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## Characteristics of Older Patient with Haemophilia

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### 1. Introduction

The mankind is living longer due to improved quality of life, better healthcare service worldwide and less infant mortality. Progressive demographic ageing of the older population is a global process. The 80 or over age group is growing faster than any young segment of the older population

#### 1.1 Life expectancy in patients with haemophilia

Until 1960 haemophilia was a life-threatening disease with limited treatment options as splints, icepacks and bed rest. With the discovery of factor concentrates the life of haemophilia patients changed dramatically better. They improved quality of life and prolong life expectancy (Mejia-Carvajal, 2006). Median life expectancy in males with severe haemophilia was 11 years in the early 20th century, increased to the range of 55 to 63 years in the 1970s (Plug, 2006; Darby, 2007). By the early 1980s life expectancy was almost 68 years (Chorba, 2001; Oldenburg, 2009). By 1990s the life expectancy in US haemophiliacs dropped to 49 years because of HIV infections. The decline in HIV-related mortality in HIV-infected persons with haemophilia reflected improvements in highly active anti-retroviral therapy (HAART). In 2001, haemophiliac life expectancy in The Netherlands reached 67 years (74 years for those without blood borne virus infections) and by 2007, the overall haemophilic life expectancy was reported to be 71 years in Italy (Plug, 2006; Tagliaferri, 2010) that is approaching the general male population. About 2% of haemophilia A and B patients surveyed in US comprehensive haemophilia treatment centres are 65 years of age or older and 15% are 45 years or older (Philipp, 2010).

#### 1.2 Quality of life in patients with haemophilia

As haemophiliacs are reaching old age new problems are arising. Except physical problems we are faced today with psychological problems in older patients with haemophilia (Siboni, 2009). They are related to family dynamics (Franchini, 2007) and early retirement. Data on health-related quality of life (HR-QoL) of elderly persons with haemophilia are scarce. Quality of life has become an important issue for physicians who are treating haemophilia patients and an increasing number of studies have analysed the HR-QoL in this population, using specific instruments for its measurement Haemo-QoL (Gringeri, 2006). Results from

multicentre study conducted in Italy in a cohort of elderly haemophiliacs ( $\geq 65$  years) have shown similar cognitive status as elderly non-haemophiliacs. Persons with haemophilia report depression and lower health-related quality of life (Siboni, 2009). These results are very important because, the health status of elderly persons with haemophilia was evaluated in a case control study. These data are consistent with studies on HR-QoL in younger haemophilia patients (Scalone, 2006).

## **2. Characteristics of older haemophiliac**

The life expectancy in persons with haemophilia is increasing and reaching almost that of the general population (Mejia-Carvajal, 2006). In many haemophilia centres, especially those in well-developed countries, old haemophilia person is not a rarity. Haematologists have little experience in managing the age related comorbidities of elderly haemophiliacs and the data are very rare. There is no evidence-based information to guide clinicians and help them to solve the problems. Population of haemophiliacs is aging slowly, giving us time to solve the problems and generate high quality data.

### **2.1 Haemophilia related comorbidities and age related diseases**

Haemophilia patients with increased age suffer the same diseases as the normal male population, especially in well developed countries with sufficient quantity of factor concentrate (Franchini, 2009). Aging is bringing to haemophilia patients not only haemophilia related complications (arthropathy and chronic viral infections) or comorbidities but also age related diseases (cardiovascular disease, malignancy, renal disease, osteoporosis, mental diseases, etc.). About 88% of the general population over the age of 65 years have one or more chronic medical conditions (Hoffman, 1995). Today, clinical experience about comorbidities in elderly haemophiliacs and their influence on the primary disorder, haemophilia are lacking.

#### **2.1.1 Arthropathy**

Haemophilia A and B are characterized in the most severe form with spontaneous bleeding into joints and muscles. Prophylactic therapy with factor concentrates has been shown, if started early, reduce the burden of haemophilic arthropathy (Dolan, 2010; Kulkarni, 2003). Administration of factor concentrate on regular basis, prophylactically demonstrated in US Joint Outcome study benefits in preventing joint damage and bleeding episodes, compared with on-demand use in children (Manco-Johnson, 2007). It is known that many adults with severe haemophilia over the age of 65 and older did not have adequate access for regular treatment until adulthood. They have established haemophilic arthropathy with typical joint deformity, muscle weakness and impaired proprioception (Nilsson, 1992; Siboni, 2009) that influence the quality of life (limitations in their daily activities, etc.). Italian study was the first to evaluate the general health status in patients with severe haemophilia, aged  $\geq 65$  years and were compared with elderly men without bleeding disorders matched for age, sex, geography and social status. Almost all patients with haemophilia had arthropathy, except two. More than half were affected in all six joints considered (57%): only one patient was affected in one joint only, five in three joints and the remaining 28 patients in more than three joints. Haemophilia patients had higher pain score and significant difference was found in the orthopaedic score between the two groups. No statistical difference was found for the number of surgical procedures but joint arthroplasty was performed in 46% of

patients with haemophilia and 7% in non-haemophilic (Siboni, et al 2009). Orthopaedic surgical procedures are usually ankle arthrodesis, osteotomy, hip and knee arthroplasty. Indications for such procedures are chronic permanent pain in arthropathic joint, disability and ineffectiveness of conservative management. There will be more revision operations that have a higher risk of bleeding, in older haemophilia patients who had their first arthroplasty about 15 years earlier. Perioperative treatment for orthopaedic surgery is administration of factor concentrate to achieve normal activity of F VIII as well as protects from development of thromboembolism.

Two approaches are applying for thromboprophylaxis: administration of low molecular weight heparins shortly after operation and under the cover of factor concentrates or using mechanical methods with early ambulation. Thromboprophylaxis is still a big question with certain controversial. Proprioceptive loss seen in elderly haemophiliacs could increase the risk of falls (Street, 2006). About 70% of elderly people with haemophilia had a high risk of falling, spontaneously or after tripling on obstacles (Siboni, 2009). Physical therapy is essential part of comprehensive care for haemophiliacs trying to preserve function of the joint and improve quality of life. They have to do functional training (hydrotherapy, walking climbing stairs, cycling, etc). Osteopenia and osteoporosis can cause increased number of serious injuries and fracture after falls (Wallny, 2007). Painful haemophilic arthropathy with reduced mobility and lack of activity may lead to a reduction of bone mass. Therefore it is recommended weight-bearing physical activities or sports, but with surgery to mobilize the patient. Calcium and vitamin D supplementation are recommended (Kovacs, 2008). Secondary prophylaxis based on two to three infusions of factor concentrates per week in adult patients with haemophilia and with few older patients  $\geq 65$  years in small retrospective studies showed marked reduction in frequency of bleeding (Tagliaferri, 2008) but arthropathy is worsening. Prophylaxis in elderly persons with haemophilia is justified and whenever possible to carry out it is improving their quality of life.

### **2.1.2 Chronic blood borne infections**

Chronic viral infections such as HIV, hepatitis B (HBV) and hepatitis C (HCV) virus are still prevalent in a subgroup of adult haemophilia patients. It is also important to emphasize the risk of development of liver cancer on the background of chronic HCV infection; particularly with genotype 1 and HIV infection, who failed to achieve a sustained viral response with pegylated interferon and ribavirin (Posthouwer, 2007). Many of them will develop liver cirrhosis and subsequent hepatocellular carcinoma (HCC) (Posthouwer, 2007, Konkle, 2009, Siboni, 2009). Hepatocellular cancer is the most prevalent cancer in the older haemophilia patients. Therefore, surveillance program with periodic ultrasound screening is recommended to detect HCC earlier in people with haemophilia and cirrhosis. Therefore, close surveillance with gastroenterologists in collaboration with hematologist should be carried out to prevent such bleeding complications.

In HIV-infected hemophilic patients, combined antiretroviral therapy (cART) significantly improved survival rate comparing to period before the introduction of this treatment in the middle 1990s. cART has also reduced the previously frequent incidence of non-Hodgkin lymphomas (Ragni, 1993, Wilde, 2002). However, cART increases the risk of the metabolic syndrome, diabetes, renal insufficiency, and atherosclerotic cardiovascular disease in non-hemophilia patients (Lundgren et al., 2008). It is likely to suspect that cART will induce the same long-term complications among HIV-infected elderly patients with hemophilia, although there are very rare data about the long-term outcome of such patient subgroup.

