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Thoughts on secondary prevention after percutaneous coronary intervention in Japan

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Currently, aspirin and statins are regarded as the bottom-line treatment regimen for secondary prevention after percutaneous coronary intervention. However, even after implementation of aspirin and statin therapy, there remains a residual risk of cardiovascular events. Endeavours to reduce cardiovascular events further have been targeted at more intensive antithrombotic and lipid-lowering therapies.

Putting the results from the previous trials into perspective, the use of more intensive antithrombotic therapy could reduce ischaemic cardiovascular events, but has consistently increased the bleeding events in patients with stable coronary artery disease (CAD) including post-PCI patients[1-3]. Furthermore, there are signs emerging of increased mortality in the case of prolonged dual antiplatelet therapy (DAPT) as compared with shorter DAPT[4]. Therefore, we should balance the benefits and risks when considering more intensive antithrombotic therapy as a secondary preventive measure in patients with stable CAD after PCI. Theoretically, more intensive antithrombotic therapy would be best suited in those patients with a high thrombotic risk but low bleeding risk, who should be identified by estimating the thrombotic and bleeding risks separately and individually. We should estimate the absolute thrombotic and bleeding risks of the individual patients by applying the appropriate risk scores to the most contemporary long-term follow-up database in the geographic and/or ethnic population of interest. Therefore, we have developed the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) thrombotic and bleeding risk scores from a large Japanese database of patients who underwent first coronary revascularisation[5]. The CREDO-Kyoto thrombotic and bleeding risk scores have demonstrated modest accuracy in stratifying the thrombotic risk and bleeding risk separately in the validation cohort from other Japanese PCI studies. We found substantial overlap of the predictors between the thrombotic and bleeding risk scores. Chronic kidney disease, atrial fibrillation, peripheral vascular disease and heart failure emerged as the common predictors for both thrombotic and bleeding events. Reflecting the overlap of the risk predictors, a large proportion of high thrombotic risk patients also had high bleeding risk. For this group of patients, a more intensive antithrombotic therapy would not be appropriate **(Figure 1)**. Patients with high thrombotic risk but low bleeding risk accounted

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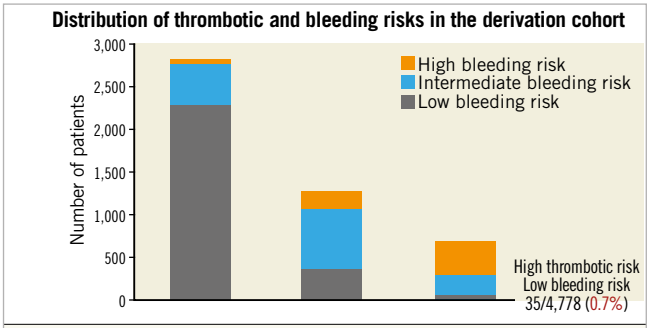

	Low thrombotic risk	Intermediate thrombotic risk	High thrombotic risk	Total
High bleeding risk	24 (0.9%)	206 (16.3%)	408 (58.9%)	638
Intermediate bleeding risk	510 (18.1%)	695 (56.0%)	250 (36.1%)	1,455
Low bleeding risk	2,288 (81.1%)	362 (28.7%)	35 (5.1%)	2,685
Total	2,822	1,263	693	4,778

Figure 1. *Distribution of thrombotic and bleeding risk based on the CREDO-Kyoto thrombotic and bleeding risk scores. A large proportion of high thrombotic risk patients also had a high bleeding risk. Patients with high thrombotic risk but low bleeding risk represented a very small proportion of the Japanese CAD population. CAD: coronary artery disease; CREDO-Kyoto: Coronary REvascularization Demonstrating Outcome study in Kyoto*

for a very small proportion of the Japanese CAD population, which could be explained by the relatively lower thrombotic risk but comparable bleeding risk in Japanese patients as compared with Western patients. Therefore, more intensive antithrombotic therapy might not be the way to go for further prevention of cardiovascular events in the vast majority of Japanese patients with stable CAD after PCI.

