

High prevalence of cardiovascular comorbidity in multiple myeloma. A Swedish register study with matched controls

Karin Larsson

karin.larsson@akademiska.se

Uppsala University

Ingigerdur Sverrisdóttir

University of Gothenburg

Sigrun Einarsdóttir

University of Gothenburg

Moshtak Karma

Södra Älvsborg Hospital

Mariana Villegas-Scivetti

University of Gothenburg

Dorota Knut-Bojanowska

Uddevalla sjukhus

Gunnar Juliusson

Lund University

Kristina Carlson

Uppsala University

Gunnar Larfors

Uppsala University

Cecilie Hveding Blimark

University of Gothenburg

Research Article

Keywords:

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11072650/v1>

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Additional Declarations: Competing interest reported. SE: Research funding from MSD. Honoraria from Sanofi.

Abstract

Introduction

Multiple myeloma (MM) is a hematological malignancy with a median age at diagnosis of 72 years. Consequently, cardiovascular comorbidity is a concern. Using Swedish population-based registries, we aim to describe cardiac comorbidities among patients at time of MM diagnosis, the incidence of new cardiovascular events (CVE) at 2-year follow-up and the risk of death, in comparison with matched controls.

Material and methods

All MM patients (n=8 672) in the Swedish myeloma registry (SMR) diagnosed 2008-2021 were included. Matched controls (n=34 561) and data on cardiovascular disease (CVD) and CVE were collected from nationwide registries. Differences in incidence and mortality were evaluated with chi-square tests and Cox regression. Ethical consent was obtained from the Swedish Ethical Review Board.

Results

At time of MM diagnosis, 45.8% of the MM patients had a registered CVD vs 35.7% of the controls, $p<0.0001$. The most frequent comorbidities were hypertension and atrial fibrillation (AF) among both patients and controls; hypertension 32.5% vs 23.3%, $p<0.0001$ and AF 11.1% vs 9.1%, $p<0.0001$. At 2-year follow-up, 17.7% of patients had AF vs 8.5% of controls, $p<0.0001$. Occurrence of AF in patients >80 years was substantial, 30.1%, vs 17.7%, $p<0.0001$. Among patients with no prior CVD, new-onset CVE was seen among 43%. Patients with CVE at 2-year follow-up had an increased risk of death vs patients without a CVE, HR 1.30 (95% CI 1.21-1.40, $p<0.0001$).

Conclusion

Almost 50% of patients had a CVD at the time of MM diagnosis. Among patients >80 years, 30% had a diagnosis of AF at 2-year follow-up. Almost half of MM patients with no CVD at time of MM diagnosis, had a CVE at 2-year follow-up. Among MM patients, CVE was associated with inferior survival, calling for awareness and guidelines for management of CVD among MM patients.

Introduction

Multiple myeloma (MM) is a hematological malignancy, with a median age at diagnosis of approximately 70 years in the Swedish myeloma registry (SMR) (1, 2). Consequently, cardiac comorbidities are expected to be frequent. In addition, specific features of MM predispose to cardiac disease; amyloid light-chain (AL) amyloidosis increases the risk of arrhythmias and congestive heart failure (CHF) (3), anemia and hypercalcemia predispose to myocardial strain and infarction (MI), CHF, and arrhythmia (4–6). Previous retrospective register studies have demonstrated a significant general comorbidity burden in comparison with matched controls at time of MM diagnosis, as well as inferior overall survival (OS)

among patients with arrhythmia, CHF and MI. However, these studies were conducted in earlier treatment eras and included patients diagnosed between 2005 and 2012 and between 1990 and 2013, respectively, thus preceding the widespread use of modern myeloma therapies (7, 8). In a cohort study from the United States (US) in 2012 including $n = 22\,076$ newly diagnosed MM patients, 63% had at least one cardiovascular disease (CVD) at time of diagnosis and 72% experienced an event during follow-up. This study did not include a control population (9).

At time of MM diagnosis, most patients need therapy. In Sweden, current induction therapy consists of a combination of 3 to 4 agents: an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), steroids and an anti-CD38 antibody. For younger, fit patients, high-dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) is recommended.

In Sweden, thalidomide and bortezomib, first-generation IMiD and PI, were approved in 2008 for first-line therapy in combination with oral melphalan and dexamethasone. Around 2010, bortezomib and dexamethasone in combination with thalidomide or cyclophosphamide were introduced as induction regimens in transplant-eligible patients. Lenalidomide was approved in 2015 and as maintenance therapy after ASCT in 2017. The addition of daratumumab (anti-CD38 antibody) to other regimes in primary therapy was approved 2020–2021. Carfilzomib, a second-generation PI, was approved as a second-line agent in 2015–2016. Thus, this study, including patients diagnosed from 2008 to 2021, mainly include patients exposed to modern agents with bortezomib backbone in first-line therapy (10).

Many of these agents have known cardiovascular adverse events (CVAE), in particular carfilzomib, IMiDs, and high-dose steroids (11, 12). Following this, real-world data on CVD and cardiovascular event (CVE) during follow-up among MM patients receiving modern therapy are warranted. Using nationwide Swedish population-based registries, we aim to i) describe cardiac comorbidity burden at the time of MM diagnosis, ii) at 2-year follow-up and iii) the impact on survival, in comparison with matched controls.

