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POPULATION-BASED STUDIES ON FAMILIALITY AND PROGNOSIS IN PATIENTS WITH MONOCLONAL GAMMOPATHIES

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Stockholm 2009
To Sunna, Kristinn, Katla and Vala
ABSTRACT

Monoclonal gammopathies constitute a group of diseases which have in common an overproduction of monoclonal immunoglobulins, M-proteins.

Clues to their etiology have been found in studies showing familial aggregation of these diseases. We included 2,144 patients with lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia (LPL/WM) and 4,458 patients with monoclonal gammopathy of undetermined significance (MGUS), their 6,177 and 14,621 first-degree relatives respectively, and controls and their relatives. We found first-degree relatives of LPL/WM, compared to first-degree relatives of controls, to have 20-fold (95% confidence interval (CI): 4.1-98), 3.0-fold (2.0-4.4), 3.4-fold (1.7-6.6), and 5.0-fold (1.3-19) increased risks of developing LPL/WM, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and MGUS, respectively. First-degree relatives of MGUS patients had increased risks of MGUS (hazard ratio (HR)=2.8; 95% CI 1.4-5.6), multiple myeloma (MM) (2.9; 1.9-4.3), LPL/WM (4.0; 1.5-11), and CLL (2.0; 1.2-2.3). These findings support shared common susceptibility genes that predispose to a variety of lymphoproliferative disorders.

We included 4,259 MGUS patients and compared their survival to that of the general population by computing relative survival ratios (RSRs). One-, 5-, 10-, and 15-year RSRs were 0.98 (95% CI 0.97-0.99), 0.93 (0.91-0.95), 0.82 (0.79-0.84), and 0.70 (0.64-0.76), respectively. Younger age at MGUS diagnosis was associated with a significantly lower excess mortality compared to older age (p<0.001). The excess mortality among MGUS patients increased with longer follow-up (p<0.0001). IgM (versus IgG/A) MGUS was associated with a superior survival (p=0.038). We also compared causes of death with 16,151 matched controls and found MGUS patients to have an increased risk of dying from both malignant transformation and non-malignant causes. Our findings are of importance in the understanding and clinical management of MGUS. The underlying mechanisms of our findings may be causally related to the MGUS, but may also be explained by an underlying disease that led to the detection of MGUS.

We conducted a study including 14,381 MM patients diagnosed in Sweden 1973-2003 to define survival patterns among MM patients. One-year survival improved (p<0.001) over time in all age groups. Improvement in 5-year (p<0.001) and 10-year (p<0.001) RSR was, however restricted to patients <70 years and <60 years, respectively. High dose melphalan with subsequent autologous stem cell support, thalidomide, and a continuous improvement in supportive care measures are probably the most important factors contributing to this finding. We also assessed the impact of socioeconomic status (SES) on survival in 14,744 patients with MM. Overall, higher white-collar workers had a lower mortality than other SES groups (p<0.005). No difference was observed in the first two calendar periods. However, in 1990-1999, self-employed (HR=1.18; 1.02-1.37), blue-collar workers (1.18; 1.04-1.32), and retired (1.45; 1.16-1.80) had a higher mortality compared to higher white-collar workers. In 2000-2005, blue-collar workers had a higher mortality (1.31; 1.07-1.60) compared to higher white-collar workers. Differences in co-morbidity, management and life-style, are likely factors to explain these findings.

We assessed the risks of venous and arterial thrombosis in 19,391 MM and 5,395 MGUS patients compared to 76,415 and 20,761 matched controls. At 1, 5 and 10 years after MM diagnosis, there was an increased risk for venous thrombosis with HR=7.9 (6.5-9.6), 4.5 (4.0-5.1), and 3.9 (3.5-4.4), respectively. The corresponding HRs for arterial thrombosis were 2.0 (1.8-2.2), 1.5 (1.4-1.6), and 1.4 (1.4-1.5). At 1, 5 and 10 years after MGUS diagnosis, we found a 3.3-fold (2.2-5.0), 2.0-fold (1.6-2.5), and 2.0-fold (1.7-2.4) increased risk of venous thrombosis. The corresponding risks for arterial thrombosis were 1.4 (1.2-1.7), 1.2 (1.1-1.3), and 1.2 (1.1-1.3). IgG/IgA (but not IgM) MGUS patients had an increased risk for venous and arterial thrombosis. These findings are of relevance for future studies and for the improvement of thrombosis prophylaxis strategies.
LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:


**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AML</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>ASCT</td>
<td>Autologous stem cell transplantation</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CLL</td>
<td>Chronic lymphocytic leukemia</td>
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<tr>
<td>DLBCL</td>
<td>Diffuse large B-cell lymphoma</td>
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<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
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<tr>
<td>EBMT</td>
<td>European group for blood and marrow transplantation</td>
</tr>
<tr>
<td>FL</td>
<td>Follicular lymphoma</td>
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<tr>
<td>FLC</td>
<td>Free light chains</td>
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<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IARC</td>
<td>International agency for research on cancer</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
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<tr>
<td>IMiDs</td>
<td>Immunomodulatory drugs</td>
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<tr>
<td>LPL</td>
<td>Lymphoplasmacytic lymphoma</td>
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<tr>
<td>MGUS</td>
<td>Monoclonal gammopathy of undetermined significance</td>
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<tr>
<td>MM</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>MP</td>
<td>Melphalan-prednisone</td>
</tr>
<tr>
<td>MPT</td>
<td>Melphalan-prednisone-thalidomide</td>
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<tr>
<td>NHL</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
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<tr>
<td>RSR</td>
<td>Relative survival ratio</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
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<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<tr>
<td>VAD</td>
<td>Vincristine-doxorubicin-dexamethasone</td>
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<tr>
<td>WM</td>
<td>Waldenström’s macroglobulinemia</td>
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</table>
1 INTRODUCTION

1.1 HISTORY

The first well described case of multiple myeloma was made by Dr. Sully in 1844, describing a 39-year-old woman, Sarah Newbury, who developed fatigue and bone pain from multiple fractures. She was diagnosed with mollities ossium (soft bones), and died four years after this discovery.\(^1\) Another patient, Thomas Alexander McBean, developed pain in his chest while on holiday in 1844. The urine of Mr. McBean was examined by Henry Bence Jones, who noted an abnormal urine protein that later was termed after his name: “I need hardly remark on the importance of seeking for this oxide of albumen in other cases of mollities osseum”.\(^2\)

Figure 1. A bone marrow aspirate from a patient with multiple myeloma, showing predominance of plasma cells

Mr. McBean was prescribed a number of treatments, including blood removal, leeches, cupping, steel, orange peel, rhubarb, and quinine, before dying in 1846. Fractured ribs were observed on autopsy and bone marrow examination revealed “round or oval cells that were one-half to twice as large as an average blood cell and contained one or two nuclei and a bright-colored nucleolus”.\(^2,3\)
The term multiple myeloma was first introduced by Dr. Rustizky in 1873\(^4\), however an accurate description of the plasma cell was not done until 1895\(^5\) and in 1900 Dr. Wright concluded that the tumor cells of myeloma consisted of plasma cells (Figure 1) or immediate descendants of these cells.\(^6\)

The unusual properties of the urine in multiple myeloma patients described by Bence Jones, turned out to be caused by light chains of monoclonal IgG, as reported by Korngold and Lipari.\(^7\) In their honour, the two types of Bence Jones proteins are called kappa and lambda.

An important discovery, made by Dr. Jan Waldenström (Figure 2) and published in 1961, was the difference between polyclonal and monoclonal gammopathies.\(^8\) He described patients, both with and without a malignancy, having a narrow band on electrophoresis, termed a monoclonal protein (M-protein). He also found patients who had a broad band, having a polyclonal increase in gammaglobulins.\(^8\)

In 1944 Jan Waldenström described two patients with abnormal bleeding, enlarged lymph nodes, anemia and thrombocytopenia, elevated erythrocyte sedimentation rate, high serum viscosity, and a predominance of lymphoid cells on bone marrow examination.\(^9\) He attributed hyperviscosity symptoms to an abnormal high-molecular-weight serum protein. These observations are now considered the first report of the disease now bearing his name, Waldenström’s macroglobulinemia (WM). The abnormal high-molecular-weight serum protein was subsequently shown to be monoclonal immunoglobulin M (IgM).\(^9\)

Jan Waldenström used the term essential hyperglobulinaemia to describe patients with an M-protein, but without evidence of multiple myeloma, WM, amyloidosis or a related disorder.\(^10\) Later it was often referred to as benign monoclonal gammopathy, but in 1978 Dr. Robert Kyle, one of the pioneers in clinical studies of monoclonal gammopathies, introduced the term Monoclonal Gammopathy of Undetermined Significance (MGUS).\(^11\)

Figure 2. Jan Gösta Waldenström (1906-1996)
LYMPHOPROLIFERATIVE DISORDERS

Lymphoid malignancies range from the most indolent to the most aggressive human malignancies. These cancers arise from different stages of differentiation of cells of the immune system, resulting in a wide range of morphologic, immunologic, and clinical findings.\textsuperscript{12}  
All lymphoid cells are derived from a common hematopoietic progenitor that gives rise to lymphoid, myeloid, erythroid, monocyte, and megakaryocyte lineages. Through the ordered and sequential activation of a series of transcription factors, the cell first becomes committed to the lymphoid lineage and then gives rise to B and T lymphocytes. About 75\% of all lymphoid leukemias and 90\% of all lymphomas are of B-cell origin.\textsuperscript{12}  
Monoclonal gammopathies involves a group of diseases which have in common a proliferation of a clone of plasma cells.\textsuperscript{13}  
The proliferation of B-cells commonly results in overproduction of monoclonal immunoglobulins, M-proteins. Under normal circumstances, maturation to antibody-secreting plasma cells is stimulated by exposure to the antigen for which the surface immunoglobulin is specific; however, in the plasma cell disorders, control of the monoclonal cell proliferation is lost.\textsuperscript{12, 14}  
The clinical manifestations of all the plasma cell disorders relate to the expansion of neoplastic cells, to the

Figure 3. A. Serum electrophoresis from a patient with an M-protein (arrow), polyclonal hypergammaglobulinemia, and normal electrophoresis.  
B. Immunofixation showing IgG kappa M-protein (arrows).
secretion of cell products (immunoglobulin molecules or subunits, lymphokines), and to some extent to the host's response to the tumor. Each M-protein consists of two heavy polypeptide chains of the same class: gamma (γ) constitutes immunoglobulin G (IgG), alpha (α) is found in IgA, mu (μ) is present in IgM, delta (δ) occurs in IgD, and IgE is characterized by epsilon (ε) heavy chains. Every M-protein is characterized by two light polypeptide chains [kappa (κ) or lambda (λ)] of the same type (Figure 3).

M-proteins can be detected in both malignant (multiple myeloma, WM, chronic lymphocytic leukemia (CLL) and other lymphomas) and pre-malignant (MGUS) conditions.
1.2 MULTIPLE MYELOMA

1.2.1 Definition

Multiple myeloma is a malignant B-cell disorder characterized by a monoclonal proliferation of plasma cells in the bone marrow (Figure 1).\(^{12, 13}\) The diagnostic criteria are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Diagnostic criteria for multiple myeloma(^{12})</th>
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<tr>
<td>Asymptomatic multiple myeloma</td>
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<tr>
<td>M-protein in serum at myeloma levels (&gt;30g/L) and/or</td>
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<td>10% or more clonal plasma cells in bone marrow</td>
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<tr>
<td>No related organ or tissue impairment or bone lesions or myeloma related symptoms</td>
</tr>
<tr>
<td>Symptomatic multiple myeloma</td>
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<tr>
<td>M-protein in serum or urine</td>
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<tr>
<td>Bone marrow clonal plasma cells or plasmacytoma</td>
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<tr>
<td>Related organ or tissue impairment</td>
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</table>

1.2.2 Epidemiology

Multiple myeloma accounts for about 1% of all malignancies and 10% of hematological malignancies.\(^{15, 16}\) It is a disease of the elderly, with a median age at diagnosis of 65-70 years, and is only occasionally diagnosed in patients below 40 years of age.\(^{15-17}\) Multiple myeloma is more common in African-Americans than in whites and less common in Asia.\(^{15, 18}\) Males are affected more commonly than females. There is a great variation in reported incidence rates around the world but it is unclear to what extent the observed differences may be explained by potential ethnic-related biological differences as well as differences with regard to access to care, case ascertainment in central registries, and other factors. Indeed, worldwide incidence rates vary from 0.4 to 8 per 100,000 person-years with higher rates in Western compared to Asian countries.\(^{19}\) In the Western world the annual age-adjusted incidence is 4.8-8 per 100,000, and in Sweden there are about 400-500 cases diagnosed annually.\(^{16}\) A steady increase in multiple myeloma incidence and mortality has been reported in some studies from US and Europe.\(^{20-22}\) Furthermore, a recent study suggests that all MM cases are preceded by MGUS (see below).\(^{23}\)

1.2.3 Etiology and pathogenesis

Although the etiology of multiple myeloma is unknown, there is evidence to support a role for genetic factors, including studies showing familial aggregation of multiple myeloma.\(^{24-29}\) In addition, racial disparities in incidence patterns for multiple myeloma support a role for germline genes in the etiology.\(^{18}\) Whether or not environmental exposure to radiation or chemicals is associated with an increased incidence of multiple myeloma is unclear.\(^{30-32}\) The association between chronic antigen stimulation and risk of multiple myeloma has been evaluated in several studies.\(^{35}\) Although the findings
have been inconsistent, there are some suggestions that autoimmunity and certain types of infectious agents could play a role.

