EDOXABAN FOR TREATING VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER. RESULTS OF HOKUSAI VTE CANCER RANDOMIZED TRIAL

Original article: *Raskob G.E., van Es N., Verhamme P., et al*. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018; 378: 615–624.

Background

Venous thromboembolism (VTE) is a frequent complication of cancer and its therapy. Treatment of patients with VTE associated with cancer is a difficult challenge, and the risk of developing recurrent thrombosis and bleeding is higher in patients with cancer than in non-oncological patients. Both complications play a big role, as they affect mortality and complications, can interact with cancer treatment, and also lead to an increase in the frequency of hospitalizations.

The results of previous studies involving cancer patients with VTE showed that the incidence of recurrent thrombosis was less with low-molecular-weight heparin (LMWH) taken for 6 months compared with vitamin K antagonists, and the risk of bleeding was similar when using these two treatment tactics. Therefore, in accordance with current clinical guidelines, LMWH is considered to be justified in such cases. However, it is unknown how effective this theapy is after 6 months. In addition, treatment with LMWH is inconvenient, as it requires daily subcutaneous injections, which limits the use of such tactics.

The use of direct oral anticoagulants (DOA) is no less effective for the treatment of patients with VTE and causes less frequent development of bleeding, as well as a lower severity of bleeding. However, the efficacy and safety of DOA has not been established in comparison with the prolonged use of LMWH for treating patients with VTE caused by cancer.

Objective

To compare two options of anticoagulant therapy: DOA or LMWH for at least 6 months and up to 12 months to test the hypothesis of the validity of anticoagulant therapy for more than 6 months.

Design

An international, multicentre, open-label, randomized trial; median follow-up in the Edoxaban group was 211 days (interquartile range IQR from 76 to 357 days), 184 days in the Dalteparin group (IQR from 85 to 341 days, p=0.01).

Patients

The study included adult patients with acute deep vein thrombosis DVT (both with clinical manifestations and revealed during the examination) located in the popliteal, femoral, iliac vein or in the inferior vena cava; in the presence of pulmonary embolism (PE) involving segmental or more proximal pulmonary arteries. According to the protocol, it was required that the attending physician should intend to use LMWH for at least 6 months.

To be included into the study, the patient had to have cancer confirmation in active form or cancer diagnosed within the previous 2 years, but with the exception of basal cell or squamous cell carcinoma of the skin. It was believed that the patient had an active form of cancer if the cancer was diagnosed within the previous 6 months, also in the case of a recurrence of cancer, local or metastatic cancer; or in case of malignant hematologic diseases, where complete remission is not achieved.

Intervention

Patients were assigned to the LMWH group for at least 5 days, followed by the therapy of Edoxaban 60 mg once a day (Edoxaban group) or to the subcutaneous Dalteparin group of 200 IU/kg body weight 1 time per day for 1 month, followed by administration of Dalteparin 150 mg/kg body weight (Dalteparin group). Such therapy continued for at least 6 months and up to 12 months.

Evaluation criteria/Clinical outcomes

The main combined indicator is the frequency of recurrent VTE or severe bleeding. Repeated VTE was diagnosed with a newly developed DVT or PE with clinical manifestations, as well as with accidentally newly diagnosed DVT or PE with the involvement of a segmental or more proximal pulmonary artery branch or with the development of fatal PE, and also in case of death of an unknown cause where it was impossible to exclude PE as the cause of death. Accidentally detected PE was diagnosed in cases where thromboembolism was established using imaging techniques that were not used in connection with the assumption of VTE development. Severe bleeding was diagnosed according to the criteria of the International Society of Thrombosis and Hemostasis in the development of clinically obvious bleeding, which was accompanied by a decrease in hemoglobin concentration in the blood by 2 g/dl or more, or necessitated the transfusion of 2 blood units or more, as well as the development of hemorrhage into vital organs or bleeding leading to death.

Results

In total, 1,050 patients were randomized. A modified analysis based on the assumption that all patients used the prescribed treatment included data on 1,046 patients. Clinical outcomes included in the main combined rate of recurrent VTE or severe bleeding in the Edoxaban and Dalteparin group developed in 12.8% and 13.5% of patients, respectively (risk ratio 0.97, 95% confidence interval (CI) 0.70 to 1.36, p=0.006 to test the hypothesis that the use of

Edoxaban is no less effective than Dalteparin, p=0.87 to test the hypothesis of a higher efficacy of Edoxaban). Repeated VTE in the Edoxaban group and in the Dalteparin group developed in 7.9% and 11.3% of patients, respectively (the absolute risk difference was 3.4, with 95% CI 7 to 0.2%, the risk ratio was 0.71 at 95% CI of 0.48 to 1.06, p=0.09). Severe bleeding in the Edoxaban group and Dalteparin group developed in 6.9% and 4%, respectively (absolute risk difference 2.9%, 95% CI 0.1% 5.6%, risk ratio 1.77, 95% CI from 1.03 to 3.04, p= 0.04).