Material and methods

Study populations

In Sweden, all citizens have a unique personal identity number (13) which can be used for documentation and identification in nationwide registries. In this study, we identified all MM patients diagnosed between 2008 and 2021 in the SMR ($n = 8\,672$).

Controls ($n = 34\,561$) were identified through the Swedish Total Population Register (14), which contains all Swedish citizens and data on sex, age and region. For each MM patient, 4 controls were chosen without any preceding hematological malignancy at time of matching date (time of MM diagnosis). The controls were matched on sex, year of birth and county of residence.

Data resources

The Swedish cancer register (SCR) (15) contains information about malignant disorders in Sweden. Since 1958, it is mandatory by law to report cancer diagnoses to the register.

The SMR was initiated in 2008 and holds clinical information about MM at time of diagnosis, type of primary therapy and survival. Patients are reported to the SMR and SCR at time of diagnosis. The completeness of SMR compared to the SCR was 97% for patients diagnosed with MM during 2008–2015 (2). The SMR serves as a population-based nationwide quality register of MM, with the purpose to improve and secure a nationwide, high standard health care for MM patients as well as a resource for studies. Data on primary therapy, HDM and ASCT as part of primary therapy are registered, but data on later lines are not registered, thus data on carfilzomib-exposed patients cannot be obtained.

To identify MM patients with cardiac comorbidity, the International Classification of Diseases (ICD) system was used. Since 1997 the ICD-10 system has been used in Sweden; i.e. all diagnoses in this study were identified using ICD-10 codes. For all patients and matched controls, the ICD-10 codes in chapter ICD-10 (I00-I99) which focuses on CVD were used to search the Patient Register(16) and the Cause of Death Register(17) for CVD diagnoses within five years prior and two years following MM diagnosis. In Table 1 data on additional relevant CVD comorbidities are presented. The Patient Register contains specialist care diagnoses and is divided into two parts: in and outpatient care, commencing in 1967 and 2000, respectively.

Table 1

Baseline data of study population and prevalence of cardiovascular comorbidity at time of MM diagnosis (matching date) and at 2 years follow-up.

Total	Patients, n (%)		Controls, n (%)
	8 672 (100)		34 561 (100)
Sex			
Male	4 982 (57.4)		19 852 (57.4)
Female	3 690 (42.6)		14 709 (42.6)
Age, median (range)	72 (20–101)		72 (20–101)
Age group n (%)			
< 65 years	2 273 (26)		9 118 (26)
65–80 years	4 590 (53)		18 294 (53)
>80 years	1 809 (21)		7 149 (21)
ISS grade, n (%)			
Low risk (I)	1 241 (20)		NA
Intermediate (II)	2 716 (44)		NA
High risk (III)	2 226 (36)		NA
Missing	2 489		
Treatment, n (%)			
Auto-SCT	2 216 (25.5)		NA
Non-auto SCT	6 035 (69.6)		NA
Missing	424 (4.9)		
Year of diagnosis			
2008–2012	2 833 (32.7)		11 306 (32.7)
2013–2017	3 198 (36.9)		12 741 (36.9)
2018–2021	2 641 (30.4)		10 514 (30.4)
Comorbidity within 5y prior to MM diagnosis	Patients, n (%)	Controls, n (%)	p
Any CVD	3 973 (45.8)	12 278 (35.7)	< 0.0001
Abbreviations: CHF: Congestive heart failure, CVD: Cardiovascular disease, CVL: Cerebrovascular disease, DM: Diabetes mellitus, ISS: International staging system, MM: Multiple myeloma, SCT: Stem cell transplantation			

Total	Patients, n (%)		Controls, n (%)
	8 672 (100)		34 561 (100)
Myocardial infarction	550 (6.3)	1 955 (5.7)	0.01
Atrial fibrillation	959 (11.1)	3 159 (9.1)	< 0.0001
Hypertension	2 817 (32.5)	8 058 (23.3)	< 0.0001
CHF	632 (7.3)	1 743 (5.0)	< 0.0001
CVL	195 (2.3)	971 (2.8)	0.004
Hyperlipidemia	596 (6.9)	2 070 (6.0)	0.002
DM type 2	828 (9.6)	2 813 (8.1)	< 0.0001
Obesity	137 (1.6)	433 (1.3)	0.02
Abbreviations: CHF: Congestive heart failure, CVD: Cardiovascular disease, CVL: Cerebrovascular disease, DM: Diabetes mellitus, ISS: International staging system, MM: Multiple myeloma, SCT: Stem cell transplantation			

To analyze mortality in CVD, the Cause of Death Register was used to identify deceased patients and controls, including date of death and main/contributing causes of death. The Cause of Death Register was initiated in 1952 and contains data on all deaths of Swedish citizens. The register holds data on date and causes of death allocated to main and contributing causes. The register has a high degree of completeness, though diagnostic accuracy varies by age and comorbidities (17).

The specific ICD-10 codes used in this study are listed in Supplementary, Table S1. The term “any CVD” refers to individuals with at least one CVD diagnosis from chapter I00-I99.

Statistical analysis

Figure 1 describes the study population outline. From 2008, the triplet with bortezomib backbone was widely introduced in clinical routine, so an analysis of exposure to different first-line treatments over time periods was not meaningful. We refer to CVD when describing prevalence at time of MM diagnosis and cardiovascular event (CVE) when presenting incidence following MM diagnosis.

