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REFERENCES

1. Nguyen V, Cimadevilla C, Estellat C, et al. Haemodynamic and anatomic progression of aortic stenosis. Heart 2015;101:943–7.

2. Clavel MA, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. J Am Coll Cardiol 2014;64:1202–13.

3. Clavel MA, Messika-Zeitoun D, Pibarot P, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler-echocardiographic and computed tomographic study. J Am Coll Cardiol 2013;62:2329–38.

4. Simard L, Côté N, Dagenais F, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? Circ Res 2017;120:681–91.

Ticagrelor Versus Clopidogrel on Myocardial Infarct Size in Patients Undergoing Primary Percutaneous Coronary Intervention

Compared with clopidogrel, ticagrelor improves clinical outcomes in patients with acute coronary syndrome (1). However, the mechanism of ticagrelor's benefits has not been fully elucidated. Although recent animal studies demonstrated that ticagrelor reduces reperfusion injury and limits myocardial infarct size (2,3), ticagrelor did not improve ST-segment elevation resolution in patients with ST-segment elevation myocardial infarction (STEMI) (4). This study sought to compare the effects of ticagrelor and clopidogrel on myocardial infarct size in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

We conducted a 2-center, prospective, randomized, open-label, blinded endpoint study. The institutional review board approved the protocol (NCT01738100), and written informed consent was obtained. From January 2013 to June 2016, a total of 110 patients with STEMI undergoing primary PCI were randomly assigned to the ticagrelor group (180-mg loading dose, 90 mg twice daily thereafter) or the clopidogrel group (600-mg loading dose, 75 mg daily thereafter) at a 1:1 ratio. Patients with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 were randomly assigned to intracoronary injection of morphine sulfate or saline at a 1:1 ratio to concurrently investigate morphine-induced cardioprotection. These second randomization data will be reported separately. The primary endpoint was myocardial infarct size assessed by cardiac magnetic resonance (CMR) imaging. Imaging acquisition and measurement of CMR were performed within 5 days after the index event as previously reported protocol in our center (5).

Evaluable CMR images were available in 45 and 50 patients of the ticagrelor and clopidogrel groups, respectively. There were no significant differences in baseline characteristics between the ticagrelor and clopidogrel groups. Angiographic and procedural findings were well balanced except pre-procedural TIMI flow grade (33 [73.3%] in the ticagrelor group vs. 42 [84.0%] in the clopidogrel group; $p = 0.20$). There was no significant difference in morphine use between the groups (48.6% vs. 55.6%; $p = 0.54$). Myocardial infarct size, the primary endpoint, and the extent of microvascular obstruction were significantly smaller in the ticagrelor group (**Table 1**). In exploratory subgroup analysis, a beneficial effect of ticagrelor was consistent regardless of morphine use (p for interaction = 0.33). Final TIMI flow grade and myocardial blush grade were comparable between the 2 groups. Although the frequency of complete ST-segment elevation resolution did not differ between the groups, peak creatinine kinase-myocardial band fraction level was also reduced in the ticagrelor group. Of patients with pre-procedural TIMI flow grade 0 to 1, beneficial effects of ticagrelor were consistent (infarct size: 22.6 ± 9.7% vs. 28.1 ± 11.0%, $p = 0.02$; microvascular obstruction: 4.4 ± 4.1% vs. 7.1 ± 6.3%, $p = 0.03$).

Platelet inhibition was comparable between the groups just before reperfusion, which was supported

TABLE 1 Study Endpoints

	Ticagrelor (n = 45)	Clopidogrel (n = 50)	p Value
Infarct size, % LV	21.5 ± 10.9	26.5 ± 11.3	0.03
Microvascular obstruction, % LV	3.0 (0-9.2)	5.3 (0.5-10.9)	0.02
Mean transmurality score	1.9 ± 0.5	2.1 ± 0.4	0.06
LV ejection fraction, %	55.2 ± 9.5	52.8 ± 8.7	0.21
Final TIMI flow grade 3	43 (95.6)	44 (88.0)	0.19
Myocardial blush grade 2/3	39 (86.6)	37 (74.0)	0.89
Complete ST-segment elevation resolution	21 (46.7)	24 (48.0)	0.90
Peak CK-MB fraction, ng/mL	170.4 (80.5-267.4)	232.7 (117.1-310.2)	0.04
$P2Y_{12}$ reaction unit	216.1 ± 83.6	231.0 ± 64.0	0.34

Values are mean ± SD, median (interquartile range), or n (%).

