primary prevention.

The use of statins for primary prevention in elderly and very elderly people

In general, the proportion of people older than 65 is significantly increasing in the world [17]. The estimated life expectancy in economically developed countries in 65 y.o. people is >20 years for women and >17 years for men [18]. The prevalence of coronary heart disease in the US by 2030 will increase by 40% (≈5 million people) only due to a change in demography. This will increase the direct costs by 198% (≈$ 70 billion). Such data should serve as a basis for increasing the proportion of healthy elderly people [19, 20]. Currently, clinical recommendations for the use of statins for primary prevention in general are not based on scientific evidence, but in most of them, with the class of recommendations I or IIa, it is considered reasonable to use drugs belonging to this class in the majority of individuals of 65 y.o. [21-25]. It should be noted that clinical recommendations vary significantly in providing tactics for assessing the risk of complications of CVD in individuals over 65 y.o, the results of such tactic can be the basis for the use of statins for primary prevention. So in the European recommendations, the risk assessment option is limited to 65 y.o, in the American – to 75 y.o. and in the recommendations adopted in the United Kingdom – 85 y.o.

A more definitive answer to the question of the tactics of using statins for the purpose of primary prevention in elderly individuals can be obtained by performing a large n = 18 000) randomized clinical trial STAREE (STAtin Therapy for Reducing Events in the Elderly). The purpose of this study is to test the hypothesis of whether taking a statin will lead to an increase in overall survival and survival without disability in healthy elderly compared with placebo (70 years and older). The end of the study is expected in December 2022. In any case, in general, most experts agree that statins should be used for primary prevention in elderly people. And in such situation, data on TTB can play a role in the choice of statin due to the need to achieve a faster effect in such cases because of the limited life expectancy of very elderly people.

The duration of the period before the development of benefits in studies of hypocholesterolemic drugs

At present time, more than 20 large randomized controlled double-blind studies have been performed to evaluate the effectiveness of statin use; and in most of them a statistically significant efficiency was noted, assessing by the main indicator of the incidence of adverse outcomes. In some of these randomized clinical trials, the effects of taking statin were compared with placebo [8, 26-38], while in others, the effectiveness of using different statins or different doses of statins of the same type was compared [39-41]. In addition, studies were performed to confirm the effectiveness of the use of hypocholesterolemic drugs, which belong to other classes (cholestyramine, gemfibrozil, ezetimibe, evolocumab alirocoumab and anacetrapeptide) [9, 42-47].

In the course of the analysis, the results of which were recently published, the TTB indicator was evaluated by visual assessment of Kaplan-Meier curves reflecting the frequency of adverse outcomes included in the main indicators that were obtained in the randomized clinical studies of lipid-lowering drugs [5]. In general, in 24 randomized clinical trials, TTB varied between 1 and 36 months (mean 13.1 months); in randomized clinical trials comparing placebo with statins (n = 14), the mean TTB was 11.1 months, and in all randomized clinical trials of statins as a whole (n = 17) – 10.3 months. In randomized clinical trials evaluating the effects of other hypocholesterolemic medications, mean TTB reached 20 months (n = 7). It should be noted that in both studies (EINSTEIN and ODYSSEY) in assessing the effects of using proprotein convertase subtilisin / kexin 9-PCSK9 enzyme inhibitors, the TTB was 12 months [45, 46].

During the analysis of the Kaplan-Meier curves for the main indicator, a summary curve was constructed for each randomized clinical trial by subtraction from the comparison group data the intervention group data (Figure 2). The point of intersection of the total curve with the X axis (the abscissa axis), reflecting the duration of the observation period during the studies, corresponded to the point of achievement of TTB for each randomized clinical trial. Such an analysis allowed to calculate only the approximation to the TTB, since it included the Kaplan-Meier curves constructed for individual studies as a whole, but not individual data on the participants in the studies. To reduce distortion, only 15 out of 24 randomized clinical trial were included in the analysis.

According to the authors of the analysis [5], the identified differences in the TTB could be affected by several factors, including such as: 1) the number of developed adverse outcomes included in the main indicator, which depends both on the size of the sample and the frequency of development of adverse outcomes; 2) the initial concentration of LDL cholesterol; 3) the severity of the decrease in LDL cholesterol; 4) indications for the use of statins (for example, such as primary prevention of CVD, coronary heart disease with a stable course, secondary prevention after acute coronary syndrome; 5) features of the drug used (statins or lipid-lowering drugs, different from statins).