Cardiovascular comorbidity at time of MM diagnosis

To calculate CVD prevalence at MM diagnosis, CVD diagnoses from 5 year prior to MM diagnosis/matching date were included. The prevalence of specific CVD comorbidities is shown in absolute numbers and percentages. In the group “any CVD”, an individual is counted once, for the purpose of estimating the proportion of MM patients and controls with at least one CVD. For specific cardiac diagnoses, an individual might be counted multiple times; for example, a patient diagnosed with hypertension and AF is counted in both groups (Table 1). To characterize the CVD burden at different

ages, patients (and their controls) were divided in three cohorts according to age at time of MM diagnosis. A sensitivity analysis of cumulative incidence was performed for “any CVD”, AF, MI and cerebrovascular lesion (CVL) in the year prior and following MM diagnosis. Furthermore, the year before and after MM diagnosis was divided in 3-months periods to investigate when in relation to MM diagnosis, the CVE occurred. Results are presented with and without lagtime of one year as well as in 3-months periods the year prior and following MM diagnosis

Cardiovascular events during follow-up

To ensure adequate data at 2-year follow-up, patients diagnosed with MM 2020–2021 and their controls were excluded.

To study the incidence of new-onset CVE following MM diagnosis, study participants were divided in two groups: those without and those with CVD comorbidity at time of MM diagnosis. In the group “any CVE”, an individual is counted once. Differences in CVE incidence between patients cohorts and controls were evaluated with chi-square tests.

Cardiovascular comorbidity and risk of death

To investigate CVD mortality, we searched the Cause of Death register for all study subjects. For deceased individuals, data on main and contributing causes of death related to CVD using the ICD-10 coding system were obtained. In a landmark analysis including patients alive at 2-year follow-up without CVD at time of MM diagnosis, we studied if new-onset CVE during the first 2 years following MM diagnosis, impacted the risk of death. Survival analysis was performed using Cox regression model. Analyses on all p values were adjusted for age, year of MM diagnosis and sex, a p value < 0.05 was considered statistically significant. Differences are shown as hazard ratios (HR) with 95% confidence intervals (CI). All analyses were performed with SAS 9.4 statistical software (SAS Inc., Cary, NC).

Ethical consideration

Ethical consent was obtained from the Swedish Ethical Review Authority (2020 – 01729 and 2021-06236-02). Since 2019 it is a single, unified government agency. Human Ethics and Consent to Participate declaration: Ethical consent is obtained as stated above. Please contact the corresponding author if more information is needed.

Results

Median age at time of MM diagnosis was 72 years and 57% were male, 60% of patients were older than 70 years at time of diagnosis. In total, including patients > 70 years, 25% received HDM and ASCT as part of primary therapy. Other baseline characteristics of the study population are outlined in Table 1. Depending on the year of MM diagnosis, the study cohort was divided into time periods; 2008–2012, 2013–2017 and 2018–2021. During these time periods, 68%, 90% and 97% received an IMiD, PI or CD38

antibody as part of primary therapy, respectively. Median follow-up for patients was 3.1 (IQR 1.4–5.6) years and 5.7 (IQR 3.1–9.2) for controls.

Cardiovascular comorbidity at time of MM diagnosis

At MM diagnosis, 45.8% of the MM patients had a history of CVD compared to 35.7% of the controls, $p < 0.0001$. The most frequent CVD comorbidity was hypertension, followed by AF, in both patients and controls: hypertension 32.5% vs 23.3%, $p < 0.0001$ and AF 11.1% vs 9.1%, $p < 0.0001$. The prevalence of CHF was 7.3% of patients vs 5.0% of controls, $p < 0.0001$. (Table 1). Among patients, the prevalence of “any CVD” at time of diagnosis among men was 47.3% vs 43.9% among women, $p = 0.002$. Among controls, 36.8% of men and 33.8% of women had a history of CVD, hypertension and AF being most prevalent in all groups. Increasing age was found to correlate with increased CVD burden, i.e. “any CVD”; among patients < 65 years 25.6% had a history of CVD, 48.4% among patients 65–80 years and 64.7% in patients > 80 years. For controls, the percentages were 16.2%, 37.2% and 56%, respectively. Among patients and controls < 65 years, AF was less frequent: 2.6% among patients and 1.9% in controls. (Supplementary, Table S2)

To estimate the risk of surveillance and register bias, we performed an analysis excluding any CVD diagnoses registered one year prior to MM diagnosis/matching date. In this analysis, 32% of the patients and 30% of the controls had history of CVD, $p < 0.01$. The highest incidence of “any CVD” and AF among MM patients was seen one year before and one year after MM diagnosis (Fig. 2a and b). To investigate the potential of bias further, we divided the year prior and after MM diagnosis into 3-month periods. The highest incidence of “any CVD” and AF was observed in the adjacent 3-month periods before and following MM diagnosis (Supplementary, Table S3, S4, Figure S1 and S2). To evaluate whether these findings merely reflected surveillance bias, we investigated the incidence of MI and CVL with the same method, demonstrating a significant increase in the 3-month period prior to MM diagnosis, $p < 0.0001$, but not following MM diagnosis for MI (Supplementary, Table S5). For CVL, the incidence was increased at 3-, and 6-months post-MM diagnosis, $p < 0.0001$, $p < 0.001$ (Supplementary, Table S6).