CK-MB = creatinine kinase-myocardial band; LV = left ventricular; TIMI = Thrombolysis In Myocardial Infarction.

by animal studies (2,3) and suggests a platelet-independent cardioprotective effect of ticagrelor. To the best of our knowledge, this study is the first to demonstrate the effect of ticagrelor on myocardial ischemia or reperfusion injury using CMR in patients with STEMI undergoing primary PCI. Our study had several limitations, including relatively small sample size, open label, performing CMR in the early period, and imbalance in initial TIMI flow grade. However, sample size calculation was based on rational background, infarct size was assessed blindly, and results of subgroup analysis were consistent. Additionally, in several important studies on infarct size, CMR was performed within 1 week.

In conclusion, we demonstrated that ticagrelor reduced myocardial infarct size and microvascular obstruction in patients with STEMI. Our data suggest that the benefit of ticagrelor may result from reducing myocardial injury, as well as preventing recurrent vascular events.

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REFERENCES

1. 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.

2. Nanhwan MK, Ling S, Kodakandla M, Nylander S, Ye Y, Birnbaum Y. Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect. Arterioscler Thromb Vasc Biol 2014;34:2078–85.

3. Ye Y, Birnbaum GD, Perez-Polo JR, Nanhwan MK, Nylander S, Birnbaum Y. Ticagrelor protects the heart against reperfusion injury and improves remodeling after myocardial infarction. Arterioscler Thromb Vasc Biol 2015;35:1805–14.

4. Armstrong PW, Siha H, Fu Y, et al. ST-elevation acute coronary syndromes in the Platelet Inhibition and Patient Outcomes trial: insights from the ECG substudy. Circulation 2012;125:514–21.

5. Kim EK, Choi JH, Song YB, et al. A protective role of early collateral blood flow in patients with ST-segment elevation myocardial infarction. Am Heart J 2016;171:56–63.

The Complex miRNAs-p53 Signaling Network in Cardiovascular Disease

I read the paper by Barwari et al. (1) with great interest and congratulate the authors on their excellent work. As the authors correctly state, microribonucleic acids (miRNAs) are the subject of intense interest in understanding and treating cardiovascular disease. However, I would like to call attention to a point that needs further clarification. A close interaction between p53 and miRNAs has been well documented. Although the ability of miRNAs in regulating the effects of p53 has been demonstrated (2), growing lists of p53 downstream miRNA targets have also been identified (3): 1) under cell stress, p53 induces the expression of miR-34 a/b/c and miR-145 to down-regulate the antiapoptotic protein expression, thus promoting apoptosis (3); 2) p53-responsive miRNAs (miR-192, miR-194, and miR-34a) are predictive indicators of heart failure after acute myocardial infarction (4); and 3) p53/Mdm2-regulated miRNAs control cardiomyocyte proliferation (5).

The findings of Barwari et al. (1) add significant information to previously published data, but evaluating the relationships between p53 and miRNAs would be useful for better understanding of the role of this complex signaling network in cardiovascular disease.

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REFERENCES

1. Barwari T, Joshi A, Mayr M. MicroRNAs in cardiovascular disease. J Am Coll Cardiol 2016;68:2577–84.

2. Xu Y, Zhu W, Wang Z, Yuan W, Sun Y, Liu H, Du Z. Combinatorial microRNAs suppress hypoxia-induced cardiomyocytes apoptosis. Cell Physiol Biochem 2015;37:921–32.

3. Li J, Aung LH, Long B, Qin D, An S, Li P. miR-23a binds to p53 and enhances its association with miR-128 promoter. Sci Rep 2015;5:16422.