Antiplatelet Therapy for ST-segment Elevation Myocardial Infarction: Highlight of 2020 Focused Update of the 2012 Guidelines of the Taiwan Society of Cardiology for the Management of ST-Segment Elevation Myocardial Infarction

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Abstract

Antiplatelet therapy is the cornerstone in the management of ST-segment elevation myocardial infarction (STEMI). The 2020 Focused Update of the 2012 Guidelines of the Taiwan Society of Cardiology for the Management of ST-Segment Elevation Myocardial Infarction was recently published. This guideline recommended that the use of dual antiplatelet therapy with aspirin and P2Y12 inhibitor is necessary for STEMI patients to reduce further ischemic risks. Concerning about the choice of P2Y12 inhibitor, ticagrelor or standard-dose prasugrel (60 mg loading dose, 10 mg daily dose) are both indicated for STEMI patients undergoing primary percutaneous coronary intervention (PCI). For patients with high bleeding risk features, clopidogrel may be considered to reduce the bleeding risk. In addition, reduced-dose prasugrel (20 mg loading dose, 3.75 mg daily dose) may also be considered in STEMI patients undergoing primary PCI based on Asian data. We hope the implementation of this guideline's recommendations can improve clinical outcomes for STEMI patients in Taiwan.

Keywords: ST-segment elevation myocardial infarction, antiplatelet therapy, guideline

Introduction

Concomitant use of aspirin and clopidogrel in acute coronary syndrome (ACS) patients has been shown to reduce major cardiovascular events compared with aspirin alone in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study,[1] and dual antiplatelet therapy (DAPT) with aspirin and clopidogrel have been listed as standard therapy in ACS patients for many years. In the 2012 Taiwan STEMI Guideline, clopidogrel was also listed as the

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only P2Y12 inhibitors for ST-segment elevation myocardial infarction (STEMI) patients.[2] However, comparing with clopidogrel, new P2Y12 inhibitors including ticagrelor and prasugrel, both showed greater efficacy in reducing ischemic events at the cost of increasing bleeding risks. Therefore, to balance the ischemic and bleeding risk in STEMI patients, the choice of different P2Y12 inhibitors has become an important issue in clinical treatment. Last year, the 2020 Focused Update of the 2012 Guidelines of the Taiwan Society of Cardiology for the Management of ST-Segment Elevation Myocardial Infarction was published.[3] This purpose of this review article is to highlight the recommendations of antiplatelet therapy from this focused update guideline. We hope to summarize these recommendations and to review the background scientific evidences.

Clopidogrel

Two large randomized control trials have demonstrated that adding clopidogrel to aspirin reduced ischemic and mortality rates in STEMI patients with different reperfusion strategies.[4,5] In Taiwan, four observation studies further confirmed that treating ACS patients with DAPT (aspirin and clopidogrel) for 9-12 months improved ischemic and mortality risks, regardless receiving percutaneous coronary intervention (PCI) or not.[6-9] About the issue of clopidogrel loading doses, some studies showed that 600 mg loading dose lead to higher and faster platelet inhibition than 300 mg in patients who received elective PCI.[10,11] However, in the CURRENT–OASIS 7 trial, similar ischemic events with higher bleeding risks were noted in ACS patients loading with clopidogrel 600 mg, comparing with patients receiving 300 mg loading dose.[12] A meta-analysis including 25,383 subjects receiving PCI demonstrated that patients with 600 mg clopidogrel loading dose had lower rates of major cardiovascular events comparing to patients receiving 300 mg loading, and the major bleeding rates were similar between these 2 groups.[13] Based on current evidences, both 300 mg and 600 mg clopidogrel loading doses are recommended for STEMI patients. However, the onset of clopidogrel is relatively slow in ACS patients because it needs a 2-steps metabolism to be transferred from an inactive prodrugs to an active metabolites.[14] In addition, the percentage of cytochrome P450 2C19 polymorphism and clopidogrel resistance is common in ACS patients, which could be associated with increased cardiovascular events.[15,16] Some observational studies even demonstrated that Asian population have higher percentage of CYP2C19 reduced function alleles carrier than Caucasian subjects. Therefore, newer P2Y12 inhibitors (prasugrel and ticagrelor) were developed to improve these drawbacks of clopidogrel.[17,18]

