Main results of the ESC Congress 2013, Amsterdam: moving or standstill in cardiology?

E. E. van der Wall

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At the Congress of the European Society of Cardiology (ESC) 2013, Amsterdam, many new trials were presented at the four Hot Line Sessions. Nine of these trials were simultaneously published in the New England Journal of Medicine (NEJM). In the Scientific Supplement of the Dutch daily newspaper, the NRC, it was put forward that seven out of the nine trials produced 'negative' results, leading to the general comment by the NRC that the scientific progress in cardiovascular medicine has halted: '*there are no further successes to report in cardiology*' (NRC Weekend, September 7/8, W7).

Let's have a short look at the nine trials reported at the ESC Congress and simultaneously published in the NEJM.

The two positive trials

- 1) PRAMI. *Randomised Trial of Preventive Angioplasty in Myocardial Infarction; the PRAMI Investigators*. The PRAMI study compared culprit artery PCI-only with full revascularisation in patients with ST-elevation myocardial infarction (STEMI). The trial was stopped prematurely by the Data Monitoring Committee when a planned interim analysis showed a clear benefit *in favour of preventive PCI*. They showed an absolute risk reduction of 14 per 100 patients in the preventive PCI group (HR 0.35, $p < 0.001$) and a *relative risk reduction of 65 %*. It was concluded that preventive PCI reduces the risk of cardiac death, subsequent MI or refractory angina by about two-thirds. Although it remains to be questioned how the preventive PCI lesion ought to be chosen during the acute

setting, it has to be emphasised that PRAMI offers a *promising new interventional approach*.

- 2) SERAPHIN. *Macitentan and morbidity and mortality in pulmonary arterial hypertension; the SERAPHIN Investigators*. A total of 250 patients were randomly assigned to placebo, 250 to the 3-mg macitentan dose, and 242 to the 10-mg macitentan dose. The hazard ratio for the 3-mg macitentan dose as compared with placebo was 0.70, $p = 0.01$, and the hazard ratio for the 10-mg macitentan dose as compared with placebo was 0.55, $p < 0.001$. Worsening of pulmonary arterial hypertension was the most frequent primary endpoint event. It was concluded that macitentan significantly *reduced morbidity and mortality* among patients with pulmonary arterial hypertension in this event-driven study.

The seven negative trials

- 1) ACCOAST. *Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes; the ACCOAST Investigators*. The ACCOAST study included 4033 patients with non-ST-elevation myocardial infarction (NSTEMI) who were randomised to prasugrel pretreatment versus standard prasugrel loading dose at the time of PCI. The enrolment was stopped early due to an increased rate of major bleeding in the pretreatment arm in the absence of a benefit in terms of ischaemic events. Accordingly, the primary endpoint was similar in the pretreatment arm and in the control group (10.0 vs. 9.8 % respectively). TIMI major bleeding rates were 2.6 and 1.4 %, respectively ($p = 0.006$). It was concluded that, among patients with NSTEMI who were scheduled to undergo catheterisation, pretreatment with prasugrel did not reduce the rate of major ischaemic events up to

E. E. van der Wall (✉)
Interuniversity Cardiology Institute of the Netherlands
(ICIN) - Netherlands Heart Institute (NHI), P.O. Box 19258, 3501
DG Utrecht, the Netherlands
e-mail: Ernst.van.der.wall@icin.knaw.nl