The development of multiple myeloma is a complex process involving genetic changes in the plasma cell as well as supportive conditions by the bone marrow microenvironment. Among the earliest genetic events are translocations of the immunoglobulin heavy chain gene locus, which leads to dysregulation of oncogenes at translocation partner regions. Additional molecular events include epigenetic changes and activation of oncogenes. Multiple myeloma cells interact with bone marrow stromal cells and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signalling as well as cytokine production such as interleukin-6 and vascular endothelial growth factor. It also includes induction of angiogenesis, the suppression of cell-mediated immunity. The resultant interactions of myeloma cells, bone marrow stromal cells, and microvessels contribute to tumor growth, survival, and resistance to drugs.

1.2.4 Clinical signs and symptoms

The clinical signs and symptoms in multiple myeloma patients may be caused by direct tumor growth or the monoclonal products. Approximately 8% of all multiple myeloma patients are asymptomatic at diagnosis. Bone pain, usually involving the back or ribs, is the most common symptom in multiple myeloma patients, and is caused by a proliferation of myeloma cells, activation of osteoclasts and suppression of osteoblast activity. A common clinical problem in patients with multiple myeloma is susceptibility to bacterial infections, and more than 75% of patients will have a serious infection at some time in their course. The most common infections are pneumonias and infections of the urinary tract. Neurological abnormalities generally are caused by regional tumor growth compressing the spinal cord or cranial nerves, but can be caused by the treatment itself. A common laboratory finding is a normocytic and normochromic anemia, which is present in about 70-80% of patients. It is related both to the replacement of normal marrow by myeloma cells and to the inhibition of hematopoiesis by tumor induced factors. Renal failure occurs in about 25% of myeloma patients. Tubular damage caused by the excretion of light chains is almost always present. Other contributing causes are hypercalcemia, glomerular deposits of amyloid, hyperuricemia, infections, use of nonsteroidal anti-inflammatory agents (NSAIDs) for pain, contrast dye for imaging, bisphosphonates, and occasional infiltration of the kidney by myeloma cells. Hypercalcemia, found in one fourth of multiple myeloma patients, is a results of lysis of the bone and can cause acute and chronic complications.

1.2.5 Treatment and prognosis

Asymptomatic multiple myeloma patients do not benefit from early treatment. In 1975, Durie and Salmon introduced a staging system (the Durie/Salmon system) based on several prognostic factors, such as type and concentration of the M-protein, hemoglobin, calcium, creatinine, and number of skeletal lesions. Since then a number of prognostic factors have been identified, such as C-reactive protein, albumin, β2-microglobulin, and serum free light chains (FLC). The recently published International Staging System, is a simple prognostic model for symptomatic multiple myeloma patients, and is based on serum albumin and β2-microglobulin in three stages.
Among other established prognostic factors for multiple myeloma patients are cytogenetic abnormalities such as hypoploidy, chromosome 13q and 17p deletions, t(4;14) and t(14;16). Furthermore, other factors such as age at diagnosis, performance status, and response to therapy are of importance.

### Table 2. International staging system for multiple myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median survival (months)</th>
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<tbody>
<tr>
<td>I</td>
<td>Serum β2-microglobulin &lt;2.5 mg/L and Serum albumin &gt; 35 g/L</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>Not stage I or III</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2-microglobulin &gt; 5.5 mg/L</td>
<td>29</td>
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</table>

Before the introduction of alkylating agents in the management of multiple myeloma, as in the cases of Sarah Newbury and Mr. McBean, the median survival of symptomatic patients was less than 1 year. Melphalan-prednisone (MP) treatment has been the mainstay of multiple myeloma therapy, since its introduction more than 40 years ago, and results in a median overall survival between 24 and 48 months (Figure 4). Interferon alfa (IFN-α) was introduced in the late 1970s, and was used as a single agent or in combination with chemotherapy. In a meta-analysis, IFN-α was reported to increase survival by approximately 4 months. In the 1980s, the vincristine, doxorubicin, and dexamethasone (VAD) regimen was reported to induce high response rates in multiple myeloma patients. Prolonged myelosuppression restricted the use of high-dose chemotherapy. Eventually, autologous stem cell transplantation (ASCT) was introduced in multiple myeloma therapy in the 1980s. Later, a double transplantation procedure was also shown to prolong survival in certain subgroups. There are indications that ASCT treatment applied after induction therapy or at the time of relapse prolongs overall survival, although it is not curative. Others have found similar overall survival with ASCT and conventional treatment. The impact of allogeneic stem cell transplantation remains restricted, given that only 5% to 10% of patients are candidates for this procedure because of age-related issues, comorbidity, toxicity, and donor availability. Studies on reduced-intensity conditioning in multiple myeloma are promising, with some but not all indicating a survival benefit.

Clinical trials have reported thalidomide (T) therapy to be associated with an increased multiple myeloma survival. It is effective in relapsed/refractory disease, as induction therapy before ASCT, and as maintenance. Additionally, four out of five studies comparing MP-T with MP have indicated a superior outcome with MPT. However only two have shown improvement in overall survival. Bortezomib, a proteasome inhibitor, has been shown to induce good responses and prolong survival in multiple myeloma patients. It is effective in relapsed/refractory disease, as induction therapy before ASCT and in combination with MP. In addition, lenalidomide, an analogue of thalidomide, has significant anti-myeloma activity. Two phase III, randomized, double-blind, multicentre trials compared lenalidomide/high-dose dexamethasone with placebo/high-dose dexamethasone in previously treated myeloma patients. In both studies, the
lenalidomide containing arms were associated with a better response and overall survival. Lenalidomide has also been tested in combination with chemotherapy, with good results.\textsuperscript{107, 108}

The above cited treatment agents have without doubt improved the survival of multiple myeloma patients. However, as randomized clinical trials have strict inclusion as well as exclusion criteria, it is not certain that these treatments options have benefited the general multiple myeloma population.

The new agents have increased the arsenal of available therapies, also with new mechanisms of action. Consequently, new panoramas of side effects have arisen. Among those is the occurrence of venous thromboembolism in patients treated with the immunomodulatory drugs (IMiDs), thalidomide and lenalidomide,\textsuperscript{109-120} not observed with bortezomib treatment.\textsuperscript{121} Compared to the general population, individuals affected with multiple myeloma have been reported to be at higher risk of developing deep vein thrombosis (DVT).\textsuperscript{122} Most studies involving the IMiDs have observed the most profound risk during the first months following multiple myeloma diagnosis and when combining IMiDs with high-dose corticosteroids or chemotherapy.\textsuperscript{109, 110, 113-120} Additionally, there have been a few case reports indicating that the use of IMiDs in multiple myeloma patients might be associated with an increased risk of developing arterial thrombosis.\textsuperscript{123-128} To our knowledge, no prior large study has been conducted to evaluate risk of arterial thrombosis among MGUS and multiple myeloma patients. The underlying mechanisms of the observed excess thromboembolism are largely unknown and more research is needed. However, the elevated risk of thromboembolic events associated with modern multiple myeloma therapy has stimulated multiple research groups to initiate efforts to uncover the etiology of thrombosis in plasma cell disorders.\textsuperscript{129-133}

![Figure 4. Timeline showing the introduction of the major therapeutic agents/procedures in multiple myeloma](attachment:figure4.png)
1.3 LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTRÖM’S MACROGLOBULINEMIA

1.3.1 Definition

Lymphoplasmacytic lymphoma (LPL)/Waldenström’s macroglobulinemia (WM) is a non-Hodgkin lymphoma (NHL) subtype characterized by small B-lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow, lymph nodes, and spleen (Figure 5).\textsuperscript{12, 134, 135} WM can be distinguished clinically from LPL on the basis of a detectable monoclonal (IgM) immunoglobulin spike of any concentration in serum.\textsuperscript{134} Also, using fluorescent in situ hybridization analysis, LPL tumor cells have frequent t(9;14)(p13;q32) translocations, while WM tumor cells appear to be diploid or near diploid and often have deletions of 6q21.\textsuperscript{136}

![Figure 5. Bone marrow aspirate from a patient with Waldenström’s macroglobulinemia, showing predominance of lymphoplasmacytoid cells and small lymphocytes](image)

1.3.2 Epidemiology

In the general population, LPL/WM is a very rare disease, accounting for only 1-2% of all hematological malignancies, reflected in an incidence rate of 3 to 4 cases per million
people per year. Although the underlying mechanisms are unclear, males and whites are at higher risk of developing LPL/WM. The median age at diagnosis is around 70 years. The disease is more common in patients of European descent than in those of African descent.

1.3.3 Etiology and pathogenesis

Currently, the causes of LPL/WM are unknown. However, there are emerging data to support a role for genetic and immune-related factors in the etiology of LPL/WM. The first report on familiality in WM was published in 1962, and since then a number of multiply affected families, as well as case-control and cohort studies, have been published showing familial clustering of LPL and WM. Recently, Treon et al. characterized clinicopathological patterns of familial disease in a hospital-based series of 257 WM patients and found that 19% of the patients had at least one first-degree relative affected with WM or another B-cell disorder. A genomewide linkage analysis of 11 high-risk WM families (122 individuals, including 34 WM patients and 10 IgM MGUS patients) found the strongest evidence of linkage on chromosomes 1q and 4q when patients with WM and IgM MGUS were both considered affected. Other locations suggestive of linkage were found on chromosomes 3 and 6. No study has quantified and evaluated the risks for LPL/WM, multiple myeloma, MGUS and other lymphoproliferative malignancies in relatives of LPL/WM patients.

A few studies have reported evidence of somatic immunoglobulin gene mutations, suggesting that the WM cells originate from B-cells that have undergone repeated antigenic stimulation and selection in the germinal centers of lymphoid follicles. A few epidemiological studies have been conducted to assess the role of chronic antigenic stimulatory conditions in relation to risk of developing LPL/WM. In one study, personal history of autoimmune disease was not associated with subsequent risk of developing WM. Additionally, two large nationwide studies based on U.S. veterans designed to explore the role of antigenic stimulation in the pathogenesis of WM have been published. In the first study, hepatitis C virus infection was found to confer a 20-30% increased risk of NHL overall and a 3-fold higher risk of WM. In the second study, a 2- to 3-fold elevated risk of WM in individuals with a personal history of an autoimmune disease was found and notably elevated risks associated with hepatitis, human immunodeficiency virus infection, and rickettsiosis.

Based on long-term follow-up data from the Mayo Clinic, a personal history of the precursor condition MGUS of the IgM class, is associated with an average 1-1.5% annual risk of developing WM (see below).