Moreover, chronic viral infections such as HCV and HIV can also alter the complex inflammatory process of atherosclerosis and coronary heart disease by itself. Checking serum lipid, glucose, and creatinine at regular intervals is suggested.

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### 2.1.3 Inhibitors

Data from large nationwide haemophilia population (Darby, 2004) provided estimates of the rate of development of inhibitors and showed the cumulative risk of haemophilia A inhibitors at 50 years is 30% and 36% at 75 years. Patients with milder forms of haemophilia may develop inhibitors at advanced age when they receive intensive replacement therapy preoperatively or for invasive procedures. Other risk factors for inhibitor development in mild to moderate haemophilia are certain mutations, like Arg531Cys and exposure to continuous infusion of factor concentrate (Eckhart, 2009).

The treatment of acute bleeding in older severe haemophilia A patients with inhibitors is administration of activated prothrombin concentrate (APCC) and recombinant factor VIIa. Rapid control of bleeding is the key to reducing bleeding complications and thereby preserving joint and musculoskeletal function in haemophilia patients with inhibitors (Šalek, 2011). Risk of thrombotic complication with bypassing agents is a question especially with advanced age. There are a few articles about safe administration of rFVIIa to elderly haemophilia patients with inhibitors (Rivolta, 2009; Leebeck, 2004). There is just one report about the successful immune tolerance induction (ITI) in one old haemophilia patient (60-years old) and high responding inhibitors (Rivolta, 2009). Review article published by Franchini (Franchini, 2008) found that about half of the haemophilia patients with inhibitors resistant to previous immune tolerance regimens are rescued by rituximab treatment. The highest probability to obtain complete response to rituximab was observed for adult haemophilia patients with mild to moderate haemophilia with median age of 50.5 years. Presence of inhibitors in older patient with haemophilia and their treatment represent still today a significant challenge.

### 2.1.4 Renal disease (urogenital disease)

Chronic kidney disease probably develops with increasing prevalence among older people with hemophilia because of multiple concomitant risk factors such as HIV infection and combined antiretroviral treatment, hematuria, structural renal damage, and use of antifibrinolytic drug. (Kulkarni, 2003).

Another important aspect of aging is erectile dysfunction resulting not only from the normal aging process, but also from co-morbidities such as painful chronic joint damage affecting sexual desire and conditions that affect erectile function, such as arteriosclerosis and



hypertension (Gianotten, 2009). The use of multiple drugs for the treatment may also compromise sexual function. Prostatic hypertrophy is also a frequent problem in elderly people with haemophilia. Genitourinary diseases and prostatic hypertrophy may facilitate the onset of hematuria as well.

### 2.1.5 Malignancy

The literature data showed clearly that liver cancer and lymphoma represent the most prevalent malignancy in haemophilia population. They are usually associated with HCV and HIV positivity. Hepatocellular carcinoma is very important cause of death among haemophiliacs with a reported standardized mortality ratio of 17.2 (Plug, 2006) and 13.51 (Darby, 2007). Risk factors for hepatocellular carcinoma assessed in multicentre Italian study were presence of liver cirrhosis, elevated alpha fetoprotein, current HCV infection and age over 45 (Tradati, 1998). There are many studies which do not found an increased incidence of other malignancies in haemophilia compared with general population. Moreover, two population studies found a lower incidence of cancer in severe haemophilia (Walker, 1998; Darby, 2007). *In vitro* study has shown that congenital prothrombotic disorders facilitate metastasis. Haemophiliac mice form less metastasis from experimental melanomas what could be explained with less formation of thrombin (Bruggemann, 2008). It seems that congenital bleeding disorders may have a protective effect against formation of metastasis on murine cells (Langer, 2006). Elderly patients with haemophilia will develop malignancies like normal elderly population; prostate, skin and gastrointestinal cancer (Franchini, 2009).

Treatment schemes for malignant tumours in older haemophilia patients are similar to non-haemophiliac although the inherited coagulation disorder might increase the risk of bleeding during chemo and radiotherapy. Factor replacement therapy is needed for invasive diagnostic and therapeutic procedures and prophylactic factor administration is mandatory for surgery (Mannucci, 2009; Dolan, 2010). At the moment it is not completely clear how intensive replacement therapy should be in a situation of treatment carcinoma in elderly haemophiliacs. There are no recommendations about optimal treatment of elderly haemophiliac with malignancy, except some case reports (Lambert, 2008; Toyoda, 2001). Our group publish a case of 51-year old patient with severe haemophilia A with low-titre inhibitors and multiple relapsing non-melanoma skin cancer. The management of such patients could be very intriguing and require a multidisciplinary approach (Zupančič Šalek, 2009). Age indicated screening tests for malignoma of prostate and colon are justified also in the population of elderly haemophiliacs but under the cover of prophylactic treatment with factor concentrates. Very important fact about haemophilia patients is that they are usually excluded from participating in clinical trials which are evaluating new anticancer drugs because of the potential adverse effects of haemostatic system. Definitely, treatment of older haemophilia patient with malignancy is a complex issue.

### 2.1.6 Pain control

Pain control is extremely important for improvement quality of life among people with haemophilia, especially due to chronic joint damage. Haemophilic arthropathy and related morbidity is still present major concern among haemophilic population. Therefore, chronic pain is prevalent in the elderly people with haemophilia, and even drug addiction is not rare. Possible adverse effects of widely used paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) may become more clinically significant with aging; gastroduodenal toxicity, paracetamol-associated liver dysfunction (particularly associated

with chronic liver disease due to excessive alcohol consumption and/or viral infections), hypertension, and renal insufficiency (Davies et al., 2006). However, paracetamol is still the first choice for pain management among haemophilia patients, and when it is not effective to control pain, cyclo-oxygenase-2 (COX-2) inhibitors are preferred to NSAIDs (Mannucci, 2009). Other possibilities are narcotics such as codeine- and morphine-containing drugs (Mannucci, 2009). Moreover, additional useful option for pain control is referral to a pain management clinic, as well as pre-emptive physiotherapy and hydrotherapy to improve joint stability.

### **2.1.7 Cardiovascular disease in elderly patients with hemophilia**

Haemophilia is reported to be protective against development of coronary heart disease due to the hypocoagulable state of such patients (Rosendaal, 1990). However, people with haemophilia could have other common risk factors for cardiovascular diseases, such as hypertension, smoking, obesity, dyslipidaemia, and diabetes. Additionally, HIV infection and cART may *per se* increase the risk for metabolic and cardiovascular disease, as it was stated earlier. Indeed, it was reported recently an increasing number of deaths in haemophilia patients as a consequence of ischemic heart disease (Plug, 2006), together with increasing prevalence of ischemic heart disease among haemophilia patients 60 years of age and older (Kulkarni, 2005). Moreover, it is important to educate haemophilia patients about the cardiovascular risk factors, and on the benefit of living a healthy lifestyle (Mannucci, 2009).

## **2.2 Assessment of atherosclerotic risk factors in patients with haemophilia**

### **2.2.1 Introduction**

Myocardial and cerebral infarctions are the leading causes of death around the world (Murray, 1997). Due to its public health importance, numerous studies have examined risk factors for atherosclerosis. Due to rare reports about risk factors in haemophilia patients we present data from risk assessment in haemophiliacs.

### **2.2.2 Subjects and methods**

During a 10-year period 410 patients with haemophilia A and B were followed in National Haemophilia Centre in University Hospital. Eight died, two of infection, three of bleeding, two of liver disease and one of malignancy. None of them died due to coronary or cerebrovascular diseases and there were no drop-outs during the follow-up. Of the surviving 402 patients, 336 (84%) had haemophilia A and 66 (16%) haemophilia B. A cohort of 117 haemophilia patients who attended regular check-ups consented to participate in our risk factors study. 104 (89%) had haemophilia A and 13 (11%) haemophilia B. Control group consists of 48 age-adjusted healthy male non-haemophiliac volunteers who did not have anamnestic or clinical signs and symptoms of coronary heart disease or other complications of atherosclerosis.

