Effect of exogenous insulin on platelet reactivity in patients with acute ischemic vascular events

Qi Ma[1], xiaodan Wen[1], Qian Wang[1], Yunlian Xue[2], and Li'an Huang[3]

[1]Guangdong Geriatrics Institute
[2]Guangdong Provincial People's Hospital
[3]Jinan University First Affiliated Hospital

May 26, 2020

Abstract

Objective: Recent studies have shown that insulin therapy increased the risk of major cardiovascular adverse events, and the changes of platelet reactivity may be responsible for the clinical outcomes. We attempted to explore the effect of exogenous insulin on platelet function in patients with type 2 diabetes mellitus who were suffering from acute vascular events. Methods: We collected data of 540 diabetes patients with acute ischemic vascular events from the hospital information system. Their platelet reactivity has been reported by the maximum amplitude of adenosine diphosphate-induced platelet-fibrin clots (MAADP) of thromboelastography. The effect of antidiabetic drugs on platelet reactivity was analyzed retrospectively. Stratified regression analysis was carried out to gradually adjust for the demographic data, genetic factors, lifestyle, biochemical indicators, antiplatelet regimen, etc. Results: Univariate linear regression analysis showed that sex, age, body mass index, smoking, low-density lipoprotein, platelet count, CYP2C19*2, antiplatelet regimens, and insulin were related to MAADP. After multiple factors were adjusted, the effect of insulin therapy (95% CI: 0.022-0.664; p =0.036) on MAADP was always statistically significant. Conclusions: Exogenous insulin effects significantly on the level of MAADP in diabetic patients with acute ischemic vascular events, which may be not conducive to antiplatelet therapy.

What is already known about this topic?

- According to the guidelines, insulin therapy is the first choice for diabetes patients in the acute stage of ischemic cardiovascular and cerebrovascular events.
- Previous studies have shown that insulin not only has hypoglycemic effect, but also has an effect of anti-platelet aggregation on heathy subjects.
- Thromboelastography is a useful tool to evaluate anti-platelet effect, and MA_{ADP} is one of key index to guild the anti-platelet therapy.

What does this article add?

- Result of stratified regression analysis shows exogenous insulin (95% CI: 0.022-0.664; p =0.036) effects significantly on the level of MA_{ADP} in diabetic patients treated with antiplatelet therapy, while glimepiride(p =0.873), metformin(p =0.816) and acarbose(p =0.076) has little effect on MA_{ADP}.
- Recent studies have shown that insulin therapy increased the risk of major cardiovascular adverse events, and the effect of insulin on platelet function may be partially responsible for that.
-

Introduction

Type 2 diabetes mellitus (T2DM) is an important independent risk factor for cardiovascular and cerebrovascular diseases.[1]Insulin has been widely used in the treatment of T2DM patients, and it has made obvious effect on improving blood glucose level. But, according to several research conclusions published recently, both insulin treated DM and non-insulin treated DM patients have greater risk of major adverse cardiovascular events (MACE) and mortality compared with non-DM patients, and insulin treated DM suffered greater risk than non-insulin treated DM,[2-7] including short-term and long-term risks.[3, 7, 8] Nevertheless, it is unclear about any causality suggestion between insulin treatment and outcomes. As well known, Insulin has antiplatelet effect as well as hypoglycemic effect,[9, 10] normally, it should reduce the occurrence of MACE, but the fact is opposite. Therefore, the relationship between insulin therapy and platelet function has gradually become an important research direction. In a randomized trial, Vivas et al thought that intensive glucose control with insulin in patients with an acute coronary syndrome reduced platelet reactivity during hospitalization.[11] Nevertheless, after 12 months of follow-up, platelet aggregation following adenosine diphosphate stimulation showed no differences between optimized glucose control with insulin and conventional control groups.[12] Westerbacka et al found that platelet-inhibitory actions of insulin under conditions mimicking thrombus formation are blunted or absent in obese or insulin resistance subjects.[13] In order to further explore the relationship between insulin therapy and platelet function, this study was carried out.