1.3.4 Clinical signs and symptoms

The clinical manifestations associated with LPL/WM can be related to those of direct organ tumour infiltration and in WM, IgM-related hyperviscosity and deposition of IgM in various tissues. Approximately 25% of patients are asymptomatic at diagnosis, and can be followed clinically without specific treatment. Patients most commonly present with complaints of fatigue, weakness, and weight loss. Almost 80% of symptomatic patients with WM present with a low hemoglobin, most often due to extensive bone marrow infiltration or related to an increase in plasma volume. Leukopenia can be present at diagnosis, but the platelet count is typically not decreased.
The most common physical findings are lymphadenopathy and hepatosplenomegaly.154 WM patients can develop a peripheral neuropathy.155 Most commonly, the symptoms are of a slowly progressive, symmetric, and predominantly sensory peripheral neuropathy.156 These can be caused by the M-protein, by myel-in-associated glycoprotein antibodies, and by treatment.139 Approximately 15% of WM patients present with symptoms and signs of the hyperviscosity syndrome,153, 157 with symptoms including headache, visual blurring, epistaxis, and rarely coma.158 Patients can also develop symptoms and signs of congestive heart failure. Secondary to serum hyperviscosity, patients often have dilated and tortuous retinal veins and may develop bilateral optic disc swelling.159 The physical properties of the IgM paraprotein can produce symptoms. Patients with cryoglobulinemia may complain of cold hypersensitivity, noting that exposure to low temperatures precipitates urticaria, purpura, acral cyanosis, or Raynaud phenomenon.160 Furthermore patients can develop symptoms related to both tissue deposition of IgM and its autoantibody activity.161, 162

1.3.5 Treatment and prognosis

LPL/WM is today an incurable disease. Asymptomatic patients can be followed clinically without specific therapy.151, 152 A few prognostic scoring systems have been described, most including factors such as age, β2-microglobulin, albumin, number of cytopenias, lactate dehydrogenase, hemoglobin, concentration of the M-protein, and more.152, 163, 164 According to these simple scoring systems the survival has been shown to vary, from 21% 5-year survival in the highest risk group to 87% in the lowest. Median survival varies greatly based on prognostic factors, and ranges from 5 to 10 years in different series.139, 151, 152, 163-165 Recently the International Scoring System for WM identified five adverse variables in WM patients acquiring therapy; high age, low hemoglobin, low platelet count, high β2-microglobulin, and high M-protein concentration.166 Importantly, these risk factors can be used with the many new drugs used in the treatment of patients with WM (see below).

Only in the presence of symptoms related to the disease should treatment be initiated, and therapy is directed toward prevention and/or symptomatic treatment of the associated clinical symptoms.167 The IgM level per se should not influence the decision to start treatment. Eventually, most patients with manifestations related to the IgM component will require systemic therapy. However, in patients with clinical manifestations of hyperviscosity, plasma exchange plays a significant role, especially in newly diagnosed patients who need urgent therapy. Long-term maintenance plasmapheresis can also be considered in patients that are intolerant to or failing systemic treatment.168

First line treatment of symptomatic WM patients has traditionally been based on single-agent therapy with alkylating agents (chlorambucil, cyclophosphamide) or purine analogues (fludarabine, cladribine).169-171 These agents can be used in older individuals and have response rates of 30-80% depending on whether used as primary treatment or in relapsed disease. These agents induce very few complete remissions. Recently the anti-CD20 antibody rituximab has been shown to have single agent activity and induce responses in 44% of WM patients.172 There are no data from prospective randomized studies to guide the choice between alkylating agents, nucleoside analogues, and rituximab for first line therapy of WM. During recent years, combination therapy have resulted in good overall response rates but low complete
response rates.\textsuperscript{173, 174} Also, as has been shown in multiple myeloma, the treatment with novel agents, such as thalidomide and bortezomib are effective in WM, both as single agents and in combination with other drugs.\textsuperscript{175-179}

Studies evaluating the effect of ASCT in LPL/WM have been promising with low toxicities and high response rates.\textsuperscript{167, 180, 181} However randomized clinical trials are lacking. Studies on allogeneic stem cell transplantation have shown effect but with considerable treatment related mortality.\textsuperscript{167, 180, 181}
1.4 MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

1.4.1 Definition

MGUS denotes the presence of an M-protein on electrophoresis in patients without evidence of multiple myeloma, WM, amyloidosis or other lymphoproliferative disorders. MGUS is characterized by the following: a serum M-protein concentration less than 30 g/L; less than 10% clonal plasma cells in the bone marrow; little or no M-protein in the urine; absence of lytic bone lesions and no related anemia, hypercalcemia or renal failure (Table 3). 

<table>
<thead>
<tr>
<th>Table 3. Diagnostic criteria for MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-protein in serum &lt;30 g/L</td>
</tr>
<tr>
<td>Bone marrow clonal plasma cells &lt;10% and low level of plasma cell infiltration in a trephine biopsy</td>
</tr>
<tr>
<td>No myeloma-related organ or tissue impairment or bone lesions</td>
</tr>
<tr>
<td>No evidence of other B-cell proliferative disorder</td>
</tr>
</tbody>
</table>

1.4.2 Epidemiology

The prevalence of MGUS is highly dependent on age. In a Swedish study, approximately 1% of persons older than 50 years of age and about 3% of those older than 70 years were found to have MGUS. According to data from the Mayo Clinic, the prevalence is 5.3% in people older than 70 years. The median age at diagnosis is 70 years. The age adjusted prevalence of MGUS in African-Americans is threefold greater than in whites.

1.4.3 Etiology and pathogenesis

The etiology of MGUS is unknown. There are some studies indicating a role for a genetic susceptibility of MGUS, including multiply affected families. There are limited data on familial aggregation of relatives of MGUS patients. Additionally, differences in racial disparity patterns have been observed in MGUS, suggesting genetic or environmental causes. Recently a study group observed an association with pesticides use and risk of MGUS. As discussed above, there is evidence for an association between chronic antigen stimulation and risk of multiple myeloma. Whether this is true for MGUS is currently unknown, and needs to be studied further. A recent study on U.S. veterans found an increased risk of MGUS among patients with a prior personal history of immune-related conditions.

Only a minority of MGUS patients will develop a lymphoproliferative disease, see below. Studies on cytogenetic abnormalities in MGUS have found similar changes in multiple myeloma and MGUS. What causes the dysregulation the leads to a manifest disease, however is not known.
1.4.4 Prognosis

Approximately 1-1.5% of patients with MGUS progress each year to multiple myeloma, WM, amyloidosis or other lymphoproliferative disorders. Predictors for multiple myeloma development include concentration (higher indicating increased risk of progress) and type of M-protein, with IgM and IgA having higher rate of progression than IgG. The presence of urine M-protein is not considered a risk factor. Recently FLC has also been shown to be an important predictor of progression in MGUS patients. Although there have been several investigations focusing on the risk for developing lymphoproliferative tumors following a diagnosis of MGUS, there is only limited available data on survival patterns among MGUS patients. Data from the Mayo Clinic show that the median survival of MGUS patients was about 45% lower at 15 years of follow-up than that of a comparable US population. In a prior study from North Jutland County in Denmark, 1,324 MGUS patients diagnosed 1978-1993 were found to have a 2-fold higher mortality compared to the general population. Similarly, a hospital-based single center study from the Netherlands including 1,464 MGUS patients reported inferior survival than a matched cohort. These and other smaller studies have reported the dominant causes of death among MGUS patients to be hematological malignancies, solid tumors, cardiovascular diseases, and infections. However, to our knowledge, no population-based large study has been conducted to determine excess mortality patterns and simultaneously assess causes of death in MGUS patients compared to controls.

The risk of venous thromboembolism has also been explored among MGUS patients. Two small studies observed that 6.1% and 7.5% of MGUS patients developed venous thromboembolic disease. Additionally, IgG MGUS patients were less prone to develop thromboembolic disease. In another study based on a single VA healthcare system, Cohen and Sarid found no statistical difference in the venous thromboembolic rate among 166 MGUS patients compared to 465 patients who had tested negative for M-protein by serum protein electrophoresis. In a large study based on inpatient data of more than 4 million U.S. veterans, we identified 2,374 cases of MGUS of whom 31 developed DVT (crude incidence 3.1 per 1000 person-years). Compared to controls, this translated into a significantly 3-fold excess risk of DVT among MGUS patients.
2 AIMS

Overall aim

To characterise familial and prognostic features of monoclonal gammopathies in Sweden

Specific aims

To quantify the risk for lymphoproliferative disorders among first-degree relatives of patients with LPL/WM and MGUS

To define outcome of patients with MGUS in Sweden over a long time period, to define prognostic factors for survival and to compare causes of death to matched controls

To define outcome of patients with multiple myeloma in Sweden over a long time period, to define prognostic factors for survival and to relate the survival pattern to trends in management strategies over time

To estimate the effect of socioeconomic status on survival in multiple myeloma

To quantify the risk of arterial and venous thrombosis in patients with multiple myeloma and MGUS
3 FAMILIAL STUDIES (I, II)

3.1 PATIENTS, CONTROLS AND METHODS

In the present studies, we make use of some of the unique Swedish population-based registers (see below), in order to test a series of hypothesis regarding monoclonal gammopathies. Since 1958, all physicians and pathologists/cytologists in Sweden are obliged by law to report each incident case of cancer that they diagnose and/or treat, to the centralized nationwide Swedish Cancer Registry. The Registry contains information on diagnosis, sex, date of birth, date of diagnosis, and region/hospital where the diagnosis was made. In a recent validation study focusing on lymphoproliferative malignancies diagnosed 1964-2003, we found the completeness and the overall diagnostic accuracy of the Registry to be >90-95%. For NHL, Hodgkin lymphoma (HL), and multiple myeloma the accuracy and completeness of the Cancer Registry was very high (>93%). For WM and CLL, the diagnostic accuracy was 93% and 84%, respectively. The completeness was similarly high for multiple myeloma and NHL (>95%), but lower for WM (68%) and CLL (88%).

We established a nationwide LPL/WM cohort (I) by the following approaches: first we identified all LPL/WM patients diagnosed 1958-2005 from the nationwide Swedish Cancer Registry. Given the under-ascertainment described above, we also retrieved information on all incident cases through a national network, which included all outpatient units in major hospital-based hematology/oncology centers in Sweden. Third, we identified all LPL/WM patients reported in the Swedish Inpatient Registry, which captures information on individual patient-based discharge diagnoses and discharge listings from inpatient (since 1964) and outpatient care (since 2000), with a very high coverage. For all LPL/WM patients, we obtained information on sex, date of birth, date of diagnosis, and region/hospital where the diagnosis was made.

We also established a nationwide MGUS cohort (II) by retrieving information on all incident patients through the national network described above. Second, we identified all MGUS patients who were reported in the Swedish Inpatient Registry. For all MGUS patients, we obtained information on sex, date of birth, date of diagnosis, and region/unit where the diagnosis was made. When available, we also collected information on MGUS isotype and concentration of the M-protein at diagnosis.

For each LPL/WM (n>2,500) and MGUS (n>5,000) patient, four population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All controls had to be alive at the time of the diagnosis for the corresponding case and without a diagnosis of a previous hematological malignancy at the date of the corresponding case’s diagnosis.

The Swedish Multigenerational Registry contains information on first-degree (parent-sibling-offspring) relations for Swedish residents (index-individuals) born 1932 or later and alive in 1960. Relatives also have to be alive in 1960, but are not restricted with regard to birth cohort. Adoption and half-siblings are flagged. The degree of completeness is high (>90% for index-individuals born after the mid 1930s and >99% for those born later than 1950), although somewhat lower among individuals moving into and out of Sweden between 1960 and 1990. From the Swedish Multigenerational Registry, we obtained information on all first-degree relatives (parents, siblings, and offspring) of LPL/WM and MGUS cases and controls. As a final
step, we conducted record-linkages with the Swedish Cancer Registry, the nationwide LPL/WM cohort, and the nationwide MGUS cohort to obtain information on lymphoproliferative malignancies and MGUS among first-degree relatives of all LPL/WM and MGUS patients and controls.

3.1.1 Statistical analyses

The statistical approach in papers I and II, is based on a model proposed by Liang and has been described in detail. For analyses of cancer outcomes, we classified relatives as “affected” if they had a primary cancer registration with the tumor of interest. For analyses of LPL/WM or MGUS outcomes, we classified relatives as “affected” if they had an LPL/WM or MGUS diagnosis in our cohort. Here, the age or age at onset of disease in a relative of a proband is modeled by a proportional hazards model. Familial aggregation for each condition is evaluated by testing the hazard ratio (HR) of being a relative of a case compared with being a relative to a control. The model was fitted to the data using the PHREG procedure in SAS v8.02. We use relative risks to denote the hazard ratio defined above, with 95% confidence intervals (CI). In our database, every case is a “proband” and thus families with more than one case appear twice in the dataset. The robust sandwich covariance matrix accounts for dependencies among family members, including dependence due to the overlapping family clusters. We tested separately for increased risk for MGUS, multiple myeloma, LPL/WM, NHL (excluding LPL/WM), CLL, and HL in relatives.

