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EDITORIAL COMMENT

Is Stent Thrombosis a Genetic Disease?*

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Despite a significant decrease of its incidence, stent thrombosis (ST) remains the most feared complication of percutaneous coronary intervention (PCI). The physiopathology of ST is not fully understood but involves many factors including the patients' comorbidities including diabetes, chronic renal failure, or inflammatory disease; the type and intensity of antiplatelet therapy; patients' compliance; the complexity of PCI; the success of procedure; and the stent platform itself. In the 1990s, before the introduction of $P2Y_{12}$ inhibitors and despite a combination of various antithrombotic agents such aspirin, heparin, and vitamin K antagonist, the rate of ST was 1 in 4 patients, which was not acceptable for the medical community and the future of PCI.[1] The advent of $P2Y_{12}$ inhibitors (ticlopidine initially then after clopidogrel) saved the PCI approach by markedly cutting the rate of early ST to an acceptable rate of 3% to 4% during the first month. However, clopidogrel is a prodrug that requires a complex hepatic biotransformation leading to an active metabolite of the drug. Loss-of-function allele CYP2C19*2 has been identified as a very important contributor of the variability of clopidogrel with a negative impact on adverse clinical outcomes including ST.[2-4] Potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel) were consequently developed to provide a more intense $P2Y_{12}$ inhibition without a detrimental effect of genetic polymorphisms of the CYP2C19 on platelet inhibition leading to first-line treatment in the acute coronary syndrome (ACS) setting.[5,6] Thus, an individualized approach based on systematic CYP2C19 genotyping was tested to adapt the choice of $P2Y_{12}$ inhibitors (from potent $P2Y_{12}$ inhibitors to clopidogrel in patients without CYP2C19 loss of function allele). This approach of de-escalation has been associated with favorable results in ACS, and this strategy could be proposed depending on patient's risk profile and availability of genotyping (Class IIb, Level of Evidence: B of the European guidelines).[7]

On the other hand, technical aspects of the PCI procedure and the properties of the stent platform are crucial. First generation of the drug-eluting stent (DES) (cypher and taxus) has been associated with a high rate of late and very late ST.[8] The use of the newest generation of DES with technical improvements (reduced strut thickness, biocompatible polymer, abluminal polymer, shorter duration of polymer resorption, and dose of antiproliferative drug) reduces by half the risk of late and very late ST compared with early-generation DES.[9,10]

In the recent years, the development of intravascular imaging in clinical practice, particularly optical coherence tomography, led to a better understanding of the physiopathology of ST and underlined additional causes of ST related to the procedure. Indeed, mechanisms of ST were dominated by stent malapposition, confirmed in more than one-third of patients, stent underexpansion, neoatherosclerosis, and uncovered struts.[11-13] A systematic use of optical coherence tomography in ST context allows to identify a technical cause in almost all patients and lead to a change of the planed procedure in more than half of the patients.[11]

Henceforth, the better comprehension of ST mechanisms and the improvement of the drugs and stent implantation have contributed to considerably reduced rate of both early and late ST to <1% (**Figure 1**). However, ST is not eradicated and has exposed patients to severe complications requiring a complete and individualized patient evaluation.

In this issue of *JACC: Advances*, Shoji et al[14] have conducted a case-control study in order to identify all