Methods

Study population

We collected data on 801 patients with type 2 diabetes suffering from acute ischemic cardio-cerebral vascular events, including acute coronary syndrome (ACS) and acute ischemic stroke (AIS), at the Guangdong Provincial People's Hospital and Guangdong Geriatrics Institute during the past four years from the hospital information system(seen in Figure. 1). All enrolled patients must be within one week from onset to admission, and were treated with dual antiplatelet therapy (DAPT, including clopidogrel (Plavix) and aspirin).

Exclusion criteria:

patients with atrial fibrillation, cerebral embolism, hemorrhagic stroke, thrombocytopenia, thrombocytosis, platelet dysfunction, type 1 diabetes, coagulation dysfunction, severe liver disease, hematopoietic dysfunction, chronic kidney disease ([?]stage 3), pregnancy, or malignant tumors and patients treated with anticoagulant agents or thrombolytic or novel antiplatelet drugs within one week before admission. Patients with partial clinical data or laboratory results were also excluded.

Data collection and organization:

Data collection:

Staff employed in the statistics office of our hospital conducted a data search based on important fields, such as diagnosis, laboratory results, and primary clinical medications.

Data arrangement:

Data such as diagnosis, laboratory results, and clinical medications were integrated into the same data file based on "patient identification number & hospitalization date" by Excel for Windows; thus, a medical database was established.

Data elimination:

To avoid selective bias and confounding factors, we chose the data from patients treated with a single hypoglycemic drug. Data with a small sample, such as patients treated with short-acting insulin, dipeptidyl peptidse-4 inhibitors, repaglinide, or thiazolidinedione, were eliminated. Moreover, patients with insulin duration <7 days were excluded, and for core data such as the maximum amplitude of adenosine diphosphate-induced platelet-fibrin clots (MA_{ADP}), the outliers were eliminated, the criteria were -3 [?] z [?] 3.

These details are shown in Figure. 1.

Data supplementation:

We reviewed medical documents and supplied some demographic data (height, weight, etc.), lifestyle data (smoking, drinking, etc.), and data on past medical history and drugs taken before admission. For those who did not have a detailed record, we contacted the patient by phone.

Data verification:

All core data were carefully verified by 2 staff members.

Antiplatelet therapy regimen:

According to clinical record data, all patients included presented two groups, Conventional DAPT (clopidogrel 75 mg daily, aspirin 100 mg daily) should be carried out at least 7 days before admission. For those who did not take any antiplatelet drugs before admission or only took one antiplatelet drug, they received intensive DAPT (clopidogrel 300 mg daily, aspirin 300 mg daily) after admission. The clopidogrel taken by patients was a reference listed drug, not a generic drug.

CYP2C19 Genotyping

As stated in the published article, [14] CYP2C19 was determined in our hospital by a genotyping kit (DNA Microarray, BaiO Inc., Shanghai, China).CYP2C19*2 mutations include 681GA and 681AA, while CYP2C19*3 mutations include 636GA and 636AA.

Thromboelastography (TEG)

Thrombelastograms (TEGs) reflects not only thrombin generation kinetics and fibrinnetwork formation during clot generation but also platelet function.[15] MA_{ADP} refers to the maximum fibrin clot strength induced by adenosine diphosphate(ADP), and is an important indicator in TEG. The quantitative assessment of MA_{ADP} measured by TEG can assess the patient's response to oral antiplatelet therapy and can be related to the prognosis of cardiovascular and cerebrovascular events,[15-17] and with the increase of MA_{ADP}, the risk of thrombosis increased or the antiplatelet effect was poor.[18] In the study, we adopted MA_{ADP} measured by TEG as a main indicator to evaluate patients' effect on antiplatelet treatment.

Blood samples that were collected from patients at least 6 h after they received intensive treatment or 7 days after they received regular antiplatelet therapy were sent for analysis in vacutainer tubes containing 3.2% trisodium citrate. The vacutainer tubes were filled to capacity and inverted 3–5 times to ensure complete mixing of the anticoagulant. Thrombelastography® uses four channels to detect the effects of antiplatelet therapy acting via the arachidonic acid and ADP pathways. A detailed description of this method has been outlined previously.[19] The TEG® 5000 Thrombelastograph® Hemostasis Analyzer System (Haemoscope Corporation, Niles, USA) and automated analytical software were used to measure the physical properties.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 23 software. The Kolmogorov-Smirnov test (KS test) was used to perform normal distribution analysis for all measurement data. Data that were fit for analyses were transferred to the normal distribution. Continuity variables are expressed as the mean ± the standard deviation (SD). Each candidate risk factor was analyzed by univariate linear regression analysis, and $P < 0.1$ was defined as the screening criterion. Then, stratified regression analysis was carried out to gradually adjust for the demographic data, genetic factors, lifestyle, biochemical indicators, antiplatelet regimen, etc., and to analyze the effects of hypoglycemic treatment on MA_{ADP} tested by TEG. $p < 0.05$ was defined as statistically significant.