Body mass index was calculated and patients were considered to have normal weight if their BMI was below 25, overweight if the BMI was 25-29.9 and obese if the BMI was 3.0 or higher (Flegal, 1998). Blood pressure was measured and according to the WHO/ISH criteria, patients were considered having arterial hypertension if their systolic blood pressure was 140 mmHg or higher, diastolic blood pressure was 90 mmHg or higher or if they were taking antihypertensive medications (WHO/ISH, 1999). Serum concentrations of glucose,

creatinine, uric acid, fibrinogen, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol were determined using standard methods and commercially available reagents (Horvat, 2003). Homocysteine concentration and lipoprotein (a) was also determined. Framingham risk index was determined as described by Grundy and co-workers (Grundy, 1999). The ten-year risk of developing coronary heart disease in individuals without symptomatic atherosclerosis is determined taking into account their sex, age, total-cholesterol, HDL-cholesterol, systolic blood pressure, treatment of arterial hypertension and smoking. Four risk levels are recognised: low, moderate, high and very high. The expected incidence of coronary and ischaemic cerebrovascular disease morbidity and mortality for patents with haemophilia was calculated as follows. The number and age for male patents discharged from Croatian hospitals with diagnosis of myocardial infarction, coronary heart disease and cerebrovascular infarction were abstracted from official publications of the Croatian Institute for Public Health (Ljubičić, 2002). Thus calculated age adjusted morbidity and mortality rates were used to determine the expected morbidity and mortality of patients with haemophilia during the 10-year observation period.

### 2.2.3 Results

The tested cohort did not differ from the whole group of patients with haemophilia in respect to age and haemophilia type. More patients with haemophilia than control subjects smoked (44 vs. 33%). This difference was even more pronounced in the group of patients with severe haemophilia (46%) but did not reach statistical significance. Patients with haemophilia had slightly lower BMI than normal controls. Again this difference was more pronounced in patients with severe disease but again, did not reach statistical significance. The incidence of abnormal BMI was similar in all analysed groups. Patients with haemophilia had similar systolic but higher diastolic blood pressure than control subjects. This difference was significant for the subgroup of patients with severe disease but not for the subgroup of patients with moderate or mild disease. The incidence of diastolic hypertension was higher in the group of patients with haemophilia than in the control group. Again, this difference was highly significant for the subgroup with severe disease but barely failed to reach significance for the subgroup of patients with moderate or mild disease. The incidence of systolic hypertension was higher in the group of patients with severe disease than in the control group (Figure 1.) The difference between all subjects with haemophilia and control subjects barely failed to reach statistical significance. These data suggest that arterial hypertension is more frequent in patients with haemophilia, especially in those with severe disease.

Patients with haemophilia did not differ from control subjects in respect to blood glucose, fibrinogen, uric acid and homocysteine concentrations, but they had lower total cholesterol, triglycerides and creatinine concentrations. The difference was even more pronounced in the subgroup of patients with severe haemophilia who also had lower LDL-cholesterol than controls. Patients with mild to moderate disease had higher HDL-cholesterol than controls. The incidence of abnormal serum glucose, fibrinogen, creatinine, uric acid and homocysteine levels was similar between groups. Controls had more frequently abnormal total cholesterol, HDL-cholesterol and triglycerides concentrations than patients with haemophilia. They had also more often abnormal total-cholesterol, LDL- cholesterol and triglycerides concentrations than patients with severe disease; an abnormal HDL-cholesterol and triglycerides concentrations than patients with mild to moderate disease.



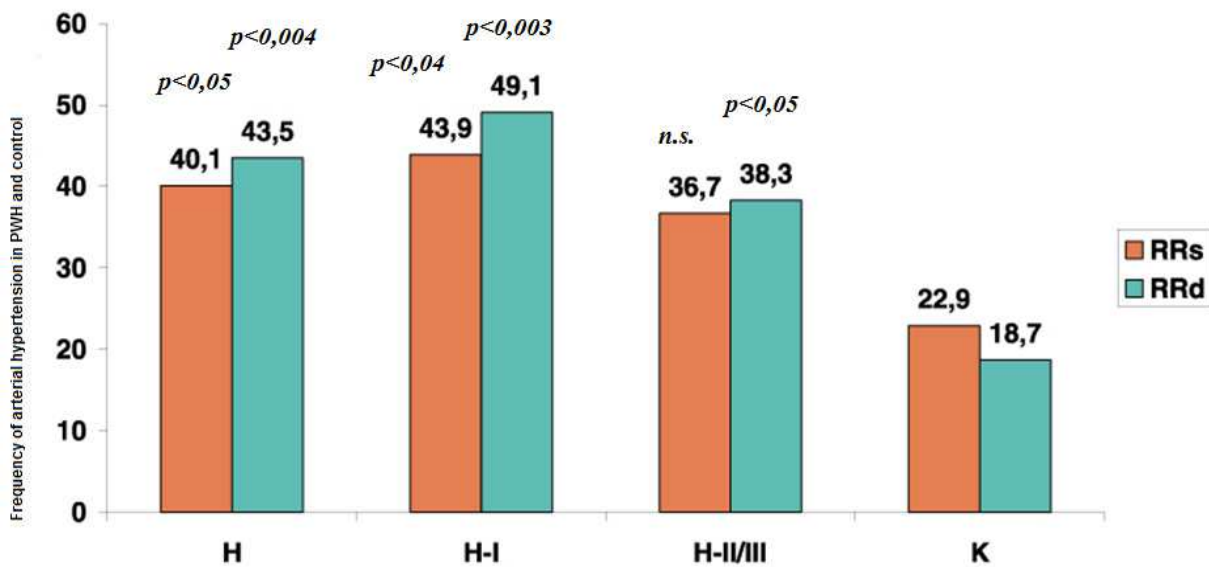


Fig. 1. Frequency of arterial hypertension in patients with haemophilia and control (Legend: red column: systolic blood pressure; blue column: diastolic blood pressure; RRs – systolic blood pressure; RRd dyastolic blood pressure, H: all haemophilia patients, H-1: severe haemophilia patients; H-II moderate haemophilia patients; H-III mild haemophilia patients)

This indicates that patients with haemophilia, especially those with severe disease have lower cholesterol and triglyceride concentrations than control subjects. In patients with mild to moderate haemophilia the increase in total cholesterol is accompanied by an increase in HDL-cholesterol, resulting in a similarly low-risk lipid profile as in those with severe disease.

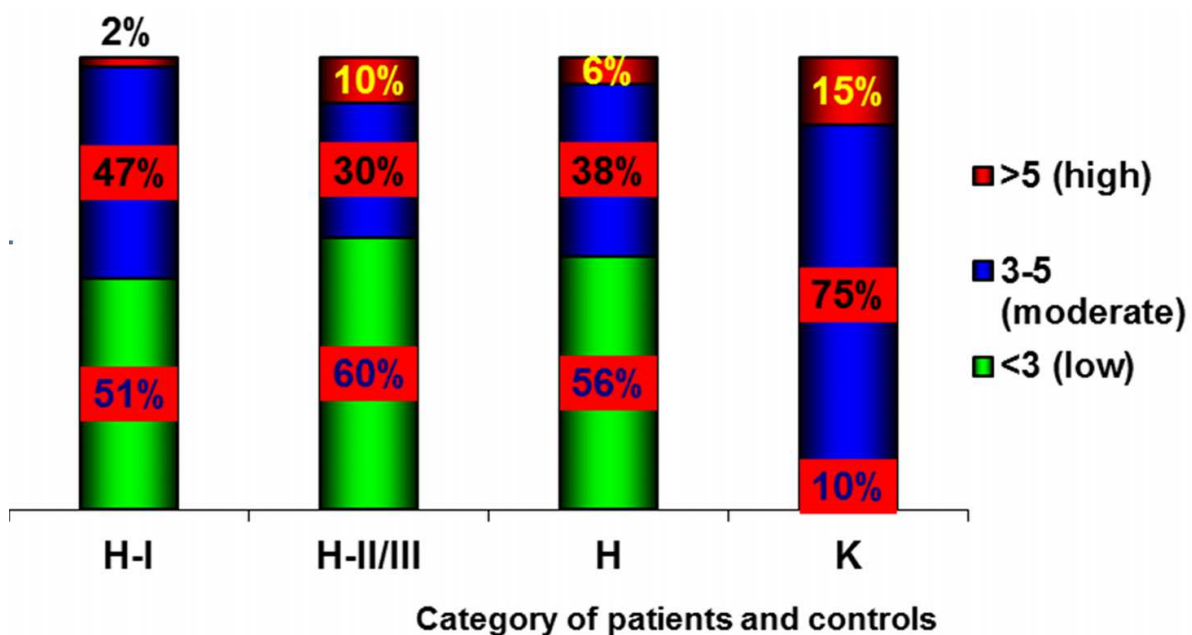


Fig. 2. Risk assessment of coronary heart disease according to LDL/HDL ratio. (Legend: H-I: severe haemophilia; H-II/III: mild and moderate haemophilia; H: all haemophilias patients and K .controls.)

