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# Diabetes mellitus: the scary killer haunting silently

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Diabetes mellitus is a serious and costly health issue reaching epidemic proportions in the developed world. The crude prevalence of diabetes is increasing over time as the population ages, being projected that nearly 9% of adults in Europe will have diabetes by the year 2025[1]. Importantly, of the 60 million European adults currently estimated to be affected by diabetes, over 50% are unaware of their condition[2]. The fourth leading cause of death in Europe, diabetes is strictly linked with a broad array of clinical presentations, including cardiovascular disease, stroke, nephropathy and neuropathy[2]. Cardiovascular disease, in particular, accounts for ~80% of deaths in diabetic patients[3]. Coronary artery disease in diabetes mellitus patients is described by being diffuse and typically has a rapid progression[4]. Revascularisation procedures in diabetic patients are usually associated with worse outcomes than those performed in patients without diabetes[5]. This is related to multiple factors including the numerous metabolic disturbances which affects these high risk patients and ultimately determine their greater tendency towards a pro-atherothrombotic status[6]. Given the evolution of percutaneous techniques and adjunctive antithrombotic regimens in recent years, there is a need to examine novel data to specifically look into the impact of diabetes on survival following percutaneous coronary intervention.

In this issue of EuroIntervention, Norhammar et al report the results of a subanalysis from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)[7]. Distinctive characteristics of this registry include data collection from 29 centres on over 60,000 patients (10,857 with diabetes mellitus) undergoing percutaneous coronary intervention between 2002 and 2007, independence from commercial funding, data quality monitoring and verification, follow up information obtained from national registries. These features make the SCAAR Registry an attractive and timely opportunity to obtain real world insights on subgroups less specifically represented in the literature. Importantly, the very large sample size allows for a powered assessment of hard events rather than angiographically-driven endpoints.

At a median follow up of 1,012 days, the authors found confirmatory evidences that diabetes mellitus is associated with a crude two-fold increased risk of death. The magnitude of the risk slightly decreased to 1.6 after adjustment for the multiple confounders existing between patients with and without diabetes, including differences in baseline comorbidities, indications, and extent of atherosclerotic disease. The association with mortality was consistent across different clinical presentations, with a linear increase from 1.4 in case of ST elevation myocardial infarction to 1.7 in patients with non-ST elevation acute coronary syndromes and 2.0 in patients with stable angina. Age softened, but did not abolish, the impact of diabetes, as the relative risk fell from 2.1 in patients < 65 years to 1.5 in those > 74 years.

The SCAAR report however raises some issues relevant to contemporary practice and study design. Firstly, attention should be paid when generalising observational data to a different case mix. Drug eluting stents were used in 36% and 28% of patients presenting with and without diabetes, respectively[7]. These rates are quite different from those higher observed elsewhere[8]. This is important as patients expected to benefit most from drug eluting stents are those at increased risk of restenosis[9]. The study did not primarily focus on the impact of drug eluting stents on mortality in diabetics, although the authors discuss some benefits of stenting regardless of the type of stent used. Nevertheless, it remains unclear the degree to which these results apply to a higher use of drug eluting stents in different cohorts. In addition, whether complete revascularisation by percutaneous techniques or revascularisation by coronary artery bypass graft may be more effective in reducing mortality of patients with diabetes is similarly

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unsolved and warrants specifically designed investigations. Second, the study demonstrates that the independent risk associated with diabetes mellitus increases with time up to four years, regardless of clinical presentation. The combined use of aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors in a considerable proportion of patients did not apparently contribute to fill this mortality gap between 2002 and 2007. Trying to sort out explanations for this observed treatment failure is challenging. Indeed, our incomplete comprehension of the multitude of mechanisms underlying the tendency towards accelerated progression of atherosclerosis seen in diabetic patients is a limiting factor. Although major efforts have been devoted in obtaining mechanistic explanations for recurrent adverse events in diabetics, the lack of striking effects by therapies committed to address these issues outline the need for novel strategies. While novel approaches focusing on physiopathology, genetics and patient education must be encouraged to broaden the area of investigation, there is currently a renewed interest in pharmacology of antithrombotic therapies. The utility of this approach seems intuitive, as it is well recognised that platelets, which are key in atherothrombotic disease processes, from patients with diabetes are more prone to be hyper-reactive despite use of recommended secondary prevention treatment regimens[5,10]. In the SCAAR Registry more potent platelet blockade by means of inhibition of the final mediator of platelet aggregation, the glycoprotein IIb/IIIa receptor, was of potential benefit only in diabetic patients presenting with ST elevation myocardial infarction, which counted for ~25% of the total population[7]. Prasugrel, a third generation oral thienopyridine with potent antiplatelet effects, has shown to be an attractive treatment alternative as it was associated with a 30% relative reduction at 15 months of the primary combined endpoint (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in diabetics compared with clopidogrel, which is larger than the 14% observed in non-diabetics[11]. Notably, prasugrel was associated with a mortality benefit compared with clopidogrel in patients who survived their first cardiovascular event[12]. Benefits were not overshadowed by increased risk of bleeding compared to clopidogrel, resulting in superior net clinical benefit for prasugrel in patients with diabetes (26%) than in those without (8%)[11]. These data suggest that the more intensive antiplatelet efficacy provided with more potent platelet P2Y12 receptor inhibitors may be of particular benefit to patients with diabetes. Ongoing studies looking at other pivotal signalling pathways upregulated in patients with diabetes, such as thrombin mediated processes which also play a key role in inflammatory reactions known to be heightened in diabetes, may provide further insights on how to optimise their pharmacological management[13].

A last point is relevant to reporting of the subgroup analysis focusing on diabetes mellitus. In the study from Norhammar et al, specific data on diabetes status are limited[7]. No specific information on type 1 or 2 diabetes is available. In addition, there is a lack of data on clinical and laboratory information about the clinical course of diabetic patients, including fasting glucose, A1c levels, micro- and macrovascular complications and comorbidities. The authors discussed some impact of insulin use in a proportion of patients enrolled from 2005 to 2007, and suggested that the need for insulin plays a major role in linking diabetes with mortality. However, it is unclear from these data whether insulin use is causally linked with higher rates of mortality or rather contributes to identify a higher-risk subgroup. More details on issues surrounding diabetes mellitus would have been very informative, especially to understand whether handling improved glucose control may truly have an impact on long term mortality.

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