The present study was approved by the Human Ethics Committee of Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences (No. GDREC2017280H) and adhered to the tenets of the Declaration of Helsinki.

Results

Baseline Characteristics

A total of 540 patients were enrolled in the study (Table 1): 230 patients did not receive any hypoglycemic therapy, 100 patients received insulin therapy alone, 54 patients took glimepiride, 65 patients received metformin, and 91 patients received acarbose. There were 400 males (74.1%), 181 patients (33.5%) with AIS, and 359 patients (66.5%) with ACS.

Univariate linear regression analysis

First, univariate linear regression analysis was performed, and the following statistically significant candidate risk factors screened by $p < 0.1$ were included (as shown in Table 2): sex, age, body mass index (BMI), smoking, low-density lipoprotein (LDL), platelet count, CYP2C19*2, antiplatelet regimen and insulin.

Stratified regression analysis

Then, we adopted stratified regression to analyze the effects of hypoglycemic regimens on MA_{ADP} tested by TEG by adjusting for antiplatelet therapy regimens and demographic, genetic, biochemical, and lifestyle factors. By drawing a partial regression scatter plot and the scatter plot of the studentized residual and predicted values, a linear relationship between each risk factor and the square root of MA_{ADP} was determined.

Independent of each observation, values (Durbin-Watson test value is 1.928) were validated, and equal variance of data was confirmed by plotting the scatter plot between the studentized residual and the unnormalized predicted value.

The regression tolerance of all variables was greater than 0.1, and the variance inflation factors were less than 10; thus, there was no multicollinearity between variables. In the outlier test, there was no observed value where the studentized residual was greater than 3 times the standard deviations, data leverage values were less than 0.2, and there was no value where the Cook distance was greater than 1. The QQ diagram suggests that the research data satisfy the normal hypothesis.

After adjusting for candidate factors, we found that insulin therapy, antiplatelet therapy, sex, age, platelet count, and CYP2C19*2 were statistically significant. In the initial model, R^2=0.016, F (4,534) = 2.181 ($p = 0.070$),only the hypoglycemic regimen (insulin therapy alone, sulfonylurea, metformin, acarbose) was included, and insulin alone was statistically significant ($p = 0.009$). After adjusting for antiplatelet therapy , in Model 2, R^2 =0.028, F (5,534) = 3.042 ($p = 0.010$), insulin therapy (p =0.015) and antiplatelet therapy (p =0.012) were statistically significant. After Model 3 was corrected for demographic data and lifestyle-related

factors (sex, age, BMI, smoking), $R^2 = 0.083$, F (9, 530) = 5.325 ($p < 0.001$) insulin therapy (p =0.030) was still statistically significant; when we continued to compare physicochemical indexes (platelet count and LDL), insulin therapy (p =0.021) remained statistically significant, Model 4, $R^2 = 0.097$, F (11,528) = 5.171 ($p < 0.001$). Finally, we corrected for the genetic factors (CYP2C19*2), and insulin therapy (p =0.036) remained statistically significant, Model 5, R^2 =0.110, F (12, 527) = 5.432 ($p < 0.001$). In conclusion, after multiple factors were adjusted for, the effect of insulin therapy (p =0.036) on MA_{ADP} was always statistically significant. The specific results are shown in Table 3.