Prasugrel

Prasugrel (60 mg loading and 10 mg daily dose) is one of the newer P2Y12 inhibitors, which has higher and faster platelet inhibitory effects than clopidogrel.[19] In the TRITON–TIMI 38 trial, 13,608 ACS patients were randomized to prasugrel or clopidogrel, which demonstrated that prasugrel reduced ischemic risk by 18% when comparing with clopidogrel [hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.73-0.93], at the cost of increased major bleeding events by 40% (HR 1.40, 95% CI 1.05-1.88).[20] Further analysis for STEMI subgroup showed consistent benefits of ischemic risks reduction in patients receiving prasugrel (HR 0.79, 95% CI 0.65-0.97), regardless of the PCI timing.[21] However, a post-hoc analysis showed that in patients with ischemic stroke or transient ischemic attack (TIA), prasugrel was associated with a trend of increased major bleeding ($p = 0.06$) and a net clinical harm. In addition, no clinical benefit of prasugrel was also noted in patients aged than 75 years old or whose body weight were less than 60 kg.[20] As a result, it is contraindicated to give prasugrel in patients with prior history of stroke or TIA, and it should also be prescribed cautiously for patients with old age or low body weight.

It is worth of noticing that reduced-dose prasugrel (20 mg loading and 3.75 mg daily dose) is available in Taiwan and Japan for the concern of higher bleeding risk in Asian populations. The clinical evidence base of the reduced-dose prasugrel comes from the PRASFIT-ACS trial, which has similar study designs with the TRITON-TIMI 38 study and was conducted in Japan. However, different from the TRITON-TIMI 38 study, patients with prior stroke or TIA were excluded in this trial. At last, 1,363 ACS patients were randomized in this study, and 50% of the study population were STEMI patients. Patients receiving reduced-dose prasugrel had 23% ischemic risk reduction (HR 0.77, 95% CI 0.56-1.07) comparing to patients receiving clopidogrel. This results were similar to the data of the TRITON-TIMI 38 trial, even though not reaching statistically significance, which may be due to the smaller patient sample size in this study. In addition, when comparing with clopidogrel, prasugrel was associated with similar risk of non-coronary artery bypass graft (CABG) major bleeding.[22] About the real world data of the reduced-dose prasugrel, the PRASFIT-Practice I study is a post-marketing survey in Japan, which recruited 732 ACS patients who received both PCI and reduced-dose prasugrel from 2014 to 2015, and 60% of the study subjects were STEMI patients. During the observational period of time, the rate of major cardiovascular events was 3.1%, and the rate of major bleeding was 1.6%, which indicated the efficacy and safety of this regimen.[23] Another large national wide registry conducted in Japan recruited 62,737 ACS patients receiving PCI in 2016, and 12,016 patients in the clopidogrel and prasugrel groups respectively were selected for comparison after propensity score matching. The percentages of STEMI patients were 30.7% in the clopidogrel and 32.6% in the prasugrel groups. In this study, similar rates of mortality and stent thrombosis were noted between these 2 groups. However, patients receiving reduced-dose prasugrel was observed to have higher bleeding risk [odds ratio (OR) 1.65, 95% CI 1.10-2.51]. In the STEMI patients, prasugrel was still associated with a trend of higher bleeding risk when comparing to clopidogrel (0.67% vs. 0.47%; OR 1.44, 95% CI 0.76-2.78).[24] Therefore, further studies are necessary in the future to clarify the efficacy and safety of reduced-dose prasugrel in Asian ACS patients.

