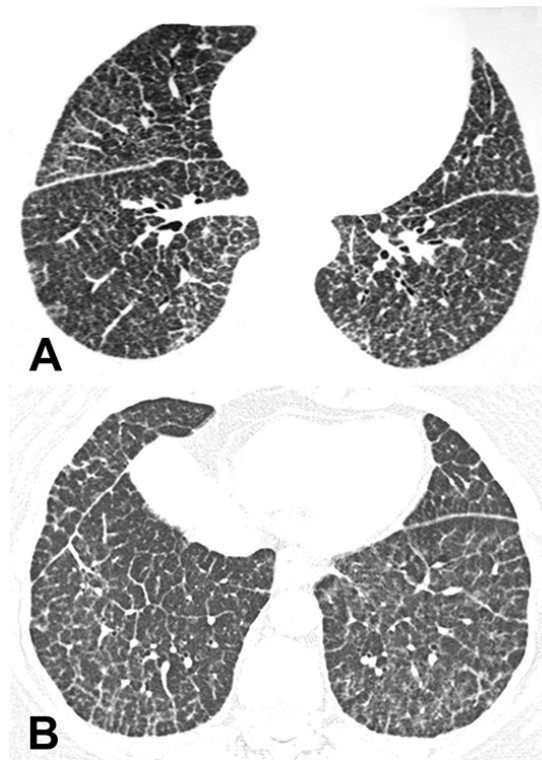


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MODIFIED BOVA SCORE IN PULMONARY EMBOLISM

•  
DISEASE BURDEN OF HCV IN THE NETHERLANDS

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NON-ARTICULAR FELTY'S SYNDROME

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# Continuous intraperitoneal insulin infusion (CIPII) for type 1 diabetes: Effective therapy but a case of bad timing?

J.A.M.J.L. Janssen

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In healthy subjects, insulin secreted by the pancreas is transported to the liver where a relevant amount (30-80%) is retained and degraded.<sup>1</sup> The remaining insulin bypasses the liver and reaches the peripheral tissues through the systemic circulation. As a consequence, in healthy subjects the liver/peripheral tissue insulin concentration ratio ranges from 3:1 up to 9:1 during insulin secretion bursts.<sup>2</sup> In type 1 diabetic patients administration of exogenous insulin is critical to achieve acceptable metabolic control. However, normal physiology is not restored by the standard intermittent subcutaneous (SC) insulin administration or continuous subcutaneous insulin infusions (CSII): with these two treatment options insulin will arrive at the peripheral tissues and the liver in similar concentrations.<sup>2</sup> This results in relative peripheral tissue hyperinsulinaemia and relative liver hypoinsulinaemia, which contrasts with the situation after endogenous insulin secretion.<sup>2</sup> Continuous intraperitoneal insulin infusion (CIPII) has been available for more than 30 years but has only been used in very few patients around the world. With CIPII, insulin is directly infused into the intraperitoneal space where it is absorbed via the capillaries of the visceral peritoneum into the portal vein.<sup>3,4</sup> Because it is absorbed directly into the portal system, there is a more physiological insulin distribution with a high hepatic uptake and relatively low peripheral plasma insulin concentrations compared with SC insulin injections and CSII.<sup>5</sup> Intraperitoneal-administered insulin takes approximately 15 min to reach its peak effect and allows blood glucose values to return to the baseline level more rapidly, producing more physiological insulin profiles compared with SC insulin injections.<sup>6</sup> Other possible positive effects include improvement of the impaired glucagon secretion and enhanced hepatic glucose production in response to hypoglycaemia.<sup>4</sup> In this issue Van Dijk et al. present a prospective observational case-control study in type 1 diabetes patients

in which they compared glycaemic control and quality of life during long-term CIPII therapy with a control group treated with SC insulin therapy.<sup>7</sup> They observed that glycaemic control during CIPII therapy was non-inferior to SC insulin therapy. In addition, the perceived health status among patients treated with CIPII was stable, but was poor compared with the patients treated with SC insulin.<sup>7</sup> Therefore, Van Dijk et al. concluded that at present the costs of CIPII outweigh the advantages of CIPII for the majority of patients and they advocated CIPII only as a last-resort treatment for selected patients with type 1 diabetes.<sup>7</sup> As the authors frankly admitted in the Discussion section of their paper, the non-randomised observational design is an important limitation of their study. In addition, at baseline the CIPII-treated patients in the study by Van Dijk et al., although matched for age and sex, had developed significantly more diabetic microvascular complications and had a longer duration of diabetes (29 vs. 26 years) than the SC control group.<sup>7</sup> This could – at least partly – explain the lower perceived health status in the CIPII-treated patients compared with the SC insulin group.

