Chapter 6

Erythropoiesis-stimulating agents and cardiovascular events in patients with myelodysplastic syndrome and multiple myeloma

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Abstract

Introduction Erythropoiesis-stimulating agent (ESA) treatment has been associated with an increased risk of venous thromboembolism (VTE) in patients with solid tumors and with an increased risk of cardiovascular events in patients with chronic kidney disease. The ESA-related risk of VTE, myocardial infarction (MI) and stroke in patients with multiple myeloma (MM) or myelodysplastic syndrome (MDS) remains unclear and was therefore assessed in this study.

Methods We conducted a population-based cohort study in Denmark, using medical databases to identify 1357 MDS patients and 2301 MM patients diagnosed 2004 - 2011. Time-dependent Cox regression was performed to compute hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE, MI, and stroke associated with ESA treatment. Analyses were adjusted for age, sex, MDS prognosis group, comorbidities and treatments.

Results Incidence rates per 1,000 person-years for VTE, MI and stroke were 10.9, 7.6 and 17.8 in MDS patients, and 22.1, 10.0 and 8.9 in MM patients without ESA treatment, respectively. MDS patients with ESA treatment had an almost twofold increased risk of MI and stroke (HR 1.98 (95% CI 0.91-4.31) and 1.95 (95% CI 1.13-3.36), respectively), compared with MDS patients without ESAs. HR for VTE in MDS patients using vs. not using ESAs was 1.10 (95% CI 0.48-2.53). In MM patients with ESAs compared with patients without ESAs, HRs were 1.43 (95% CI 0.88-2.34) for VTE, 1.38 (95% CI 0.66-2.88) for MI and 1.81 (95% CI 0.94-3.48) for stroke.

Conclusion ESA use is a risk factor for cardiovascular events in both MDS and MM patients.

Introduction

Erythropoiesis-stimulating agents (ESAs) are used to treat anemia, in order to reduce the need for red blood cell transfusions.[1] After ESAs first proved successful in treating anemia in patients with chronic kidney disease, ESAs were also implemented in the treatment of anemia associated with malignancies.[1] In the past decade, several meta-analyses including trials of patients with mainly solid tumors, have reported an up to 1.17-fold increased mortality risk associated with ESA treatment.[2-4] As well, an increased risk of venous thromboembolism (VTE) has been reported in cancer patients treated with ESAs.[5] Concurrently, higher doses of ESAs and higher hemoglobin targets have also been associated with increased mortality and cardiovascular risk in patients with non-malignant chronic kidney disease.[6]

As a consequence, ESA treatment in patients with solid tumors is now restricted to certain patients with chemotherapy induced anemia.[1;7] However, ESA treatment is widely used in patients with the hematological neoplasms myelodysplastic syndrome (MDS) and multiple myeloma (MM). MDS patients generally are believed to be at low risk of VTE, mainly because of the high incidence of thrombocytopenia and anemia[8] and a previous case-crossover study reported no increased risk of VTE in MDS patients treated with ESAs.[9] However, an earlier phase II trial in low-to-intermediate risk MDS patients was halted early because three out of seven patients developed a VTE.[10] Also, a higher incidence of VTE with ESA treatment in patients with MM has been reported.[11;12]

The hemato-oncology literature has concentrated mainly on the effect of ESAs on VTE events.[13] An effect of ESAs on cardiovascular events, as described in patients with chronic kidney disease, is infrequently reported. A meta-analysis showed a 1.7-fold increased risk of a combination of venous and arterial thrombotic events in ESA-treated patients,

mainly with solid tumors, compared with cancer patients who did not receive ESA treatment.[4] It is difficult to deduce the contribution of myocardial infarction (MI) and stroke. No increased risk of combined arterial and venous thrombotic events with ESA treatment was reported in an earlier study of MM patients.[14] In the current study, we therefore aimed to examine the association between ESA use and cardiovascular events in patients with MM and MDS in a large population-based cohort study. To that end, we calculated the ESA-related risk of VTE, MI and stroke separately.

Methods

We conducted a population-based cohort study in Denmark, linking individual-level records among different Danish registries using the central personal registry (CPR) number.[15;16] This unique and permanent identification number is assigned to all Danish residents alive on, or born after 1968 or at the time of immigration. In Denmark, the National Health Service provides universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals.

