Consult. Confirm. CONTROL:

with NovoSeven® (Recombinant Factor VIIa) in acquired haemophilia (AH)[1]

Henry, 78 years old, *presented with severe and extensive skin bruising and blood in the stool. Henry had no prior history of bleeding.*

This advertisement is intended for Healthcare Professionals

Your primary treatment objective in AH is to STOP THE BLEED*

NovoSeven® is one of the first-line treatment options in AH based on:†[2,3]

• Rapid bleed control with consistently high efficacy[4-11] • Established tolerability profile[1,4,12-15] • Simple, rapid reconstitution and administration‡ and convenient storage[1]

*Published guidelines also recommend eradicating the inhibitor with immunosuppressive therapy.
†Other first-line haemostatic treatments are also recommended.
‡NovoSeven® vial-to-vial reconstitution 2–5 mins to infuse.

Prescribing Information NovoSeven® Eptacog alfa (activated); recombinant Factor VIIa (rFVIIa) **Please refer to Summary of Product Characteristics for full information. Presentation:** Powder (vial) and solvent (pre-filled syringe) for solution for injection. Available in packs containing 1, 2, 5 or 8 mg rFVIIa (8 mg only available in the UK). **Uses:** Treatment of bleeding episodes and prevention of bleeding during surgery or invasive procedures in patients with:- congenital haemophilia with inhibitors to coagulation FVIII or FIX > 5 BU or who are expected to have a high anamnestic response to FVIII or FIX; - acquired haemophilia; - congenital FVII deficiency; - Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available. **Dosage:** The rFVIIa is dissolved in the accompanying solvent before use. After reconstitution the solution contains 1 mg rFVIIa/ml. Administer by intravenous bolus injection over 2-5 minutes; must not be mixed with infusion solutions or given in a drip. NovoSeven® should be administered as early as possible after the start of a bleeding episode. *Haemophilia A or B with inhibitors or expected to have high anamnestic response* Initial dose of 90 µg/kg body weight. Duration of, and interval between, repeat injections dependent on severity of haemorrhage or procedure/surgery performed. Paediatric population: Clinical experience does not warrant a general differentiation in dosing between children and adults. Children have faster clearance than adults and higher doses may be needed to obtain similar plasma concentrations as in adults. For mild to moderate bleeding episodes (including home therapy): Two dosing regimens can be recommended: i) Two to three injections of 90 µg/kg body weight administered initially at 3-hour intervals. If further treatment is required, one additional dose of 90 µg/kg can be administered. ii) One single injection of 270 µg/kg body weight. Duration of home therapy should not exceed 24 hours. Only after consultation with the haemophilia treatment centre can continued home treatment be considered. For serious bleeding episodes, initial dose 90 µg/kg body weight; dose every two hours until clinical improvement. If continued therapy indicated, dosage interval can be increased successively. Major bleeding episode may be treated for 2-3 weeks or longer if clinically warranted. For invasive procedures/surgery administer initial dose of 90 µg/kg body weight immediately before the procedure. Repeat dose at 2-3 hour intervals for first 24-48 hours. In major surgery continue dosing at 2-4 hour intervals for 6-7 days. Dosage interval may then be increased to 6-8 hours for further 2 weeks. Treatment may be up to 2-3 weeks until healing has occurred. *Acquired haemophilia* Initial dose of 90 µg/kg body weight. Further injections may be given if required. Initial dose interval should be 2-3 hours. Once haemostasis achieved, the dose interval can be increased successively *Factor VII deficiency* For bleeding episodes and for invasive procedures/surgery, in adults and children, administer 15-30 µg/kg body weight every 4-6 hours until haemostasis achieved. Adapt dose and frequency to individual. Limited clinical experience in long term prophylaxis has been gathered in paediatrics below 12 years of age, with severe clinical phenotype. *Glanzmann's thrombasthenia* For bleeding episodes and for invasive procedures/surgery administer 90 µg/kg body weight (range 80-120 µg) every 2 hours (1.5-2.5 hours). At least three doses should be administered to secure effective haemostasis. For patients who are not refractory platelets are first line treatment. In all conditions the dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred. **Contra-indications:** Known hypersensitivity to active substance, excipients, or to mouse, hamster or bovine protein may be a contraindication to the use of NovoSeven®. **Precautions:** Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. For severe bleeds NovoSeven® should only be administered in hospitals specialised in the treatment of patients with coagulation factor FVIII or FIX inhibitors or in