Framingham risk index. The distribution of risk groups did not differ between patients with haemophilia and control subjects. However, some of the patients with severe disease had a high or very high risk of developing coronary heart disease. None such cases could be seen in the control group (Figure 2).

If the morbidity of myocardial infarction and ischaemic cerebrovascular infarction, calculated as described in "Methods" section, would be the same in patients with haemophilia as it is in the general Croatian population, during the ten-year observation period 18 patients would be expected to develop myocardial infarction and 10 ischaemic cerebrovascular infarction. However, none occurred. These differences are highly statistically significant. If the mortality of coronary heart disease, myocardial infarction or cerebrovascular infarction, calculated as described in section "Methods" , would be the same in patients with haemophilia as it is in the general Croatian population, during the ten-year observation period 8 patients would be expected to die of coronary heart disease, 4 of myocardial infarction and 4 of cerebrovascular infarction. None of them died. These differences are statistically significant. These data indicate that patients with haemophilia have a significant lower incidence of complications of atherosclerosis than the general population.

The concentration of lipoprotein (a) as well as the proportion of subjects with abnormal levels is higher in the group of patients with haemophilia than in the controls. The difference is more pronounced in the subgroup of patients with mild to moderate disease, while the difference between patients with severe haemophilia and controls fails to reach statistical significance (Figure 3).

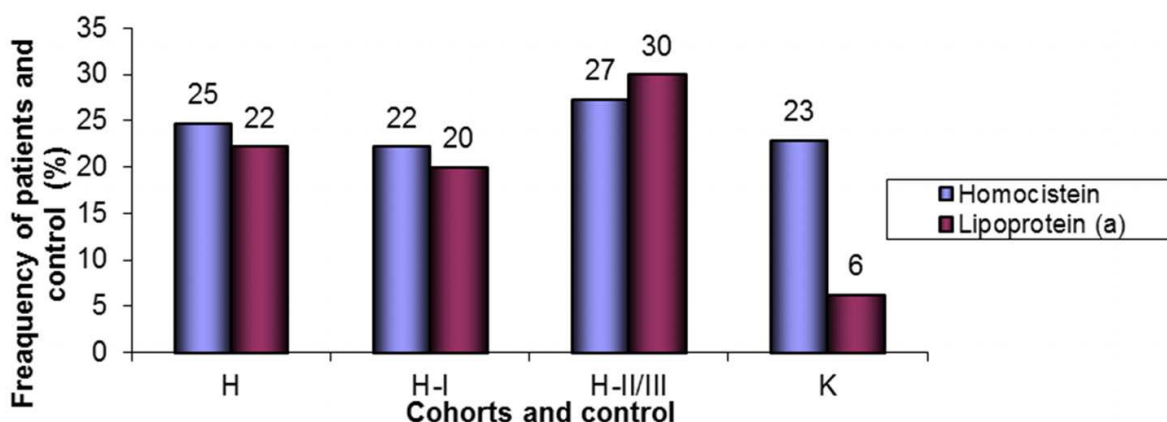


Fig. 3. Frequency of abnormal values for homocysteine and lipoprotein (a) (Legend: H-I: severe haemophilia; H-II/III: mild and moderate haemophilia; H: all haemophilia patients and K: controls.)

### 2.2.3.1 Risk factors

Our results suggest that patients with haemophilia smoke somewhat more frequently than the subjects from the control group or the general Croatian population. Two studies, one Dutch and the other Italian study with patients with haemophilia have reached the same conclusion (Rosendaal et al 1990; Bilora, 1999). This is most probably due to psychological changes induced by the presence of a chronic disease and the enforced sedentary life style. Our patients have a slightly lower BMI than healthy subjects. The same was found in the Dutch study. Again, this is more probably a result of reduced muscle mass in patients with haemophilia, caused by their sedentary life style, than their superior health consciousness.

The incidence of hypertension in the group of patients with haemophilia was 48%, while it was 20% in the control group. The latter incidence is surprisingly low, probably due to the fact that the control subjects had to be free from any signs and symptoms of disease due to atherosclerosis. An epidemiological study performed in 2 898 Croatian subjects found a 32% incidence of hypertension, still lower than in patients with haemophilia (Turek, 2001). The increase in blood pressure we observed was even more pronounced in patients with severe haemophilia and was already present in the youngest group aged between 18 and 29 years. This might suggest that haemophilia somehow causes hypertension. The underlying mechanisms are completely unclear and further research is needed. Renal damage is certainly not the cause.

Patients with haemophilia have more favourable lipid profiles than control subjects. Again, similar findings were obtained by Rosendaal. Lowest cholesterol levels are seen in patients with severe haemophilia. In patients with milder disease total cholesterol is increased, but so is HDL-cholesterol, resulting in a lipid profile that is still favourable than in control subjects. Since we have no reason to believe that patients with haemophilia adhere to a more healthy diet than average person, we agree with the explanation of Rosendaal and col. That this difference is due to a reduced liver synthetic capacity caused by an increased exposure to foreign proteins and transfusion related viral diseases.

Increased homocysteine levels were seen in 25 % of patients with haemophilia and 23% control subjects. These proportions are not statistically different, but are higher than those published for other populations. The reason for this is not clear.

Patient with haemophilia has increased lipoprotein (a) levels. There are reports indicating that lipoprotein (a) levels are reduced in haemophilia patients with AIDS, and that the incidence of increased lipoprotein (a) levels in children with haemophilia is not different from that observed in the general population (Matsuda et al 1994). There are no reports on the concentration of lipoprotein (a) in adult, HIV negative, patients with haemophilia. Since these concentrations are genetically determined and not influenced by diet, studies in other populations are needed to determine whether the increase is characteristic for haemophilia or specific for tested population (Scanu, 1992).

#### **2.2.3.2 Global risk assessment**

The Framingham risk index is a reliable predictor of the ten-year risk for the development of coronary heart disease for persons who did not have prior complications of atherosclerosis (Grundy, 1998). It is used in USA guidelines for arterial hypertension and hypercholesterolemia treatment. It is still one of the best and most validated global risk assessment tools for risk factors for coronary heart disease in patients with haemophilia. According to the Framingham risk index, patients with haemophilia are similar to the control group. While the global assessment is similar, there are important differences in risk profiles. Patients with haemophilia have more favourable lipid profiles, but tend to smoke and have arterial hypertension more frequent than control subjects. Still, some of the patients with severe haemophilia have high risk features, while none such subjects were found in the control group. If the difference in newly recognized risk factors, such as lipoprotein (a) levels, would be taken into account, the increase in risk in the haemophilia group would be even more pronounced.

#### **2.2.3.3 Coronary heart disease and cerebrovascular morbidity and mortality**

The expected coronary and cerebrovascular morbidity and mortality in the group of patients with haemophilia is probably underestimated. The difference between the expected and

observed coronary heart disease and cerebrovascular morbidity and mortality in patients with haemophilia is highly significant. The same phenomenon was observed by other authors in other countries. This indicates that patients with haemophilia have a reduced risk of developing and dying of myocardial infarction, coronary heart disease and ischaemic cerebrovascular infarction.