Data sources

The Danish Cancer Registry (DCR) contains records of all incident cases of malignant neoplasms in Denmark since 1943 and provides details on histology, morphology, and cancer stage at diagnosis.[17] Throughout our study period, tumors were classified according to the tenth revision of the International Classification of Diseases (ICD–10).

The Danish National Patient Registry (DNPR) provides information on all non-psychiatric hospital inpatient admissions since 1977, and on all outpatient clinic and emergency room visits since 1995.[18] Each in-patient hospital discharge or outpatient visit is recorded with one primary diagnosis and up to 19 secondary diagnoses classified according to ICD–8

through 1993 and ICD–10 thereafter. Surgical and treatment information is coded according to a Danish classification (1977 through 1995) and a Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (from 1996 on).

The National Health Service Prescription Database (NHSPD) includes information on reimbursed prescriptions redeemed at community and outpatient pharmacies since January 1, 2004.[19] Each time a prescription is redeemed at a pharmacy, the date, the types and quantity of the prescribed drug (according to the Anatomical Therapeutic Chemical Classification System (ATC)) is transmitted to the database.

The Danish Civil Registration System (CRS), established in 1968, contains information on gender, residence, and date of death and emigration, with daily updates.[16]

Study cohort

The study included all adult patients (age ≥18 years) with a first-time diagnosis of MDS or MM in the DCR during the period 1 July 2004 - 31 December 2011 (codes in Appendix). MDS was in this study categorized as 'standard prognosis', 'poor prognosis', and 'other', based solely on the ICD-10 diagnoses (codes in Appendix).

Exposure

ESA treatment was defined as a time-dependent exposure according to data in the DNPR (codes in Appendix). Start of ESA treatment was defined as the first date on which the specific ESA treatment code appeared (Appendix). Generally MDS and MM patients would be provided with free-of-charge ESAs from the hospital departments that treat their diseases. However, in order to investigate if any patients were prescribed ESA treatment through community pharmacies, we also performed a cross check with the NHSPD (codes in Appendix). The cross check did not yield additional patients who were treated with

ESAs. Patients and person-years were considered unexposed before starting ESA treatment and exposed from start of ESA treatment until end of follow-up.

Covariates

Sex and age were extracted from CRS. Diabetes mellitus, chronic kidney disease and cardiovascular disease were identified from the DNPR. In order to increase the sensitivity of diagnoses of diabetes mellitus and cardiovascular diseases, we also searched the prescription database (NHSPD) for any previous dispensing of diabetic medication and medication of cardiovascular diseases. Statin use was also obtained from the NHSPD. Anti-thrombotic therapy was also identified from the NHSPD and checked with a treatment code from the DNPR. Chemotherapy, treatment with azaticidin, thalidomide or lenalidomide, any other immunomodulating therapy and radiation therapy were obtained from the DNPR (all codes and definitions provided in the Appendix).

Follow-up & outcome

The DNPR was also used to identify the outcomes of interest: VTE, MI, and stroke. Patients diagnosed with VTE, MI or stoke only in the emergency room setting were excluded from the analysis, due to the expected low positive predictive value of the working diagnoses. For each analyzed event, patients who were diagnosed with that specific event before start of follow-up were excluded from the analyses. For the primary analysis, follow-up started on the MDS or MM diagnosis date. Patients were followed until the first date of the specific outcome, emigration, death, or end of follow-up on 31 December 2012, whichever came first. Mortality data were obtained from the CRS.[16]

Statistical analyses

Baseline characteristics were stratified for MDS and MM patients with and without ESA treatment at baseline. Age was expressed as median with interquartile range, and categorical data as percentages. Rates of VTE, MI, and stroke

were calculated and expressed as the number of events per 1,000 person-years. Time-dependent Cox regression analysis was performed to compute hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were adjusted for sex, age, MDS risk group (only for analyses including MDS patients), diabetes mellitus, chronic kidney disease, cardiovascular disease, statin and anti-thrombotic agent use at baseline. Additional adjustment (adjustment b) was made for time-updated concurrent treatments: chemotherapy, azacitidin, thalidomide or lenalidomide, immunomodulating therapy, and radiation therapy (all codes and definitions provided in the Appendix).

