

## Page Proof Instructions and Queries

**Journal Title:** European Journal of Preventive Cardiology (CPR)

**Article Number:** 780497

Thank you for choosing to publish with us. This is your final opportunity to ensure your article will be accurate at publication. Please review your proof carefully and respond to the queries using the circled tools in the image below, which are available by clicking “Comment” from the right-side menu in Adobe Reader DC.\*

Please use *only* the tools circled in the image, as edits via other tools/methods can be lost during file conversion. For comments, questions, or formatting requests, please use . Please do *not* use comment bubbles/sticky notes .



\*If you do not see these tools, please ensure you have opened this file with Adobe Reader DC, available for free at [get.adobe.com/reader](http://get.adobe.com/reader) or by going to Help > Check for Updates within other versions of Reader. For more detailed instructions, please see [us.sagepub.com/ReaderXProofs](http://us.sagepub.com/ReaderXProofs).

No.	Query
	Please confirm that all author information, including names, affiliations, sequence, and contact details, is correct.
	Please review the entire document for typographical errors, mathematical errors, and any other necessary corrections; check headings, tables, and figures.
	Please confirm that the Funding and Conflict of Interest statements are accurate.
	Please ensure that you have obtained and enclosed all necessary permissions for the reproduction of artistic works, (e.g. illustrations, photographs, charts, maps, other visual material, etc.) not owned by yourself. Please refer to your publishing agreement for further information.
	Please note that this proof represents your final opportunity to review your article prior to publication, so please do send all of your changes now.
AQ: 1	please check the change to the end of the last sentence in the main text. Should something have followed 'driven' in the original?
AQ: 2	Ref. 6: please complete the title.
AQ: 3	Figure 1: please check the added definitions.
AQ: 4	Please provide volume and page range for the ref. 4.



# The decline of rate and mortality of acute myocardial infarction. Almost there, still a long way to go

**Federico Lombardi<sup>1</sup>, Heikki Huikuri<sup>2</sup>, Georg Schmidt<sup>3</sup>  
and Marek Malik<sup>4</sup>; on behalf of e-Rhythm Study Group of EHRA**

In the last decades, reduction of both hospitalizations and mortality due to acute myocardial infarction (AMI) has been reported in many developed countries and attributed, at least in part, to risk modification at population level.<sup>1–3</sup> Several other mechanisms, such as prompt and effective coronary revascularization, have also been shown to be instrumental in the improvement of patient prognosis. Indeed, a growing number of patients is now appropriately managed in the acute and post-acute phase of the index event. Evaluation of residual myocardial ischaemia as well as appropriate administration of drugs, including statins, beta-blockers, ACE inhibitors and dual antiplatelet therapy, represent the mainstream of therapeutical management for most of these patients.

In this issue of the journal, Sulo et al.<sup>4</sup> has updated information on trends of incident AMI in Norway according to data of the ‘Cardiovascular Disease in Norway 1994–2014’ project. They observed a yearly decline of AMI diagnoses by 2.6% and 2.8% in men and women, respectively, that contributed to the reduction of both AMI hospitalization and mortality. Declining rates were observed in all age groups. In 18% of men and 23.3% of women, the first AMI was fatal and in 20.1% of cases, the death occurred at home, work place, public places, nursing home or during transportation. As appropriately recognized by the authors, the observational design of the study prevents an appropriate evaluation of the factors responsible for the observed changes. It is likely that modifications in the levels of some risk factors, such as smoking or uncontrolled arterial hypertension, might have played a positive role.

Whilst there might be regional differences and the data presented by Sulo et al.<sup>4</sup> might not be entirely representative of other countries, similar trends can also be observed in other developed countries.<sup>3</sup> Hence it is appropriate to ask whether the contemporary clinical care is on the right track and whether we should expect further reduction of mortality due to AMI in the

forthcoming years. In our opinion, this is unlikely for several reasons.

Despite organizational and medical management advances of the acute phase of AMI that contributed to a significant decline of in-hospital mortality, death rates before hospital admission and after hospital discharge have not decreased as we would have wished. As shown by Sulo et al.,<sup>4</sup> the mortality due to ventricular fibrillation that characterizes the early phase of acute coronary syndrome and prevents admission and proper treatment of patients remains high and is only partially affected by medical and healthcare organization strategies.<sup>5</sup> Drugs such as beta-blockers, angiotensin-converting enzyme inhibitors and statins may show their preventive effects on the electrophysiological and haemodynamic changes associated with an acute coronary event only in patients in whom cardiac diagnosis has already been made. This leaves the so-called apparently healthy subjects particularly vulnerable. Present knowledge allows risk modifications in the general population to be proposed but they require interventions that are difficult to apply without a consistent support and funding from national healthcare systems. In this context, the 2016 European Guidelines on cardiovascular (CV) disease prevention in clinical practice<sup>6</sup> recommended ‘systematic CV risk assessment in men >40 years of age and in women >50 years of age or post-menopausal with no known CV risk factors may

<sup>1</sup>UOC Cardiologia, Fondazione IRCCS Ospedale Maggiore Policlinico, University of Milan, Italy