Obviously, the benefits in the treatment group will not appear until at least several unfavorable outcomes develop. The number of adverse outcomes depends on the number of patients who have a risk of developing the outcome (sample size) and the frequency of development of such an outcome. For example, in the course of a study that will develop 200 outcomes during the first 6 months, there is a higher probability of early detection of benefits compared to a

study in which only 20 outcomes will develop over the same period.

On the other hand, it can be assumed that there is a correlation between the severity of LDL cholesterol lowering and the degree of risk reduction of CVD complications. During the analysis of the results of a randomized clinical study of statins, it was found that a decrease in the level of LDL cholesterol in the blood for every 1 mmol/l corresponds to a decrease in the relative risk of CVD complications by 22% [48]. In the course of performing statin studies, compared with studies of non-statin lipid-lowering drugs, with a decrease in LDL cholesterol concentration for every 1 mmol / L during the first year of reducing the relative risk, CVD complications were 9%, and in subsequent years by 22-28% [48]. In general, it can be assumed that the more pronounced the decrease in the number of unfavorable outcomes, the smaller will be the TTB. However, the results of the analysis of the diagram indicated a weak connection between such indicators [5].

The initial concentration of LDL cholesterol is also theoretically possible to be considered as a factor that influences on TTB. For each specific decrease in the concentration of LDL cholesterol in percentages, the absolute decrease in LDL cholesterol level will increase with an increase in the initial LDL cholesterol concentration, that is, a higher baseline LDL-C is accompanied by a more pronounced absolute LDL decrease. A very high baseline level of LDL cholesterol was noted in the LRC-CPPT trial (Lipid Research Clinics Coronary Primary Prevention Trial) [42] and in the 4S study (Scandinavian Simvastatin Survival Study) [26]. However, in none of them TTB was particularly short. After receiving the results of the 4S study for ethical reasons, it was considered inappropriate to leave untreated patients with such a high level of LDL cholesterol. Given that both of these studies completed with a positive result, we can consider that TTB is not associated with the initial LDL cholesterol.

The characteristics of the study participants are likely to affect the TTB. In a cohort of patients with acute coronary syndrome, the incidence of adverse outcomes is significantly higher than in a cohort of patients with a stable course of coronary heart disease. A higher frequency of such outcomes at an earlier stage after randomization could be a predictor of a smaller TTB.

The use of statins can have positive effects at an early stage after the beginning of their administration due to a positive effect on several pathophysiological links of the disease in patients with acute coronary syndrome, including such as endothelial dysfunction, inflammation, platelet reactivity, and increased blood coagulability [6, 49]. It is widely believed that the use of statins in such patients has a positive effect on the risk of developing of CVD complications in the early stage after the beginning of their use precisely because of such mechanisms. In this regard, it should be recalled that in the implementation of a large randomized clinical trial IMPROVE-IT (44) on the evaluation of the efficacy of the addition of ezetimibe compared with placebo to simvastatin in patients newly diagnosed with acute coronary syndrome, TTB was not short, that is, the use of a hypolipidemic drug not from statins class, was not accompanied by an earlier onset of the clinical effect. It is known that in the absence of acute coronary syndrome, TTB was similar in persons without an established diagnosis of coronary heart disease and in patients with a stable course of coronary heart disease. In the course of performing statin studies for primary prevention, TTB varied over a very wide range from 1 to 30 months [33, 35].

And finally, the most difficult and important question is: does the TTB depend on which particular drug is used to reduce the LDL cholesterol concentration? The available evidence data supports the hypothesis that taking particular statin effects the TTB.

The results of the analysis performed by P.J. Barter and D.D. Waters [5] indicate that, overall, in 17 randomized clinical trials of statins, TTB was on average 10.3 months, while in 7 randomized clinical trials of lipid-lowering drugs belonging to other classes it was on the average 20 months. The results of a separate analysis of a randomized clinical trial in which different statins were studied indicated that, with atorvastatin, TTB was less compared with the use of other statins. In the course of 6 randomized clinical trials evaluating the efficacy of atorvastatin, TTB was an average of only 4.75 months, while 11 randomized clinical trials evaluating the effect of other statins had on average 13.4 months of TTB.

Why the administration of atorvastatin leads to smaller TTB? Previously, the possible factors that determine the decrease in TTB, were specified in this article. There is data that active metabolites are formed during the metabolism of atorvastatin, which act as antioxidants, and have a beneficial effect on lipoproteins [50-52]. The presence of comparable metabolites for such effects was not observed [5]. In particular, there are experimental studies showing that only active metabolites of atorvastatin specifically inhibit the oxidation of small dense particles of LDL cholesterol [51].