Two sensitivity analyses were performed to check the robustness of our results. First, as ESA treatment is most often started shortly after diagnosis, and the duration of ESAs' effect is under debate, follow-up was restricted to the first two years following MDS or MM diagnosis. The second sensitivity analysis was restricted to patients receiving chemotherapy, since this would create a more homogeneous group of patients. In this sensitivity analysis, follow-up was started on the date of chemotherapy initiation.

All analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Data Protection Agency (record number 2011-41-5755).

Results

Descriptive characteristics of the study population

In total, 1357 patients with MDS and 2301 patients with MM were identified. Baseline characteristics are shown in Table 1. Slightly more patients in both groups were male and median age was 76 years in MDS patients and 71 years in MM patients. ESA-treated patients were more likely to have a previous diagnosis of cardiovascular disease, diabetes mellitus, or chronic kidney disease. Anti-thrombotic agent use at baseline was similar in patients with and without ESA treatment. As expected, most MM patients were treated with chemotherapy during follow-up.

Incidence rates overall and in subjects without ESA treatment

Table 2 displays the number of events and incidence rates of VTE, MI, and stroke per 1,000 person-years. In MDS patients, a total of 29 VTEs, 28 MIs and 59 strokes were observed in at least 2734 person-years of follow-up, depending on the event of interest. For MM patients, the total number of person years was at least 5584, and 127 VTEs, 59 MIs and 57 strokes were observed. The incidence rate of VTE was 10.9 per 1,000 person years in MDS patients without ESA treatment and twice as high in MM patients without ESA treatment, at 22.1 per 1,000 person years. The incidence rate of stroke was higher in MDS patients than in MM patients, with 17.8 per 1,000 person-years and 8.9 per 1,000 person-years in MDS and MM patients without ESA treatment respectively.

ESA-treated patients

As displayed in Table 2, crude incidence rates of MI and stroke were higher in ESA-treated patients compared with patients without ESA treatment. The unadjusted and adjusted HRs for VTE, MI, and stroke during the total follow-up period are shown in Table 3. While the fully adjusted HR of VTE for ESA-treated MDS patients compared to MDS patients without ESA

Table 1. Characteristics of patients with myelodysplastic syndrome and multiple myeloma diagnosed between 1 July 2004-31 December 2011

	Myelodysplastic syndrome		Multiple myeloma	
	No ESA	ESA	No ESA	ESA
Number of patients	831	526	1876	425
Age*	76.3 (65.1-82.0)	76.0 (68.3-83.0)	70.4 (62.4-78.3)	71.8 (64.1-79.2)
Male	57.5	58.4	55.9	56.9
Cardiovascular disease	70.0	73.4	65.5	71.3
Diabetes mellitus	12.9	16.2	9.2	12.7
Chronic kidney disease	4.6	5.3	9.4	15.3
Statin use	20.2	26.0	23.1	29.6
Anti-thrombotic agents	20.0	20.5	14.7	15.3
MDS groups				
standard prognosis	19.3	24.7	.	.
poor prognosis	12.8	12.5	.	.
other	68.0	62.7	.	.
Chemotherapy during FU	26.5	32.3	72.2	94.8
Radiation therapy during FU	6.5	7.4	28.6	24.2
Immunomodulating drugs during FU	5.8	17.1	66.0	91.5

Values are presented as percentages or *median (interquartile range).
MDS: myelodysplastic syndrome, ESA: erythropoiesis-stimulating agent, FU: follow-up.

treatment was 1.10 (95% CI 0.48-2.53), ESA-treated MDS patients had an almost twofold higher risk of MI (HR 1.98 (95% CI 0.91-4.31)) and stroke (HR 1.95 (95% CI 1.13-3.36)). Among MM patients, ESA treatment was associated with a higher risk of all cardiovascular events, although all confidence intervals included equivalence. HRs were 1.43 (95% CI 0.88-2.34) for VTE, 1.38 (95% CI 0.66-2.88) for MI and 1.81 (95% CI 0.94-3.48) for stroke. Overall, additional adjustment for time-updated concurrent treatments (adjustment b) affected estimates only minimally.