Overall, in the Edoxaban and Dalteparin group, 39.5% and 36.6% of the patients died, respectively. Most of deaths were associated with cancer. Six patients in each group died of causes associated with VTE or bleeding.

Conclusion

1. Edoxaban was no less effective than subcutaneous Dalteparin injections in influencing the risk of developing adverse outcomes included into the main combined rate of recurrent venous thromboembolism or severe bleeding.

2. In the Edoxaban group, compared with the Dalteparin group, the frequency of recurrent venous thromboembolism was lower, but the incidence of severe bleeding was higher.

EFFECTS OF DUAL ANTIPLATELET THERAPY FOR 6 MONTHS AND 12 MONTHS AND MORE IN PATIENTS WITH ACUTE CORONARY SYNDROM AFTER PERCUTANEOUS CORONARY INTERVENTION. RESULTS OF OPEN-LABEL, RANDOMIZED SMART-DATE TRIAL

Original article: *Hahn J.Y., Song Y.B., Oh J.H., et al.* 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomized, open-label, non-inferiority trial. Lancet. 2018 Mar 9. doi: 10.1016/S0140-6736(18)30493-8. [Epub ahead of print]

Background

In accordance with current recommendations, the use of a dual antiplatelet therapy (DAPT), including Aspirin and $P2Y_{12}$ inhibitor, is considered valid after implantation of a drug-eluting stent in a patient with acute coronary syndrome (ACS). However, there are only limited data on the optimal duration of DAPT in patients with ACS who underwent percutaneous coronary intervention (PCI).

Objective

To check the hypothesis that in patients with ACS, who have undergone PCI, the use of DAPT for 6 months will be no less effective compared to DAPT for 12 months or more.

Design

A multicentre, open-label, randomized clinical trial performed at 31 South Korea research centers to test the hypothesis of no less effective DAPT for 6 months compared to DAPT for 12 months or more; duration of follow-up is 18 months.

Patients

Patients with forms of ACS such as unstable angina, acute myocardial infarction (MI) without ST-segment elevation, and acute MI with ST-segment elevation were included into the study. To be included into the study, patients had to have at least one site of coronary artery lesions with a diameter ranging from 2.25 to 4.25 mm and stenosis 50% or more according to a visual assessment in which PCI with stenting could be performed.

The main exclusion criteria were: intolerance or contraindications to the use of Aspirin, Clopidogrel, Heparin, Biolimus, Everolimus, Zotarolimus or contrast agent; active pathological bleeding; severe bleeding during the previous 3 months; surgical operation with a large amount of intervention for the previous 2 months; hemorrhagic diathesis or coagulopathy in the anamnesis; life expectancy is less than 2 years; estimated planned surgical intervention within 12 months, as well as participation in other studies to evaluate the effectiveness of drugs or devices.

Intervention

During the PCI patients were distributed to the group of DAPT for 6 months and the group of DAPT for 12 months or more in a ratio 1:1. At the time of the study, Prasugrel and Ticagrelor were available in South Korea, so at some point randomization was performed using stratification, depending on the type of $P2Y_{12}$ inhibitor. In addition, to reduce the possibility of a systematic error associated with the use of stents of a certain type, patients were also distributed to groups of stents of one of three types also in a ratio of 1:1:1: Zotarolimus coated stents (Resolute Integrity, Medtronic Vascular, Santa Rosa, California, USA), Everolimus coated stents (Xience Prime, Abbott Vascular, Santa Clara, California, USA) and Biolimus A9 coated stents (BioMatrix Flex, Biosensors Inc, Newport Beach, California, USA). Only stents of a certain type could be installed into coronary arteries in accordance with the results of randomization. However, implantation of other stents was also possible in the case of unavailability of a stent of the appropriate type or in cases when, in the opinion of the doctor, implantation of another stent is more justified in the patient's interests.

All patients took a loading dose of Aspirin 300 mg and Clopidogrel 300 or 600 mg no later than 12 hours before PCI, except for patients who had previously taken such antiplatelet agents. And, if the patient could not take the loading dose for 12 hours before the intervention, the loading dose of Clopidogrel 600 mg was prescribed as early as possible before the PCI. After PCI, Aspirin (100 mg once a day) and Clopidogrel (75 mg once a day) were prescribed for an indefinitely long time according to the results of randomization (6 months or 12 months or more). As mentioned earlier, Prasugrel and Ticagrelor were available in South Korea during the study. In this regard, from December 2014 reception of a loading dose of Prasugrel equal to 60 mg followed by 10 mg per day or a loading dose of Ticagrelor equal to 180 mg, followed by administration of 90 mg twice a day could be used instead of Clopidogrel. After the intervention, all patients were recommended to use the optimal drug therapy, including statins, beta-blockers and blockers of the renin-angiotensin system, in the presence of indications consistent with modern clinical recommendations. After the initial PCI, patients were examined 1, 6, 12 and 18 months later.