Cardiovascular events during follow-up

At 2-year follow-up for all MM patients (with and without prior CVD at time of MM diagnosis) the prevalence of “any CVE” was 60.7% ($n = 4\,505$) vs 27.3% among controls. The most frequent CVEs were hypertension, 39.6% among MM patients vs 16.8% among controls, $p < 0.0001$; and AF, 17.7% vs 8.5%, $p < 0.0001$. (Supplementary Table S7) The occurrence of AF in MM patients > 80 years (before and after MM diagnosis) at 2-year follow-up was substantial, 30.1% vs 17.7% among controls, $p < 0.0001$.

For MM patients with no history of CVD at the time of MM diagnosis, 43% of the patients developed a CVE within 2 years vs 14% among controls ($p < 0.0001$). The most frequent CVEs among patients and controls were hypertension 24.9% vs 8.3%, AF 8.2% vs 2.7% and CHF 5.6 vs 1.6%; $p < 0.0001$, $p < 0.0001$, $p < 0.0001$. (Supplementary Table S8)

Cardiovascular comorbidity and risk of death

Adjusted for age, year of MM diagnosis and sex, a CVD diagnosis at time of MM diagnosis increased the risk of death by 28% (HR = 1.28, 95% CI 1.21–1.35, $p < 0.0001$) (Supplementary Figure S3).

In the landmark analysis at 2-year follow-up the risk of death was higher in patients with CVD comorbidity at the time of MM diagnosis vs no CVD comorbidity. (Fig. 3). Among MM patients without CVD comorbidity at time of MM diagnosis, a new-onset CVE at 2-year follow-up was associated with increased risk of death, HR 1.29 (95% CI, 1.17–1.42, $p < 0.0001$). The impact of a new-onset AF on the risk of death was similar; the risk of death was increased in patients diagnosed with AF within 2-years follow-up vs patients without prior AF, HR 1.18 (95% CI 1.03–1.35, $p < 0.05$). (Supplementary, Figure S4)

During follow-up, $n = 5\,441$ MM patients died. Out of these, 35.5% had at least one CVD diagnosis registered as main and/or contributory cause of death, CHF being the most prevalent with 17% as a cause, followed by AF with 9%, and ischemic heart disease with a total of 9%. (Supplementary Table S8)

Discussion

In this large population-based retrospective study including 8 672 patients with MM diagnosed between 2008 and 2021 with matched controls, we found a substantial CVD comorbidity burden at MM diagnosis, with increased CVD prevalence at time of diagnosis and incidence during follow-up among patients compared to controls. The occurrence of cardiovascular comorbidity at MM diagnosis was highest among patients > 80 years, with 64.7% presenting with at least one cardiac comorbidity, 47.7% with hypertension and 22% with AF. At 2-year follow-up, 30% of patients > 80 years had an AF diagnosis vs 17.7% among controls. Among patients with no CVD at time of MM diagnosis, 43% was found to have a new-onset CVE at 2-year follow-up.

Previous population-based data on CVD among newly diagnosed MM patients are few and were conducted prior to the modern MM therapy era with PI and IMiDs (7, 8). Prevalence data on AF among MM patients include a large retrospective study of National Inpatient Sample database in the US, investigating AF prevalence in different cancer subtypes among adult cancer patients admitted to hospital, divided into three age groups: patients < 65 years, 65–80 years and > 80 years. Patients with MM admitted to hospital were found to have an increased risk of AF compared to other cancer types, especially in the two younger age groups. In admitted MM patients > 80 years, the prevalence of AF was 28.2%, i.e. comparable with our prevalence data of 30.1%. In the US study, no correlations to MM characteristics or MM therapy were analyzed. Among all cancer patients with AF, the hospitalization cost, duration of stay and importantly, mortality, was increased vs patients who were admitted without AF (18).

A main observation in our study is the substantial cardiovascular comorbidity present among patients > 80 years, where 65% had history of CVD (including hypertension) at MM diagnosis. Importantly, 30% had a history AF at 2-year follow-up. Furthermore, CVD comorbidity at MM diagnosis was associated with

inferior survival vs patients without CVD. A similar pattern was observed when analyzing the impact of new-onset of any CVE including AF among patients without prior CVD.

To assess whether our control cohort was representative of the population, we compared our data with Swedish reports on AF from the Patient register and found that the prevalence of AF was comparable to that of our study control population across all age groups (19, 20).