Sensitivity analyses

When the analyses were restricted to two years of follow-up, results for MDS patients were in line with the main results

Table 2. Incidence rates of venous thromboembolism, myocardial infarction and stroke per 1,000 person-years

		Myelodysplastic syndrome			Multiple myeloma		
	ESA	events	person-years	IR (95% CI)	events	person-years	IR (95% CI)
VTE	no	20	1843	10.9 (6.1-15.6)	106	4793	22.1 (17.9-26.3)
	yes	9	960	9.4 (3.3-15.5)	21	791	26.6 (15.2-37.9)
MI	no	14	1852	7.6 (3.6-11.5)	49	4903	10.0 (7.2-12.8)
	yes	14	930	15.1 (7.2-23.0)	10	797	12.6 (4.8-20.3)
Stroke	no	32	1800	17.8 (11.6-23.9)	43	4817	8.9 (6.3-11.6)
	yes	27	934	28.9 (18.0-39.8)	14	828	16.9 (8.1-25.8)

IR: incidence rate (per 1,000 person-years at risk), CI: confidence interval, VTE: venous thromboembolism, MI: myocardial infarction, ESA: erythropoiesis-stimulating agent.

Table 3. HRs for ESA-treated patients compared with patients not treated with ESA during complete follow-up

	Myelodysplastic syndrome			Multiple myeloma		
	HR (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]
VTE	0.98 (0.43-2.21)	1.05 (0.46-2.41)	1.10 (0.48-2.53)	1.57 (0.97-2.54)	1.62 (0.99-2.63)	1.43 (0.88-2.34)
MI	2.17 (1.01-4.62)	1.97 (0.91-4.25)	1.98 (0.91-4.31)	1.74 (0.86-3.55)	1.36 (0.66-2.82)	1.38 (0.66-2.88)
stroke	2.03 (1.19-3.47)	1.94 (1.13-3.33)	1.95 (1.13-3.36)	2.24 (1.20-4.19)	1.89 (0.99-3.61)	1.81 (0.94-3.48)

[a] Adjusted for sex, age, diabetes mellitus, MDS prognosis group (in case of MDS), chronic kidney disease, cardiovascular disease, statin use and antithrombotic therapy at baseline.

[b] Additionally adjusted for chemotherapy, radiotherapy, immunomodulating therapy, and antithrombotic therapy as time-dependent covariates.

MDS: myelodysplastic syndrome, HR: hazard ratio, CI: confidence interval, VTE: venous thromboembolism, MI: myocardial infarction, ESA: erythropoiesis-stimulating agent.

Table 4. HRs for ESA-treated patients compared to patients not treated with ESAs during the first two years of follow-up

	Myelodysplastic syndrome			Multiple myeloma		
	HR (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)	HR (95% CI)[a]	HR (95% CI)[b]
VTE	0.60 (0.17-2.19)	0.69 (0.19-2.54)	0.74 (0.20-2.74)	1.95 (1.11-3.44)	1.96 (1.11-3.49)	1.78 (1.00-3.17)
MI	2.04 (0.83-5.01)	1.83 (0.74-4.54)	1.95 (0.78-4.85)	2.55 (0.94-6.89)	1.91 (0.69-5.28)	2.10 (0.75-5.92)
stroke	1.80 (0.96-3.37)	1.73 (0.92-3.28)	1.73 (0.91-3.29)	1.91 (0.71-5.10)	1.52 (0.56-4.15)	1.53 (0.55-4.20)

[a] Adjusted for sex, age, diabetes mellitus, MDS prognosis group (in case of MDS), chronic kidney disease, cardiovascular disease, statin use, and anti-thrombotic therapy at baseline.

[b] Additionally adjusted for chemotherapy, radiotherapy, immunomodulating therapy, and anti-thrombotic therapy as time-dependent covariates.

MDS: myelodysplastic syndrome, HR: hazard ratio, CI: confidence interval, VTE: venous thromboembolism, MI: myocardial infarction, ESA: erythropoiesis-stimulating agent.