Ticagrelor

Ticagrelor (180 mg loading and 90 mg twice daily dose) is the other newer P2Y12 inhibitor, which is active in platelet function inhibition without the need through hepatic metabolism. Therefore, it has faster onset and greater platelet inhibitory activity than clopidogrel. Moreover, the binding of ticagrelor to P2Y12 receptor is reversible. Therefore, the offset of ticagrelor is also faster than that of clopidogrel after drug discontinuation.[25] The PLATO study randomized 18,624 ACS patients to ticagrelor and clopidogrel, and ticagrelor was shown to reduce the risk of composite primary outcomes including CV death, MI, or stroke by 16% (HR 0.84, 95% CI 0.77-0.92). However, as a more potent platelet activity inhibitor, ticagrelor was also shown to be associated with increased risk of non-CABG major bleeding (4.5% vs. 3.8%, p = 0.03).[26] The subgroup analysis showed that the benefits of ticagrelor over clopidogrel was consistent in STEMI patients. The risks of MI, total mortality and definite stent thrombosis were also reduced significantly in STEMI patients receiving primary PCI, and the major bleeding rates were similar between 2 groups in this population.[27] For STEMI patients receiving fibrinolytic therapy, another TREAT study also showed that ticagrelor was associated with similar 30-days TIMI major bleeding and 12 months ischemic / bleeding risks when comparing to clopidogrel.[28,29] In addition to randomized control trials, the SWEDEHEART registry recruited 45,073 ACS patients in Sweden from 2010 to 2013 and provided the largest clinical evidence of real world data. Consistent with the results from the PLATO study, ticagrelor

comparing to clopidogrel in this registry was associated with a 15% composite ischemic risk reduction (HR 0.85, 95% CI 0.78-0.93) but a 20% risk increment of re-admission with bleeding (HR 1.20, 95% CI 1.04-1.40).[30] However, about the efficacy and safety of ticagrelor in Asian ACS population, heterogeneous and conflicting results were demonstrated from relatively small randomized control trials and observational studies.[31-36] In Taiwan, three observational studies demonstrated that ticagrelor reduced ischemic risks in ACS patients when comparing to clopidogrel, and the major bleeding risks were similar between these two drugs.[37-39]

Comparisons between P2Y12 inhibitors

A meta-analysis compared the efficacy and safety of newer P2Y12 inhibitors including ticagrelor and prasugrel to cliopidogrel in STEMI patients receiving primary PCI. It showed that ticagrelor / prasugrel were associated with reduced risks of all-cause mortality, major adverse cardiovascular events (MACE), and stent thrombosis. In addition, the bleeding risks were similar between newer P2Y12 inhibitors and clopidogrel.[40] In another meta-analysis, ticagrelor and prasugrel were both associated with lower risk of MACE than clopidogrel in STEMI patients undergoing primary PCI, and prasugrel was even associated with lower MACE and mortality rates at 1 year than other P2Y12 inhibitors.[41] A retrospective data claim study enrolled 40706 acute myocardial infarction patients undergoing PCI from 2010 to 2015 in Korea, and 35% were STEMI patients. Both ticagrelor and prasugrel reduced 30-day mortality risks comparing to clopidogrel in this study.[42] Another real world data from KAMIR-NIH registry also showed that newer P2Y12 inhibitors including prasugrel and ticagrelor were associated with higher MACE-free rate than clopidogrel in ACS patients, and the results were consistent in the STEMI subgroup.[43] For head to head comparisons between ticagrelor and prasugrel, a retrospective study using Truven Commercial and Medicare Supplemental claims database from 2011-2016 analyzed 10,073 ACS patients treated with prasugrel or ticagrelor respectively. In this study, ticagrelor was associated with lower rates of ischemic and bleeding risks comparing to prasugrel.[44] However, in the ISAR-REACT 5 study, 4,018 ACS patients were randomized to prasugrel and ticagrelor, and 41% were STEMI subjects. Comparing to ticagrelor, prasugrel reduced composite ischemic risks including death, MI, or stroke significantly, and the bleeding rates were similar between these two groups.[45]

Summary

According to current clinical evidences, ticagrelor or standard-dose prasugrel should be the prior choices of P2Y12 inhibitors in STEMI patients. However, for patients with high bleeding risk, it is also reasonable to choose clopidogrel rather than newer P2Y12 inhibitors if the concerns about bleeding outweigh ischemia risks. In general, high bleeding risk characteristics include old age, chronic kidney disease, low body weight, anemia, prior major bleeding or intra-cranial hemorrhage history, or concurrent use of oral anti-coagulant. Moreover, reduced-dose prasugrel (20 mg loading and 3.75 mg daily maintenance dose) may also be considered for STEMI patients undergoing PCI in Taiwan according to Asians' data. In summary, to get the maximal clinical net benefit, the choice of P2Y12 inhibitors and their doses should be individualized to balance the ischemic and bleeding risks in Asian STEMI patients.