The prevalence of hypertension in our data is lower than expected among both patients and controls, compared with other data; a study by the American Heart Association from 2015 reported a prevalence of hypertension of 65% among individuals ≥ 60 years in the United States (US) (21). Our lower prevalence, 32.2% among patients and 23.3% in controls, are possibly explained by register bias since Swedish general practitioners (GP) do not report diagnoses to the Patient Register. We suspect hyperlipidemia might follow the same pattern. To investigate the potential of registration and surveillance bias further, we analyzed the incidence of “any CVD”, AF, MI and CVL in 3-month periods in the year prior to and following MM diagnosis. We added MI and CVL since these diagnoses are primarily registered in-hospital. During the adjacent 3-month period prior to MM diagnosis, a significant increase in MI among MM patients vs controls was found. A similar tendency was found for CVL (patients vs controls) during the same period. We also performed a sensitivity analysis excluding any CVD diagnoses registered within one year prior to MM diagnosis; the prevalence at diagnosis diminished to 32% among patients vs 30% among controls. To conclude, the increase in CVD among MM patients already at MM diagnosis might partly be explained by registration and surveillance bias during work-up for MM diagnosis, but due to the significant differences in MI and CVL during the same periods adjacent to MM diagnosis, it cannot be ruled out that MM and/or its therapy enhances the risk of CVD. Possible mechanisms that might increase CVD and AF risk in patients with MM include AL amyloidosis, high plasma viscosity, anemia, renal failure (22) as well as CVAEs during follow-up.

Data on CVE in real-world MM patients during follow-up are largely derived from older studies. In 2016, Kistler et al. investigated cardiac disease incidence in a large cohort of previously treated MM patients receiving MM therapy with at least 3 MM drugs (including PI and/or IMiD) vs a control population with no diagnosis of MM. Among MM patients the prevalence of any cardiac event was 60.1% vs 54.6% among controls ($p < 0.0001$). The MM cohort also had an increased risk of CVAE, including dysrhythmias (AF not specified). As in our study, no specific analyses were performed to study CVD incidence following specific regimens or steroid doses. To note, the study contained a young MM population derived from an insurance database with a median age of 62 years (23). For MM patients eligible for HDM and ASCT, a recent study including 801 patients undergoing ASCT during 2016–2022 demonstrated a cumulative incidence of AF at 90 days post ASCT of 5.5% and 9.0% at 3 years. Age > 65 years, obesity and prior AF were independent predictors of AF onset post-ASCT. Notably, developing AF after ASCT increased the risk of all-cause and non-relapse mortality (24). These data, in combination with our data on high prevalence of AF among the elderly and the observed increased risk of mortality, underlines that AF among MM patients need further investigation to determine whether certain therapies should be avoided or preferred in specific groups.

Our data are of particular interest since they characterize baseline cardiac comorbidity in the modern era of MM therapy. Several of the mainstays of modern MM therapy drugs, notably PIs (particularly carfilzomib), IMiDs and dexamethasone have been linked to CVAEs (11). A meta-analysis including 4 164 patients included in 29 trials with carfilzomib found an incidence of 8.68% all grade CVAEs, with high grade (3 or more) of 4.92%, concomitant IMiD use further increased the CVAE incidence (25). A phase 3 trial, Endeavour, compared carfilzomib and dexamethasone vs bortezomib and dexamethasone, demonstrating increased CVAEs in the carfilzomib arm (10.7%) than in the bortezomib arm (4.7%) (26). Cardiotoxicity with IMiDs has been reported with higher rates if combined with dexamethasone; the risk of MI was 1.98% vs 0.57% (27). Most data are from clinical trials and since frail and/or elderly patients rarely meet the inclusion criteria, data are sparse in this group (28). Importantly, data on CVD in patients treated with and without dexamethasone remain limited. Studies on AF and steroids have previously shown an increased risk of AF in doses higher than prednisolone 7.5 mg daily (29), equivalent to a weekly dexamethasone dose of 8 mg, thus below the standard therapeutic dose in MM. In the current era of quadruplets the additional effect of dexamethasone to IMiDs, PI and CD38 antibodies, is questioned. An analysis published in 2025 of the SWOG 0777 and SWOG 121 trials, evaluating primary therapy with lenalidomide and dexamethasone +/- bortezomib +/- elotuzumab, found no difference in PFS or OS when comparing patients receiving full-dose dexamethasone with patients receiving dose reductions (due to toxicities). Notably, 69% of patients experienced dose reductions of dexamethasone (30).

In 2022, the European Society of Cardiology published general guidelines in cardio-oncology on how to screen, prevent, monitor and manage CVD among cancer patients (31). Specific guidelines for MM patients and CVD, when available, are built on expert opinions (6, 11), which recommend liberal usage of baseline electrocardiogram (ECG), ultrasonic cardiography (UCG) and measurement of cardiac biomarkers such as troponin and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) before initiating carfilzomib or other cardiotoxic agents (6, 12). For carfilzomib, hypertension and CHF are not uncommon and blood pressure should be monitored before each infusion (12). A recently published paper from the phase II GMMG-CONCEPT trial, prospectively evaluated the predictive value of NT-proBNP and high-sensitivity troponin I (hsTropI) in high-risk MM patients receiving first-line treatment with isatuximab, carfilzomib, lenalidomide and dexamethasone. The two biomarkers were obtained before start of cycle 1 (baseline) and subsequently during the treatment cycles. Approximately 50% had at least one CVD at baseline. New-onset and/or worsening of CVD was reported in 32% of the patients, the majority being hypertension, AF and CHF. Notably, elevated levels of NT-proBNP were common prior to therapy but were not found to predict new-onset or worsening of CVD (32). Thus, studies on other biomarkers and/or risk scores would be helpful in the clinical setting.