The main effect of interest in this analysis is the risk associated with being a relative of a case compared with being a relative of a control. However, we were also interested in testing whether other factors, such as sex, type of relative, and age of disease onset in the case probands, affected case-control comparisons.

3.2 RESULTS AND DISCUSSION

3.2.1 Familial aggregation of LPL/WM and MGUS (I, II)

We identified 2,144 LPL/WM (1,539 WM [72%] and 605 LPL [28%]) patients with linkable relatives (80.3%) diagnosed in Sweden, 8,279 population-based matched controls, and linkable first-degree relatives of patients (n=6,177) and controls (n=24,609) (I). We found first-degree relatives of LPL/WM patients to have 20-fold (95% CI: 4.1-98.4), 3.0-fold (2.0-4.4), 3.4-fold (1.7-6.6), and 5.0-fold (1.3-18.9) increased risks of developing LPL/WM, NHL, CLL, and MGUS, respectively (Table 4).

We identified 4,458 MGUS patients diagnosed in Sweden (1967-2005) with linkable relatives (82.5%), 17,505 population-based controls, and first-degree relatives of patients (n=14,621) and controls (n=58,387) (II). Compared to relatives of controls, relatives of MGUS patients had increased risks of MGUS (HR=2.8; 95% CI 1.4-5.6), multiple myeloma (2.9; 1.9-4.3), LPL/WM (4.0; 1.5-11), and CLL (2.0; 1.2-2.3) (Table 4). Relatives of patients with IgG/IgA MGUS had a 4.0-fold (1.7-9.2), 2.9-fold (1.7-4.9), and 20-fold (2.3-170) elevated risk of developing MGUS, multiple myeloma, and LPL/WM, respectively. Relatives of IgM MGUS patients had 5.0-fold (1.1-23) increased CLL risk.
Although many cancers show familial clustering, identifying the predisposing germ line genes is challenging. Familial aggregation of a disease is a necessary but not sufficient condition to infer a contribution of heredity, and identifying such families has led to elucidation of the genetic basis for numerous conditions. Besides our findings (I, II), there is substantial evidence that lymphoproliferative malignancies have familial components to their etiology.

Previous studies have consistently shown significantly increased risks of NHL associated with a family history of lymphoma or other hematopoietic malignancy. In a study including 70,006 first-degree relatives of 26,089 NHL cases and 161,352 first-degree relatives of 58,960 matched controls, relatives of NHL patients were found to have significantly increased risk of NHL and HL (Table 4). Furthermore, in a recent study we evaluated risk of lymphoma subtypes among first-degree relatives of 2,668 follicular lymphoma (FL) patients, 2,517 diffuse large B cell lymphoma (DLBCL) patients, and 6,963 HL patients compared to first-degree relatives of controls. Relatives were at the highest risk for developing the same lymphoma subtype as the proband. DLBCL was 10-fold increased among relatives of DLBCL patients, FL was 4-fold increased among relatives of FL patients and HL was 4-fold increased among relatives of HL patients, implying that germline susceptibility genes are relatively specific to lymphoma subtype. However the effect of unidentified environmental factor can not be excluded.

A number of multiply affected families, as well as case-control and cohort studies, have been published showing familial clustering of LPL and WM. Together with previous studies, our findings (I) support a role for shared common susceptibility genes that predispose to LPL/WM and certain lymphoproliferative disorders. Additionally, a genomewide linkage analysis of 11 families at high risk for WM found the strongest evidence of linkage was found on chromosomes 1q and 4q.

Only recently, we evaluated the familial risk of CLL including almost 10,000 CLL patients and their close to 27,000 first-degree relatives, and showed that first-degree relatives of CLL patients had an 8.5-fold increased risk for CLL, which is similar to that observed in another study. Furthermore we found a significantly increased risk for NHL, including LPL/WM, and hairy cell leukemia. However there was no excess risk of HL, multiple myeloma or MGUS (Table 4). These studies support the role of germline genes underlying risk of CLL and related malignancies. Regions of the genome likely to contain susceptibility genes have been identified from linkage studies in high-risk families. Specific genes have been implicated from candidate gene studies and a genome-wide association study. However, specific mutations causing susceptibility have not been identified.

As pointed out, there is evidence to support a role for genetic factors, including studies showing familial aggregation of multiple myeloma and familial aggregation of MGUS. In addition, racial disparities in incidence patterns for MGUS and multiple myeloma support a role for germline genes in the etiology of multiple myeloma. We performed a study including 13,896 multiple myeloma patients and 54,365 matched controls, and first-degree relatives of cases (n=37,838) and controls (n=151,068). We found that first degree-relatives of multiple myeloma patients, compared to first degree relatives of controls, had a 2-fold increased risk of multiple myeloma, MGUS, and acute lymphoblastic leukemia (Table 4). In a recent study from the Mayo Clinic, first-degree relatives of multiple myeloma patients had a 2-
fold increased risk of MGUS, suggesting a familial aggregation of MGUS and multiple myeloma.\textsuperscript{224}

Similarly, we found relatives of MGUS patients (compared to relatives of controls), to have an increased risk of MGUS, multiple myeloma, LPL/WM, and CLL (II). In accordance with our study, the study from the Mayo Clinic, involving relatives of 97 MGUS cases, found a 2.6-fold increased risk of MGUS.\textsuperscript{224} Additionally, recent studies have suggested that there is a familial aggregation of solid tumors (malignant melanoma and prostate cancer) with multiple myeloma and MGUS.\textsuperscript{26, 27} In our study on relatives of multiple myeloma patients we observed a significantly increased risk for all solid tumors combined, as well as bladder cancer.\textsuperscript{223} Similarly, relatives of MGUS patients had an increased risk of all solid tumors combined, and specifically bladder cancer and spinal cancer, but not prostate cancer or malignant melanoma.\textsuperscript{225} These results again support a role for germline susceptibility genes, shared environmental influences, or an interaction between both in multiple myeloma and MGUS, and possibly even solid tumors.

| Table 4. Relative risks for lymphoproliferative diseases among first-degree relatives of patients with non-Hodgkin lymphoma, lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia, chronic lymphocytic leukemia, multiple myeloma, and MGUS (compared with relatives of matched controls) |
|---------------------------------------------------------------|-------|-------|-------|-------|-------|-------|
| Probands condition                                           | NHL   | LPL/WM| CLL   | HL    | MM    | MGUS (II) |
|                                                              | HR    | HR    | HR    | HR    | HR    | HR       |
|                                                              | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) | (95% CI) |
| Non-Hodgkin lymphoma\textsuperscript{222}                   | 1.7   | -     | 1.3   | 1.4   | 1.1   | -        |
|                                                              | (1.4-2.2) | -     | (0.9-1.9) | (1.0-2.0) | (0.8-1.5) | -        |
| Lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia (I) | 3.0   | 20.0  | 3.4   | 0.8   | 1.6   | 5.0      |
|                                                              | (2.0-4.4) | (4.1-98.4) | (1.7-6.6) | (0.3-2.2) | (0.8-3.2) | (1.3-18.9) |
| Chronic lymphocytic leukemia\textsuperscript{218}            | 1.9   | 4.0   | 8.5   | 1.5   | 1.2   | 1.4      |
|                                                              | (1.5-2.3) | (2.0-8.2) | (6.1-11.7) | (0.96-2.3) | (0.9-1.8) | (0.9-2.2) |
| Multiple myeloma\textsuperscript{223}                       | 1.1   | 1.4   | 1.1   | 0.9   | 2.1   | 2.1      |
|                                                              | (0.9-1.4) | (0.7-2.8) | (0.8-1.7) | (0.6-1.4) | (1.6-2.9) | (1.5-3.1) |
| MGUS (II)                                                    | 1.1   | 4.0   | 2.0   | 1.3   | 2.9   | 2.8      |
|                                                              | (0.8-1.5) | (1.5-11) | (1.2-2.3) | (0.6-2.9) | (1.9-4.3) | (1.4-5.6) |

Abbreviations: NHL=Non-Hodgkin lymphoma, LPL/WM=Lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia, CLL=chronic lymphocytic leukemia, HL=Hodgkin lymphoma, MM=multiple myeloma, MGUS=monoclonal gammopathy of undetermined significance, HR=Hazard ratio, CI=confidence interval

These two studies (I, II) and other recent large population-based studies from Scandinavia have provided insight to familial aggregation of lymphoproliferative diseases. While the risk of a specific subtype is most prominently increased in relatives, risks are also increased for other lymphoproliferative diseases, suggesting that certain genes are associated with increased risk for multiple lymphoproliferative diseases. This means that linkage and association studies should look for genes specific to subtypes as well as genes shared among subtypes. The power to detect common susceptibility genes with smaller effects has been facilitated by the ability to conduct genome-wide studies with very densely spaced genetic markers. Additionally, as stated above, one can not exclude that the observed familial aggregation could in part be due to unidentified environmental factors.
It is important to consider the clinical implications of the above discussed associations. First-degree relatives of patients with lymphoproliferative diseases are at an increased *relative risk* of developing various subtypes of lymphoproliferative diseases, with the highest risk for the same disease as the proband. However, because of the low baseline risk of most of these lymphoproliferative malignancies in the general population, the *absolute risk* for a first-degree relative to develop the same disease or another lymphoproliferative disorder is still very low. Furthermore, early detection of indolent lymphomas in particular, is not likely to affect outcome since most asymptomatic patients typically are not treated. Additionally, although relatives of patients with a lymphoproliferative disease are at increased risk for developing MGUS (I), the average transformation rate from MGUS to multiple myeloma or WM is only about 1-1.5% per year. Consequently, at this time, it is not recommended to screen for lymphoproliferative or plasma cell dyscrasias among family members outside clinical research studies.
4 PROGNOSTIC STUDIES (III-VI)

4.1 PATIENTS, CONTROLS AND METHODS

We included patients from the nationwide MGUS cohort diagnosed 1986-2005 (described on page 23) (III). For all MGUS patients, we obtained information on sex, date of birth, date of diagnosis, and region/hospital where the diagnosis was made. When available, we also collected information on MGUS isotype and concentration of the M-protein at diagnosis. To minimize the influence of a potentially undetected lymphoproliferative malignancy, MGUS patients who died or were diagnosed with a lymphoproliferative malignancy within 6 months following MGUS diagnosis were excluded from the MGUS cohort. Using the nationwide Cause of Death Registry, we obtained information on date and cause of death for all subjects (MGUS patients and controls, see below) that had deceased up to December 31, 2006. We grouped causes of death into categories based on the International Classification of Diseases classification versions 9 and 10.

In studies IV and V we included information on all multiple myeloma patients reported to the Swedish Cancer Registry (see page 23) from 1973 to 2003 (IV) and 2005 (V). Information was gathered for sex, date of birth, date of diagnosis, date of death, and hospital where the patient was diagnosed. Stem cell transplantations performed in Sweden are reported to the European Group for Blood and Marrow Transplantation (EBMT) register, which was established in 1974. Information on the number of stem cell transplantations in multiple myeloma patients reported from Swedish centers during the study period was obtained from the EBMT register. Additionally, in study V we included patients with acute myeloid leukemia (AML) diagnosed from 1973 to 2005. We used occupational status as a proxy for socioeconomic status (SES), gathered from the Swedish National Census Databases, established from nationwide and mandatory censuses conducted in 1960, 1970, 1980 and 1990. SES was divided into seven groups (higher white-collar worker, lower white-collar worker, self-employed, farmer, blue-collar worker, retired, and unknown).

We identified all multiple myeloma patients diagnosed between 1965 and 2005 (VI). Also we included MGUS patients diagnosed in Sweden between 1965 and 2005. For each multiple myeloma and MGUS patient (III, VI), four population-based controls (matched by sex, year of birth, and county of residence) were chosen randomly from the Swedish Population database. All controls had to be alive at the time of multiple myeloma or MGUS diagnosis for the corresponding case and without a previous diagnosis of any hematological malignancy at the date of the corresponding case’s diagnosis.