close collaboration with a physician specialised in treatment of haemophilia. No clinical experience with administration of single dose of 270 µg/kg body weight in elderly patients. Home therapy should not exceed 24 hours. Possibility of thrombogenesis or induction of DIC in conditions in which tissue factor could be expected in circulating blood, e.g. advanced atherosclerotic disease, crush injury, septicaemia, or DIC. Since NovoSeven® may contain trace amounts of mouse, bovine and hamster proteins there is a remote possibility of the development of hypersensitivity. Monitor FVII deficient patients for prothrombin time and FVII coagulant activity; suspect antibody formation if FVIIa activity fails to reach expected level or bleeding not controlled with recommended doses. Thrombosis in FVII deficient patients receiving NovoSeven® during surgery has been reported but risk is unknown. Avoid simultaneous use of prothrombin complex concentrates, activated or not. Based on a non-clinical study it is not recommended to combine rFVIIa and rFXIII. **Interactions: (Irish requirement only)** Risk of a potential interaction between NovoSeven® and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided. Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is however limited. **Fertility, pregnancy and lactation:** Only administer to pregnant women if clearly needed. Not known if excreted in human milk; a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoSeven® should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven® therapy to the woman. Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility. **Side Effects:** The frequencies of both serious and non-serious adverse drug reactions are: Uncommon (≥ 1/1,000, < 1/100): venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia); rash (including allergic dermatitis and rash erythematous); pruritus and urticaria; therapeutic response decreased - it is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage; pyrexia. Rare (≥1/10,000, <1/1,000): disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT; coagulopathy; hypersensitivity; headache; arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia); angina pectoris; nausea; injection site reaction including injection site pain; increased fibrin degradation products; increase in alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known. Not known: anaphylactic reaction; intracardiac thrombus, flushing; angioedema. *Inhibitory antibody formation:* Post-marketing there have been no reports of inhibitory antibodies against NovoSeven® or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven® has been reported in post-marketing observational registry of congenital FVII deficient patients. Patients with FVII deficiency, formation of antibodies against NovoSeven® and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). Risk factors may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived FVII, severe mutation of FVII gene, and overdose of NovoSeven®. Patients with FVII deficiency treated with NovoSeven® should be monitored for FVII antibodies. *Thromboembolic events:* When NovoSeven® is administered outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (5.6% in patients treated with NovoSeven® versus 3.0% in placebo-treated patients) has been shown in trials conducted outside current approved indications. Safety and efficacy of NovoSeven® have not been established outside approved indications; NovoSeven® should not be used in these cases. Thromboembolic events may lead to cardiac arrest. *Patients with acquired haemophilia:* Clinical trials showed certain adverse drug reactions were more frequent (1% based on treatment episodes): arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products. The Summary of Product Characteristics should be consulted for a full list of side effects. **Marketing Authorisation numbers:** NovoSeven® 1 mg (50 KIU) EU/1/96/006/008 NovoSeven® 2 mg (100 KIU) EU/1/96/006/009 NovoSeven® 5 mg (250 KIU) EU/1/96/006/010 NovoSeven® 8 mg (400 KIU) EU/1/96/006/011 (UK only) **Legal Category:** POM **(UK ONLY)- Basic NHS Price:** NovoSeven® 1 mg £525.20 NovoSeven® 2 mg £1,050.40 NovoSeven® 5 mg £2,626.00 NovoSeven® 8 mg £4,201.60 For complete prescribing information, please refer to The Summary of Product Characteristics which is available: **For Ireland from** - www.medicines.ie or by email from info@novonordisk.ie or from Medical Department, Novo Nordisk Limited, 1st Floor, Block A, The Crescent Building, Northwood Business Park, Santry, Dublin 9, Ireland; Tel: 1 850 665 665 **For UK from** – www.medicines.org.uk or from Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA; Tel: 01293 613555 or Fax: 01293 613535

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Adverse events should be reported. Information about adverse event reporting is available at www.hpra.ie Adverse events should be reported to the Novo Nordisk Medical department; Tel: 1 850 665 665.