Evaluation criteria/Clinical outcomes

- The main combined indicator is the total mortality, the incidence of myocardial infarction or stroke within 18 months after PCI, performed for ACS in patients, the data for which were included in the analysis, performed on the assumption that all patients had the prescribed treatment.

- Additional indicators: individual components of the main indicator; the frequency of a definite or probable stent thrombosis and the frequency of development of type 2-5 bleeding by the criteria of an academic consortium of researchers within 18 months after the initial intervention.

Main results

Between September 5, 2012 and December 31, 2015, 2,712 patients were included into the study, in the DAPT group for 6 months and in the DAPT group for 12 months or more, 1,357 and 1,355 patients, respectively. In the DAPT group for 6 months and in the DAPT group for 12 months or more, Clopidogrel was taken as an inhibitor of $P2Y_{12}$ by 79.7% and 81.8% of patients, respectively.

- Adverse clinical outcomes included into the main combined index of total mortality, incidence of myocardial infarction, or stroke within 18 months after PCI, performed for ACS in patients whose data were included in the analysis based on the assumption that all patients followed the prescribed therapy, developed in 63 and 56 patients, respectively (the cumulative incidence of these outcomes reached 4.7% and 4.2%, respectively, the difference in absolute risk was 0.5%, the upper limit 95% of (CI) reached 1.8%, p=0.03 for the analysis performed to test the hypothesis of no less effective DAPT for 6 months compared to DAPT for 12 months or more at a pre-existing 95% CI for such an analysis of 2.0).

- Despite the absence of statistically significant differences between the results in the 6-month DAPT and DAPT for 12 months or more for total mortality (2.6% and 2.9% respectively, the risk ratio is 0.90 at 95% CI from 0.57 to 1, 42, p=0.90) and the incidence of stroke (0.8% and 0.9%, respectively, risk ratio 0.92, 95% CI 0.41 to 2.08, p=0.84), MI was statistically significantly more likely to develop in the 6 months DAPT group compared to DAPT for 12 months or more (1.8% and 0.8%, respectively, the risk ratio was 2.41, with 95% CI 1.15 to 5.05 p=0.02). Moreover, stent thrombosis in the groups of DAPT for 6 months and 12 months or more developed in 1.1% and 0.7% of patients, respectively (risk ratio 1.50 at 95% CI 0.68 to 3.35; p=0.32).

- The incidence of bleeding of types 2-5 according to the classification and criteria of the academic consortium of researchers in the DAPT group for 6 months and the DAPT group for 12 months or more was 2.7% and 3.9%, respectively (risk ratio 0.69 at 95% CI from 0.45 to 1.05, p=0.09).

- The results of the analysis, performed depending on the treatment actually applied, were similar to the results of the analysis performed on the assumption that all patients received the prescribed treatment.

Conclusion

1. Increased risk of myocardial infarction with the use of dual antiplatelet therapy for 6 months and wide confidence interval limits according to the analysis done to test the hypothesis of no less efficacy of the use of dual antiplatelet therapy for 6 months in comparison with dual antiplatelet therapy for 12 months and more do not allow to make a conclusion that the shortened period of dual antiplatelet therapy is safe in patients with acute coronary syndrome, who underwent percutaneous coronary intervention and installation of drug eluting stents.

2. The prolonged use of dual antiplatelet therapy in patients with acute coronary syndrome in the absence of an excessively high risk of bleeding should remain the standard approach to the treatment of such patients.

EFFECTS OF TICAGRELOR VS CLOPIDOGREL IN PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION TREATED WITH PHARMACOLOGICAL THROMBOLYSIS. RESULTS OF TREAT RUNDOMIZED STUDY

Original article: *Berwanger O., Nicolau J.C., Carvalho A.C., et al.* Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients with ST-Elevation Myocardial Infarction: A Randomized Clinical Trial. JAMA Cardiol. 2018 Mar 11. DOI: 10.1001/jamacardio.2018.0612. [Epub ahead of print].

Background

Primary percutaneous intervention on the coronary arteries is considered the preferred tactic for achieving reperfusion in patients with acute myocardial infarction with ST-segment elevation (STEMI). However, there are many places in the world with no possibility of proper treatment for patients with STEMI in accordance with modern clinical recommendations. In this regard, in many patients with STEMI, fibrinolytic therapy (FT) is performed as the initial tactic of achieving reperfusion. The results of two large randomized clinical trials indicated that the use of dual antiplatelet therapy with Aspirin and Clopidogrel leads to reduction in the incidence of severe complications of cardiovascular events (CVD).