#### **2.2.4 Haemophilia and atherosclerosis**

The reduction of complications of atherosclerosis in patients with haemophilia is not due to a reduction in known risk factors. It is tempting to assume that the inability to produce a stable thrombus, i.e. haemophilia itself, is the cause. Our results and the published data suggest that haemophilia protects patients against atherosclerosis and complications but it is still not clear whether this is due only to the lack of thromboembolic incidents occurring late in the process of atherogenesis.

### **2.3 Osteoporosis**

#### **2.3.1 Introduction**

Since the world's population is ageing, osteoporosis has become one of the major socioeconomic problems in the western world. As a consequence of reduced bone mass and decline in neuromuscular function, the risk of osteoporotic fractures is rising with the advancing age, both in men and in women. Fractures of the spine, proximal femur and a distal forearm are described as typical for osteoporosis; nevertheless, almost all types of bone fractures are increased in patients with reduced bone mineral mass. Many factors influence bone mass accumulation in early life, and maintenance of that mass in adult age, including genetic factors, hormonal status, physical activity and calcium intake. Besides genetics, which has the highest impact on bone mass accumulation and maintenance, the changes of hormonal status in ageing woman have been described to have strong impact on bone mineral mass.

#### **2.3.2 Osteoporosis in haemophilia patients**

Recently, bone mineral mass has become an issue of interest in patients with haemophilia. Although there are only sparse data about osteoporotic fractures in haemophilia patients, we can expect increase in number of osteoporotic fractures in the future due to ageing of haemophilia population. Morbidity and mortality of osteoporotic fractures in haemophilia patients are very high, and those patients need special care (Rodriguez-Merchan, 2002.). Moreover, it has been shown that patients with haemophilia and reduced bone mass have lower quality of life (Khawaji, 2010.). Studies addressing bone mineral mass in haemophilia patients mainly focused on patients with severe haemophilia. Because haemophilia is rare disease, total number of studied patients is relatively low.

#### **2.3.3 Incidence of reduced bone mass in haemophilia patients**

The incidence of reduced mineral bone mass among patients with haemophilia differs between studies. Our results, in a study where we evaluated 58 patients with haemophilia, showed reduced bone mass in 56% of patients with haemophilia. Those results are comparable with findings of Nair, who described reduced bone mass in 50% of patients with severe haemophilia (Nair, 2007). On the other hand, some authors showed reduced bone mass in 86% patients with severe and moderate haemophilia (FVIII<3%) (Katsarou,

2009), and in 70% of patients with severe haemophilia (Gerstner, 2009, Wallny, 2007). The reason for difference between those results is uncertain.

The data about incidence of reduced bone mineral mass in patients with moderate or mild haemophilia are sparse. Our results showed increased loss of bone mineral density in patients with mild and moderate haemophilia (FVIII>1%). In comparison of bone mass between patients with severe and patients with mild or moderate haemophilia, the difference was noted in values of bone mineral density measured at femoral neck, representing cortical bone, where patients with mild and moderate haemophilia had higher values (Boban, unpublished data). See Figure 4.

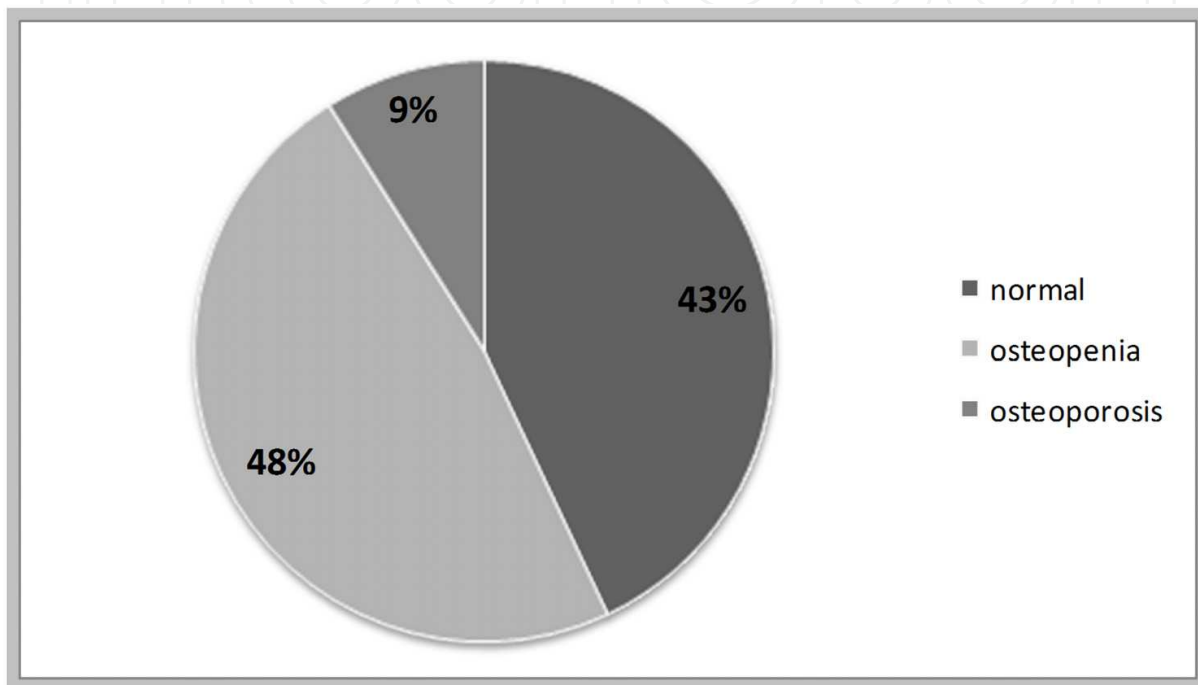


Fig. 4. Prevalence of osteopenia and osteoporosis in patients with haemophilia.

### 2.3.4 Physical activity

Several risk factors for developing osteoporosis in patients with haemophilia have been recognized. Besides genetics, reduction of physical activity during childhood and adult age has been suggested to have major impact on bone metabolism in haemophilia patients. However, the exact pathogenesis of developing reduced bone mineral mass in haemophilia patients is still obscure. Patients with haemophilia seem to achieve lower peak bone mineral mass when compared to healthy controls. In favour of this hypothesis, studies showed reduced bone mineral density among children with severe haemophilia (Barnes, 2004, Abdelrazik, 2007., Nair, 2007., Tlacuilo-Parra, 2008.). The major impact on bone formation during childhood and adolescents has physical activity and, moreover, weight-bearing exercises. Patients with haemophilia avoid physical activity due to acute bleedings into joints, chronic pain, development of arthropathy, and fear of possible injury. The study showed that 77% of young haemophiliacs are inactive; with the high correlation of inactivity and reduced bone mass (Tlacuilo-Parra, 2008).

The role of physical activity in maintaining or even improving bone mass in adult age is questionable. The only study that evaluated influence of physical activity on bone mass in



adult haemophilia patient did not show any correlation between those two parameters (Khawaji, 2010.). However, we must point out that patients enrolled in the mentioned study had normal bone mineral mass.

### **2.3.5 Joint status and prophylactic therapy**

The strong relationship has been established between reduced bone mass and joint status in young patients with haemophilia (Abdelrazik, 2007), as well as among adult haemophiliacs (Nair, 2007., Katsarou, 2009.). Joint status was evaluated using clinical score as described by the Orthopedic Advisory Council of the World Federation of Haemophilia (Rodriguez-Merchan EC, 2003.) and by the Pettersson scores (Pettersson, 1994). Total joint score had independent prognostic value for development of bone loss (Nair, 2007., Katsarou, 2009). In our study number of target joints was evaluated as a prognostic factor for development of bone loss. No correlation was found between bone mass and number of target joints (Boban, unpublished data).

Prophylactic therapy, however, seems to prevent bone mineral loss. Prophylactic therapy significantly reduces the risk of developing haemophilic arthropathy, thus avoiding immobilization, crippling, and chronic pain (Manco-Johnson, 2007). Young patients with haemophilia that received prophylactic therapy had only slightly reduced bone mass (Barnes, 2004). Moreover, adult patients with haemophilia that received prophylactic treatment since childhood had bone mass comparable to patients with mild haemophilia (Khawaji, 2009.).

