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.

Eun Kyoung Kim, MD, PhD
Taek Kyu Park, MD
Jeong Hoon Yang, MD, PhD
Young Bin Song, MD, PhD
Jin-Ho Choi, MD, PhD
Seung-Hyuk Choi, MD, PhD
Woo Jung Chun, MD, PhD
Yeon Hyeon Choe, MD, PhD
***Hyeon-Cheol Gwon, MD, PhD**
***Joo-Yong Hahn, MD, PhD**

*Heart Vascular Stroke Institute, Samsung Medical Center
Sungkyunkwan University School of Medicine
#81 Irwon-ro, Gangnam-gu
Seoul 06351
South Korea
E-mail: jyhahn@skku.edu OR hc.gwon@samsung.com

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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.

***Salvatore Patanè, MD**

*Cardiologia Ospedale San Vincenzo - Taormina (Me)
Azienda Sanitaria Provinciale di Messina
Contrada Sirina
98039 Taormina (Messina)
Italy
E-mail: patane-@libero.it

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REPLY: The Complex miRNAs-p53 Signaling Network in Cardiovascular Disease

We appreciate the comments by Dr. Patanè on our review on microribonucleic acids (miRNAs) in cardiovascular disease. To concisely summarize the current knowledge and give our opinion on the way ahead, we have selected key publications that illustrate the great potential of this type of noncoding RNA. The vast number of studies that have been published in the past decade in this field require a balance between addressing the full breadth of cardiovascular disease, and a thorough critical appraisal of these fields.

With this in mind, we briefly touch on miRNA effects on cardiomyocyte apoptosis and regeneration. We highlight the study by Boon et al. (1), reporting a regulatory function of miR-34a on cardiomyocyte survival. These results build on previous studies with an oncological focus, reporting this miRNA to be induced by p53 and acting as a proapoptotic signal (2). On the other hand, miRNAs such as miR-590 and miR-199a were shown to promote cardiomyocyte proliferation through cell cycle re-entry (3). miR-199a has also been shown to reduce p53-mediated apoptosis in hypoxic cardiomyocytes (4). These studies illustrate the role that miRNAs seemingly play in apoptosis and proliferation, including the p53 pathway.

Steering cardiomyocytes toward regeneration can certainly be seen as a "Holy Grail" for heart failure therapy, and we applaud all efforts to further elucidate the mechanisms that are at play. On the other hand, there are profound differences in both miRNA expression and structural protein regulation between the (regenerative) zebrafish heart and the (proliferative) neonatal mouse heart compared with the adult mouse heart and human cardiomyocytes that lack these endogenous repair mechanisms (5). In our review, we aim to emphasize the systemic effects of miRNAs that come as a consequence of their expression across tissues and cell types. This is just as true for p53-related actions of miRNAs as it is for any others, on one hand protecting against dysplasia and on the other hand restricting repair of dysfunctional tissue in the failing heart. The lack of techniques that selectively target miRNAs in the heart remains a major impediment to clinical utility. Therefore, we argue for comprehensive evaluation of miRNA effects that takes into account their ubiquitous expression.

Temo Barwari, MD
Abhishek Joshi, BA, BMBCh
***Manuel Mayr, MD, PhD**
*King's British Heart Foundation Centre
King's College London
125 Coldharbour Lane
London SE5 9NU
United Kingdom
E-mail: manuel.mayr@kcl.ac.uk

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Deep Learning With Unsupervised Feature in Echocardiographic Imaging

We read with interest the paper by Narula et al. (1) in which supervised machine learning (ML) was applied to speckle tracking echocardiography (STE) to differentiate hypertrophic cardiomyopathy from athlete's heart. The authors demonstrated the potential of ML in echocardiographic imaging by performing 3 ML algorithms included artificial neural networks, support vector machines, and random forests using 9 subsets for training and then 1 subset for prediction. In the realm of Big Data, ML is revolutionizing the echocardiographic imaging. Recently, preliminary data showed that ML algorithms using STE data might be useful for assessment of left ventricular filling pressures (2). In addition, Sengupta et al. (3)