Information on occurrence and date of arterial (coronary artery disease and cerebrovascular disease) and venous [DVT and pulmonary embolism (PE)] thrombosis was obtained from the Swedish Patient Registry, using the 7th, 8th, 9th, and 10th revisions of the International Classification of Diseases. All conditions were analyzed both individually and grouped into categories. Through linkage with the Cause of Death Registry and the Registry of Total Population, we collected information on vital status until December 31, 2006. From the Swedish Medical Products Agency we gathered information on the number of patients that were prescribed thalidomide and lenalidomide during the study period.
4.1.1 Statistical analyses

Relative survival ratios (RSRs), were computed as measures of MGUS and multiple myeloma survival (III, IV). RSR provides a measure of total excess mortality associated with a diagnosis of MGUS or multiple myeloma. One-, 5-, 10-, and 15-year RSRs can be interpreted as the proportion of MGUS or multiple myeloma patients who survived their disease at 1, 5, 10, and 15 years, respectively. RSR is defined as the observed survival in the patient group (where all deaths are considered events) divided by the expected survival of a comparable group from the general population, which is assumed to be free of the disease in question. Expected survival was estimated using the Ederer II method from Swedish population life-tables stratified by age, sex, and calendar time.


Poisson regression was used to model excess mortality. The estimates from this model are interpreted as excess mortality ratios; an excess mortality ratio of 1.5, for example, for males/females indicates that males experience 50% higher excess mortality than females.

By using the Cause of Death Registry we identified and compared causes of death between MGUS patients and controls using Cox’s proportional hazards regression.

We estimated survival in relation to type of occupation using the Kaplan-Meier method (V). Secondly, the relative risk of death (any cause and cause specific) in relation to SES and calendar period were estimated using Cox’s proportional hazards regression. We conducted both univariate and multivariate analyses, adjusted for sex, area of residence at diagnosis (in six geographical regions), age at diagnosis (≤54, 55-64, 65-72, 73-78, 79-83, or ≥84 years) and calendar period at diagnosis (1973-79, 1980-89, 1990-99, and 2000-2005). To investigate whether mortality in relation to SES had changed over time, we also conducted analyses stratified by calendar period.

In study VI, Cox’s proportional hazard models were used to compare 1-, 5-, and 10-year risks for thrombosis in multiple myeloma and MGUS patients compared to controls. The proportional hazards assumption for variables used in the models was assessed by visual inspection of the hazard function. Individuals entered the risk period at the date of diagnosis of multiple myeloma or MGUS or the dates of diagnosis of the corresponding matched case, for controls. Censoring events were death, emigration, or the end of the data acquisition period (December 31, 2006). For the analyses of MGUS cases and controls we also censored individuals at the time of diagnosis of multiple myeloma or WM. Individuals were not censored if they developed a cardiovascular condition other than the one being tested since they will still be at risk for developing the specific cardiovascular condition subsequently. Adjusted HRs and 95% CIs were estimated overall and separately for men and women. Adjustment variables included in the models were gender, age at diagnosis, and year of diagnosis. Cox proportional hazard models were stratified by the covariates to assess interactions and formal interaction p-values were also calculated.
Hazard curves for MGUS or multiple myeloma patients and matched controls were estimated using the Kaplan-Meier method. Survival curves were compared using the log-rank test.

### 4.2 RESULTS AND DISCUSSION

#### 4.2.1 Survival and cause of death among MGUS patients (III)

In this study, a total of 4,259 MGUS patients (diagnosed 1986-2005) and 16,151 population-based controls were included. The median age at MGUS diagnosis was 70 years (range 22-79 years). The median follow-up time was 5.6 years and 1,565 (37%) deaths were observed among the MGUS patients. As stated previously, prior studies have observed a lower life expectancy in MGUS patients. The cumulative RSRs for the MGUS cohort after 5 and 10 years follow-up was 0.93 and 0.82, respectively (Table 5). We observed an increasing excess mortality rate with time from diagnosis, which was not observed in a study from Denmark.

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>&lt;50 years (n=396)</th>
<th>50-59 years (n=668)</th>
<th>60-69 years (n=1,005)</th>
<th>70-79 years (n=1,372)</th>
<th>≥80 years (n=818)</th>
<th>All patients (n=4,254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year RSR</td>
<td>0.99 (0.97-1.00)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.99 (0.97-1.00)</td>
<td>0.98 (0.97-0.99)</td>
<td>0.97 (0.94-0.99)</td>
<td>0.98 (0.97-0.99)</td>
</tr>
<tr>
<td>5-year RSR</td>
<td>0.98 (0.96-1.00)</td>
<td>0.96 (0.93-0.98)</td>
<td>0.97 (0.94-0.99)</td>
<td>0.92 (0.89-0.95)</td>
<td>0.82 (0.75-0.89)</td>
<td>0.93 (0.91-0.95)</td>
</tr>
<tr>
<td>10-year RSR</td>
<td>0.93 (0.89-0.96)</td>
<td>0.93 (0.89-0.96)</td>
<td>0.85 (0.80-0.89)</td>
<td>0.74 (0.68-0.80)</td>
<td>0.60 (0.44-0.77)</td>
<td>0.82 (0.79-0.84)</td>
</tr>
<tr>
<td>15-year RSR</td>
<td>0.90 (0.81-0.95)</td>
<td>0.77 (0.65-0.86)</td>
<td>0.74 (0.63-0.84)</td>
<td>0.59 (0.42-0.78)</td>
<td>0.74 (0.11-2.41)</td>
<td>0.70 (0.64-0.76)</td>
</tr>
</tbody>
</table>

In the cause of death analyses, as expected, we observed major causes of excess mortality to be multiple myeloma, WM, and other lymphoproliferative diseases (Table 6). Furthermore, compared to controls, we found MGUS patients to have an increased risk of dying due to amyloidosis, bacterial infections, ischemic heart disease, other heart disorders (mainly congestive heart failure, heart valve diseases, cardiomyopathy, and arrhythmias), liver diseases (typically, liver failure and cirrhosis), benign hematological disorders (most frequently hemolytic anemia and aplastic anemia), and renal diseases (mainly renal failure and glomerular diseases) (Table 6). Previous studies have reported the dominant causes of death among MGUS patients to be hematological malignancies, solid tumors, cardiovascular diseases, and infections. Thus we confirmed an increased risk of dying from lymphoproliferative disorders, and in addition we found an excess risk of death in myeloid (mainly AML) malignancies and a wide variety of non-malignant disorders. It cannot be ruled out that the observed increased risk of dying due to bacterial infections, renal and heart diseases, at least in
some cases, might be reflections of early multiple myeloma, amyloidosis or another lymphoproliferative malignancy.

We found age to be an important predictor of prognosis, and younger age at MGUS diagnosis was associated with a significantly lower excess mortality (p<0.001), which is in accordance to that observed in a Dutch but not the Danish study. The main causes of death in younger patients were lymphoproliferative malignancies, amyloidosis, and liver disorders, whereas cardiovascular diseases dominated in elderly MGUS patients.

Table 6. Causes of death among MGUS patients and controls and hazard ratios and 95% confidence intervals as measures of excess risk of dying among MGUS patients versus controls

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>MGUS patients</th>
<th>Controls</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>1,565</td>
<td>4,405</td>
<td>1.5</td>
<td>1.4-1.6</td>
</tr>
<tr>
<td>Any cancer</td>
<td>469</td>
<td>954</td>
<td>2.0</td>
<td>1.8-2.2</td>
</tr>
<tr>
<td>Any hematological malignancy</td>
<td>259</td>
<td>21</td>
<td>54.2</td>
<td>31.6-93.0</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>185</td>
<td>1</td>
<td>553</td>
<td>77-3946</td>
</tr>
<tr>
<td>Waldenström’s macroglobulinemia</td>
<td>18</td>
<td>0</td>
<td>∞</td>
<td>N.A.</td>
</tr>
<tr>
<td>Other lymphoproliferative malignancies</td>
<td>20</td>
<td>12</td>
<td>6.5</td>
<td>2.8-15.1</td>
</tr>
<tr>
<td>Myeloid malignancy</td>
<td>36</td>
<td>8</td>
<td>22.9</td>
<td>8.9-58.7</td>
</tr>
<tr>
<td>Any solid tumor</td>
<td>210</td>
<td>933</td>
<td>0.9</td>
<td>0.8-1.1</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>24</td>
<td>0</td>
<td>∞</td>
<td>N.A.</td>
</tr>
<tr>
<td>Infection</td>
<td>79</td>
<td>236</td>
<td>1.4</td>
<td>1.0-1.8</td>
</tr>
<tr>
<td>Bacterial</td>
<td>19</td>
<td>24</td>
<td>3.4</td>
<td>1.7-6.7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>46</td>
<td>158</td>
<td>1.1</td>
<td>0.8-1.6</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>N.A.</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>52</td>
<td>1.2</td>
<td>0.6-2.2</td>
</tr>
<tr>
<td>Heart disease</td>
<td>460</td>
<td>1,441</td>
<td>1.3</td>
<td>1.2-1.5</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>319</td>
<td>1,053</td>
<td>1.3</td>
<td>1.1-1.4</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>141</td>
<td>388</td>
<td>1.5</td>
<td>1.2-1.8</td>
</tr>
<tr>
<td>Vascular</td>
<td>192</td>
<td>644</td>
<td>1.2</td>
<td>1.0-1.4</td>
</tr>
<tr>
<td>Pulmonary embolism/deep vein thrombosis</td>
<td>15</td>
<td>49</td>
<td>1.3</td>
<td>0.7-2.5</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>125</td>
<td>444</td>
<td>1.1</td>
<td>0.9-1.4</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>52</td>
<td>151</td>
<td>1.3</td>
<td>0.9-1.9</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>57</td>
<td>154</td>
<td>1.6</td>
<td>1.1-2.2</td>
</tr>
<tr>
<td>Bowel disease</td>
<td>35</td>
<td>108</td>
<td>1.4</td>
<td>0.9-2.1</td>
</tr>
<tr>
<td>Liver disease</td>
<td>14</td>
<td>26</td>
<td>2.1</td>
<td>1.1-4.2</td>
</tr>
<tr>
<td>Biliary/Pancreatic disorder</td>
<td>8</td>
<td>20</td>
<td>1.9</td>
<td>0.7-4.6</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>53</td>
<td>191</td>
<td>1.0</td>
<td>0.7-1.4</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>13</td>
<td>26</td>
<td>1.2</td>
<td>0.6-2.5</td>
</tr>
<tr>
<td>Endocrine/Metabolic disorder</td>
<td>30</td>
<td>98</td>
<td>1.3</td>
<td>0.9-2.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23</td>
<td>85</td>
<td>1.2</td>
<td>0.7-1.9</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>13</td>
<td>2.2</td>
<td>0.8-5.7</td>
</tr>
<tr>
<td>Benign hematological disease</td>
<td>16</td>
<td>9</td>
<td>6.9</td>
<td>2.7-18.0</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>33</td>
<td>216</td>
<td>0.6</td>
<td>0.4-0.9</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>28</td>
<td>102</td>
<td>1.3</td>
<td>0.8-2.0</td>
</tr>
<tr>
<td>Renal disease</td>
<td>45</td>
<td>62</td>
<td>3.2</td>
<td>2.0-4.9</td>
</tr>
</tbody>
</table>

Abbreviations: MGUS=monoclonal gammopathy of undetermined significance, CI=confidence interval, NA=not applicable

We found IgM (versus IgG/A) MGUS to be associated with a superior survival (p=0.038). However, in the Dutch study no difference in survival by MGUS subtype was observed. Contradictory to our findings, IgM MGUS has been reported to have a higher risk of malignant transformation compared to IgG MGUS. In our study, we found similar cause of death patterns by MGUS subtype, except that MGUS patients who subsequently died due to WM were predominantly IgM MGUS and those who
died from multiple myeloma were typically IgG/IgA MGUS. High M-protein concentration at diagnosis has been reported to predict a poor outcome in multiple myeloma and MGUS.\textsuperscript{41, 150, 193} We did not observe such an association between M-protein concentration at diagnosis and survival, in accordance with another MGUS study.\textsuperscript{197}

We included MGUS patients diagnosed in an outpatient setting in standard clinical practice. Consequently, our findings are relevant to clinicians managing MGUS patients, since MGUS is associated with an excess mortality, not only restricted to multiple myeloma and other lymphoproliferative disorders, but also other non-malignant diseases.