This study has several strengths, primarily its large, population-based patient cohort with matched controls and the use of nationwide Swedish registries. In addition, due to the Swedish public health care system, all citizens have free access to modern health care, including agents for MM as well as for CVD including primary prophylaxis, making comparisons and generalizations possible. The main limitations of this study include its retrospective design and the potential influence of surveillance and registration

bias, as previously discussed. Although first-line therapy is recorded in the SMR, information on possible subsequent lines, specific treatment regimens, cumulative steroid exposure and the presence of concomitant AL amyloidosis is not available. In our cohort, 26% of MM patients underwent ASCT in first-line setting, including patients above 70 years. Missing data was noticed for almost 5% of the patients. This might be due to data cut-off date for patients diagnosed during 2021 (the annotation regarding the primary therapy report had not yet been dispatched from the SMR). Additionally, the covid-19 pandemic might have led to less intensive therapy in 2020–2021 and finally 26% of MM patients were < 65 years at time of MM diagnosis. The survival associations were based on register data and not adjusted for renal disease, performance status or disease severity. Residual confounding cannot be excluded, and causality cannot be inferred. Whether any of these CVE events could have been mitigated or prevented is unknown. Analyzing causes of death, data need to be interpreted with caution since the Cause of Death Register has known limitations in correct diagnoses especially in elderly with comorbidities and chronic diseases such as MM (17).

Our data and current literature demonstrate that CVD, in particular hypertension and AF, is common among MM patients, especially in patients > 80 years. Importantly, patients with previous CVD following MM diagnosis are at increased risk of death. Strategies to decrease the risk of CVAE or CVE and manage CVD risk factors are warranted. Data on dexamethasone dose reduction and/or steroid-free regimens are promising, and follow-up data are of clinical interest. In the rapidly changing field of MM therapy, treatment guidelines on optimal management of MM and concomitant cardiac comorbidities, are needed to minimize complications and optimize survival chances.

Declarations

Declarations

Competing Interests

SE: Research funding from MSD. Honoraria from Sanofi.

Funding

The study was financed by grants from the Swedish state under the agreement between Swedish government and the county councils, the ALF-agreement (Region Uppsala and Gothenburg).

Clinical Trial Number

Not applicable.

The Author Contribution

KL wrote the project plan and the main manuscript. The study design was discussed and design with GL, CHB and IS. GL analyzed the data, made the figures and the tables. CHB sought ethical approval for the MMBase project. All authors (KL, GL, CHB, IS, SE, MK, MVS, DKB, GJ and KC) have critically reviewed, edited and approved the manuscript.

Author Contribution

KL wrote the project plan and the main manuscript. The study design was discussed and design with GL, CHB and IS. GL analyzed the data, made the figures and the tables. CHB sought ethical approval for the MMBase project. All authors (KL, GL, CHB, IS, SE, MK, MVS, DKB, GJ and KC) have critically reviewed, edited and approved the manuscript.

Data Availability

For original data, please contact the corresponding author. As per Swedish law, individual participant data will not be shared.