Ticagrelor is a reversible and long-acting antagonist of the receptor for adenosine diphosphate $P2Y_{12}$, which leads to a more rapid and sustained suppression of $P2Y_{12}$ receptors compared to Clopidogrel. In the PLATO (Platelet Inhibition and Patient Outcomes) study, Ticagrelor as compared to Clopidogrel resulted in a statistically significant reduction in mortality from complications of vascular disease, the incidence of myocardial infarction (MI), or stroke in the absence of an increased risk of developing severe bleeding in general.

Despite such advantages of Ticagrelor, PLATO did not include patients who underwent FT within the previous 24 hours. Concerns about the use of Ticagrelor in this situation relate to a possible increase in the risk of severe bleeding, especially intracranial hemorrhage (ICH) or fatal hemorrhage. In patients with STEMI, bleeding increases the risk of severe CVD complications and death.

Objective

To evaluate the efficacy of Ticagrelor use in comparison with Clopidogrel in patients with STEMI who underwent thrombolytic therapy.

Design

An international, multicenter, open-label, randomized trial using a blind method in assessing adverse clinical outcomes; duration of follow-up is 30 days.

Patients

The study included patients (younger than 75) with STEMI according to electrocardiography (in men – elevation of the ST segment from the isoelectric line by 1 mm or more in two consecutive leads from the extremities or thoracic leads, in women – elevation by 1.5 mm in leads V_1- V_3 and 1 mm in leads from the extremities) who applied for medical care within 24 hours after the development of clinical manifestations of the disease and underwent FT.

The main exclusion criteria: the presence of any contraindications to the use of Clopidogrel, the use of anticoagulants, an increased risk of bradycardia and concomitant therapy with strong inhibitors or inducers of cytochrome P-450 3A.

Intervention

Patients were assigned to the Ticagrelor group in a 1:1 ratio with a 180 mg loading dose or to Clopidogrel group using a loading dose of 300 to 600 mg at the earliest possible time after development of STEMI and not later than 24 hours. Randomization was performed using a blind method using a program available on the Internet. Block randomization with displaced blocks of 6 patients in each block was applied, as well as stratification, depending on the research center. It was allowed to include in the study patients who took Clopidogrel before randomization.

In the case of distribution into the Ticagrelor group, the use of a saturating dose was recommended, and in patients of Clopidogrel group, if the percutaneous intervention was performed on the coronary arteries, they could optionally take 300 mg according to local recommendations. The maintenance dose of Ticagrelor was 90 mg 2 times a day, Clopidogrel 75 mg once a day.

All patients in the case of tolerability took acetylsalicylic acid 75-100 mg per day. In patients who previously did not take it, the use of a loading dose of acetylsalicylic acid 162-325 mg was recommended. The decision to use another type of treatment for myocardial infarction and subsequent revascularization was made according to an attending physician.

Evaluation criteria/Clinical outcomes

The main safety index: the incidence of severe bleeding according to the TIMI classification (Thrombolysis in Myocardial Infarction).

Additional safety indicators: the incidence of severe or mild bleeding by PLATO criteria and the criteria of a consortium of academic researchers, as well as clinically significant minor bleeding or mild bleeding by the TIMI criteria.

Main results

The mean age of patients was 58±9.5 years; 71.1% were men; 57.3% were of the European race.

Within 30 days after randomization, severe bleeding according to the TIMI classification in the Ticagrelor group and Clopidogrel group was noted in 0.73% and 0.69% of patients, respectively (absolute difference 0.04% at 95% confidence interval (CI) 0.49 to 0.58%, p<0.001 for the analysis performed to test the hypothesis of no less high safety of Ticagrelor).

The frequency of severe bleeding according to the criteria of PLATO and hemorrhages of the 3-5th type according to the criteria of the consortium of academic researchers in the Ticagrelor group and Clopidogrel group was 1.2% and 1.38% respectively (absolute difference 0.18% at 95% 0.89 to 0.54%, p=0.001 for the analysis performed to test the hypothesis of an equally high safety of Ticagrelor). In the Ticagrelor group and the Clopidogrel group, there was a similar incidence of fatal bleeding (0.16% and 0.11%, respectively, p=0.67) and ICH (0.42% and 0.37%, respectively, p=0.82) . The incidence of mild and minimal bleeding was higher in the Ticagrelor group than in the Clopidogrel group.

The combined mortality from complications of vascular disease, the incidence of myocardial infarction or stroke in the Ticagrelor group and Clopidogrel group was 4% and 4.3%, respectively (odds ratio 0.91, 95% CI 0.67 to 1.25; p=0.57).

Conclusion

For 30 days of observation in patients with acute myocardial infarction with ST-segment elevation under the age of 75, the delayed administration of Ticagrelor after fibrinolytic therapy was no less safe than Clopidogrel in terms of the risk of severe bleedings according to the TIMI classification.