CIPII is usually started late in the course of diabetes in highly selected populations with often a rather complex background and disease history. Most of these patients have 'brittle diabetes', i.e. failure to reach adequate glycaemic control despite intensive insulin therapy with multiple daily injections (MDI) or CSII and/or having frequent hypoglycaemic episodes. This was also the case for the patients included in the study by Van Dijk et al.<sup>7</sup> In spite of inclusion of highly selected populations in most studies, a systematic review of the literature showed that CIPII is effective in type 1 diabetes in lowering and maintaining HbA1c levels, with strong evidence from randomised studies but low evidence from observational studies.<sup>8</sup> Shisko et al. demonstrated that the route of insulin delivery plays an important role in glycaemic control.<sup>9</sup> They compared the effects of CIPII (via the umbilical vein)

with insulin administered as CSII and with 'standard' intermittent SC therapy in 36 newly diagnosed young type 1 diabetes (i.e. diabetes duration of 1-3 weeks).<sup>9</sup> Six months after the start of treatment, glycaemic control was almost normal in the patients in the CII group compared with those in the CSII group (HbA<sub>1c</sub>: 5.3% vs. 7.9%).<sup>9</sup> In addition, glycaemic excursions and the frequency of hypoglycaemia was significantly less during CII than with CSII. Moreover, CII was more effective than CSII in elevating total insulin-like growth factor-I (IGF-I) levels and decreasing IGF-binding protein-1 (IGFBP-1) levels and growth hormone (GH) secretion than CSII while it has recently been reported that the IGF-I bioactivity, which is more sensitive for monitoring the effects of therapeutic interventions than total IGF-I, was higher (i.e. more normal) in patients treated with CII compared with CSII.<sup>9,10</sup> This shows that the route of insulin administration also plays an important role in the normalisation of the GH-IGF-I axis in type 1 diabetes. It has been further hypothesised that the low circulating IGF-I bioactivity in type 1 diabetes usually observed during SC insulin therapy results in chronically insufficient protective effects by IGF-I in the kidneys, eyes and neurons, and thus the progression of diabetic microvascular complications with ageing.<sup>11</sup> Therefore, intraperitoneal insulin administration may not only be beneficial by improving glucose control but also by correcting the alterations in the IGF system in type 1 diabetes.<sup>12</sup>

In their paper, Van Dijk et al. concluded that for the majority of patients the actual costs of CII in the management of type 1 diabetes seem, at the moment, to outweigh the advantages of CII. They advocated the use of CII only as a last-resort treatment option for highly selected patients with type 1 diabetes, who have been unable to reach the current treatment goals with current SC insulin therapy.<sup>7</sup> However, many years of poor metabolic control of type 1 diabetes – as was already present at baseline in the diabetic patients included in the study by Van Dijk et al. – may have induced long-lasting harmful effects. These effects will not be arrested promptly and/or recovered completely after the start of CII. From epidemiological studies, it has become clear that after many years of poor metabolic control, there is less opportunity to positively influence the development and progression of diabetic complications in type 1 diabetes. On the contrary, based on the long-term results of the DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC) study, the concept of glycaemic legacy has been proposed: strict glycaemic control in the very early phase of type 1 diabetes generates a legacy effect that may confer protection against or a delay in the long-term diabetic complications.<sup>13,14</sup> By mimicking more normal physiological insulin secretion

than current therapies, CII is in my opinion still a promising treatment option for type 1 diabetes that once again deserves clinical attention. However, until now, the long-term effects of CII treatment when initiated at the very start of type 1 diabetes have never been studied. Therefore, new well-designed studies should be initiated to determine whether CII treatment started early in the course of diabetes can decrease morbidity and improve quality of life and in the long-term – compared with current treatment options – is superior in reducing diabetes complications.

