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EDITORIAL

Different perspectives on outcomes in patients with non-ST-elevation myocardial infarction when observed in clinical trials and in real life

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This editorial refers to 'Modes and timing of death in 66 252 patients with non-ST-segment elevation acute coronary syndromes enrolled in 14 TIMI trials'†, by D.D. Berg *et al.*, on page 3810.

Non-ST-elevation acute myocardial infarction (NSTEMI) is currently the most common manifestation of coronary artery disease. In the 1980s, the pathophysiology of the condition was elucidated by showing the underlying ruptured atherosclerotic plaque with superimposed thrombotic material leading to impeded coronary blood flow by severe stenosis, temporary occlusions and downstream embolization of thrombotic material leading to myocardial injury.[1] Initially the diagnosis mainly relied on ECG changes but, since the 1990s, elevation of troponin has been the key diagnostic finding.[2] Since the beginning of the 1990s, a series of randomized clinical trials have established that treatment with aspirin, P_2Y_{12} inhibitors, statins, and early revascularization under the protection of anticoagulation improves survival and reduces the risk of re-infarction.[3–11] After this success story, it is appropriate to ask which might be the remaining problems that need to be addressed in order to improve outcomes further.

In the current issue of the *European Heart Journal*, investigators from the TIMI-study group network present the accumulated survival results in 66 252 patients with 3147 deaths during a median of 12 (interquartile range 7–17) months of follow-up included in 14 prospective randomized clinical trials (RCTs) of patients with NSTEMI between 1989 and 2014 (*Table 1*).[12] Despite the fact that few of the current treatment regimens were established during the first 10 years, the total mortality was strikingly low at 1.4% at 1 month and 4.3% at 1 year (*Figure 1*). The causes of death were cardiovascular in 75% of cases, with sudden death (SD) constituting 36%, myocardial infarction (MI) 23%, and heart failure (HF) 19%, with MI being the dominating cause before and SD after 30 days. The authors' conclusion of the study is that SD represents the largest proportion of deaths after 30 days among patients enrolled in cardiovascular clinical trials with NSTEMI and that further investigations aimed at developing specific treatment to reduce SD following NSTEMI may be critical to reducing late mortality. It is important to point out that the authors emphasize the lack of generalizability of observational studies in RCT populations and that selection bias is an especially important consideration in this mortality analysis, since higher risk patients were excluded from most of the trials. The authors therefore appropriately state that their findings are most directly relevant to designing future cardiovascular trials and developing novel therapies to reduce mortality following NSTEMI. Because of the selected enrolment of lower risk patients, further investigations are needed to explore in more depth whether these RCT-based outcome data are relevant for real-life patients with NSTEMI.

Interestingly, the real-life outcomes in patients with NSTEMI from the same time period, 1995–2014, from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry are simultaneously published in the current issue of this journal.[13] The SWEDEHEART registry continuously includes all patients admitted with a suspected or definite acute coronary syndrome to the participating hospitals, which since 2003 includes all 72 hospitals providing care for acute cardiac diseases. Between 1995 and 2014 there were 205 693 patients with NSTEMI.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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Table 1 Baseline characteristics in the TIMI NSTEMI 14 RCT cohort and the SWEDEHEART NSTEMI cohort

Cohort	TIMI 14 RCT NSTEMI	SWEDEHEART NSTEMI
Time	1994–2014	1995–2014
Number of patients	66 252	205 693
Days to inclusion median (IQR)	1 (1–4)	0 (0–0)
Follow-up days median (IQR)	372 (218–521)	365 (365–365)
Number of deaths	3147	38 366
Age median (IQR)	63 (55–71)	74 (64–82)
Female sex, %	30.1	37.5
Male sex, %	69.9	62.5
Prior history	All trials	Range over the years
Hypertension, %	66.4	37.1–67.9
Diabetes mellitus, %	28.2	23.4–28.8
Active smoking, %	31.3	17.9–19.8
Myocardial infarction, %	30.4	35.6–32.0
Stroke, %	4.2	10.7 – 13.6
Peripheral arterial disease, %	7.8	6.8 – 7.9
Heart failure, %	10.5	23.3 – 31.5
Prior medications	All trials	Range over the years
Beta-blocker, %	56.3	35.8–46.2
Calcium channel blocker, %	27.6	17.6–22.6
ACE-I or ARB, %	49.0	16.7–43.2
Aspirin %	71.7	39.7–48.0
Lipid-lowering agent, %	44.2	5.1–35.8

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range.