It should be noted that this analysis has a number of limitations. In particular, at the time of the divergence of the Kaplan-Meier curves, the differences between the groups in most cases did not reach the level of statistical significance and, with one exception [6], the authors of the randomized clinical trials included in the analysis did not calculate at what time the differences between the groups became statistically significant. And it is important to remember that when the statistical significance of differences between groups was revealed, the study could be terminated early [30, 33]. In addition, the definition of the point of divergence could, at least in part, be determined by subjective factors and varied depending on the graphical representation of the results of a randomized clinical trial. In particular, when diagram of possible area of divergence of the curves was presented, the results of establishing the point of divergence of the curves changed [44].

It should also be noted that the index of TTB can't be considered the only indicator of the effectiveness of the drug under study, since the duration of the preservation of the achieved effect is of great importance. It has been established that the use of statins is accompanied by a continuation of the effect even after the study was terminated, which was noted even 20 years after randomization [53]. However, this rule does not apply to all drugs used to treat CVD. For example, the benefits of using β-blockers after myocardial infarction in the absence of heart failure seems questionable [54].

Evidence that demonstrates the importance of achieving an early statin effect in patients with acute coronary syndrome

The need to achieve a rapid effect of statins in patients with acute coronary syndrome can be illustrated by data obtained during the research, the results of which confirm the rapid stabilization of atherosclerotic plaque after the use of intensive regimes of statin intake. Such studies include randomized clinical trials EASY-FIT [55] and ESCORT [56]. In the course of performing these studies using optical coherence tomography, it was found that the use of a more intensive mode of statin intake compared to less intense in patients with unstable angina leads to an increase in the thickness of the atherosclerotic plaque, indicating a more pronounced stabilization.

It is obvious that atorvastatin remains the most studied statin in patients with acute coronary syndrome, the effectiveness of which has been confirmed in the course of the MIRACL study [28] and especially PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluationand Infection Therapy-Thrombolysisin MyocardialInfarction 22) study [39]. The use of atorvastatin 80 mg per day in patients with acute

coronary syndrome for this reason remains the "gold standard" of lipid-lowering therapy in this situation.

We don't know for sure whether the more pronounced pleiotropic effects of atorvastatin can be attributed, at least in part, to a decrease in the proportion of patients receiving other TTB statins during the randomized clinical trial. However, it can be assumed that it is the pleiotropic effects that are associated with an earlier influence on the prognosis. It has been established that in patients who have recently undergone acute coronary syndrome there is a higher expression of matrix metalloproteinase (MMP) of the first type of membranes, which is considered to be an important factor of destabilization of antibodies [57, 58].

In a small randomized clinical trial involving 83 patients with acute coronary syndrome, data were obtained that the use of atorvastatin in comparison with rosuvastatin resulted in a statistically significant decrease in MMP of type 1 membranes and MMP of type 9, despite the same decrease in LDL cholesterol concentration [59]. The results of such a study suggest that atorvastatin has an additional effect on the stabilization of atherosclerotic plaques, which depends not only on the effect on the level of LDL-C in the blood and also statins may vary in the severity of pleiotropic effects. Considering the results of a fairly recent recent SECURE-PCI study (Statins Evaluation in Coronary Procedures and Revascularization), it can be assumed that for the clinical implementation of the effects of early use of a high dose of atorvastatin in acute coronary syndrome, it takes more than 30 days [60].

CONCLUSION

Thus, a recent analysis made it possible to obtain data on the fact that TTB when using statins, according to a randomized clinical trial, varies in a fairly wide range. At the same time, it can be assumed that there is no statistically significant association between TTB and the initial concentration of LDL cholesterol or the severity of its decrease by taking statins. In addition, studies that included patients with acute coronary syndrome noted an early development of the clinical effect due to the benefits of taking statins, not only related to the effect on LDL cholesterol level in the blood. In general, TTB when using statins was smaller than with the use of lipid-lowering drugs, not belonging to the class of statins. Besides, TTB was less when taking atorvastatin (Liprimar drug produced by Pfizer) compared with the use of other statins. At the same time, during randomized clinical trials of new lipid-lowering drugs, the benefits of therapy can begin to be detected only not earlier than 1-2 years after the initiation of therapy.

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