UK only

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 600 5055). Calls may be monitored for training purposes.

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NovoSeven® Recombinant Factor VIIa

Survival continues to increase in chronic lymphocytic leukaemia: a population-based analysis among 20 468 patients diagnosed in the Netherlands between 1989 and 2016

Chronic lymphocytic leukaemia (CLL) is the most frequently diagnosed and prevalent form of leukaemia among adults in Western countries (Brenner *et al.*, 2008; Kristinsson *et al.*, 2009; Van den Broek *et al.*, 2012). The gradual increase in life expectancy in Western countries over the past decades is one of the contributing factors that brought about the increasing incidence and prevalence of CLL, particularly among the elderly (Van den Broek *et al.*, 2012). Also, diagnostic procedures have been refined, leading to increased detection of CLL at an earlier stage (Bennett *et al.*, 1989). Besides, the therapeutic armamentarium of CLL has rapidly evolved with improvements in supportive care and risk-adapted therapy, and, more importantly, the advent of purine analogues, anti-CD20 agents, kinase inhibitors, and pro-apoptotic agents (Hallek, 2017). Despite the significant advances in diagnosis, prognostication, and treatment of CLL over the past decades, it is mostly unknown how these advances have impacted the survival of patients with CLL at the population level, especially among contemporarily diagnosed patients.

At present, large, representative population-based studies on this issue are scant and mostly do not encompass patients managed with first- and second-generation anti-CD20 agents, kinase inhibitors, and pro-apoptotic agents (Brenner *et al.*, 2008; Kristinsson *et al.*, 2009; Thygesen *et al.*, 2009; Van den Broek *et al.*, 2012). Therefore, the aim of this contemporary, nationwide, population-based study was to assess trends in short-term and long-term excess mortality among patients with CLL diagnosed during a 28-year period in the Netherlands.

We selected all patients with CLL diagnosed between January 1, 1989 and December 31, 2016 – with follow-up for survival until January 1, 2019 – from the nationwide population-based Netherlands Cancer Registry (NCR), using International Classification of Diseases for Oncology morphology code 9823. Details about the registry are provided in the Supporting Information (Data S1).

Relative survival rates (RSRs) were calculated for four calendar periods of diagnosis (1989–1995, 1996–2002, 2003–2008 and 2009–2016) and four age categories at diagnosis (18–59, 60–69, 70–79 and ≥80 years) and measured from the time of diagnosis to death, emigration, or end of follow-up, whichever occurred first. Relative survival (RS) is the overall survival (OS) in the patient cohort divided by the expected OS of an equivalent group from the general population, matched to the patient group by age, sex, and period (Dickman & Adami, 2006). Multivariable evaluation of RS using Poisson regression was performed to assess linear trends in RS over time and the relative excess risk of mortality. A $P < 0{\cdot}05$ indicated statistical significance. Further details about the statistical analyses are provided in Data S1. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

Baseline characteristics of 20 468 patients with CLL (median age, 69 years; range 21–101 years; 61% males) included in this study are presented in Table SI. The overall age-standardised incidence rate (ASR) of CLL gradually increased over time, but remained comparatively steady from 2003 onwards (Table SI and Figure S1). Throughout the entire study period, a consistent male predominance was observed (Table SI and Figure S1). The age-specific incidence rises sharply with older age (Figure S2).

Patients across all age groups experienced ongoing excess mortality – as compared to the general population – in all calendar periods studied (Figure 1). Nevertheless, RSRs improved with each calendar period across all age groups. The multivariable model confirmed an improvement of RS across all age groups in the most recent calendar period (2009–2016) – as compared to the calendar period 2003–2008 – and showed a poor prognostic effect of male sex (up to age 80) and a previous malignancy before CLL diagnosis (Table I).