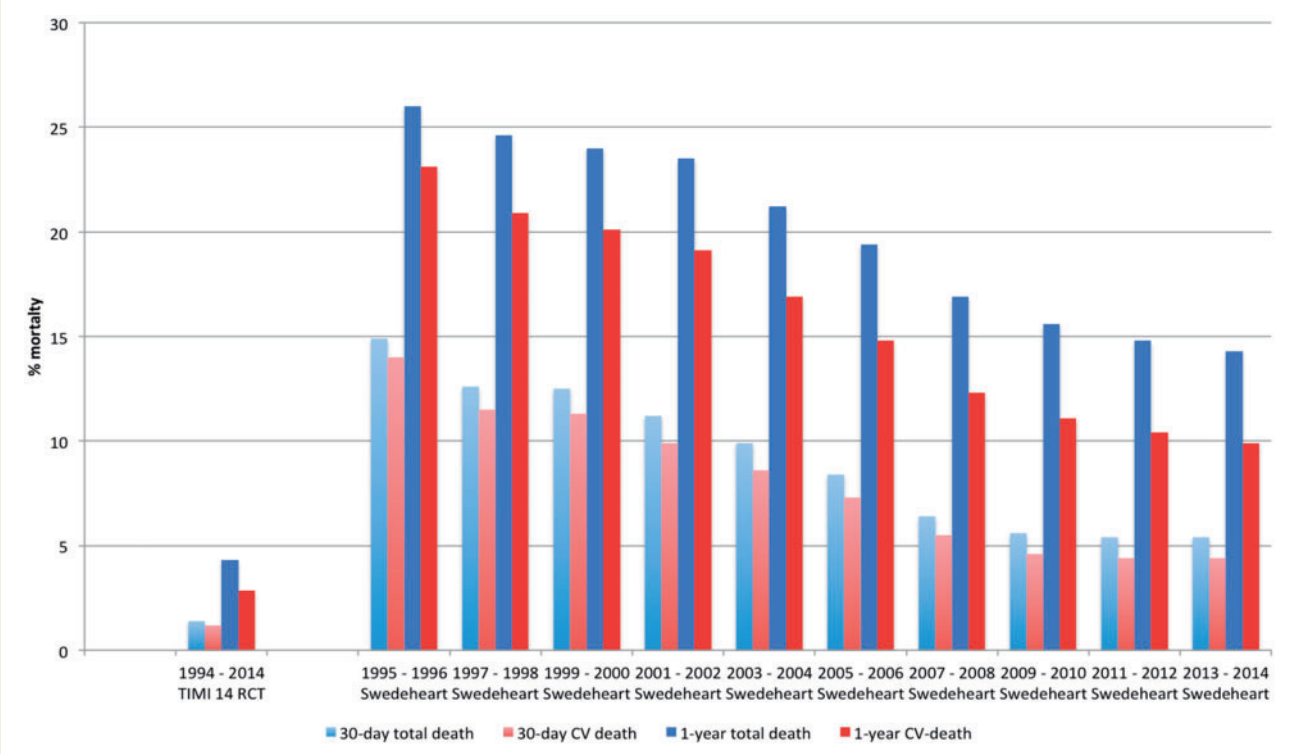

Figure 1 Total and cardiovascular (CV) mortality at 30 days and 1 year in the TIMI NSTEMI 14 RCT and the SWEDEHEART NSTEMI cohort.