Table 5. HRs for ESA-treated patients compared to patients not treated with ESAs, with follow-up starting at initiation of chemotherapy

	Myelodysplastic syndrome		Multiple myeloma	
	HR (95% CI)	HR (95% CI)[a]	HR (95% CI)	HR (95% CI)[a]
VTE	0.87 (0.21-3.64)	1.25 (0.25-6.19)	1.49 (0.91-2.45)	1.26 (0.75-2.12)
MI	1.65 (0.23-11.8)	1.48 (0.15-14.2)	1.90 (0.87-4.17)	1.43 (0.62-3.28)
stroke	1.15 (0.42-3.09)	1.33 (0.48-3.70)	2.41 (1.23-4.74)	2.08 (1.02-4.22)

[a] Adjusted for sex, age, MDS risk group (in case of MDS), diabetes mellitus, chronic kidney disease, cardiovascular disease, statin use at baseline, time-updated anti-thrombotic therapy, and type of chemotherapy.

MDS: myelodysplastic syndrome, HR: hazard ratio, CI: confidence interval, VTE: venous thromboembolism, MI: myocardial infarction, ESA: erythropoiesis-stimulating agent.

(Table 4). In MM patients the results were also similar. Although the association between ESA treatment and VTE and MI became somewhat more pronounced, confidence intervals were wide. When we repeated the analysis in the cohort of MDS patients treated with chemotherapy (Table 5), the association of ESA treatment with MI and stroke attenuated. In MM patients the results were in line with the main analysis, and the ESA-associated risk of stroke became more pronounced. The HR for stroke in ESA-treated MM patients with chemotherapy was 2.08 (95% CI 1.02-4.22).

Discussion

Our population-based cohort study showed an elevated risk of cardiovascular events in ESA-treated MM patients. In MDS patients, ESA use was also associated with cardiovascular events, mainly with stroke and MI.

In patients with MM the overall incidence rate of VTE was high, i.e. [22-26] per 1,000 person years, which is about tenfold higher than in the general population. Previous studies have reported a VTE frequency ranging from 2% up to 28% in MM patients during treatment with different regimens including thalidomide, in varying timeframes up to 2 years,[11;20] suggesting that the risk seems to depend on concurrent treatments. Especially use of the immunomodulatory agents thalidomide and lenalidomide has been associated with higher VTE risk.[21] ESA use has also been reported as a risk factor for VTE in MM patients taking immunomodulating drugs and in newly diagnosed MM patients, with a relative risk up to 3.4.[12;22] Furthermore, in MM patients taking lenalidomide and dexamethasone, concomitant ESA therapy increased the incidence from 5% to 23%.[11] However, an earlier study in MM patients taking thalidomide did not show a relation between the occurrence of thrombosis and ESA treatment,[14] and a pooled analyses of newly diagnosed MM patients enrolled in

clinical trials in Italy and the United States showed no effect of ESAs on the VTE rate.[23] Our results, taking concomitant anticoagulant and immunomodulating therapy into account, indicated a 1.4-fold increase in VTE in ESA-treated MM patients.

Risk of VTE in MDS patients does not seem much higher than that in the general population, but the contribution of ESAs or other treatments has been investigated infrequently. Available studies in MDS patients found that ESAs did not increase the VTE rate.[24;25] The reported VTE rate for MDS patients receiving lenalidomide in a postmarketing surveillance study was only 0.53%, but there were some signals of an association with ESA use.[26] In line with our results, a later study found an odds ratio of 1.2 with ESA treatment, and concluded that the safety profile of ESAs may be different in MDS patients than in patients with solid tumors.[9] Still, an increased VTE rate has been reported in MDS patients receiving ESAs in combination with thalidomide.[10]

Little is known about the occurrence of MI and stroke in the two patient groups, especially in relation with ESA use. However, compared to an age-matched general population, MM patients have a 1.5- to 2-fold increased risk of arterial thrombosis.[27] ESA treatment has been related to cardiovascular events in general oncology patients and patients with chronic kidney disease. A meta-analysis reported a 1.67-fold (95% CI 1.35-2.06) increased risk of thromboembolic events (a composite of VTE, transient ischemic attack, stroke and MI) in oncology patients treated with ESAs.[4] Only a minority of the studies in this meta-analysis included MM or MDS patients and these were mostly performed before 2002. In patients with chronic kidney disease, ESA use is related to a 1.15-fold increased risk of serious cardiovascular events, with a 1.51-fold increased risk of stroke.[6] Our results also indicate a higher risk of stroke and MI with ESA use in both MDS and MM patients.