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Figures

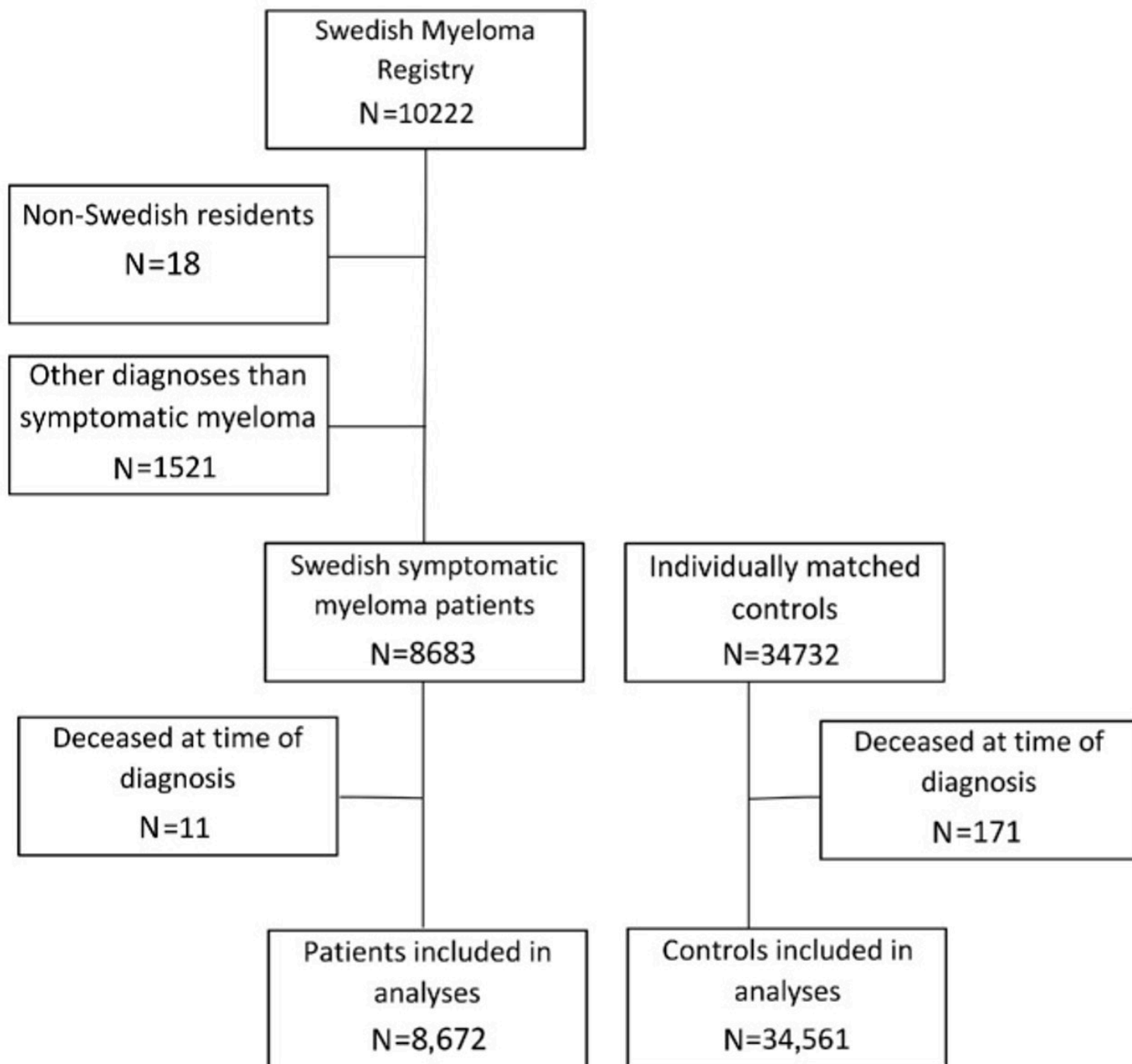
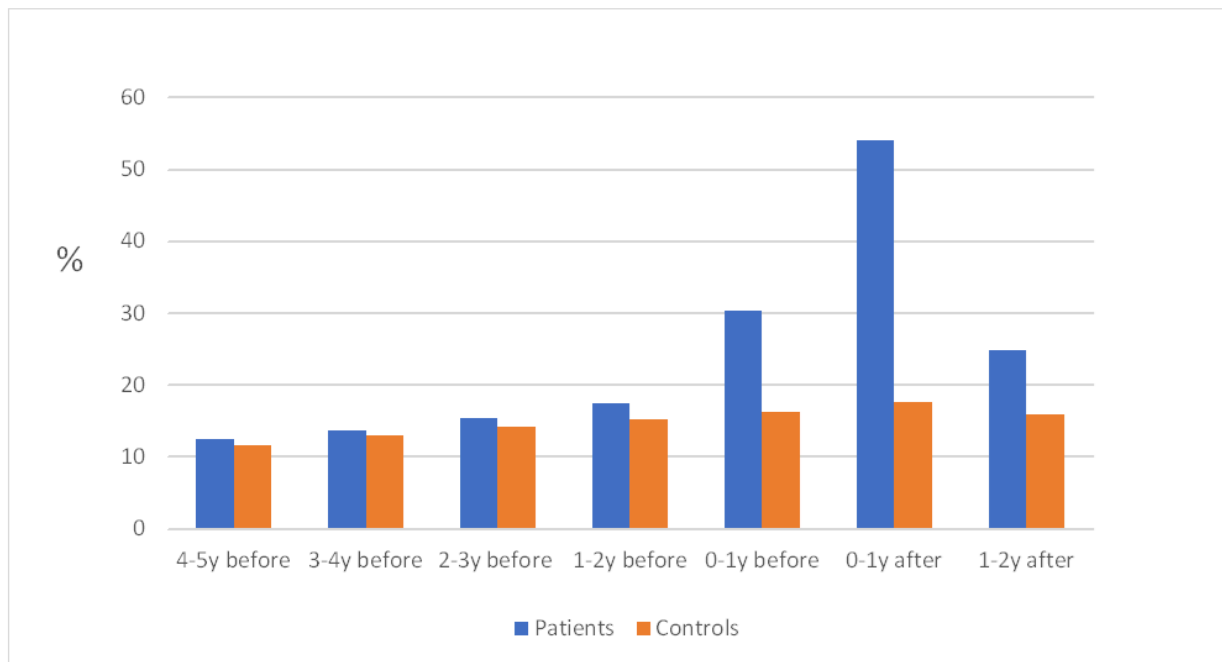


Figure 1

Study outline of the MMBaSe study (Multiple MyelomaBaSe); a linked database from population-based registers in Sweden

a)



b)