In summary, we found that individuals who were diagnosed in a clinical context with MGUS had a significantly reduced life expectancy. The rate of transformation of MGUS to multiple myeloma or other lymphoproliferative diseases is one percent per year.\textsuperscript{150, 193} However, the majority of MGUS patients are diagnosed as a result of a clinical investigation for various symptoms, and were found to die from other causes. The underlying mechanisms for the observed mortality and cause of death pattern may be causally related to the MGUS, but may also be explained by an underlying disease that led to the detection of MGUS. The excess mortality was particularly pronounced among elderly MGUS patients. The fact that cause of death patterns varied with age at MGUS diagnosis may have clinical implications.

### 4.2.2 Survival in multiple myeloma and socioeconomic status (IV, V)

A total of 14,381 multiple myeloma patients (7,643 males and 6,738 females; median age, 69.9 years; 19-101 years), were included (IV). Thirty-two percent of the patients were diagnosed at university/regional hospitals. A total of 1,285 stem cell transplantations in multiple myeloma patients were reported to the EBMT register during the study period. Of these, more than 90% were carried out during the last calendar period.

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year RSR</td>
<td>0.73 (0.71-0.75)</td>
<td>0.78 (0.76-0.79)</td>
<td>0.80 (0.78-0.81)</td>
<td>0.82 (0.80-0.83)</td>
</tr>
<tr>
<td>5-year RSR</td>
<td>0.31 (0.29-0.33)</td>
<td>0.32 (0.30-0.34)</td>
<td>0.34 (0.32-0.36)</td>
<td>0.36 (0.34-0.38)</td>
</tr>
<tr>
<td>10-year RSR</td>
<td>0.12 (0.10-0.13)</td>
<td>0.11 (0.10-0.13)</td>
<td>0.14 (0.12-0.15)</td>
<td>0.14 (0.12-0.16)</td>
</tr>
</tbody>
</table>

The RSRs for the multiple myeloma patients in relation to calendar period of diagnosis are shown in Table 7. The 1-, 5-, and-10-year RSR improved significantly throughout the study period (p<0.001).

One-year RSRs improved with calendar period in all age categories (p<0.001), suggesting that the improvements in the early management of multiple myeloma
patients has benefited all age groups. This is probably an effect of improvement in supportive care, including dialysis and intensive care, as well as multiple myeloma specific therapy. We found improvement in 5-year RSRs to be confined to patients younger than 70 years at diagnosis (p<0.001; Table 8), and 10-year RSRs improved significantly (p<0.001) in patients below 60 years at diagnosis (Table 9). This is in accordance with another population-based study from U.S. that found improved 5- and 10-year RSRs when comparing patients diagnosed 1990-1992 with 2002-2004, most pronounced in younger patients.\textsuperscript{235} In a study including patients from the Mayo Clinic, the authors also found an improvement in survival in recent years, predominantly in the younger patients.\textsuperscript{236} The underlying causes of the absence of improvement in long-term survival among elderly patients remain unclear, and are probably multifactorial including increased co-morbidity among older patients. Early mortality has been reported to be higher among elderly patients.\textsuperscript{237} In addition to the fact that patients do not tolerate aggressive treatment such as high dose therapy, it has also been proposed that elderly patients present with a more advanced disease at diagnosis.\textsuperscript{238, 239}

The disappointing lack of improvement in the oldest multiple myeloma patients is of concern. Recent randomized clinical trials suggest that combination therapies, including MP with the novel drugs, may be effective and well tolerated in this patient population.\textsuperscript{93-95, 97, 102} Innovative agents and procedures suitable for the older patient (>70 years) coupled with better prognostic markers used to guide individualized treatment in multiple myeloma are greatly needed.

| Table 8. Five-year relative survival ratios (RSR) with 95% confidence intervals in multiple myeloma stratified by calendar period and age category |
|----------------------|----------------------|----------------------|----------------------|----------------------|
| <40 years           | 0.60 (0.39-0.76)     | 0.50 (0.33-0.65)     | 0.57 (0.40-0.71)     | 0.74 (0.56-0.86)     |
| 41-50 years         | 0.47 (0.38-0.55)     | 0.46 (0.37-0.55)     | 0.49 (0.41-0.57)     | 0.65 (0.58-0.71)     |
| 51-60 years         | 0.36 (0.31-0.40)     | 0.42 (0.38-0.47)     | 0.48 (0.43-0.53)     | 0.58 (0.53-0.62)     |
| 61-70 years         | 0.34 (0.30-0.37)     | 0.33 (0.30-0.36)     | 0.36 (0.33-0.39)     | 0.37 (0.34-0.40)     |
| 71-80 years         | 0.26 (0.22-0.29)     | 0.29 (0.26-0.32)     | 0.30 (0.27-0.33)     | 0.27 (0.25-0.30)     |
| >81 years           | 0.17 (0.12-0.24)     | 0.14 (0.09-0.19)     | 0.18 (0.14-0.23)     | 0.19 (0.15-0.24)     |

The most likely major explanation for the observed improvement in long-term outcome in our study is the introduction of high dose melphalan supported by ASCT.\textsuperscript{70, 72, 239} Additionally, there was an increased use of thalidomide during the latest period under study, which may have contributed to this improvement. In the study from the Mayo Clinic, in addition to receiving thalidomide, some of their patients in most recent years have also received bortezomib and lenalidomide.\textsuperscript{236} Taken together, these studies support the results from clinical trials showing that the introduction of novel agents/procedures have led to improvement in survival for multiple myeloma patients, which may be recorded at a population level.

We found a consistently superior survival for women, in accordance with survival data from five continents released by IARC.\textsuperscript{240} Similar observations have been
made in other hematological and non-hematological malignancies, however the underlying mechanisms are unknown. Possible explanations to this finding are differences in co-morbidity and distribution of prognostic factors among males and females.

Table 9. Ten-year relative survival ratios with 95% confidence intervals in multiple myeloma stratified by calendar period and age category

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>0.53 (0.33-0.70)</td>
<td>0.25 (0.13-0.41)</td>
<td>0.33 (0.19-0.48)</td>
<td>0.42 (0.10-0.72)</td>
</tr>
<tr>
<td>41-50 years</td>
<td>0.21 (0.14-0.28)</td>
<td>0.27 (0.19-0.35)</td>
<td>0.31 (0.23-0.38)</td>
<td>0.28 (0.16-0.40)</td>
</tr>
<tr>
<td>51-60 years</td>
<td>0.17 (0.13-0.20)</td>
<td>0.16 (0.13-0.20)</td>
<td>0.21 (0.17-0.25)</td>
<td>0.33 (0.26-0.41)</td>
</tr>
<tr>
<td>61-70 years</td>
<td>0.12 (0.10-0.15)</td>
<td>0.11 (0.09-0.14)</td>
<td>0.14 (0.12-0.17)</td>
<td>0.12 (0.08-0.17)</td>
</tr>
<tr>
<td>71-80 years</td>
<td>0.06 (0.04-0.09)</td>
<td>0.07 (0.05-0.10)</td>
<td>0.10 (0.08-0.13)</td>
<td>0.08 (0.05-0.12)</td>
</tr>
<tr>
<td>&gt;81 years</td>
<td>0.06 (0.02-0.16)</td>
<td>0.08 (0.03-0.17)</td>
<td>0.07 (0.03-0.13)</td>
<td>0.01 (0.00-0.07)</td>
</tr>
</tbody>
</table>

Another predictor of prognosis in our study was hospital type where the multiple myeloma diagnosis was made, with patients diagnosed at non-University/regional compared with University/regional hospitals having a significantly higher 5- and 10-year mortality. Management in specialized/referral hematology and oncology units has been reported to improve outcome in patients with certain solid tumors, and acute lymphoblastic leukemia. In a study involving 21 centers in the U.S. the survival of multiple myeloma patients improved with increasing distance from the treatment center. However, due to the lack of detailed clinical information on individual patients in our study, one has to interpret these findings with caution. Potentially, it might reflect underlying variation with regard to diagnostic procedures, supportive care, and mechanisms involving referral bias.

Based on our findings (IV) regarding the effect of hospital-type at diagnosis and gender on survival, we were inclined to perform a study to assess the impact of SES on survival in multiple myeloma (V). We also included patients with AML, to include another hematological malignancy, with different characteristics. AML is an aggressive malignancy which requires immediate management and is potentially curable. Multiple myeloma on the other hand is in most cases an indolent lymphoproliferative disorder with little or no prospect of cure. In multiple myeloma, some authors have observed inferior survival among patients in lower socioeconomic groups, while others have not.

We identified a total of 9,165 and 14,744 patients with a first cancer diagnosis of AML and multiple myeloma, respectively (V). The median age at diagnosis was 69.2 years in patients with AML and 71.8 years in multiple myeloma. The SES distribution was similar in the two diseases. The majority of patients were blue-collar (39.5; 37.9%) and lower white-collar workers (30.9; 30.7%). The distribution of the SES groups
remained stable, with a predictable decrease in the proportion of farmers over calendar time.

In AML and multiple myeloma respectively, self-employed, farmers, blue-collar workers, and retired had an overall significantly higher mortality compared to higher white-collar workers (Table 10). Lower white-collar workers had a significantly higher mortality than higher white-collar workers in multiple myeloma but not in AML. Relative risk of death in relation to SES and calendar period is shown in Table 11. Among AML patients no association between SES and mortality was found during the first calendar period (1973-79). However, during the last three periods (1980-1989, 1990-1999, and 2000-2005), a consistently higher mortality was observed in blue-collar workers compared to higher white-collar workers.

<p>| Table 10. Relative risk of death in AML and multiple myeloma according to sex, calendar period of diagnosis, and socioeconomic status based on all-cause mortality* |
|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Socioeconomic status</strong>**</th>
<th>AML (n=9,165)</th>
<th>Myeloma (n=14,744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher white-collar worker</td>
<td>477</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Lower white-collar worker</td>
<td>2,545</td>
<td>1.14 (0.99-1.31)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>590</td>
<td>1.20 (1.07-1.36)</td>
</tr>
<tr>
<td>Farmer</td>
<td>704</td>
<td>1.18 (1.07-1.30)</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>3,141</td>
<td>1.22 (1.11-1.34)</td>
</tr>
<tr>
<td>Retired</td>
<td>447</td>
<td>1.19 (1.05-1.34)</td>
</tr>
<tr>
<td><strong>p=0.005</strong></td>
<td></td>
<td><strong>p&lt;0.005</strong></td>
</tr>
</tbody>
</table>

*Analyses were adjusted for SES, age, sex, calendar period of observation and region of residence; CI denotes confidence interval.

**Most recent classification before diagnosis, excluding individuals with unknown occupation

P-values obtained using Wald Chi-squared test

In multiple myeloma, mortality did not differ between the SES groups in the first two calendar periods (1973-1979 and 1980-1989), but in the third calendar period (1990-1999), self-employed, blue-collar workers, and retired had a significantly higher mortality compared to higher white-collar workers. In the fourth period (2000-2005), blue-collar workers had a significantly higher mortality compared to higher white-collar workers (Table 11). Probably several factors contribute to the difference in survival according to SES observed in our study. These can, although with some overlap, be separated into patient-related, tumor-related, and factors related to the health care provider.