### **2.3.6 Inhibitors**

Patients with inhibitors have significantly more joint pain with clinically and radiological worse orthopaedic status than patient without inhibitors (Morfini, 2007). Therefore, due to pathogenesis of osteoporosis in patient with haemophilia, they were expected to have lower bone mass than patients without inhibitors. Data about bone mineral mass in haemophilia patients with inhibitors in the literature are sparse. Only very few patients with inhibitors were evaluated. The study on 6 patients showed that patients with increased bone loss were statistically more likely to have a history of factor inhibitor (Gerstner, 2009). We have evaluated 9 patients with severe haemophilia and inhibitors. The results showed no difference in bone mineral mass between patients with severe haemophilia and with and without inhibitors. The discrepancy between those two studies may be explained by different treatment approaches. Moreover, in our study, no difference was found in number of target joints between patients with and without inhibitors, which can suggest effective treatment (Boban, unpublished data).

### **2.3.7 Infection with hepatitis C**

Infection with hepatitis C virus (HCV) has been recognized as a risk factor for development of increased bone loss. HCV infection can lead to chronic liver disease, and consequently to increased bilirubin levels, hypogonadims and abnormalities in vitamin D metabolism, which can have negative influence on bone turnover (Olsson, 1994, Schiefke, 2005). Influence of HCV infection on bone loss in patients with haemophilia is still unclear. Two studies (Nair, 2007, Barnes, 2004) found no significant difference in bone mass between HCV positive and negative patients. On the other hand, Wallny showed significantly lower bone mass in haemophilia patients that were HCV positive (Wallny, 2007). According to our

study, HCV infection had no influence on bone mineral mass in patients with haemophilia. Nevertheless, slight difference was seen in group of patients with mild and moderate haemophilia, where we discovered negative influence of HCV infection on bone mineral (Boban, unpublished data).

### **2.3.8 Quantitative ultrasound of the heel**

Dual energy X-ray absorptionmetry (DXA) is the golden standard for measurement of bone mineral mass. Quantitative ultrasound (QUS) of the heel is emerging as a new, low cost screening technique that is able to identify risk of osteoporotic fractures. The QUS parameters, BUA (broadband sound attenuation) and SOS (speed of sound) depend not only on mineral bone mass, but also on micro architecture and physical properties of bone tissue. A number of studies showed that the values of parameters measured with QUS are lower in woman with the history of osteoporotic fractures, regardless of the bone mineral density determined by DXA (Hernandez, 2004, Gluer, 2004). Thus, QUS parameters are independent risk indicator for hip fractures. Our study observed reduced bone properties among patients with severe hemophilia determined by QUS. On the other hand, patients with mild and moderate hemophilia had QUS values comparable to healthy controls. Sensitivity and specificity of QUS in finding reduced bone mineral density was 70,4% and 64%, respectively. However, among studied population we observed no history of osteoporotic fractures. Therefore, we could not assess QUS as the method for identifying risk of osteoporotic fractures in patients with haemophilia (Boban, unpublished data).

### **2.3.9 Haemophilia and bone mineral density**

Assessment of frequency of osteoporosis/osteopenia in patients with haemophilia A/B has been undertaken in National Haemophilia Centre. Results showed that patients with haemophilia have high risk of developing osteoporosis and osteopenia, which is dependent on severity of haemophilia, but not on presence of FVIII inhibitors or hepatitis C infection. Quantitative ultrasound of the heel, after modification of T- cut off values, showed high sensitivity and specificity for detection of reduced bone mineral density in haemophilia patients.

## **3. Conclusion**

The improved diagnosis and comprehensive care of patients with hemophilia around the world have introduced the new problems of an aging patients with hemophilia and other co-morbidities. It is obvious that population of people with hemophilia is getting older, approaching life expectancy that of the general male population; at least in countries that can afford regular replacement therapy with coagulation factor concentrates.

Such improvement of life expectancy among people with hemophilia is due to several factors: advances in hemophilia replacement treatment, comprehensive care, home treatment and prophylaxis, as well as due to advances in general health care improvement.

Two investigations have been set in Hemophilia Centre. The first one was conducted about the frequency of classical risk factors of coronary heart disease in patients with haemophilia A and B as well as new risk actors - homocysteine and lipoprotein (a).

The frequencies of atherosclerotic complications are less expressed in haemophilia patients than expected from the data of the normal Croatian population

The results of investigated risk factors of CHD in patients' with haemophilia reveal the importance to follow up in spite of the protection of haemophilia in clinical manifestations of atherosclerosis.

Recently, Biere-Rafi (Biere-Rafi, 2011) also published data about cardiovascular risk assessment in haemophilia patients. They found that the number of hemophiliacs with hyperglycaemie (24%) and hypertension (51%) was higher than in the controls. It is comparable with our results that hemophiliacs have more arterial hypertension than the control group. Also, they have lower level of low-density lipoprotein (LDL) than control what is also comparable with our results.

Considering high prevalence of patients with cardiovascular risk factors, active screening for these factors is recommended.

The second investigation assessed the frequency of osteoporosis/osteopenia in patients with haemophilia A/B (see 2.3.9.).

The aging haemophilia population will have much co-morbidities like older general population, however with specific complex requirements due to bleeding tendency. There are well established guidelines of care for the younger people with hemophilia, but it is necessary to have guidelines of care for aging hemophilia patients as well.

#### 4. References

- Abdelrazik, N.; El-Ziny, M.; Rabea, H. (2007). Evaluation of bone mineral density in children with hemophilia: Mansoura University children hospital (MUCH) experience, Mansoura, Egypt. *Hematology*, Oct;12(5): 431-7.
- Barnes, C WP.; Egan, B.; Speller, T.; Cameron, F.; Jones, G.; Ekert, H.; Monagle, P. (2004.) Reduced bone density among children with severe hemophilia. *Pediatrics*, Aug;114 (2): e177-81.
- Biere-Rafi, S.; Baarslag, MA.; Peters, M.; Kruip, MJHA.; Kraaijenhagen, RA.; Heijer, MD.; Buller, HR. and Kamphuisen, PW. (2011) Cardiovascular risk assessment in haemophilia patients. *Thrombosis and Haemostasis*. 105:274-278.
- Bilora,F.; dei Rossi,C.; Girolami,B.; Casonato, A.; Zanon,E.; Bertomoro, A.; Girolami, A.(1999). Do haemophilia A and von Willebrand disease protect against carotid atherosclerosis? A comparative study between coagulopathies and normal subjects by means of carotid echo-colour Doppler scan. *Clin Appl Thormb Haemost* 5:232-235
- Birch C, La F. (2008) Haemophilia, clinical and genetic aspects. Urbana: University of Illinois, 1937.
- Bruggemann, LW.; Versteeg, HH.; Nieres, TM.; Reitsma, PH.; and Spek, CA. (2008) Experimental melanoma metastasis in lungs of mice with congenital coagulation disorders. *J Cell mol Med* 12(6B): 2622-2627.
- Chorba, TL.; Holman, RC.; Clarke, MJ.; Evatt, BL. (2001) Effects of HIV infection on age and cause of death for persons with Haemophilia A in the United States. *Am J Hematol*. 66:229-240.
- Dalldorf,FD.; Taylor,RE.; Blatt,PM. (1981) Artherosclerosis in severe haemophilia. *Arch Pathol Lab Med*. 10:652-654.
- Darby, SC.; Keeling, DM.; Spooner, RJ. et al. (2004) UK Haemophilia Centre Doctors' Organization. The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977-99. *J Thromb Haemost*.2:1047-1054.