In this contemporary, nationwide, population-based study, we demonstrated that the overall ASR of CLL gradually increased until it remained comparatively steady from 2003 onwards. Similar trends were observed in Denmark and Sweden (Kristinsson *et al.*, 2009; Thygesen *et al.*, 2009). The initial increase can probably be explained by several factors. First, general practitioners and hospital-based physicians might nowadays be more diligent in requesting routine blood tests, potentially leading to the enhanced detection of early, asymptomatic CLL. Furthermore, the incidence of CLL might be overestimated, because most patients diagnosed with Rai stage 0 or I before 2008 can be reclassified into monoclonal B-cell leukaemia according to the most recent diagnostic criteria (Hallek *et al.*, 2008). On the other hand, the incidence might be underestimated in these earlier calendar periods, because CLL is most frequently diagnosed by flow cytometry

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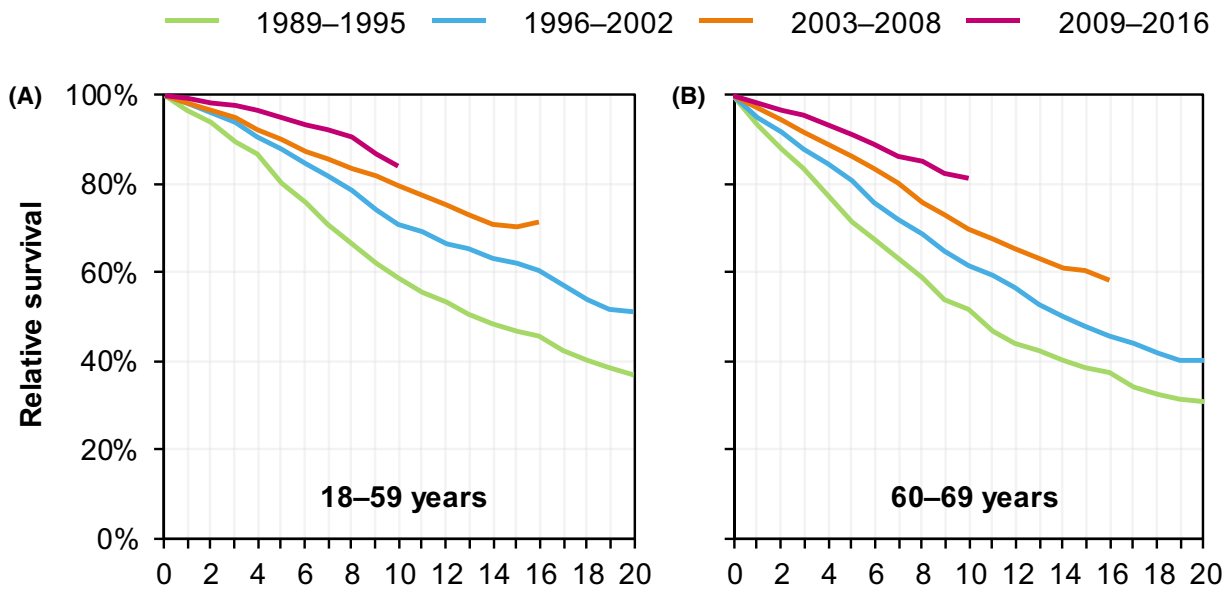
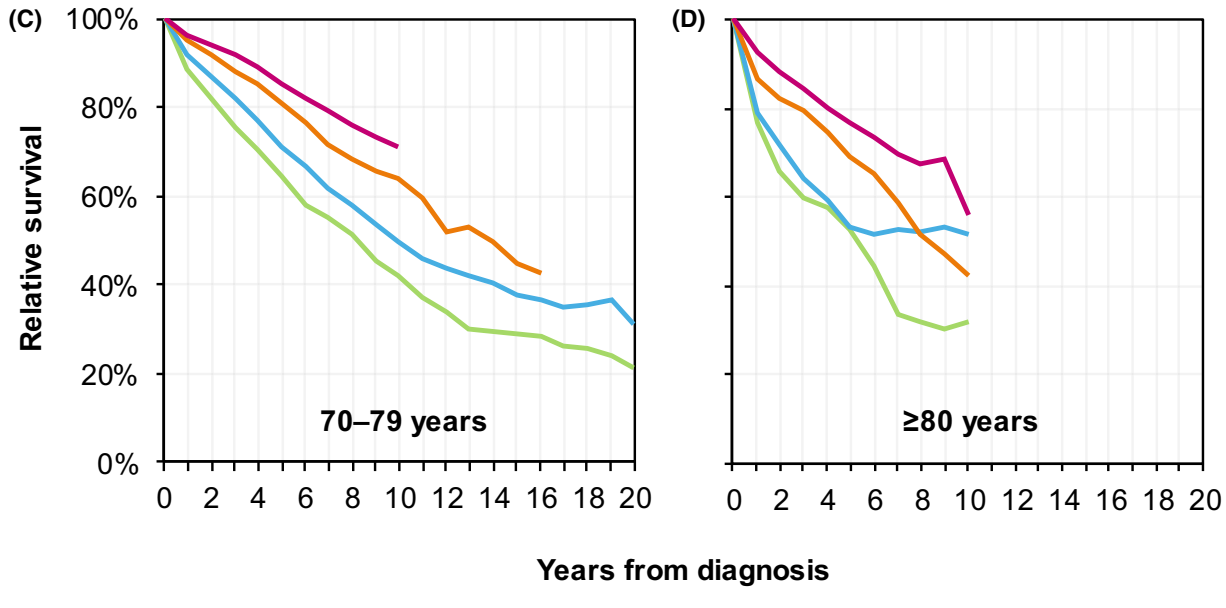