A number of mechanisms have been proposed for the increase in cardiovascular events with ESA therapy.[28] The higher blood viscosity induced by ESAs could increase the risk of thrombotic events, but this is mainly reported for above-normal hematocrit levels, such as in patients with polycythemia vera.[29] ESAs also have been associated with vasoconstriction, may activate vascular endothelium, and could increase blood pressure.[30] In addition, ESAs have been associated with pro-thrombotic changes, including increased platelet counts, lower levels of protein C and S, and increased thrombin generation.[31;32]

Our study is notable for the large number of patients identified from population-based registries covering the complete Danish population. As well, the accuracy of a number of ICD-10 codes and quality of VTE diagnosis in the DNPR has been validated and the positive predictive value was found to be very high.[33;34] Furthermore, any misclassification would probably be non-differential and would lead to underestimation, since ICD-10 codes and diagnosis are unlikely to differ by ESA use. A concern is that the exact end date of ESA treatment and its effects are unknown. In our analyses we assumed that patients were exposed from the start of ESA treatment until the end of follow-up. It is noteworthy that sensitivity analyses restricting follow-up to two years yielded similar results.

The validity of our findings also depends on proper adjustment for confounding. Our HRs were adjusted for an array of confounding factors, including comorbidities and concurrent therapies such as anticoagulant therapy and immunomodulating drugs. However, as with all observational studies, residual confounding cannot be excluded.[35] Unfortunately, we lacked detailed information on laboratory parameters, including Hb and platelet values. Because low-risk MDS patients are most often treated with ESAs in clinical practice, we also adjusted for type of MDS in our analyses. If we did assume that higher-risk MDS confers a higher risk of cardiovascular events, the HRs calculated in our study would

likely underestimate the true ESA effect in the MDS patient group. On the other hand, other symptoms not resulting in a specific diagnosis - such as suspected angina pectoris - and estimated prognosis that influence treatment decisions could result in confounding by indication and overestimated HRs. Among MM patients, patients with bone marrow failure, renal failure, and elderly frail patients not appropriate for other treatment typically are treated with ESAs. These more fragile patients are generally at higher risk of any adverse event. If any residual confounding were present, our results were probably overestimated for this group.

In conclusion, we found that ESA use was associated with cardiovascular events in both MDS and MM patients. Identification of patients who will benefit most from ESA treatment is an important goal for future research.

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Appendix

Study population

Multiple Myeloma:	ICD-10: C90.0
Myelodysplastic syndrome:	ICD-10: D46
• standard prognosis:	ICD-10: D46.0, D46.1 and D46.6
• poor prognosis:	ICD-10: D46.2 and D46.5
• other: ICD-10:	D46.4, D46.7 and D46.9

Exposure

Erythropoiesis-stimulating agents:
BOHE10; ATC: B03XA01, B03XA02, B03XA03

Outcomes

VTE:	ICD-8 451.00 and 450.99; ICD-10: I80.1, I80.2, I80.3 and I26
MI:	ICD-8: 410; ICD-10: I21
Stroke:	ICD-8: 431-434; ICD-10: I61, I63, and I64

Covariates

Cardiovascular disease:	ICD-8: 393-398, 400-404, 410-414, 427.09, 427.10, 427.19; ICD-10: I05-I09, I10-I15, I20-I25, I50; ATC: C09, B01AC06, N02BA01, C07, C08, C03, C01DA, C10AA, B04AB, C02.
Chronic kidney disease:	ICD-8: 249.02, 250.02, 582, 583, 584, 590.09, 593.20, 753.10, 753.19, 792; ICD-10: E10.2, E11.2, E14.2, N03, N05, N11.0, N14; N16, N18-N19, N26.9, Q61.1-Q61.4.
Diabetes mellitus:	ICD-8:249-250 (except 249.02 and 250.02); ICD-10: E10-E11 (except E10.2 and E11.2), O24 (except O24.4), H36.0; ATC: A10B, A10A.
Statin use:	ATC: C10AA
Anti-thrombotic therapy:	BOHA03; ATC: B01A
Chemotherapy:	BWHA
Radiation therapy:	BWG
Immunomodulating therapy:	BWHB
Lenalidomide:	BWHB82; ATC: L04AX04
Thalidomide:	BWHB81; ATC L04AX02
Azacitidin:	BWHA256