- Darby, SC.; Kan, SW.; Spooner, RJ.; Giangrande, PLF.; Hill, FGH.; Hay, CRM.; Lee, CA.; Ludlam, CA.; and Williams, M. (2007) Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*, 110:815-825.
- Davies, NM.; Reynolds, JK.; Undeberg, MR.; Gates, BJ.; Ohgami, Y.; Vega-Villa, KR. (2006) Minimizing risks of NSAIDs: cardiovascular, gastrointestinal and renal. *Expert Rev Neurother*. 6(11):1643- 1655.
- Dolan, G. (2010) The challenge of an ageing hemophilia population. *Haemophilia*. 16 (Suppl.5), 11-16.
- Eckhart, Cl.; Menke, LA.; van Ommen, CH., et al. (2009).Intensive peri-operative use of factor VIII and the Arg593cys mutation are risk factors for inhibitor development. *J Thromb Haemost*.7:9228-929.
- Flegal, KM.; Carroll, MD.; Kuczmarski, RJ.; Johnson, CL. (1998). Overweight and obesity in the United States. Prevalence and trends, 1960-1994. *Int J Obes*. 22:39-47.
- Franchini, M.; Mengoli, C.; Lippi, G.; Targher, G.; Montagnana, M.; Salvagno, GL.; Zaffanello, M.; & Cruciani, M.(2008) Immune tolerance with rituximab in congenital haemophilia with inhibitors: a systematic literature review based on individual patients' analysis. *Haemophilia* 14, 903-912.
- Franchini, M.; Manzato, F.; Salvagno, G.L.; et al. (2009). Prophylaxis in congenital hemophilia with inhibitors: the role of recombinant activated factor VII. *Semin Thromb Hemost*, 35:814-819.
- Franchini, M.; Lippi, G.; Montagnana, M.; Targher, G.; Zaffanello, M.; Salvagno, GL.; Rivolata, GF.; Perna, C.D.; and Tagliaferri, A. (2009) Haemophilia and cancer: a new challenge for hemophilia centers . *Cancer Treatment Reviews*, 35, 374-377.
- Franchini, M.; and Mannuccio ,PM. (2009) Co-morbidities and quality of life in elderly persons with haemophilia. *British J Haematology*, 148;522-533.
- Franchini,M.; Tagliaferri, A.; Mannucci, PM. (2007) The management of haemophilia in elderly patients. *Clin Interv Aging* 2:361-368.
- Gerstner, G. D. M.; Tom A, Worman ,C.; Schultz, W.; Recht, M.; Stopeck, AT. (2009).Prevalence and risk factors associated with decreased bone mineral density in patients with haemophilia. *Haemophilia*. Mar;15(2): 559-65.
- Gianotten, WL.; Heijnen, L. (2009) Haemophilia, aging and sexuality. *Haemophilia*. 15(1):55-62.
- Gringeri,A.; Mantovani, L.; & von Mackensen, S. (2006) Quality of life assessment in clinical in haemophilia treatment. *Haemophilia*. 12 (Suppl.3), 22-29.
- Grundy, SM., Balady,GJ.; Criqui,MH.; et al. (1998). Primary prevention of coronary heart disease:guidance from Framingham. *Circulation* 97:1876-1887
- Grundy, SM. (1999). Primary prevention of coronary heart disease: Integrating risk assessment with intervention. *Circulation* 100:988-98.
- Guidelines Subcommittee (1999). World Health Organisation - International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 7:151-83.
- Gluer, CC.; Eastell, R.; Reid, DM.; et al. (2004). Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in population-based sample: The OPUS study. *J Bone Miner Res* 19:782-793.



- Hernandez, JL.; Marin, F.; Gonzalez-Macias, J.; et al. (2004). Discriminative capacity of calcaneal quantitative ultrasound and fracture risk factors in postmenopausal women with osteoporotic fractures. *Calcif Tissue. Int* 74:357-365.
- Hoffman, C.; Rice, D.; and Sung, HY. (1995) Persons with chronic conditions, their - and costs. *JAMA* 276:1473-1479.
- Horvat, D.; Zrinski-Topić, R.; Bilić, A.; Stavljenić-Rukavina, A. (2003). Determination of HDL-C concentration: the importance of hypertriglyceridaemia for the choice of the method. *Biochemia Medica*, 3-4:137-43 (In Croatian)
- Katsarou, O T E.; Chatzismalis Provelengios, S.; Adraktas, T.; Hadjidakis, D.; Kouramba, A.; Karafoulidou, A. (2009.) Increased bone resorption is implicated in the pathogenesis of bone loss in hemophiliacs: correlations with hemophilic arthropathy and HIV. *Annals of Hematology*, Jun 2.
- Konkle, BA.; Kessler, C.; Aledort L, et al. Emerging clinical concerns in the ageing haemophilia patient. *Haemophilia*. 2009;15(6):1197-1209.
- Khawaji, M A K.; Berntorp, E. (2009). Long-term prophylaxis in severe haemophilia seems to preserve bone mineral density. *Haemophilia*, Jan;15(1): 261-6.
- Khawaji, M.A.J.; Akesson, K.; Berntorp, E. (2010). Physical activity for prevention of osteoporosis in patients with severe haemophilia on long-term prophylaxis. *Haemophilia*, 1-7.
- Khawaji, M.; Astermark, J.; Von Mackensen, S.; et al. (2011). Bone density and health-related quality of life in adult patients with severe haemophilia. *Haemophilia*, Mar;17(2):304-11.
- Kovacs, CS. (2008) Hemophilia, low bone mass, and osteopenia/osteoporosis. *Transf Apher Sci*. 38:1079-1083.
- Kulkarni, R.; Soucie, JM.; and Evatt, B. (2003). Hemophilia Surveillance System Project Investigators. Renal disease among males with haemophilia. *Haemophilia*. 9;703-710.
- Kulkarni, R.; Soucie, JM.; Evatt, B.(2003). Renal disease among males with haemophilia. *Haemophilia* 9(6):703-710.
- Kulkarni, R.; Soucie, JM.; Evatt, BL; (2005). Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart disease among males with hemophilia. *Am J Hematol*. 79(1):36-42.
- Lambert, C.; Deneys, V.; Pothen, D. & Hermans, C. (2008) Safety of bevacizumab in mild haemophilia B. *Thrombosis and Haemostasis*, 99. 963-964.
- Langer, F.; Amirhosravi, A.; Ingersoll, SB. et al. (2006) Experimental metastasis and primary tumor growth in mice with haemophilia A. *J Thromb Haemost*. 4(5): 1056-1062.
- Leebeck, FWG.; Kappers-Klunne, MC.; & Jie, KSG. (2004) Effective and safe use of recombinant factor VIIa (Novo Seven) in elderly mild haemophilia A patients with high-titre antibodies against factor VIII. *Haemophilia*, 10, 250-253.
- Lundgren, JD.; Battegay, M.; Behrens, G; et al. (2008). European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med*. (2):72-81.
- Ljubičić, M.; Kuzman, M. et al (2002) Croatian health-statistic annals for year 2002. Croatian Institute for Public Health, Zagreb, 2002
- Mannucci, PM.; Schutgens, REG.; Santagostino, E. and Mauser-Bunschoten, EP. (2009) How I treat age-related morbidities in elderly persons with hemophilia. *Blood*. 114:5256-5263. Manco-Johnson, MJ.; Abshire, TC.; Shapiro, et al. (2007) Prophylaxis versus