## DISCLOSURES

None.

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# Intraperitoneal versus subcutaneous insulin therapy in the treatment of type 1 diabetes mellitus

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## ABSTRACT

**Background:** Continuous intraperitoneal insulin infusion (CIPII), a last-resort type 1 diabetes mellitus (T1DM) treatment, has only been investigated in small or controlled studies. We aimed to investigate glycaemia and quality of life (QoL) with CIPII versus subcutaneous (SC) insulin therapy during usual T1DM care.

**Methods:** A prospective, observational case-control study. CIPII-treated cases were matched to SC controls. The primary endpoint was a non-inferiority assessment (pre-defined margin of -5.5 mmol/mol) of the baseline adjusted difference in HbA1c between groups during a 26-week follow-up. Secondary outcomes included QoL, clinical and biochemical measurements.

**Results:** In total, 183 patients were analysed (CIPII n = 39 and SC n = 144). The HbA1c difference between treatment groups was -3.0 mmol/mol (95% CI -5.0, -1.0), being lower in the SC group. Patients using SC insulin therapy spent less percentage of time in hyperglycaemia (-9.3% (95% CI -15.8, -2.8)) and more in euglycaemia (6.9% (95% CI 1.2, 12.5)) as compared with CIPII-treated patients. Besides a 3.6 U/l (95% CI 1.2, 6.0) lower concentration of alanine aminotransferase with CIPII, no biochemical and clinical differences were present. Most QoL scores were lower at baseline among CIPII-treated patients. However, besides lower health status, there were no differences in the baseline-adjusted general and diabetes-specific QoL and treatment satisfaction.

**Conclusion:** Although patients using CIPII had a higher glycaemic profile compared with patients using SC insulin

therapy, the HbA1c difference was non-inferior. Overall, health status was lower among CIPII-treated patients, although diabetes-specific QoL and treatment satisfaction was similar to subcutaneously treated patients.

## KEYWORDS

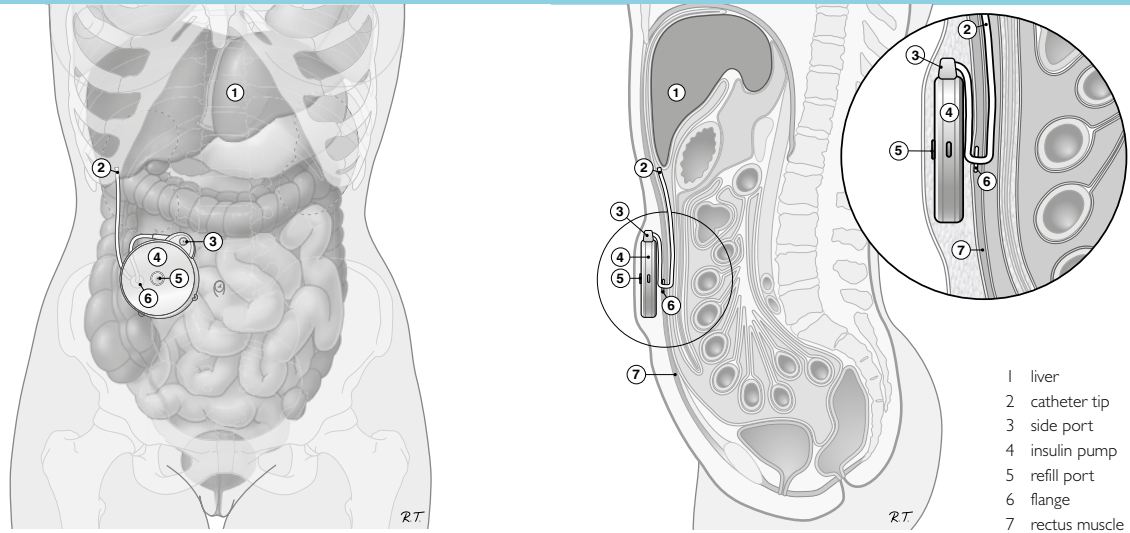
Glycaemia, intraperitoneal insulin, subcutaneous insulin, type 1 diabetes mellitus, quality of life