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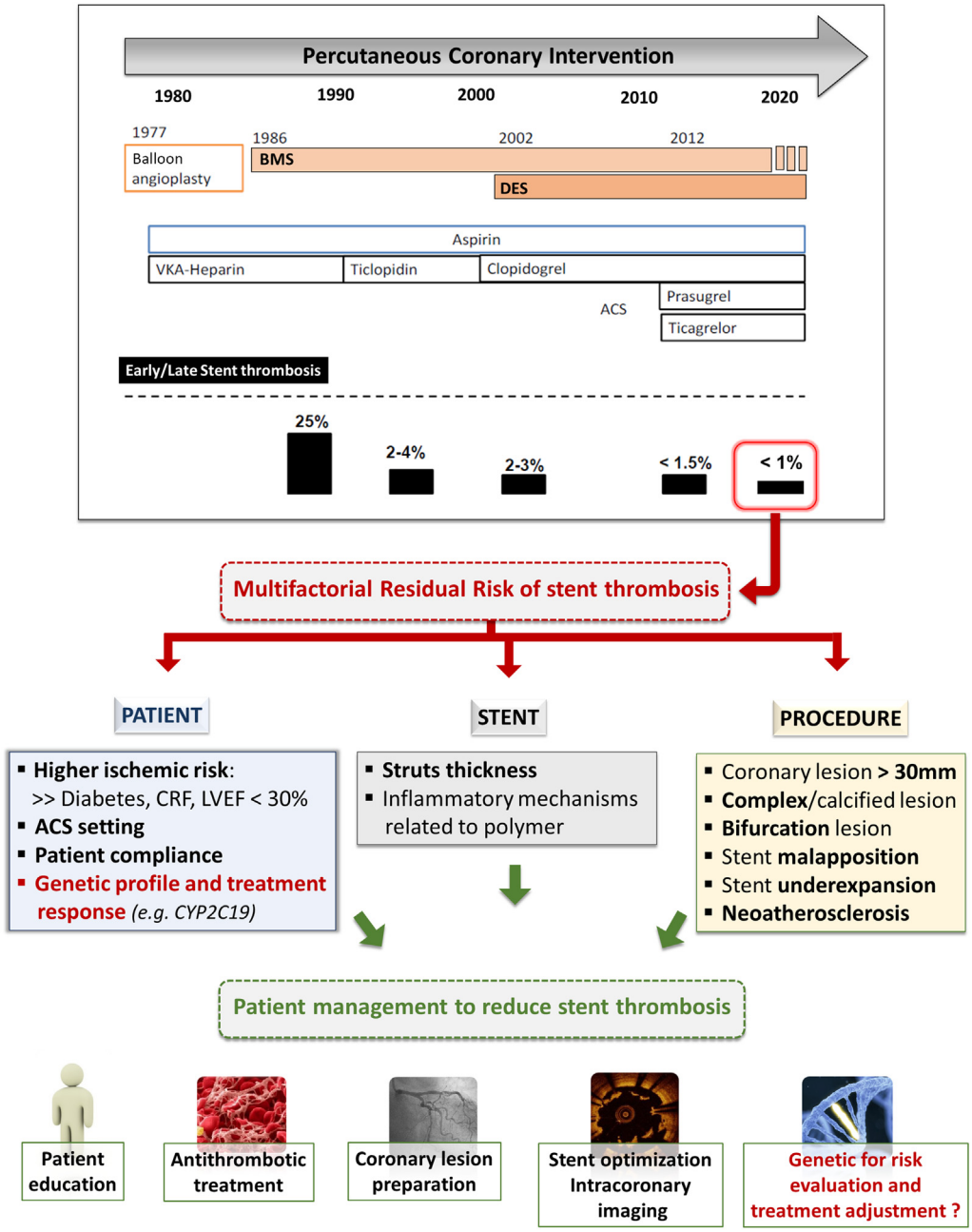
FIGURE 1 Better Comprehension of ST Mechanisms, Improvement of the Drugs and Stent Implantation Have Contributed to Considerably Reduced Rate of Both Early and Late ST to <1%



ACS = acute coronary syndrome; BMS = bare-metal stent; CRF = chronic renal failure; DES = drug-eluting stent; LVEF = left ventricular ejection fraction.

the genetic factors associated with ST using genome-wide association (GWAS). This type of genetic study has achieved great success in identifying genetic susceptibility to understand the pathogenesis of many complex diseases. In this case-control study, the prospective 15-center JCD-KICS (Japan Cardiovascular Database Keio Interhospital Cardiovascular Studies) registry was used to identify 132 patients

with an history of ST (early or late/very late) of whom 42 patients were alive and continuing clinical follow-up. Two different control groups comprising the Biobank Japan patients were used; the first group included patients admitted for ACS, and the second one included patients suffering from stable angina. None of the well-known genetic factors previously identified in the absorption, in the metabolism of clopidogrel or in platelet function,[15] were found, whereas 2 new susceptibly markers were described. Polymorphisms located within NSD1 (nuclear receptor-binding SET domain protein-1) were associated with early ST, and polymorphisms located within GRIN2A (glutamate ionotropic receptor) were associated with late and very late ST. The authors have proposed some potential physiopathological hypotheses to explain the link between these polymorphisms and ST as impairment of DNA methylation resulting in abnormal proliferation of endothelial cells and platelet aggregation or change in Ca2+ responses enhancing cell proliferation, but further dedicated studies are warranted to confirm these hypotheses. The determination of the authors to identify a specific risk profile of ST based on the genetic analysis and independently of coronary lesion and PCI should be appreciated, but the conclusions of this GWAS study must be interpreted with a lot of precautions.