Among patient-related factors an income or economic barrier contributing directly to our findings is quite unlikely given the equal access to health care in Sweden. In multiple myeloma there are two studies on the association between SES
Population-based studies on familiality and prognosis in monoclonal gammopathies

and distance from treatment center and survival with contradictory results.\textsuperscript{248, 254} One other potential reason for the observed SES associated differences in survival is patient’s delay in seeking medical attention, which has been noted in other malignancies.\textsuperscript{255} This factor may to a certain extent contribute to the differences in outcome observed in multiple myeloma patients. In support for this notion is a reported increased early mortality among multiple myeloma patients who delayed seeking medical care.\textsuperscript{257} However, in another study, 17\% of multiple myeloma patients sought medical attention after 6 or more months of symptomatic disease, a delay which did not translate into a decreased overall survival.\textsuperscript{256}

### Table 11. Relative risk of death in AML and multiple myeloma in relation to socioeconomic status, by calendar period*

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>AML (n=9,165)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher white-collar worker</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Lower white-collar worker</td>
<td>1.04 (0.76-1.42)</td>
<td>1.14 (0.95-1.38)</td>
<td>1.29 (1.10-1.51)</td>
<td>1.14 (0.92-1.40)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>1.19 (0.84-1.70)</td>
<td>1.29 (1.03-1.62)</td>
<td>1.14 (0.93-1.39)</td>
<td>1.06 (0.80-1.39)</td>
</tr>
<tr>
<td>Farmer</td>
<td>1.10 (0.78-1.53)</td>
<td>1.11 (0.89-1.37)</td>
<td>1.32 (1.07-1.62)</td>
<td>1.29 (0.96-1.74)</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>1.10 (0.80-1.50)</td>
<td>1.26 (1.05-1.51)</td>
<td>1.23 (1.05-1.45)</td>
<td>1.28 (1.04-1.57)</td>
</tr>
<tr>
<td>Retired</td>
<td>1.00 (0.71-1.42)</td>
<td>1.20 (0.93-1.54)</td>
<td>1.57 (1.19-2.08)</td>
<td>1.54 (1.00-2.39)</td>
</tr>
<tr>
<td><strong>Multiple myeloma (n=14,744)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher white-collar worker</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Lower white-collar worker</td>
<td>0.95 (0.73-1.24)</td>
<td>1.12 (0.96-1.30)</td>
<td>1.08 (0.96-1.22)</td>
<td>1.18 (0.96-1.44)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>1.07 (0.80-1.44)</td>
<td>1.02 (0.85-1.21)</td>
<td>1.18 (1.02-1.37)</td>
<td>1.13 (0.87-1.46)</td>
</tr>
<tr>
<td>Farmer</td>
<td>0.92 (0.70-1.22)</td>
<td>1.06 (0.90-1.25)</td>
<td>1.16 (1.00-1.35)</td>
<td>1.15 (0.88-1.52)</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>0.95 (0.73-1.24)</td>
<td>1.12 (0.96-1.30)</td>
<td>1.18 (1.04-1.32)</td>
<td>1.31 (1.07-1.60)</td>
</tr>
<tr>
<td>Retired</td>
<td>1.07 (0.81-1.43)</td>
<td>1.15 (0.95-1.39)</td>
<td>1.45 (1.16-1.80)</td>
<td>1.40 (0.90-2.17)</td>
</tr>
</tbody>
</table>

*Analyses were adjusted for SES, age, sex, calendar period of observation and region of residence; CI denotes confidence interval.
**Most recent classification before diagnosis, excluding individuals with unknown occupation.

Patients with co-morbid disorders are less likely to receive or tolerate intensive therapy, which may reduce survival.\textsuperscript{257, 258} In addition, lifestyle factors, physical activity, overweight, tobacco or alcohol use, factors which are influenced by SES\textsuperscript{259-261} may also have an impact on the patient’s tolerance to diagnostic and therapeutic procedures.

Tumor-related factors, such as stage or tumor burden at diagnosis have been suggested as possible explanations for the differences in cancer survival according to
SES. In multiple myeloma, patients in lower socioeconomic groups were more likely to present with an advanced disease stage. The health care provider’s attitude towards management may differ according to socioeconomic group. One such factor could be a delay in establishing the correct diagnosis. In one multiple myeloma study, a duration of symptoms of more than 6 months was observed prior to diagnosis in 40% of patients, among whom more than 50% had initially consulted a general practitioner. Furthermore physicians might be prone to perform a more extensive medical work-up/screening in patients in higher socioeconomic groups with subsequent earlier detection of disease. However, there is still uncertainty regarding the impact of doctor’s delay on survival.

The SES related difference in survival in multiple myeloma was only observed during the two most recent calendar periods (1990-1999 and 2000-2005), and this difference was most pronounced in the latter period. Before that time, treatment of multiple myeloma was mainly restricted to MP and interferon-α. During the last 15 years, new procedures such as high-dose melphalan with ASCT and active agents like thalidomide, bortezomib, and lenalidomide have been introduced. In study IV we found an increasing number of ASCTs performed in multiple myeloma patients after 1994. Furthermore, thalidomide was increasingly used in Sweden from 1999. It is possible that patients in higher SES groups get earlier access to these newer agents and procedures, with an established impact on survival, in part explaining the growing survival differences observed after the year 1990. Further studies are needed to better define the underlying factors of our findings.

4.2.3 Thrombosis in multiple myeloma and MGUS (VI)

A total of 19,391 multiple myeloma patients, 5,395 MGUS patients, and 76,415 and 20,761 controls to multiple myeloma and MGUS, respectively, were included in the study. The median age at multiple myeloma diagnosis was 71 years (range 19-101 years) and MGUS diagnosis 71 years (range 22-100 years). A total of 1,756 patients received thalidomide 2000-2005 and 103 patients were prescribed lenalidomide 2003-2005. Before the year 2000, thalidomide was given to less than 100 multiple myeloma patients.

In the present study we found, as previously reported in our study based on U.S. veterans and from clinical trials, an increased risk of DVT and PE in multiple myeloma, with the highest risk during the first year (Table 12). The reason for the observed increased risk of venous thrombosis in multiple myeloma is not completely understood. Many factors can contribute to this excess risk, including type of therapy, immobilization, surgery, infections, indwelling central venous catheters, use of erythropoietin, acquired and inherited hypercoagulable state which are known risk factors for venous thrombosis. Procoagulant antibody formation, interference of paraprotein with fibrin, activated protein C resistance and damage to the endothelium have also been suggested. However, because the highest risk of venous thrombosis was observed in the first year following diagnosis, it seems reasonable that the hypercoagulable state, at least in part, could also reflect accelerated neoplastic activity and tumor burden, perhaps in combination with unknown influences caused by treatment. Furthermore, secretion of interleukin-6 and tumor necrosis factor can activate coagulation pathways. Finally, Factor VIII and von Willebrand factor levels have been shown to be elevated among multiple myeloma patients.
Studies focusing on IMiDs and venous thrombosis risk in multiple myeloma have reported the cumulative incidence to vary between about 2% to 75%, with greatest risk in previously untreated patients receiving combination therapy. In fact, single agent therapy with thalidomide in newly diagnosed and relapsed/refractory patients has not been associated with an increased risk, nor has lenalidomide, used in relapsed/refractory patients.

In our study, we estimated the risk of thrombosis both before and during the IMiD era. Although not statistically significant, we found multiple myeloma patients who were treated in the pre-IMiD-era to have a 7.5-fold higher risk of venous thrombosis compared to controls, whereas patients treated after the introduction of the IMiDs had an 11.4-fold risk.

In the absence of data from randomized clinical trials, addressing which patients should receive thrombosis prophylaxis and which agent to use, the available evidence come from studies involving other malignancies as well as indirect evidence from clinical trials with IMiDs using different prophylactic strategies. In a recent consensus...

Table 12. Hazard ratios and 95% confidence intervals for selected arterial and venous thrombosis among 19,391 multiple myeloma patients (vs. 76,415 matched controls)

<table>
<thead>
<tr>
<th>Disease/grouping</th>
<th>1-yr follow-up</th>
<th>5-yr follow-up</th>
<th>10-yr follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MM pts</td>
<td>Ctrls</td>
<td>HR* (95% CI)</td>
</tr>
<tr>
<td><strong>Specific diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep venous</td>
<td>146</td>
<td>81</td>
<td>7.7 (5.9-10.1)</td>
</tr>
<tr>
<td>thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>150</td>
<td>85</td>
<td>7.5 (5.7-9.8)</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>375</td>
<td>785</td>
<td>2.1 (1.8-2.4)</td>
</tr>
<tr>
<td>disease**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular***</td>
<td>232</td>
<td>557</td>
<td>1.9 (1.6-2.2)</td>
</tr>
<tr>
<td><strong>Groupings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thrombosis¹</td>
<td>541</td>
<td>1235</td>
<td>2.0 (1.8-2.2)</td>
</tr>
<tr>
<td>Venous thrombosis²</td>
<td>285</td>
<td>156</td>
<td>7.9 (6.5-9.6)</td>
</tr>
<tr>
<td>Any disease (combined)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males and females</td>
<td>809</td>
<td>1374</td>
<td>2.6 (2.4-2.9)</td>
</tr>
<tr>
<td>Males</td>
<td>457</td>
<td>834</td>
<td>2.5 (2.2-2.8)</td>
</tr>
<tr>
<td>Females</td>
<td>352</td>
<td>540</td>
<td>2.9 (2.5-3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: MM=multiple myeloma, HR = hazard ratio, CI = confidence interval; pts = patients; ctrls = controls;
*Adjusted for age, sex and calendar period at diagnosis; **Angina pectoris, unstable angina, and myocardial infarction; ***Cerebral infarction, TIA, and cerebral hemorrhage
¹Angina pectoris, unstable angina, myocardial infarction; ²Deep venous thrombosis, pulmonary embolism.
paper, an expert group recommended prophylactic strategy for multiple myeloma patients treated with IMiDs according to a risk-assessment model. The group recommended aspirin for patients with 1 or no risk factors for venous thrombosis. Low-molecular-weight heparin was recommended for those with two or more individual/myeloma-related risk factors and for patients receiving concurrent high-dose dexamethasone or doxorubicin. Full-dose warfarin was considered an alternative.

In accordance with prior smaller studies as well as our recent study based on U.S. veterans, we found MGUS patients to have an increased risk of venous thrombosis (Table 13). It is possible that the observed increased risk may be due to undiagnosed asymptomatic multiple myeloma or WM. However, we did not find the risk for multiple myeloma or WM progression to differ among MGUS patients with (versus without) a diagnosis of venous thrombosis. This is in contrast to the study by Sallah et al. Also the underlying mechanisms may be causally related to the MGUS, but may also be explained by an underlying disease that led to the detection of MGUS, as suggested by a recent study.

| Table 13. Hazard ratios and 95% confidence intervals for selected arterial and venous thrombosis among 5,395 MGUS patients (vs. 20,761 matched controls) |
|-------------------------------------------------|--------|--------|--------|
| Disease/grouping                               | 1-yr follow-up | 5-yr follow-up | 10-yr follow-up |
|                                                 | MGUS    | Ctrl   | MR*    | 95% CI  | MGUS    | Ctrl   | MR*    | 95% CI  | MGUS    | Ctrl   | MR*    | 95% CI  |
| Specific diseases                               |         |        |        |         |         |        |        |         |         |         |        |         |         |
| Deep venous thrombosis                          | 29      | 26     | 3.6    | 2.1-6.2 | 69      | 112    | 3.1    | 2.2-4.4 | 91      | 172    | 2.8    | 2.1-3.8 |
| Pulmonary embolism                              | 33      | 28     | 3.7    | 2.2-6.4 | 78      | 137    | 2.1    | 1.6-2.8 | 114     | 218    | 2.0    | 1.5-2.6 |
| Coronary artery disease**                       | 156     | 307    | 2.3    | 1.8-2.8 | 429     | 1294   | 1.4    | 1.3-1.6 | 649     | 2048   | 1.4    | 1.2-1.5 |
| Cerebrovascular***                              | 104     | 270    | 1.4    | 1.1-1.7 | 298     | 1090   | 1.1    | 0.9-1.2 | 438     | 1685   | 1.1    | 1.0-1.2 |
| Groupings                                       |         |        |        |         |         |        |        |         |         |         |        |         |         |
| Arterial thrombosis\(^1\)                       | 233     | 539    | 1.4    | 1.2-1.7 | 645     | 2128   | 1.2    | 1.1-1.3 | 957     | 3258   | 1.2    | 1.1-1.3 |
| Venous thrombosis\(^2\)                         | 55      | 51     | 3.3    | 2.2-5.0 | 132     | 242    | 2.0    | 1.6-2.5 | 186     | 377    | 2.0    | 1.7-2.4 |
| Any disease (combined)                          |         |        |        |         |         |        |        |         |         |         |        |         |         |
| All patients                                    | 286     | 580    | 1.6    | 1.4-1.9 | 754     | 2297   | 1.3    | 1.2-1.4 | 1096    | 3510   | 1.3    | 1.2-1.4 |
| Males                                          | 166     | 363    | 1.6    | 1.3-1.9 | 421     | 1344   | 1.2    | 1.1-1.4 | 606     | 2006   | 1.3    | 1.2-1.4 |
| Females                                        | 120     | 217    | 1.8    | 1.4-2.3 | 333     | 953    | 1.4    | 1.2-1.6 | 490     | 1504   | 1.4    | 1.3-1.6 |

Abbreviations: MGUS=monoclonal gammopathy of undetermined significance, HR = hazard ratio, CI = confidence interval; ctrl = controls; *Adjusted for age, sex and calendar period at diagnosis; **Angina pectoris, instable angina, and myocardial infarction; ***Cerebral infarction, TIA, and cerebral hemorrhage