Discussion

Studies have shown that insulin-treated diabetic patients have increased platelet aggregation.[20-22]Postprandial P-selectin increased by 23% with the activation of platelet activator, and postprandial P-selectin expression increased to 57%, but if 0.1 U/kg insulin was given before a meal, postprandial platelet activation was significantly related to the higher insulin level in postprandial blood.[23] Further studies have found that this increase in postprandial platelet activation was activated by the thromboxane pathway after high postprandial insulin levels.[24] In our study, it was found that the effects of glimepiride, metformin, or acarbose on MA_{ADP} tested by TEG were not statistically significant in diabetic patients with acute ischemic vascular events, and insulin therapy may increase the level of MA_{ADP}tested by TEG and even promote the risk of platelet aggregation. This conclusion may partly explain the increased cardiovascular risk in diabetic patients treated with insulin.[2-6, 8]

In healthy people, insulin at physiological concentrations plays a role in the inhibition of platelet aggregation: insulin promotes NO synthesis[25], and NO induces an increase in cGMP while promoting the upregulation of cGMP and cAMP-dependent pathways.[26] NO also increases the effect of prostacyclin, which synergistically reduces platelet aggregation[25]. In addition, insulin itself reduces platelet aggregation by inhibiting ADP- or thrombin-induced calcium mobilization and platelet-collagen interactions.[27]

Compared with the effect of physiological concentration, the effect of exogenous insulin under pathogenic conditions on platelets is opposite. The antiplatelet aggregation effect of insulin by increasing the cGMP concentration of platelets is impaired in obese diabetic patients.[9] Similarly, for diabetic patients with insulin resistance, the inhibitory effect of insulin on platelet aggregation is weakened or even disappears.[13] First, insulin-resistant diabetic patients have reduced platelet surface insulin receptors and decreased sensitivity, which makes platelets overactivated.[28] Second, calcium levels in platelets are elevated by insulin stimulation, leading to further activation and aggregation of platelets.[26] Third, hyperinsulinemia induces an increase in tissue factor levels and promotes thrombus formation.[29] Platelet tissue factor synthesis in T2DM patients is resistant to inhibition by insulin.[30]Angiolillo *et al* proved that the P2Y12-dependent and P2Y12-independent pathways of platelet reactivity were altered in T2DM patients compared with nondiabetic patients, and insulin-treated DM patients had greater ADP-induced platelet aggregation compared with non-insulin-treated DM patients.[20] Therefore, the loss of responsiveness to insulin together with increased signaling through P2Y12 may explain the hyperactivity of platelets in patients with T2DM.[31]

In addition, for healthy people, insulin can inhibit the collagen pathway of platelet aggregation and increase the cGMP concentration in platelets; however, for insulin-resistant patients, insulin cannot inhibit the interaction between platelets and collagen at all, and it cannot increase the cGMP concentration in the platelets of obese subjects.[13]

Several limitations should be considered in this study. Firstly, we conducted a retrospective analysis in the study, it is difficult to distinguish whether the patients included were suffering from insulin resistance. This is also the focus of our prospective research in the future. Secondly, we only included partly oral hypoglycemic agents to analyze.

Conclusions

In conclusion, exogenous insulin increased the level of MA_{ADP} in patients with acute ischemic vascular events , and MA_{ADP} tested by TEG represents the function of platelet aggregation,[18] its elevation may affect the prognosis of ischemic cardiovascular and cerebrovascular diseases to some extent.[15, 16] In other words, platelets with T2DM patients are more susceptible to activation under the action of insulin. Therefore, when T2DM patients suffer from acute cardiovascular and cerebrovascular disease, we should prescribe exogenous insulin cautiously for hypoglycemic treatment. Nevertheless, a further prospective study needs to be performed.

Declaration of Competing Interest

No conflict of interest.

Funding

This work was supported by Science and Technology Planning Project of Guangdong Province (No. 2017ZC0273)

ORCID iD

Qi. Ma*https://orcid.org/0000-0002-5593-1983* .

Li'an.Huang*https://orcid.org/0000-0002-0416-7532*.

References

1.Norhammar A, Mellbin L and Cosentino F. Diabetes: Prevalence, prognosis and management of a potent cardiovascular risk factor.*Eur J Prev Cardiol* 2017; 24: 52-60. DOI: 10.1177/2047487317709554.

2.Chandrasekhar J, Dangas G, Baber U, et al. Impact of insulin treated and non-insulin-treated diabetes compared to patients without diabetes on 1-year outcomes following contemporary PCI. *Catheter Cardiovasc Interv* 2020 2020/03/13. DOI: 10.1002/ccd.28841.

3.Bawamia BR, Egred M, Jackson M, et al. Percutaneous coronary intervention for left main stem disease: Impact of diabetes mellitus on mortality. *Catheter Cardiovasc Interv* 2020 2020/03/07. DOI: 10.1002/ccd.28818.