More intensive lipid-lowering therapy is much safer than more intensive antithrombotic therapy. Based on the several previous "more versus less statins" trials, the current American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommends high-intensity statin therapy in patients with clinical atherosclerotic cardiovascular disease[6]. However, high-intensity statin therapy is not widely implemented in daily clinical practice, particularly in Asia, at least partly because there has been no previous "more versus less statins" trial in Asia. We conducted a large randomised controlled trial comparing high-dose (4 mg/day) versus low-dose (1 mg/day) pitavastatin in 13,054 Japanese patients with stable CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease [REAL-CAD]), which is the largest ever "more versus less statins" trial, and the first trial of this type conducted in Asia. High-dose as compared with low-dose pitavastatin significantly reduced the risk of the primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or unstable angina requiring emergency hospitalisation) (4.3% versus 5.4%, respectively, HR 0.81, 95% CI: 0.69-0.95, p=0.01)[7]. The favourable effect of high-dose pitavastatin was demonstrated regardless of the baseline low-density lipoprotein cholesterol (LDL-C) level. Relative risk reduction for the primary endpoint in the REAL-CAD trial conducted in Japan was remarkably comparable to that in the Treating to New Targets (TNT) trial conducted outside Japan, although the absolute event rate was much higher in the TNT trial than in the REAL-CAD trial **(Figure 2)**[8]. A positive result in a large randomised controlled trial does not always lead to a strong recommendation to adopt the tested intervention in real clinical practice. However, in the case of high-dose statins, we should strongly recommend adopting it in Japanese clinical practice, considering the robust risk reduction seen in Japanese patients, proven safety of long-term statin use during more than 30 years of clinical experience, its reasonably low cost, and the issue of "what is the optimal statin dose?".

Beyond the high-intensity statins, the efficacy of non-statin LDL-C-lowering agents in reducing cardiovascular events has long been debated. A few years ago, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that ezetimibe inhibiting intestinal absorption of cholesterol significantly reduced cardiovascular events with a 6.4% relative risk reduction in 18,144 patients with acute coronary syndrome (ACS)[9]. More recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and ODYSSEY Outcomes trials demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab, respectively) promoting LDL receptor recycling significantly reduced cardiovascular events with a 15% relative risk reduction in 27,546 patients with atherosclerotic cardiovascular disease and in 18,924 patients with ACS[10]. These non-statin LDL-C-lowering agents also appeared to be safe, and might be promising for secondary prevention in very high-risk patients. However, in real-world clinical practice, the decision to implement more intensive intervention should be based on consideration of the efficacy (relative risk reduction) and safety of a given intervention, absolute cardiovascular event risk of a given patient, and the cost of the intervention. The role of more