## INTRODUCTION

Treatment of type 1 diabetes mellitus (T1DM) consists of insulin administration or pancreas (islet cells) transplantation. In most patients, insulin is administered subcutaneously using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) using an external pump. Although most patients achieve acceptable glycaemic control using subcutaneous (SC) insulin, some patients fail to reach adequate glycaemic control or have frequent hypoglycaemic episodes.<sup>1</sup> Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump (*figure 1*) is a treatment option for such patients.

Of the three randomised clinical studies that compared CIPII with SC insulin treatment in T1DM patients, two reported short-term HbA1c improvements of 8 to 14 mmol/mol [0.76 to 1.28%] without an increase in hypoglycaemic episodes and one did not find any differences between



**Figure 1.** Illustration of the implantable pump system in situ (derived from Haveman et al.<sup>28</sup>).

therapies.<sup>2-4</sup> CIPII has also been reported to lead to small improvements in health status, general quality of life (QoL) and treatment satisfaction as compared with SC therapy.<sup>5,6</sup> Nevertheless, during the subsequent six years of follow-up among patients treated with CIPII, the short-term improvements in both HbA<sub>1c</sub> and QoL reported in the randomised studies disappeared and levelled with the values these patients had during intensive SC insulin therapy, while improvements in the number of hypoglycaemic episodes and treatment satisfaction remained present.<sup>7</sup>

Since CIPII with an implantable pump is currently an invasive and costly treatment for selected patients, there is a clear need for data regarding the effects of treatment with CIPII as compared with SC insulin therapy during usual care. However, available randomised studies have a short duration (9 to 16 months) and a small number of selected participants (n = 10 to 24), and most available observational studies lack a sufficiently powered control group.<sup>8-10</sup> In order to gain more information about glycaemic control, QoL and level of treatment satisfaction among T1DM patients treated with CIPII versus SC insulin therapy during usual care circumstances, we performed a prospective, observational case-control study.

## MATERIALS AND METHODS

### Study design

An investigator-initiated, prospective, observational matched case-control study to compare the effects of CIPII versus SC insulin therapy on glycaemic control, QoL (including perceived health status, emotional well-being and diabetes-related QoL and diabetes-specific distress) and treatment satisfaction. The study was designed to test the

hypothesis that CIPII would be non-inferior to SC insulin therapy in T1DM patients during a 26-week follow-up period. Patient recruitment took place in Isala (Zwolle, the Netherlands) and the Diaconessenhuis Hospital (Meppel, the Netherlands).

### Patient selection

Cases were subjects on CIPII therapy using an implanted insulin pump (MIP 2007D, Medtronic/Minimed, Northridge, CA, USA) for the past four years without interruptions of > 30 days, in order to avoid effects related to initiating therapy. Inclusion criteria for cases to participate in this study were identical to those of a prior study in our centre and have been described in detail previously.<sup>2</sup> In brief, patients with T1DM, aged 18 to 70 years with an HbA<sub>1c</sub> ≥ 58 mmol/mol (7.5%) or ≥ 5 incidents of hypoglycaemia glucose (< 4.0 mmol/l) per week, were eligible.

The SC control group was age and gender matched to the cases and consisted of both MDI and CSII users. Eligibility criteria for controls were T1DM, SC insulin as mode of insulin administration for the past four years without interruptions of > 30 days, HbA<sub>1c</sub> at time of matching ≥ 53 mmol/mol (7.0%) and sufficient mastery of the Dutch language.