\(^1\)Angina pectoris, instable angina, myocardial infarction, TIA, cerebral infarction; \(^2\)Deep venous thrombosis, pulmonary embolism
Trials with thalidomide in patients with other diagnoses than multiple myeloma have been inconsistent with regard to risk of thrombosis. In patients with WM treated with IMiDs, there was no observed increased risk of venous thrombosis.\textsuperscript{177, 272, 273} Further studies are needed to elucidate this issues. However consistent with these findings, we found that patients with IgM MGUS did not have an increased risk for thrombosis while patients with IgG/IgA MGUS had a 2-fold increased risk for venous thrombosis. Although the exact mechanisms are unclear, together with prior observations, data suggest that there might be a biological difference between IgG/IgA and IgM MGUS with regard to risk of thromboembolism. However, there are reports on patients treated with thalidomide for other malignancies observing increased risk of thrombosis.\textsuperscript{274-278}

We found a significantly increased risk of arterial thrombosis in patients with multiple myeloma and MGUS. More specifically, the risks for coronary artery disease and cerebrovascular disease were elevated among MGUS and multiple myeloma patients (Tables 12 and 13). In patients with multiple myeloma the risk for arterial thrombosis was significantly elevated both before and after the introduction of the IMiDs. However, we observed only a non-significantly higher risk after the year 2000. Some case reports have described an association with IMiDs and arterial thrombosis.\textsuperscript{123-128} Our observations are of importance for the understanding of the pathogenesis of thromboembolism in plasma cell dyscrasias. In fact, the observed excess risk for both arterial and venous thrombosis suggests that there might be some shared biological features, most probably involving platelet activation. Although arterial and venous thrombosis are traditionally considered to have separate pathogenesis, with arterial thrombi comprising mainly of platelets, whereas venous thrombi consist mainly of fibrin and red blood cells, there is evidence for an overlap.\textsuperscript{279} This is further supported by reports suggesting that aspirin is an effective prophylactic agent in venous thrombosis in multiple myeloma.\textsuperscript{117, 280, 281} Additionally some authors have found evidence of platelet aggregation\textsuperscript{280} and activation caused by thalidomide, that is abrogated by aspirin.\textsuperscript{282} Future investigations are needed to clarify underlying mechanisms of our observations.
5 METHODOLOGICAL ISSUES

5.1 BIAS

The objective of most epidemiologic research is to obtain a valid and precise estimate of the effect of potential cause on the occurrence of disease. Errors in estimation are traditionally classified as either random or systematic. Systematic errors in estimates are commonly referred to as biases, and validity being the opposite of that. Thus an estimate that has little systematic error may be described as valid. Similarly, an estimate that has little random error may be described as precise. In our study we used population-based registries to test hypothesis regarding monoclonal gammopathies. As for every cohort study, these results are potentially subject to bias.

5.1.1 Selection bias

Selection bias is defined as the error introduced when the study population does not represent the target population. One example is ascertainment bias, which can result from procedures used to select subjects and from factors that influence study participation. In our studies, we used register-based cohort design, based on population-based high-quality data. Most of the registries were established before and independent of our studies. Furthermore data are reported prospectively to the registries.

In the studies involving hematological malignancies, we obtained information of patients from the Swedish Cancer Registry. In our validation study of lymphoproliferative malignancies in the cancer registry, we found a high degree of diagnostic accuracy for the studied malignancies. We found some underreporting of the more indolent diseases, most pronounced in elderly patients in earlier calendar periods. Importantly, the ascertainment of WM was found to be only 68%. Given this, we added information of LPL/WM from our nationwide network involving most hematology/oncology hospital-based units in Sweden (described before). The same procedure was used to establish the MGUS cohort. It is possible that our cohorts of MGUS and LPL/WM patients comprise a selection of cases that are not representative of the whole population (ascertainment bias), and that more patients with aggressive diseases are referred to the hospitals for clinical work-up. However, in the familial studies (I, II) there are no data to support that familial aggregation varies with severity of disease, and furthermore we performed sensitivity analyses based on source and found essentially the same results. In studies III and VI, we included MGUS patients from the network described above. As some cases were obtained from the Inpatient Registry, and thus were admitted to hospital for another cause, we excluded these patients from the analyses. However, it can not be excluded that our findings may to some degree be explained by a selection of MGUS cases that were referred from the primary care for further work-up, and thereby included in our cohort. It is thus possible that a fraction of cases, with a more favourable outcome were not included in our analyses, leading to a bias away from the null. However given the fact that bone marrow examination are not performed by primary care physicians in Sweden, and that we believe that most patients with an M-protein are refereed for evaluation to hematology/oncology hospital-based units, we believe our cohorts to be representative of the MGUS population in Sweden.
5.1.2 Information bias

Information bias occurs when the subjects to be compared have been identified, and the bias is caused by measurement errors in the information needed. As stated above, our studies are based on already established registries, independent of our study. Thus, the information used and studies should not be different for cases versus controls. The fact that a subject has a known disease, for example MGUS, may influence whether and which information is registered. One example is detection bias, when an exposure influences the diagnosis of the outcome. It is conceivable that the registered cause of death in MGUS patients differ to that registered for controls (III). A physician, that is aware of the MGUS diagnosis, may have more information on the deceased, compared to the controls, which can influence the reported cause of death, leading to misclassification.

Another possible information bias is that both multiple myeloma and MGUS cases are followed at the hematology and oncology units, and thus may be more prone to being admitted for various signs and symptoms, thus being registered in the Inpatient Registry (VI). This will lead to surveillance bias, with the probability of hospitalization of cases and controls being different.

Lead time bias is the error introduced by the added time of illness produced by a diagnosis of a condition in its latency period. The observed improvement in survival in multiple myeloma patients (V) may be influenced by an increased access to healthcare and earlier detection of the disease over time. However, because the incidence as well as the median age at diagnosis of multiple myeloma were very stable in the second, third, and fourth calendar periods, respectively, and multiple myeloma survival was observed to be particularly improved in the most recent calendar periods, we feel comfortable with our interpretation of the results. Similarly, the superior survival in patients of higher SES, might be explained by an earlier diagnosis (lead time bias), during an asymptomatic phase of multiple myeloma (V).

5.1.3 Confounding

Confounding occurs when a variable is a risk factor for an effect among non-exposed persons and is also associated with the exposure under study in the source population. Additionally, a confounding factor must not be affected by the exposure or the disease; it cannot thus be an intermediate step in the causal pathway between the exposure and the disease.

In our studies we have used a registry-based design, and have not information on potential confounders. However in most of the studies, we have a matched design and adjusted for age, sex and calendar period of diagnosis. The observation of an increased mortality of MGUS patients may to a large extent be explained by underlying disease that led to the identification of the M-protein and is associated with an excess mortality (confounding by indication). Similarly, in study V, people of lower SES may have more co-morbid disorders and are less likely to receive or tolerate intensive therapy, which may reduce survival. In addition, lifestyle factors, physical activity, overweight, tobacco or alcohol use, factors which are influenced by SES may also have an impact on the patient’s tolerance to diagnostic and therapeutic procedures. Finally, in study VI, we do not have information on underlying disease, such as known risk factors for thrombosis. Our observation of an increased risk of thrombosis among
MGUS patients may, as stated above, be explained by underlying disease and not be causally related to the MGUS.
6 SUMMARY AND CONCLUSIONS

Familial studies (I, II)

First-degree relatives of LPL/WM patients have an increased risk of developing LPL/WM, NHL, CLL, and MGUS, but not multiple myeloma and HL. First-degree relatives of MGUS patients have an increased risk of MGUS, multiple myeloma, LPL/WM, and CLL, but not NHL and HL. Our findings support shared common susceptibility genes that predispose to a variety of lymphoproliferative disorders.

Prognostic studies (III-VI)

MGUS patients experience a decreased life expectancy compared to the general population, most pronounced in the elderly. IgM (versus IgG/A) MGUS was associated with a superior survival. MGUS patients had an increased risk of dying due to hematological diseases and non-malignant conditions. These findings may be causally related to the MGUS, but may also be explained by underlying diseases that led to the detection of MGUS.

Survival of multiple myeloma patients has improved in recent years. Five- and ten-year multiple myeloma survival has increased in younger patients (younger than 60 to 70 years). High dose melphalan with subsequent ASCT, thalidomide, and a continuous improvement in supportive care measures are probably the most important factors contributing to the improvement in multiple myeloma survival. Patients with higher socioeconomic status have a superior survival compared to lower, most evident after 1990. Differences in co-morbidity, management, and life-style, are likely factors to explain the observed survival differences.

Patients with multiple myeloma and MGUS have an increased risk of venous and arterial thrombosis. IgG/IgA (but not IgM) MGUS patients had an increased risk for venous and arterial thrombosis. Thrombosis among MGUS patients did not predict progression to multiple myeloma or WM. Our results are important for future studies designed to explore this excess risk and of potential impact for the development of thrombosis prophylaxis strategies for multiple myeloma and possibly MGUS patients.
7 ACKNOWLEDGEMENTS

There are many people that have helped me along the way and I want to express my sincere gratitude to all who supported me in my work. In particular, I wish to thank:

Magnus Björkholm, my main supervisor. It is a privilege to have you as my supervisor. Special thanks for wide and in-depth scientific guidance, for introducing me to the world of science, for including me in your research group, for helping me develop critical thinking. Also thanks for never ending advice about science, clinical problems, methods, wording, boat maintenance, and insurance companies. And all the stories. Thank you for making this thesis and all our work together a great fun.

Ola Landgren, my co-supervisor. You have been a great supervisor. Thank you for believing in me, for always having new and exciting ideas, for strategic advice, and tips on the secrets of science, for pushing me to carry on and plan more studies, for thousands of e-mails, and for great fun at hematology meetings.

Jan Sjöberg, my clinical tutor, for being a great tutor, for two-men journal clubs, for gossip, for clinical discussions, and Swedish mispronunciations (mine, not yours).

Per Ljungman, for providing excellent conditions for combining research and clinical working at the Division of Hematology.

All my colleagues and friends at the Division of Hematology, for friendship and support and fruitful discussions.

Åsa Derolf, my co-author, co-PhD-student, my friend, for great collaboration, corridor-discussions on everything (including some epidemiology but mainly other stuff) and great fun.

Ingemar Turesson, for being a great co-worker, for including so many patients and data to our studies, and for being thorough and critical at all times. Also thanks to all physicians and pathologists that provided information on their patients, in particular Anders Wahlin, Cecilie Blimark, Ulf-Henrik Mellqvist, Anja Porwit-McDonald and many more.

The staff at MEP, in particular Paul W Dickman for great collaboration, including statistical assistance. Many thanks also to Sandra Eloranta, Therese ML Andersson, and Gustaf Edgren for statistical help.

My co-authors at the National Institute of Health. Especially to Lynn R Goldin for all work we have done together, for statistical and database construction. Also I’d like to thank Mary Lou McMaster, Ruth M Pfeiffer, Jill Koshiol, and Neil Caporaso for great collaboration.
My friends and co-scientists, Andri Steinþór Björnsson, Bjarni Páll Ingason, Gunnar Tómasson, and Þorvarður Jón Löve. For a great friendship, and for discussions on science, life, happiness and stuff.

My Icelandic friends living in Sweden. For hundreds of dinners, late nights, laughs, and everything that can’t be said in a book like this.

The basketball team, for not breaking my arms or legs, and for letting me win.

Charlotta Ekstrand, for help in collecting information and filling in all case report forms, great data management, and an amazing speed. Also I thank Lisa Camner and Molly Collin for invaluable ascertainment of MGUS data.

Shiva Ayobi and the staff at the Swedish Socialstyrelsen for help with data linkage.

Ninni Petersen, Marinette Blücher, Marie-Louise Mountzoglou, and Sandra Brown for all secretarial help, and especially Ninni Petersen for all help and for pushing me to be on time.

My family in Iceland, in particular my parents and my sisters for all their faith in me and encouragement.

And finally to Sunna, Kristinn, Katla and Vala. For everything. This thesis is dedicated to you.

This thesis was supported by grants from the Swedish Cancer Society, Karolinska Institutet Foundations, the Stockholm County Council, the Intramural Research program of the NIH and Roche.
8 REFERENCES

Population-based studies on familiality and prognosis in monoclonal gammopathies


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