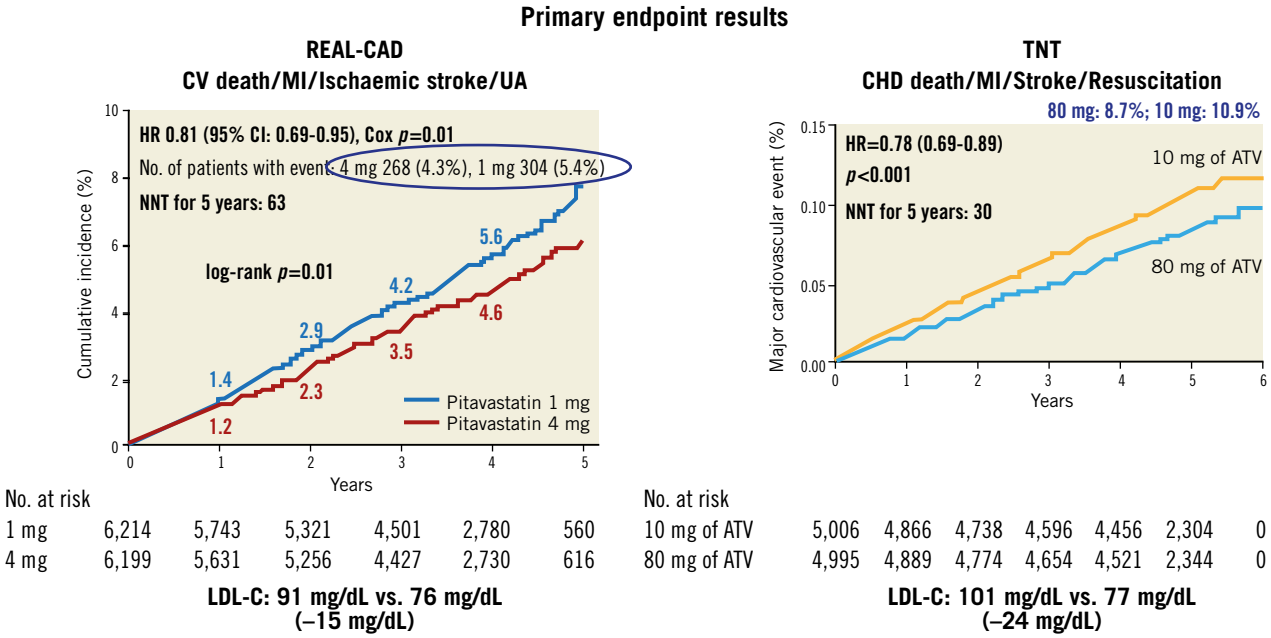

Figure 2. *Primary endpoint results in the REAL-CAD and TNT trials. ATV: atorvastatin; CHD: coronary heart disease; CI: confidence interval; CV: cardiovascular, HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; NNT: number needed to treat; REAL-CAD: Randomised Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease; TNT: Treating to New Targets; UA: unstable angina*

intensive lipid-lowering interventions beyond "high-intensity statin" therapy would be very limited in Japanese CAD patients, in whom the cardiovascular event risk is relatively low, and therefore the cost-effectiveness balance is unfavourable for these expensive interventions.

Conflict of interest statement

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References

1. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. *N Engl J Med.* 2014;371:2155-66.

2. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med.* 2015;372:1791-800.

3. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar A, Fox KAA, Parkhomenko AN, Ertl G, Störk S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S; COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med.* 2017;377:1319-30.

4. Toyota T, Shiomi H, Morimoto T, Natsuaki M, Kimura T. Short versus prolonged dual antiplatelet therapy (DAPT) duration after coronary stent implantation: A comparison between the DAPT study and 9 other trials evaluating DAPT duration. *PLoS One.* 2017;12:e0174502.

5. Natsuaki M, Morimoto T, Yamaji K, Watanabe H, Yoshikawa Y, Shiomi H, Nakagawa Y, Furukawa Y, Kadota K, Ando K, Akasaka T, Hanaoka KI, Kozuma K, Tanabe K, Morino Y, Muramatsu T, Kimura T; CREDO-Kyoto PCI/CABG Registry

Cohort 2, RESET, and NEXT trial investigators. Prediction of Thrombotic and Bleeding Events After Percutaneous Coronary Intervention: CREDO-Kyoto Thrombotic and Bleeding Risk Scores. *J Am Heart Assoc.* 2018 May 22;7(11).

6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129:S1-45.

7. Taguchi I, Iimuro S, Iwata H, Takashima H, Abe M, Amiya E, Ogawa T, Ozaki Y, Sakuma I, Nakagawa Y, Hibi K, Hiro T, Fukumoto Y, Hokimoto S, Miyauchi K, Yamazaki T, Ito H, Otsuji Y, Kimura K, Takahashi J, Hirayama A, Yokoi H, Kitagawa K, Urabe T, Okada Y, Terayama Y, Toyoda K, Nagao T, Matsumoto M, Ohashi Y, Kaneko T, Fujita R, Ohtsu H, Ogawa H, Daida H. Shimokawa H, Saito Y, Kimura T, Inoue T, Matsuzaki M, Nagai R. High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial. *Circulation.* 2018;137:1997-2009.

8. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425-35.

9. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372:2387-97.

10. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med.* 2017;376:1713-22.