Recommendation

- Ticagrelor (180 mg loading dose, 90 mg twice daily), prasugrel (60 mg loading dose, 10 mg daily dose), or clopidogrel (300-600 mg loading dose, 75 mg daily dose) is recommended in STEMI patients undergoing primary PCI unless contraindicated and ticagrelor or prasugrel is

preferred to clopidogrel. (COR I, LOE B)

- Clopidogrel rather than ticagrelor or prasugrel may be onsidered in patients with increased bleeding risk features. (COR IIa, LOE C)
- Reduced dose of prasugrel (20 mg loading dose, 3.75 mg daily dose) may be considered in STEMI patients undergoing PCI based on Asian data. (COR IIa, LOE B)

References

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without STsegment elevation. *N Engl J Med* 2001;345:494-502.
2. Li YH, Yeh HI, Tsai CT, et al. 2012 Guidelines of the Taiwan Society of Cardiology (TSOC) for the management of ST-segment elevation myocardial infarction. *Acta Cardiol Sin* 2012;28:63-89.
3. Li YH, Lee CH, Huang WC, et al. 2020 Focused Update of the 2012 Guidelines of the Taiwan Society of Cardiology for the Managementof ST-Segment Elevation Myocardial Infarction. *Acta Cardiol Sin* 2020;36:285-307.
4. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo controlled trial. *Lancet* 2005;366:1607-21.
5. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.
6. Cheng CI, Chen CP, Kuan PL, et al. The causes and outcomes of inadequate implementation of existing guidelines for antiplatelet treatment in patients with acute coronary syndrome: the experience from Taiwan Acute Coronary Syndrome Descriptive Registry (T-ACCORD Registry). *Clin Cardiol* 2010;33:E40-8.
7. Chiang FT, Shyu KG,Wu CJ, et al. Predictors of 1-year outcomes in the Taiwan Acute Coronary Syndrome Full Spectrum Registry. *J Formos Med Assoc* 2014; 113:794-802.
8. Chen SC, Hsiao FY, Lee CM, et al. Duration of dual antiplatelet therapy following percutaneous coronary intervention on rehospitalization for acute coronary syndrome. *BMC Cardiovasc Disord* 2014;14:21.
9. Li YH, Chiu YW, Cheng JJ, et al. Duration of clopidogrel-based dual antiplatelet therapy and clinical outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention - a real-world observation in Taiwan from 2012 to 2015. *Circ J* 2019;83:1317-23.
10. Gurbel PA, Bliden KP, Zaman KA, et al. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel LoadingWith Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study. *Circulation* 2005;111: 1153-9.
11. von Beckerath N, Taubert D, Pogatsa-Murray G, et al. Absorption, etabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISARCHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) trial. *Circulation* 2005;112:2946-50.
12. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;363:930-42.
13. Siller-Matula JM, Huber K, Christ G, et al. Impact of clopidogrel loading dose on clinical outcome in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Heart* 2011;97:98-105.
14. Schömig A. Ticagrelor--is there need for a new player in the antiplatelet-therapy field? *N Engl J Med* 2009;361:1108-11.
15. Matetzky S, Shenkman B, Guetta V, et al. Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction. *Circulation* 2004;109:3171-5.
16. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel aftermyocardial infarction: a cohort study. *Lancet* 2009;373:309-17.
17. Hu XP, Xu JM, Hu YM, et al. Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in Chinese people. *J Clin Pharm Ther* 2007;32: 517-24.
18. Veiga MI, Asimus S, Ferreira PE, et al. Pharmacogenomics of CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5 andMDR1 in Vietnam. *Eur J Clin Pharmacol* 2009;65:355-63.
19. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;116:2923-32.
20. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute

coronary syndromes. *N Engl J Med* 2007;357:2001-15.
21. Udell JA, Braunwald E, Antman EM, et al. Prasugrel versus clopidogrel in patients with ST-segment elevation myocardial infarction according to timing of percutaneous coronary intervention: a TRITON-TIMI 38 subgroup analysis (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38). *JACC Cardiovasc Interv* 2014;7:604-12.
22. Saito S, Isshiki T, Kimura T, et al. Efficacy and safety of adjusteddose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *Circ J* 2014;78:1684-92.
23. Nakamura M, Iizuka T, Sagawa K, et al. Prasugrel for Japanese patients with acute coronary syndrome in short-term clinical practice (PRASFIT-Practice I): a postmarketing observational study. *Cardiovasc Interv Ther* 2018;33:135-45.
24. Akita K, Inohara T, Yamaji K, et al. Impact of reduced-dose prasugrel vs. standard-dose clopidogrel on in-hospital outcomes of percutaneous coronary intervention in 62,737 patients with acute coronary syndromes: a nationwide registry study in Japan. *Eur Heart J Cardiovasc Pharmacother* 2019;pii: pvz056.
25. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009; 120:2577-85.
26. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
27. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patientswith ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 2010;122:2131-41.
28. Berwanger O, Nicolau JC, Carvalho AC, et al. Ticagrelor vs clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: a randomized clinical trial. *JAMA Cardiol* 2018;3:391-9.
29. Berwanger O, Lopes RD, Moia DDF, et al. Ticagrelor versus clopidogrel in patients with STEMI treated with fibrinolysis: TREAT trial. *J Am Coll Cardiol* 2019;73:2819-28.
30. Sahlén A, Varenhorst C, Lagerqvist B, et al. Outcomes in patients treated with ticagrelor or clopidogrel after acutemyocardial infarction: experiences from SWEDEHEART registry. *Eur Heart J* 2016;37:3335-42.
31. Goto S, Huang CH, Park SJ, et al. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronarysyndrome -- randomized, double-blind, phase III PHILO study. *Circ J* 2015;79: 2452-60.
32. Park DW, Kwon O, Jang JS, et al. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. *Circulation* 2019;140:1865-77.
33. Tang X, Li R, Jing Q, et al. Assessment of ticagrelor versus clopidogrel treatment in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Cardiovasc Pharmacol* 2016;68:115-20.
34. Xin YG, Zhang HS, Li YZ, et al. Efficacy and safety of ticagrelor versus clopidogrel with different dosage in high-risk patients with acute coronary syndrome. *Int J Cardiol* 2017;228:275-9.
35. Park KH, Jeong MH, Ahn Y, et al. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea Acute Myocardial Infarction Registry-National Institute of Health. *Int J Cardiol* 2016;215:193-200.
36. Wang H, Wang X. Efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese patientswith acute coronary syndrome. *Ther Clin Risk Manag* 2016;12:1101-5.
37. Chen IC, Lee CH, Fang CC, et al. Efficacy and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: a multicenter retrospective pilot study. *J Chin Med Assoc* 2016;79:521-30.
38. Lee CH, Cheng CL, Yang KYH, et al. Cardiovascular and bleeding risks in acute myocardial infarction newly treated with ticagrelor vs. clopidogrel in Taiwan. *Circ J* 2018;82:747-56.
39. Lee CH, Tsai TH, Lin CJ, et al. Efficacy and safety of ticagrelor compared with clopidogrel in patients with end-stage renal disease with acute myocardial infarction. *Am J Cardiovasc Drugs* 2019;19:325-34.
40. Sun J, Xiang Q, Li C, et al. Efficacy and safety of novel oral P2Y12 receptor inhibitors in patients with ST-segment elevation myocardial infarction undergoing PCI: a systematic review and metaanalysis. *J Cardiovasc Pharmacol* 2017;69:215-27.
41. Rafique AM, Nayyar P,Wang TY, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a network meta-analysis. *JACC Cardiovasc Interv* 2016;9:1036-46.

42. Kim C, Shin DH, Ahn CM, et al. The use pattern and clinical impact of new antiplatelet agents including prasugrel and ticagrelor on 30-day outcomes after acute myocardial infarction in Korea: Korean Health Insurance Review and Assessment Data. *Korean Circ J* 2017;47:888-97.
43. Choe JC, Cha KS, Ahn J, et al. Comparison of prescription rates and clinical outcomes in acute coronary syndrome patients who underwent percutaneous coronary intervention using different P2Y12 inhibitors in a large observational study. *Int J Cardiol* 2019;274:21-6.
44. Dawwas GK, Dietrich E, Winchester DE, et al. Comparative effectiveness and safety of ticagrelor versus prasugrel in patients with acute coronary syndrome: a retrospective cohort analysis. *Pharmacotherapy* 2019;39:912-20.
45. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med* 2019;381:1524-34.