<sup>2</sup>University of Oulu, Finland

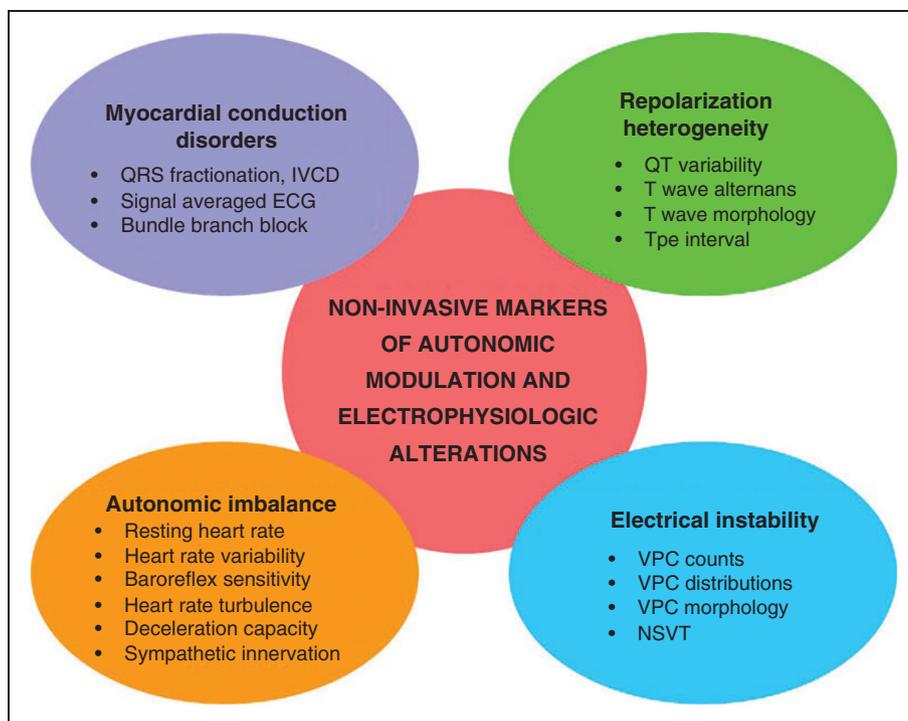
<sup>3</sup>Technische Universität München, Germany

<sup>4</sup>Imperial College, London, UK

**Corresponding author:**

Federico Lombardi, UOC Cardiologia, Fondazione IRCCS Ospedale Maggiore Policlinico, University of Milan, Via F. Sforza 35, 20122 Milan, Italy.

Email: federico.lombardi@unimi.it



**Figure 1.** Non-invasive parameters that can be derived from short- or long-term electrocardiographic recordings and have been used for risk stratification. Adapted from Camm et al.<sup>8</sup> and Sassi et al.<sup>9</sup>

IVCD: intraventricular conduction delay; ECG: electrocardiogram; VPC: ventricular premature contraction; NSVT: non-sustained ventricular tachycardia [AQ3].

be considered' and that 'It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment'. We already have adequate algorithms for an automatic analysis of 12-lead electrocardiograms to detect gross alterations consistent with previous AMI, left ventricular hypertrophy and bundle branch block as well as with subtle abnormalities including, for example, QRS fragmentation and repolarization changes. All these electrocardiographic deformities have been associated with an increased mortality risk.<sup>7</sup> A nation-wide screening programme of this size would be substantial and the cost and management of such huge amounts of data is a major limiting factor for its implementation. However, waiting for better times does not provide any benefit.

The second area of unmet need is the mortality reduction after hospital discharge. Appropriate and extensive coronary revascularization, together with optimal medical therapy have been associated with a reduction in mortality after the index event. The use of implantable cardioverter defibrillators on high-risk patients has also contributed to the observed mortality reduction. Nevertheless, as indicated in all reports, our capabilities of identifying patients at high arrhythmic risk is poor and, in most clinical settings, we only

rely on echocardiographic evaluation of left ventricular ejection fraction. In the last 30 years, most of the efforts to develop and validate non-invasive markers of arrhythmic risk in post-AMI patients have been frustrated by negative or contrasting results. Consequently, no indication for non-invasive evaluation of arrhythmic risk excluding imaging techniques is contained in the recent ESC guidelines for the management of AMI patients presenting with ST segment elevation.<sup>5</sup> How to explain this when considering the number of methodologies indicated in Figure 1, including heart rate variability, heart rate turbulence, baroreflex sensitivity that have been tested in post-AMI patients and associated with an increased mortality risk?<sup>8</sup> We have recently addressed this issue<sup>9</sup> by considering two major points. On the one hand, these non-invasive methodologies have been repeatedly excluded in large clinical trials and in new population screening programmes despite the simplicity of obtaining high quality digital electrocardiographic signals. On the other hand, most of the new methodologies developed in the last 10 years utilize analyses of complex systems that increase the gap between biomedical researchers and clinical cardiologists. Solving unmet clinical needs obviously requires more active and more interlinked inter-disciplinary driven collaboration. [AQ1]

### Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### References

1. Smolina K, Wright FL, Rayner M, et al. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: Linked national data-base study. *BMJ* 2012; 344: d8059.
2. O'Flaherty M, Buchan I and Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: Why have CVD mortality rates declined so much since the 1960s? *Heart* 2013; 99: 159–162.
3. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: Cardiovascular disease statistics 2017. *Eur Heart J* 2018; 39: 508–577.
4. Sulo G, Iglund J, Vollsett SE, et al. Trends in incident acute myocardial infarction in Norway: An updated analysis through 2014 using national data from CVDNOR projects. *Eur J Prev Cardiol* 2018; ■■: ■■–■■ [AQ4].
5. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction patients presenting with ST segment elevation. *Eur Heart J* 2018; 39: 119–177.
6. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol* 2016; 23: NP1–NP96 [AQ2].
7. Malik M, Buxton AE, Huikuri H, et al. Noninvasive electrophysiology in risk assessment screening. *Heart Rhythm* 2018; in press.
8. Camm AJ, Malik M, Bigger JT, et al. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; 93: 1043–1065.
9. Sassi R, Cerutti S, Lombardi F, et al. Advances in heart rate variability signal analysis: Joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace* 2015; 17: 1341–1353.