- 30 days but did increase the rate of major bleeding complications. As a result, the ACCOAST trial provides clear evidence for a practice established in many cardiology centres and supported by current guidelines.
- 2) TASTE. *Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction*, by Fröbert *et al.* In the TASTE trial patients were randomised to manual thrombus aspiration ($n=3621$) followed by percutaneous coronary intervention (PCI) or to PCI only ($n=3623$). There was no significant difference in the primary endpoint, all-cause 30-day mortality (2.8 % in the thrombus aspiration group vs. 3.0 % in the PCI only group), suggesting that routine thrombus aspiration provides *no benefits*. The *neutral* results were consistent across all subgroups; however the results may not be extrapolated to high-risk populations since there was a mortality of 2.9 % among patients who were underwent randomisation vs. 10.6 % among those who did not.
 - 3) Hokusai-VTE. *Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism; the Hokusai-VTE Investigators*. In the Hokusai-VTE (venous thromboembolism) study more than 8200 patients were randomised to edoxaban or warfarin. A total of 4921 patients presented with deep-vein thrombosis, and 3319 with pulmonary embolism. At 1 year, edoxaban was *non-inferior* to warfarin with respect to the primary efficacy outcome recurrent symptomatic venous thromboembolism, which occurred in 130 patients in the edoxaban group (3.2 %) and 146 patients in the warfarin group (3.5 %). It was concluded that yet another oral factor Xa inhibitor has shown to be *as effective as warfarin* for preventing recurrences in VTE patients and *with a lower risk of bleeding*.
 - 4) RE-ALIGN. *Dabigatran versus Warfarin in Patients with Mechanical Heart Valves; the RE-ALIGN Investigators*. The RE-ALIGN study included 1) patients who had undergone aortic- or mitral-valve replacement within the past 7 days and 2) patients who had undergone such replacement at least 3 months earlier. The starting dose of dabigatran (150, 220 or 300 mg twice daily) was based on renal function and adjusted during the study based on plasma levels. The trial was terminated prematurely after the enrolment of 252 patients due to an *excess of both thromboembolic and bleeding rates* in the dabigatran group in both study populations. Ischaemic stroke occurred in 9 patients (5 %) in the dabigatran arm compared with no patients in the warfarin group. Major bleeding, all pericardial bleeding, occurred in 7 patients (4 %) and 2 patients (2 %), respectively. It was concluded that *dabigatran cannot be used as an alternative to warfarin* in patients who require anticoagulation after the implantation of a prosthetic heart valve.
 - 5) SAVOR-TIMI53. *Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus; the SAVOR-TIMI 53 Steering Committee and Investigators*. A total of 16,497 patients with type 2 diabetes with an HbA1c ≥ 6.5 % and <12.0 % on any background antidiabetic treatment and history of established cardiovascular disease were randomised 1:1 to saxagliptin 5 mg daily or matching placebo. SAVOR-TIMI 53 failed to demonstrate that the occurrence of major adverse cardiac events is reduced by saxagliptin compared with placebo. Saxagliptin did, however, *improve* glycaemic control and prevented progression of microalbuminuria. In addition, SAVOR-TIMI 53 *provided reassuring information* on non-cardiovascular *safety* since no increase in infections, bone fractures, malignancies or pancreatitis was observed.
 - 6) EXAMINE: *Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes; the EXAMINE Investigators*. In the EXAMINE trial alogliptin (DPP-4 inhibitor) was compared with placebo in type 2 diabetes patients with recent ACS who are receiving standard of care for diabetes and secondary cardiovascular prevention. The primary endpoint was a composite of first occurrence of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. A total of 5380 patients were enrolled and followed up for 40 months. The primary endpoint occurred in 305 patients assigned to alogliptin (11.3 %) versus 316 patients assigned to placebo (11.8 %) ($p<0.001$ for non-inferiority). Overall, the incidence of death, myocardial infarction and stroke in type 2 diabetes patients were not reduced by the DPP-4 inhibitor alogliptin. Moreover, alogliptin *did not result in an increase in adverse events* associated with DPP-4 inhibitors.
 - 7) ECHO-CRT. *Cardiac-Resynchronization Therapy (CRT) in Heart Failure with a Narrow QRS Complex; the EchoCRT Study Group*. This trial evaluated CRT in patients with NYHA class III or IV, an LV ejection fraction ≤ 35 %, a QRS <130 ms and echocardiographic evidence of LV dyssynchrony. After the inclusion of 809 patients with a mean follow-up of 19.4 months, the study was discontinued. All-cause mortality was significantly increased in the CRT group with 45 deaths (11.1 %) compared with 26 (6.4 %) in the control group ($p=0.02$), as well as cardiovascular mortality (9.2 vs. 4.2 %, $p=0.004$). Device-related serious adverse events were more frequently observed in the CRT group (13.6 %) compared with the control group (7.2 %, $p=0.003$). It was concluded that *CRT should not be used in patients with systolic heart failure with a narrow QRS complex <130 ms*.