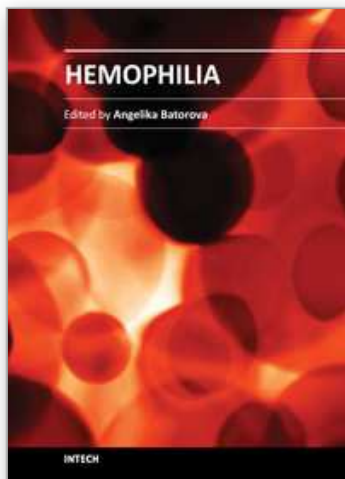
- episodic treatment to prevent joint disease in boys with severe haemophilia. *N Engl J Med.* 357;535-544.
- Matsuda, J.; Saitoh, N.; Gohecki, K.; Gotoh, M.; Tsukamoto, M. (1994) Low serum lipoprotein (a) and beta-2-lipoprotein I levels in HIV – 1 positive haemophiliacs. *Ann Hematol.* 68:315-316.
- Mejia-Carvajal, C.; Czapek, EE.; and Valentino, LA. (2006) Life expectancy in hemophilia outcome. *Journal of Thrombosis and Haemostasis.* 4, 507-509.
- Morfini, M., Haya, S., Tagariello, G., et al. (2007). European Study on Orthopaedic Status of haemophilia patients with inhibitors. *Haemophilia.* 13, 606-612.
- Murray, CJ.; & Lopez, AD. (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet.* 349:1436-1442.
- Nair, APJF.; Ghosh, K.; Madkaikar, M.; Shrikhande, M.; Nema.; M. (2007). Osteoporosis in young haemophiliacs from western India. *American Journal of Hematology.* Jun;82(6): 453-7.
- Nilsson, IM.; Berntorp, E.; Lofqvist, T. and Pettrsson, H. (1992) Twenty-five years , experience of prophylactic in severe haemophilia A and B. *J Intern Med.* 232:-25-32.
- Oldenburg, J.; Dolan, G.; Lemm, G. (2009) Haemophilia care then, now and in the future. *Haemophilia.* 15 (Suppl 1) :1-2.
- Olsson, R., Johansson, C., Lindstedt, G., et al. (1994) Risk factors for bone loss in chronic active hepatitis and primary biliary cirrhosis. *Scandinavian Journal of Gastroenterology,* 29:753-756.
- Pettersson H (1994). Can joint damage be quantified? *Semin Hematol.* 31 (Suppl 2):1-4.
- Philipp ,C. (2010). The aging patient with haemophilia: complications, comorbidities and management issues. *Hematology* 191-196.
- Plug, I.; Van Der Bom, JG.; & Peters, M.; et al. (2006) Mortality and causes of death in patients with haemophilia, 1992-2001: a prospective cohort study. *J Thromb Haemost.* 4;510-516.
- Posthouwer, D.; Makris, M.; Yee, TT.; et al. (2007). Progression to end-stage liver disease in patients with inherited bleeding disorders and hepatitis C: an international, multicenter cohort study. *Blood.* 09(9):3667-3671.
- Posthouwer D, Yee TT, Makris M, et al. (2007) Antiviral therapy for chronic hepatitis C in patients with inherited bleeding disorders: an international, multicenter cohort study. *J Thromb Haemost.* 5(8):1624-1629.
- Ragni, MV.; Belle, SH.; Jaffe, RA.; et al. (1993) Acquired immunodeficiency syndrome-associated non- Hodgkin's lymphomas and other malignancies in patients with hemophilia. *Blood.* 81(7): 1889-1897.
- Rivolta, GF.; Di Perna, C.; Franchini, M.; Riccardi, F.; Ippolito, L.; Lombardi, M. & Tagliaferri, A. (2010) Successful Immune tolerance induction with factor VIII/von Willebrand factor concentrate in an elderly patient with severe haemophilia A and a high responder inhibitor. *Blood Trans.* 8;66-68.
- Rivolta, GF.; Di Perna, C.; Franchini, M.; Ippolito, L. ; Maurizio, S.; Rocci, A. & Tagliaferri, A. (2009) Management of coronary artery disease in a severe haemophilia patient with high titre inhibitor and anaphylaxis. *Haemophilia* 15, 1159-1179.
- Rodriguez-Merchan, EC. (2010). Bone fractures in the haemophilic patient. *Haemophilia,* 8, 104-111.

- Rosendaal, FR.; Briët, E.; Stibbe, J.; van Herpen, G.; Leuven, JA.; Hofman, A.; Vandenbroucke, JP. (1990). Haemophilia protects against ischaemic heart disease: a study of risk factors. *Br J Haematol.* 75(4):525-30.
- Salek, ZS, Elezovic, I. et al. (2011). The need for speed in the management of haemophilia patients with inhibitors. *Haemophilia*, 17: 95-102.
- Salomon, O.; Steinberg, DM.; Darlik, R., Rosenberg, N; Zivelin, A.; Tamarin, I.; Ravid, B. & Seligsohn, U. (2002) Inherited factor XI deficiency confers no protection against myocardial infarction. *Thromb Haemost.* 1:658-661.
- Scalone, L.; Mantovani, LG.; Mannucci, PM.; Gringeri, A. and COCIS Study Investigators. (2006) Quality of life is associated to the orthopaedic status in hemophiliac patients with inhibitors. *Haemophilia*. 12, 154-162.
- Scanu, AM. (1992) Lipoprotein (a). A genetic risk factor for premature coronary heart disease. *J Am Med Assoc.* 267:3326-3329.
- Schiefke, I., Fach, A., Wiedmann, M., et al. (2005). Reduced bone mineral density and altered bone turnover markers in patients with non-cirrhotic hepatitis B or C infection. *World Journal of Gastroenterology*, 11:1843-1847.
- Siboni, SM.; Mannucci, PM.; Gringeri, A. et al. (2009) Health status and quality of life of elderly persons with severe haemophilia born before the advent of modern replacement therapy. *J Thromb Haemost.* 7:780-786.
- Tagliaferri, A. (2009) Hemophilia and Cancer: A New challenge for hemophilia centers. *Cancer Treatment Reviews.* 35:374-377. Tradati, F.; Colombo, M.; Mannucci, PM. et al. (1998) A Prospective multicenter study of hepatocellular carcinoma in Italian haemophiliacs with chronic hepatitis C. *Blood*, 91 (4):1173-1177.
- Tagliaferri, A.; Rivolta, GF.; Ioro, A. et al. (2010) Mortality and causes of death in Italian persons with haemophilia. *Haemophilia*. 16:437-466.
- Tlacuilo-Parra A, M.-Z. R., Tostado-Rabago, N., Esparza-Flores MA, Lopez-Guido B, Orozco-Alcala J. (2008). Inactivity is a risk factor for low bone mineral density among haemophilic children. *British Journal of Haematology*, Mar;140(5): 562-7.
- Toyoda, H.; Fukuda, Y.; Yokozaki, S.; Hayashi, K.; Saito, H. & Takamatsu, J. (2001) Safety and complications of interventional radiology for hepatocellular carcinoma in patients with haemophilia and cirrhosis. *British Journal of Haematology.* 112, 1071-1073.
- Turek, S.; Rudan, I.; Smolej-Narančić, N et al. (2001) A large cross-sectional study of health attitudes, knowledge, behavior and risks in the post-war Croatian population (The first Croatian health project) *Coll Anthropol* 25:77-96.
- Walker, IR.; and Julian, JA. (1998) Association of Hemophilia Clinic Directors of Canada. Causes of death in Canadians with haemophilia 1980 -1995. *Haemophilia* 4 (5):714-720.
- Wallny, TA. S. D.; Oldenburg, J.; Nicolay, C.; Ezziddin, S.; Pennekamp, PH.; Stoffel-Wagner, B.; Kraft, CN. (2007). Osteoporosis in haemophilia - an underestimated comorbidity? *Haemophilia*, Jan;13(1): 79-84.
- Wilde JT, Lee CA, Darby SC, et al. (2002). The incidence of lymphoma in the UK haemophilia population between 1978 and 1999. *AIDS.* 16(13): 1803-1807.

Zupancic Salek, S.; Radman, I.; Pulanic, D.; Pasic, A.; Nola, M.; and Labar. B. (2009) Treatment of multiple relapsing non-melanoma skin cancer in a patient with severe hemophilia A. *Tumori*,95:115-118.

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## **Hemophilia**

Edited by Dr. Angelika Batorova

ISBN 978-953-51-0429-2

Hard cover, 130 pages

**Publisher** InTech

**Published online** 30, March, 2012

**Published in print edition** March, 2012

This book demonstrates the great efforts aimed at further improving the care of the hemophilia, which may bring further improvement in the quality of life of hemophilia persons and their families.

### **How to reference**

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Silva Zupančić Šalek, Ana Boban and Dražen Pulanić (2012). Characteristics of Older Patient with Haemophilia, Hemophilia, Dr. Angelika Batorova (Ed.), ISBN: 978-953-51-0429-2, InTech, Available from: <http://www.intechopen.com/books/hemophilia/characteristics-of-older-patient-with-haemophilia>

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