4.Shen L, Rorth R, Cosmi D, et al. Insulin treatment and clinical outcomes in patients with diabetes and heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019; 21: 974-984. 2019/07/05. DOI: 10.1002/ejhf.1535.

5.Pepe M, Sardella G, Stefanini GG, et al. Impact of Insulin-Treated and Noninsulin-Treated Diabetes Mellitus in All-Comer Patients Undergoing Percutaneous Coronary Interventions With Polymer-Free Biolimus-Eluting Stent (from the RUDI-FREE Registry). *Am J Cardiol* 2019; 124: 1518-1527. 2019/09/25. DOI: 10.1016/j.amjcard.2019.08.015.

6.Pi SH, Rhee TM, Lee JM, et al. Outcomes in Patients with Diabetes Mellitus According to Insulin Treatment After Percutaneous Coronary Intervention in the Second-Generation Drug-Eluting Stent Era. *Am J Cardiol* 2018; 121: 1505-1511. 2018/05/13. DOI: 10.1016/j.amjcard.2018.02.034.

7.Jil M, Rajnikant M, Richard D, et al. The effects of dual-therapy intensification with insulin or dipeptidylpeptidase-4 inhibitor on cardiovascular events and all-cause mortality in patients with type 2 diabetes: A retrospective cohort study. *Diab Vasc Dis Res* 2017; 14: 295-303. 2017/03/24. DOI: 10.1177/1479164116687102.

8.Herman ME, O'Keefe JH, Bell DSH, et al. Insulin Therapy Increases Cardiovascular Risk in Type 2 Diabetes. *Prog Cardiovasc Dis* 2017; 60: 422-434. 2017/09/30. DOI: 10.1016/j.pcad.2017.09.001.

9.Anfossi G, Massucco P, Mattiello L, et al. Insulin exerts opposite effects on platelet function at physiological and supraphysiological concentrations. *Thromb Res* 1996; 82: 57-68. 1996/04/01. DOI: 10.1016/0049-3848(96)00051-5.

10.Chakraborty K and Sinha AK. The role of insulin as an antithrombotic humoral factor. *Bioessays* 2004; 26: 91-98. 2003/12/30. DOI: 10.1002/bies.10375.

11.Vivas D, Garcia-Rubira JC, Bernardo E, et al. Effects of intensive glucose control on platelet reactivity in patients with acute coronary syndromes. Results of the CHIPS Study ("Control de Hiperglucemia y Actividad Plaquetaria en Pacientes con Sindrome Coronario Agudo"). *Heart* 2011; 97: 803-809. 2011/03/08. DOI: 10.1136/hrt.2010.219949.

12.Vivas D, Garcia-Rubira JC, Bernardo E, et al. Effect of an optimized treatment with insulin on platelet reactivity after discharge in patients with an acute coronary syndrome and hyperglycemia. *Rev Esp Cardiol (Engl Ed)* 2014; 67: 22-27. 2014/04/30. DOI: 10.1016/j.rec.2013.05.020.

13.Westerbacka J, Yki-Jarvinen H, Turpeinen A, et al. Inhibition of platelet-collagen interaction: an in vivo action of insulin abolished by insulin resistance in obesity. *Arterioscler Thromb Vasc Biol*2002; 22: 167-172. 2002/01/15. DOI: 10.1161/hq0102.101546.

14.Ma Q, Chen GZ, Zhang YH, et al. Clinical outcomes and predictive model of platelet reactivity to clopidogrel after acute ischemic vascular events. *Chin Med J (Engl)* 2019; 132: 1053-1062. 2019/03/22. DOI: 10.1097/CM9.0000000000000210.

15.Tantry US and Gurbel PA. Assessment of oral antithrombotic therapy by platelet function testing. *Nat Rev Cardiol* 2011; 8: 572-579. DOI: 10.1038/nrcardio.2011.107.

16.Tang XF, Han YL, Zhang JH, et al. Comparing of light transmittance aggregometry and modified thrombelastograph in predicting clinical outcomes in Chinese patients undergoing coronary stenting with clopidogrel. *Chin Med J (Engl)* 2015; 128: 774-779. DOI: 10.4103/0366-6999.152611.