RSR	Calender period				*P* for trend*
	1989–1995	1995–2002		2009–2016	
	RSR (in%) with 95% CI				
5-year	80 (77–84)	88 (86–90)	90 (88–92)	95 (94–96)	<0·001
10-year	59 (54–63)	71 (68–74)	80 (77–82)	84 (79–88)	<0·001

	Calender period				*P* for trend*
	1989–1995	1995–2002	2003–2008	2009–2016	
	RSR (in%) with 95% CI				
5-year	72 (68–75)	81 (78–83)	86 (84–88)	91 (89–93)	<0·001
10-year	51 (48–55)	62 (58–65)	70 (67–73)	81 (77–85)	<0·001



RSR	Calender period				*P* for trend*
	1989–1995	1995–2002	2003–2008	2009–2016	
	RSR (in%) with 95% CI				
5-year	64 (61–68)	71 (68–74)	81 (78–84)	85 (83–88)	<0·001
10-year	42 (37–47)	50 (46–54)	64 (60–68)	71 (64–78)	<0·001

	Calender period				*P* for trend*
	1989–1995	1995–2002	2003–2008	2009–2016	
	RSR (in%) with 95% CI				
5-year	52 (46–59)	53 (47–60)	69 (63–75)	77 (71–82)	<0·001
10-year	32 (23–43)	51 (40–64)	42 (34–52)	56 (37–79)	<0·001

Fig 1. Relative survival of patients with chronic lymphocytic leukaemia diagnosed in the Netherlands according to calendar period of diagnosis and age at diagnosis, 1989–2016. Relative survival is shown for four calendar periods according to the following four age categories: (A) 18–59, (B) 60–69, (C) 70–79, and (D) ≥80 years. The tables present the projected 5- and 10-year relative survival rates (RSRs) with 95% confidence intervals (CIs) according to calendar period of diagnosis for the four age categories. *, *P*-value for likelihood ratio test assessing linear trends between the first and last calendar period. RSRs for patients aged ≥80 years were truncated at 10 years, since comparatively few patients in this age group were alive 10 years after their diagnosis.

Table I. Excess mortality ratio during the first 10 years after chronic lymphocytic leukaemia diagnosis across different age groups.