According to the opinion of the NRC newspaper, only the PRAMI and the SERAPHIN trial were ‘positive’ and the

remaining seven trials were ‘negative’. This warrants the following comments. First of all, the label ‘positive’ or ‘negative’ hinges on a p -value of <0.05 (p NS) or >0.05 (p significant); this has nothing to do with the clinical implication of a study, be it positive or negative. The almost definite proof of the value of a large clinical study is incorporation into the guidelines. Second, often a ‘negative’ trial is neutral rather than strictly ‘negative’. Of course, the outcome might be disappointing but even a ‘negative’ or neutral trial may provide important clinical information. Third, ‘negative’ only applies to the primary endpoint; in many instances the novel drugs studied in the above-mentioned trials were not only non-inferior but showed improved safety. The other way around, positive (i.e. statistically significant) does not directly imply superiority. Lastly, more importantly, a false impression was created by the NRC newspaper that there might not be any progress in cardiovascular medicine. This is of course far from true! To illustrate this, I will just dip into the basket of the recent ESC Congress.

Ten positive findings at the ESC Congress 2013

1) A positive study presented at Hot Line III and published simultaneously in the European Heart Journal was the COMPARE trial which showed that addition of losartan to standard of care (beta-blocking agents) in adults with Marfan syndrome significantly reduces aortic root dilatation rate in un-operated patients and aortic arch dilatation rate in patients after elective aortic root surgery. 2) The PURE (Prospective Urban Rural Epidemiological) study in over 150,000 individuals (Hot Line III), clearly showed an inverse relationship between risk factors for heart disease and actual rates of prevalence. 3) A Finnish study showed that exercise was beneficial to men with poor fitness; in 2656 men it was demonstrated that increasing the level of exercise protects against sudden cardiac death. 4) Along those lines, French participants of the Tour de France between 1947 and 2012 showed a substantially lower (41 %) mortality compared with the general male French population, again emphasising that

(even strenuous) exercise should be encouraged (Hot Line IV). 5) The CONFIRM study (Coronary CT Evaluation for Clinical Outcomes) showed that active and past smokers have a twofold risk of CAD in all three coronary arteries assessed by coronary CT. 6) With respect to aortic valve stenosis, it was shown that individuals with first-degree relatives with aortic valve disease have twice the risk to develop the condition, and that following TAVI female gender was associated with improved survival. 7) The Dutch FollowPace study showed similar survival in pacemaker recipients without concomitant cardiovascular disease as in age- and sex-matched controls in the general Dutch population. 8) The IN-TIME trial (Hot Line II) clearly showed the benefits of home-monitoring in heart failure patients, with less worsening in clinical status and improved all-cause and cardiovascular mortality. 9) In the Dutch North Holland region an emergency care program was introduced 5 years ago, involving CPR and AED training to the public, whereby the time from first emergency call has been reduced to 8 min and the overall survival rates from out-of-hospital arrest have increased to 23 %. 10) Finally, the protein copeptin (added to troponin) proved to be a new promising biomarker to triage patients with ACS. These are just a few examples of scientific progress in the cardiovascular world based on the data presented at the 2013 ESC Congress.

As mentioned above, the almost definite proof of the value of a study is incorporation into the guidelines. At the ESC Congress 2013 four new guidelines were presented on a variety of topics; 1) Cardiac Pacing, 2) Diabetes, 3) Hypertension, and 4) Stable Coronary Artery Disease (SCAD). The SCAD guideline, for example, includes 514 references; it would be interesting to find out which of the previously presented Hot Line trials have finally made it into this guideline.

To conclude, the NRC newspaper of 7/8 September was much too negative and should become more neutral in order to report the really positive findings in cardiovascular medicine. Where a heart beats, there is never a standstill!

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