17.Gurbel PA, Bliden KP, Navickas IA, et al. Adenosine diphosphate-induced platelet-fibrin clot strength: a new thrombelastographic indicator of long-term poststenting ischemic events. *Am Heart J* 2010; 160: 346-354. DOI: 10.1016/j.ahj.2010.05.034.

18.Shen W, Zhou JY, Gu Y, et al. Establishing a reference range for thromboelastography maximum amplitude in patients administrating with antiplatelet drugs. *J Clin Lab Anal* 2019: e23144. 2019/12/08. DOI: 10.1002/jcla.23144.

19.Hobson AR, Petley GW, Dawkins KD, et al. A novel fifteen minute test for assessment of individual time-dependent clotting responses to aspirin and clopidogrel using modified thrombelastography. *Platelets* 2007; 18: 497-505. DOI: 10.1080/09537100701329162.

20.Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol*2006; 48: 298-304. DOI: 10.1016/j.jacc.2006.03.038.

21.Alexopoulos D, Vogiatzi C, Stavrou K, et al. Diabetes mellitus and platelet reactivity in patients under prasugrel or ticagrelor treatment: an observational study. *Cardiovasc Diabetol* 2015; 14: 68. 2015/05/31. DOI: 10.1186/s12933-015-0232-1.

22.Yki-Jarvinen H. Nonglycemic effects of insulin. *Clin Cornerstone* 2003; Suppl 4: S6-12. 2004/02/28. DOI: 10.1016/s1098-3597(03)90061-5.

23.Spectre G, Ostenson CG, Li N, et al. Postprandial platelet activation is related to postprandial plasma insulin rather than glucose in patients with type 2 diabetes. *Diabetes* 2012; 61: 2380-2384. 2012/06/13. DOI: 10.2337/db11-1806.

24.Spectre G, Stalesen R, Ostenson CG, et al. Meal-induced platelet activation in diabetes mellitus type 1 or type 2 is related to postprandial insulin rather than glucose levels. *Thromb Res* 2016; 141: 93-97. 2016/03/20. DOI: 10.1016/j.thromres.2016.03.009.

25.Trovati M and Anfossi G. Influence of insulin and of insulin resistance on platelet and vascular smooth muscle cell function. *J Diabetes Complications* 2002; 16: 35-40. 2002/03/02.

26.Suslova TE, Sitozhevskii AV, Ogurkova ON, et al. Platelet hemostasis in patients with metabolic syndrome and type 2 diabetes mellitus: cGMP- and NO-dependent mechanisms in the insulin-mediated platelet aggregation. *Front Physiol* 2014; 5: 501. 2015/01/21. DOI: 10.3389/fphys.2014.00501.

27.Ferreira IA, Eybrechts KL, Mocking AI, et al. IRS-1 mediates inhibition of Ca2+ mobilization by insulin via the inhibitory G-protein Gi. *J Biol Chem* 2004; 279: 3254-3264. 2003/11/07. DOI: 10.1074/jbc.M305474200.

28.Udvardy M, Pfliegler G and Rak K. Platelet insulin receptor determination in non-insulin dependent diabetes mellitus.*Experientia* 1985; 41: 422-423. 1985/03/15. DOI: 10.1007/bf02004539.

29.Boden G and Rao AK. Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation. *Curr Diab Rep*2007; 7: 223-227. 2007/06/06.

30.Gerrits AJ, Koekman CA, van Haeften TW, et al. Platelet tissue factor synthesis in type 2 diabetic patients is resistant to inhibition by insulin. *Diabetes* 2010; 59: 1487-1495. DOI: 10.2337/db09-1008.

31.Ferreira IA, Mocking AI, Feijge MA, et al. Platelet inhibition by insulin is absent in type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2006; 26: 417-422. DOI: 10.1161/01.ATV.0000199519.37089.a0.

Hosted file

`Figure.docx` available at https://authorea.com/users/326519/articles/454330-effect-of-exogenous-insulin-on-platelet-reactivity-in-patients-with-acute-ischemic-vascular-events

Hosted file

`Tables.docx` available at https://authorea.com/users/326519/articles/454330-effect-of-exogenous-insulin-on-platelet-reactivity-in-patients-with-acute-ischemic-vascular-events