Age at diagnosis	Covariate	EMR*	95% CI	P†
18–59	Period of diagnosis			
	1989–1995	2·30	1·89–2·80	<0·001
	1996–2002	1·47	1·21–1·79	<0·001
	2003–2008	1	(ref)	
	2009–2016	0·62	0·48–0·81	<0·001
	Female sex	0·65	0·55–0·77	<0·001
	Previous malignancy	1·65	1·21–2·25	0·002
60–69	Period of diagnosis			
	1989–1995	2·00	1·71–2·35	<0·001
	1996–2002	1·40	1·19–1·65	<0·001
	2003–2008	1	(ref)	
	2009–2016	0·59	0·48–0·72	<0·001
	Female sex	0·60	0·52–0·68	<0·001
	Previous malignancy	1·40	1·14–1·72	0·001
70–79	Period of diagnosis			
	1989–1995	2·13	1·80–2·51	<0·001
	1996–2002	1·59	1·35–1·88	<0·001
	2003–2008	1	(ref)	
	2009–2016	0·72	0·60–0·87	0·001
	Female sex	0·59	0·52–0·67	<0·001
	Previous malignancy	1·94	1·67–2·25	<0·001
≥80	Period of diagnosis			
	1989–1995	1·88	1·50–2·34	<0·001
	1996–2002	1·44	1·14–1·82	0·002
	2003–2008	1	(ref)	
	2009–2016	0·58	0·44–0·76	<0·001
	Female sex	0·98	0·83–1·16	0·830
	Previous malignancy	1·49	1·20–1·84	<0·001

EMR, excess mortality ratio; CI, confidence interval.
*All covariates are simultaneously adjusted.
†*P*-values are compared with the reference category.

and most cancer registries primarily rely on pathology reports for case notification (Zent *et al.*, 2001). Thus, although the NCR does not solely rely on pathology reports for case notification, the ascertainment of early, asymptomatic CLL might be underestimated in the NCR in earlier periods (i.e. between 1989 and 2003).

A noteworthy finding of our study was that RS of CLL improved continuously over the calendar periods studied. This finding is congruent with results observed in the paucity of prior population-based studies from the United States (1980–2011), Germany (1997–2011), Denmark (1943–2003) and Sweden (1973–2003). Encouragingly enough, RSRs in the most recent calendar period of our study (2009–2016) surpassed those reported in the aforementioned studies (Brenner *et al.*, 2008; Kristinsson *et al.*, 2009; Thygesen *et al.*, 2009; Pulte *et al.*, 2016). Advances in supportive care (i.e. transfusions, growth factors, and antibiotics) and therapy are key factors that contributed to the improvement in RS over time. However, a normalised plateau in RS has not been reached, suggesting ongoing excess mortality for the overall patient population. Recent progress with kinase inhibitors (e.g. ibrutinib) and pro-apoptotic agents (e.g. venetoclax) might further reduce excess mortality in CLL. However, the benefit of these novel agents cannot be entirely objectivated in this study, since these modalities were not widely implemented for routine application in CLL in the Netherlands during the study period.

The main strengths of our study include the use of a nationwide population-based cancer registry with comprehensive data available for individual patients. Limitations of our study include a lack of information on cytogenetic and molecular diagnostics and treatment throughout most of the registry. Therefore, it is not possible to correct for changes in the classification of CLL over time.

In summary, in this large, contemporary, nationwide population-based study, RS improved significantly over time among patients with CLL across all age groups. The current study provides a benchmark for future research to evaluate the impact of a broader application of kinase inhibitors and anti-apoptotic agents on RS.

Acknowledgements

The authors thank the registration clerks of the NCR for their dedicated data collection. The nationwide population-based NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL).

Conflicts of interest

The authors declare to have no potential conflicts of interest regarding the present work.

Author contributions

AGD and LvdS designed the study; LvdS analysed the data; AGD supervised the data analyses; OV collected the data; LvdS wrote the manuscript with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Age-specific incidence rates of patients with chronic lymphocytic leukaemia in the Netherlands according to age, 1989–2016. Incidence rates are presented per 100 000 person-years and shown according to the following sexes: (A) males and females together, (B) males alone, and (C) females alone.

Figure S2. Age-specific incidence rates of patients with chronic lymphocytic leukaemia in the Netherlands per quinquennial years of age, 2003–2016. Incidence rates are presented per 100 000 person-years and shown according to sex. The period of 2003–2016 was chosen, as the incidence of CLL in the Netherlands remained comparatively steady as from 2003.

Table SI. Patient characteristics.

Data S1. Supplemental methods.

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