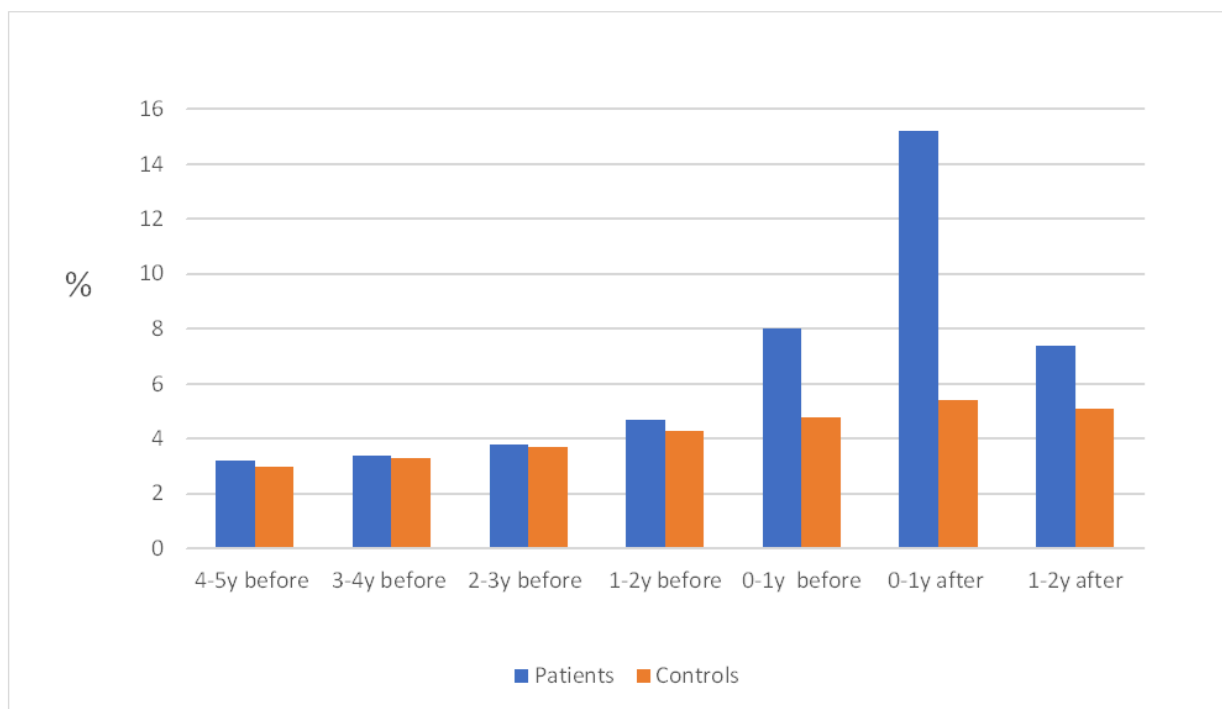


Figure 2

a) Incidence of any CVD year by year for all individuals, demonstrating a peak in incidence 1y before and 1 year after MM diagnosis. b) Incidence in AF year by year for all individuals, with similar incidence pattern.

Abbreviations: AF: Atrial fibrillation, CVD: Cardiovascular disease, CVL, MM: Multiple myeloma

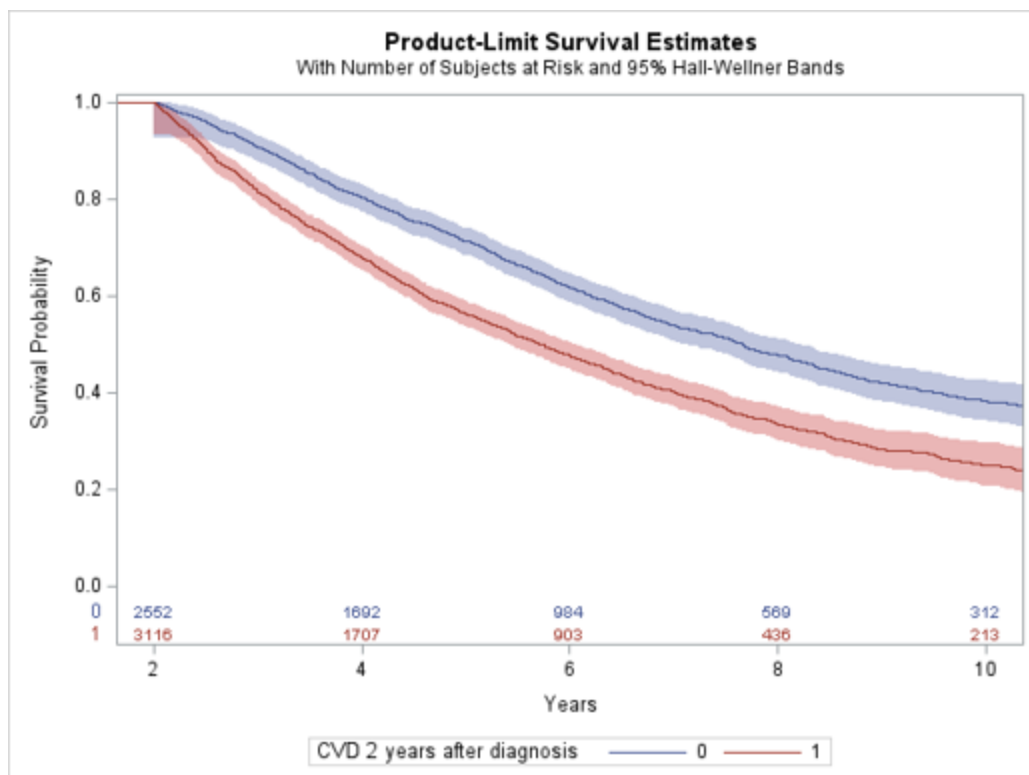


Figure 3

Survival probability during follow-up among patients with vs without CVD at time of MM diagnosis. Patients diagnosed within 2 years after MM diagnosis were excluded from the analysis.

Abbreviations: AF: Atrial fibrillation, CVD: Cardiovascular disease, CVL, MM: Multiple myeloma

Supplementary Files

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- [SupplementaryMMCVD.docx](#)