Dear Sirs,

Although morbidity and mortality from cardiovascular diseases are probably lower in haemophilia patients than in the general male population, the clinical impact of such conditions is growing in parallel with life expectancy of these individuals in the era of modern and safe concentrate replacement treatment (1–2). Therefore, the management of cardiovascular disease and of other age-related comorbidities represents a new challenge for the global care of haemophilia (2–4). In particular, treatment of acute coronary syndromes (ACS) raises concerns for the increase of bleeding risk due to the use of antithrombotic agents and revascularisation strategies, including percutaneous coronary interventions (PCI).

We report the unlucky history of a patient with severe haemophilia A and an ACS, addressing the need for clinical validation of management in this setting, balancing the actual prothrombotic condition and the inherent bleeding risk, enhanced by the treatment strategies.

This 63-year-old patient was admitted to our Centre because of persistent dyspnoea. He was a heavy smoker and suffered from severe arterial hypertension, requiring intensive pharmacological treatment (atenolol, amlodipine, ramipril and doxazosin). Diabetes mellitus had been diagnosed 15 years earlier, and the patient was on insulin treatment since five years, achieving fair metabolic control. Mild impairment of renal function with multifactorial genesis (hypertensive and diabetic vascular complications, abuse of non-steroidal antinflammatory drugs because of haemophilic arthropathy) was reported over the last five years, but a significant worsening (glomerular flow rate approximately 30 ml min⁻¹) was shown recently, leading to dietary restrictions and epeoïn supplementation. On admission, diffuse negative T-waves at electrocardiography and hypokinesia at two-dimensional echocardiography were shown. Nitrates, diuretics and low-dose (2,500 IU, then infusion 600 IU hour⁻¹) unfractionated heparin (UFH) were started. In spite of normal troponin levels, as dyspnoea and chest pain at rest recurred, after receiving 30 IU Kg⁻¹ followed by 1 IU Kg⁻1 hr⁻¹ continuous infusion of recombinant factor VIII (FVIII) concentrate (Kogenate Bayer™) and 75 mg clopidogrel, the patient underwent coronary angiography by femoral access. Factor (F)VIII plasma levels raised up to 64% at the procedure and were maintained within 20–35% thereafter. Severe multi-vessel coronary disease, hampering angioplasty and stent implantation, was detected at angiography. Moreover, the occurrence of chest pain at the procedure, together with troponin elevation and further deterioration of ejection fraction, revealed myocardial infarction. Coronary bypass-grafting intervention was planned, FVIII infusion was continued and UFH substituted for clopidogrel. The patient suddenly died on day 4, a few hours before undergoing surgery.

This clinical history supports the notion that haemophiliacs are not protected from the development of atherosclerosis and its thrombotic complications, even in the case of severe coagulation factor deficiencies (1). Thrombotic risk may largely overcome the bleeding tendency in some phases of life of haemophilia patients, in particular when cardiovascular risk factors coexist. Most reported cases of myocardial infarction in haemophilic patients are associated to factor concentrate infusions (5). This was not the case of our patient, who presented an ACS caused by severe multi-vessel coronary atherosclerotic disease.

Increasing literature interest is devoted to comorbidities and their management in the ageing haemophilia patients (1–4, 6–8) and guidelines for treatment of cardiovascular disease have been published very recently (4, 8). However, clinical validation of the proposed strategies is still lacking, as no rigorous trial is presently available and such studies are probably unfeasible in this setting. Only few case reports addressed the treatment of ACS in patients with severe haemophilia (9–15). The experienced approaches are heterogeneous and reflect these uncertainties. As a general rule from the experts’ suggestions and the available case reports, antithrombotic strategies and indications for PCI could be the same adopted in non-haemophilic patients, provided that factor deficiency is corrected by adequate replacement treatment. As achieved in our case, 60–80% should be considered safe levels in the highest bleeding risk phase, when PCI is carried out and combined anticoagulant and antiplatelet agents are administered. In this respect, factor concentrate continuous infusion was preferred to bolus injections to prevent FVIII fluctuations, with trough levels associated with bleeding risk and high harmful post-injections peak levels (14).

Table 1 summarises these and other open issues in the management of ACS in haemophilia patients. Administering antithrombotic agents with a short half-life, enabling a better management of possible bleeding complications, is likely to be a leading criterion for clinical choices in this setting. In this respect, as in our patient, UFH has been often preferred to low-molecular-weight heparin (9–11) and the direct thrombin inhibitor bivalirudin (half-life 25 minutes in patients with normal
renal function) has been safely employed as the only antithrombotic strategy during PCI in other two severe patients (12–13). Moreover some data argue for a lower risk of major bleeding complications in patients receiving bivalirudin for PCI (16).

For similar reasons, we decided for clopidogrel as antiplatelet agent in our patient. In most reported cases antiplatelet treatment has been used only after PCI (9–11), but patients receiving combined antiplatelet therapy including clopidogrel loading have been more recently reported (13–14, 17). More uncertainties concern the use of glycoprotein IIb/IIIa inhibitors (Table 1) (11, 18–19). As regards PCI procedures, radial access is considered safer than femoral puncture (8); however, the latter was not associated with bleeding complications in our and other severe haemophilia patients receiving adequate concentrate replacement (12–13). Few data are available with respect to the long-term follow-up of patients on single/combined antiplatelet treatment. In two moderate patients combined treatment was associated with increase of bleeding tendency, leading to stop clopidogrel (16, 20). Thus, factor concentrate prophylaxis is suggested, in particular in patients receiving combined antiplatelet treatment. Dose, regimens, target levels and duration are unknown but are likely to be tailored according to the patient’s characteristics (severity of factor deficiency, bleeding phenotype, other risks for bleeding) and to the clinical course. Along this line, no information is available concerning strategies of primary prevention of cardiovascular disease in haemophilia patients (Table 1). Our patient developed severe coronary atherosclerosis on the basis of multiple cardiovascular risk factors. Therefore, a careful assessment of cardiovascular risk and intensive lifestyle and pharmacological correction of risk factors are very much needed. A tailored approach to antiplatelet primary prevention could be also taken into account.

Individualisation of effective and safe antithrombotic regimens, balancing thrombotic and bleeding risk, represents an intriguing issue in patients with ACS (21). This becomes essential in haemophilia patients. As evidence-based guidelines remain an improbable task in this setting, the recently proposed suggestions for management should be employed for collecting prospective and more uniform clinical data and increasing knowledge on the efficacy and safety outcomes in this challenging treatment.

### References