The size of the analyzed population is very small, leading to potential selection and interpretation biases due to the exclusion of a majority of the 132 patients and very large CIs in the analysis.

The choice of the 2 control groups is also questionable. Patients from the Biobank Japan project were recruited between 2003 and 2008 and selected by target diseases.[16]

It is unknown how many patients from the control group underwent PCI, and it is therefore difficult to consider all these patients as control group. Moreover, it should be mentioned that GWAS studies are very interesting to identify genotype-phenotype association, but this type of analysis are prone to identify variants and gene with no direct biological relevance and also false-positive results, owing to the large number of statistical tests performed.

Important informations regarding the context of ST such as the type of dual antiplatelet therapy used, loading and maintenance dose, compliance to dual antiplatelet therapy, the context of occurrence of ST, and procedural or intravascular imaging details of the initial procedure are also lacking.

Finally, none of the well-known genetic factors associated with the genetic variability of platelet response to clopidogrel were identified in this analysis. In the largest case-control study on early ST[15] using a gene candidate approach, 3 genes involved in clopidogrel metabolism and platelet function receptor (*CYP2C19*, *ABCB1*, *ITGB3*) were independently associated with early ST. Other established clinical and angiographic factors (acuteness of PCI, complex lesions, left ventricular dysfunction, diabetes mellitus, use of proton pump inhibitors, and loading dose of clopidogrel) were also found to be associated with early ST. As a consequence, due to polyfactorial mechanisms, it appears difficult to evaluate the risk of ST based only on the genetic analysis regardless of its extent. The best approach to predict ST appears therefore to be the combination of genetic factors and nongenetic factors (clinical and angiographic).

In conclusion, important advances have been made in the comprehension of ST, leading to a better use of $P2Y_{12}$ inhibitors, to an improvement of the quality of stent implantation, and consequently to a considerable decrease in the incidence of this complication. The residual rate of ST remains low, and it is a result of a combination of multiple factors, each individual factor contributing weakly to the occurrence of this complication. Better than an approach centered on unique causal genetic factors, the permanent objective of ST eradication seems to be based on an individualized approach including clinical and angiographic factors but probably also future individual genetic profiling.

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REFERENCES

1. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. *N Engl J Med*. 1991;324:13-17.

2. Mega JL, Simon T, Collet J-P, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304:1821-1830.

3. Hulot J-S, Collet J-P, Cayla G, et al. CYP2C19 but not PON1 genetic variants influence clopidogrel pharmacokinetics, pharmacodynamics, and clinical efficacy in post-myocardial infarction patients. *Circ Cardiovasc Interv*. 2011;4:422-428.

4. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010;376:1320-1328.

5. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057.

6. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.

7. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-1367.

8. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.

9. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *J Am Coll Cardiol Intv*. 2013;6:1267-1274.

10. Räber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation*. 2012;125:1110-1121.

11. Souteyrand G, Amabile N, Mangin L, et al. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the National PESTO French Registry. *Eur Heart J*. 2016;37:1208-1216.

12. Räber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. 2018;39:3281-3300.

13. Adriaenssens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). *Circulation*. 2017;136:1007-1021.

14. Shoji S, Sawano M, Inohara T, et al. Genetic backgrounds associated with stent thrombosis: a pilot study from a percutaneous coronary intervention registry. *JACC Adv*. 2023;2:100172.

15. Cayla G, Hulot J-S, O'Connor SA, et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. *JAMA*. 2011;306:1765-1774.

16. Nagai A, Hirata M, Kamatani Y, et al. Overview of the BioBank Japan project: study design and profile. *J Epidemiol*. 2017;27:S2-S8.

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