The baseline characteristics in the SWEDEHEART NSTEMI cohort were very different from those of the TIMI RCT cohort, with earlier inclusion (on admission as compared with after, an interquartile range of 1–4 days), 11 years higher median age (74 vs. 63), a higher proportion of females (38% vs. 30%), and a 2–3 times higher prevalence of prior stroke and HF (*Table 1*). In contrast to the TIMI trials, the SWEDEHEART NSTEMI study showed the dramatic reduction in total and cardiovascular mortality over time and how this has been accomplished by implementation of the new effective medical and interventional treatments. However, still even for the cohort for the last 2 years, 2013–2014, the total and cardiovascular mortality at 1 month (5.4% and 4.4%) and 12 months (14.3% and 9.9%) were 3–4 times higher than the corresponding results in the total TIMI NSTEMI RCT cohort, i.e. at 1 month (1.4% and 1.2%) and 12 months (4.3% and 2.9%) (*Figure 1*). The SWEDEHEART NSTEMI study was not able to report different types of cardiovascular death but demonstrated continuous reductions also in re-MI, heart failure, and stroke, which were probably related to the reduction in long-term mortality during the continued life-long follow-up.[13]

What might be the causes of these vast differences in baseline characteristics and outcomes between the TIMI RCT NSTEMI cohort and the SWEDEHEART real life NSTEMI cohort? The most obvious explanations are the differences in patient selection, where SWEDEHEART includes all comers with suspected or definite NSTEMI immediately on arrival while the RCTs include selected survivors at a later stage of the disease and with many exclusion criteria leading to a substantially lower proportion of elderly patients, women, and those with early MI complications and other cardiovascular or non-cardiovascular co-morbidities (*Table 1*). It might be questioned if the higher mortality in the SWEDEHEART NSTEMI cohort was caused by a slower uptake of new medications than in the global TIMI RCT environment. However, this seems unlikely, as direct comparisons have shown similar or more rapid uptake of new treatments and similar or better outcomes in SWEDEHEART as compared with the acute cardiac care registries in UK and US healthcare.[14–16] Thus, the dominating reason for the differences between the patient populations and outcomes must be differences in patient selection.

The simultaneous presentation of these two very large and comprehensive cohorts of patients with NSTEMI included between 1994 and 2014 in prospective global RCTs or in a prospective continuous national registry with large differences in outcomes provides valuable perspectives on how to improve the understanding and treatment of the disease further. As stated many times before, a prospective RCT is ideal for comparative effectiveness of new treatments, but is usually performed in an idealized setting excluding patients at higher risk. An RCT usually has a short-term follow-up for 1–2 years, providing detailed and adjudicated information on all events. However, the overall event rates in RCTs usually are substantially lower than in an unselected populations. Therefore, neither the effectiveness nor the risk of side effects might correspond to the results in a real-life population. Unselected cohorts from continuous registries with good coverage and complete long-term follow-up better represent the natural history of disease and its short- and long-term outcomes. The remaining causes of complications in NSTEMI, e.g. SD, might be indicated by detailed observation in RCTs, although their importance needs to be validated in other trials and observational cohorts because of the selected enrolment. The continued evaluation of unmet needs and opportunities for further improvement probably are easier and more reliable in unselected registry populations.

The large differences between the real-life NSTEMI patients and those included in RCTs also emphasize concerns for the relevance of the results when testing new treatments in very selected low-risk populations. There are obvious risks that the results from a selected RCT setting are not representative of the broad complex real-life population where the effects might be both smaller and larger than in the selected RCT cohorts. The testing of new treatments mainly in lower risk populations also carries risks of losing important information on both efficacy and safety that might have important influences on the further development and eventual approval of new treatments. In order to increase the chances of clear and relevant results, all trials should be encouraged as far as possible to include the whole target population. Such a strategy is both doable and very cost-effective by performing the RCTs embedded in continuous registries rather thean using the conventional approach.[17]

Conflict of interest: L.W. has received institutional research grants from AstraZeneca, Bristol-Myers Squibb/Pfizer, Merck & Co, Roche, GlaxoSmithKline, and Boehringer Ingelheim, and consulting fees from Abbott; he holds two patents on GDF-15 licensed to Roche Diagnostics.

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