Exclusion criteria for the present study for both cases and controls included: impaired renal function (plasma creatinine ≥ 150 μmol/l or Cockcroft-Gault ≤ 50 ml/min), cardiac problems (unstable angina or myocardial infarction within the previous 12 months or NYHA class III or IV congestive heart failure), cognitive impairment, current or past psychiatric treatment for schizophrenia, cognitive or bipolar disorder, current use of oral corticosteroids or suffering from a condition which necessitated corticosteroid use more than once in

the previous 12 months, alcohol or drug abuse, current gravidity or plans to become pregnant during the study. If patients were eligible to act as SC controls, they were matched to the CIPII-treated cases based on gender and age. The ratio of participants on the different therapies (CIPII:MDI:CSII) was 1:2:2.

### Study procedures

There were four study visits. During visit 1, baseline characteristics were collected and a continuous glucose measurement (CGM) system was inserted for a period of six days. Furthermore, questionnaires were handed out and patients were asked to fill in the questionnaires concerning QoL and treatment satisfaction at home. During visit 2 (5 to 7 days later) laboratory measurements were performed, the CGM system was removed and the questionnaires were collected. During visit 3 and 4, 26 weeks after visit 1 and 5 to 7 days after visit 3, respectively, the procedures of visit 1 and 2 were repeated. During the study period all patients received usual care.

### Measurements

Demographic and clinical parameters were collected using a standardised case record form. Blood pressure was measured using a blood pressure monitor (M6 comfort; OMRON Healthcare). HbA<sub>1c</sub> was measured with a Primus Ultra2 system using high-performance liquid chromatography (reference value 20-42 mmol/mol [4.0-6.0%]). The six-day 24-hour interstitial glucose profiles were recorded using a blinded CGM device (iPro2, Medtronic, Northridge, CA, USA), inserted in the periumbilical area. Time spent in hypoglycaemia was defined as the percentage of CGM readings < 4.0 mmol/l, time in euglycaemia as the percentage of CGM readings from 4.0 to 10.0 mmol/l and time spent in hyperglycaemia as the percentage of CGM readings > 10.0 mmol/l.

Perceived health status was assessed using the 36-item Short-Form Health Survey (SF-36). Both scale and component scores (ranging from 0 to 100) were calculated.<sup>11</sup> Emotional well-being was assessed using the World Health Organisation-Five Well-Being Index (WHO-5, range 0 to 100; higher scores indicating better QoL).<sup>12-14</sup> Diabetes-related QoL was measured using the Diabetes-Related QoL (DQOL) questionnaire with four scales (range 0 to 100; higher scores indicating better QoL).<sup>15,16</sup> Diabetes-specific distress was measured using the 20-item Problem Areas In Diabetes (PAID) (range 0 to 100; higher scores indicating greater emotional distress). Treatment satisfaction was measured with the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Two DTSQ items assess perceived frequency of hyperglycaemia and hypoglycaemia, and six items comprise the treatment satisfaction scale (range 0-36; higher scores indicating higher satisfaction).<sup>17</sup>

### Outcome measures

Since CIPII is a last-resort treatment option for T1DM, CIPII-treated patients are a highly selected population with a rather complex background and disease history. In order to account for this inequality between the two treatment groups (CIPII versus SC insulin therapy), the primary endpoint was powered based on a non-inferiority assessment of the difference in HbA<sub>1c</sub> during a 26-week period, taking possible baseline differences between groups into account. Secondary outcomes included differences in QoL, treatment satisfaction and clinical and biochemical measurements. In addition, comparisons between CIPII and patients using MDI and CSII were made.

### Statistical analysis

The criteria for non-inferiority required that the upper limits of the 95% confidence intervals (CI) were above the predefined margin for the difference in HbA<sub>1c</sub>. Based on the results of previous randomised clinical trials and discussion with experts, a non-inferiority margin of -5.5 mmol/mol [-0.5%] was chosen.<sup>2-4</sup> According to a pre-specified protocol, both per protocol and intention-to-treat analysis for the primary outcome were performed. A regression model based on covariate analysis (ANCOVA) was applied in order to adjust for possible baseline imbalance in HbA<sub>1c</sub>. In the model the fixed factors CIPII and SC insulin therapy were used as determinants. The difference in scores was determined based on the  $\beta$ -coefficient of the particular (CIPII or SC, MDI or CSII) group. Significance of the  $\beta$ -coefficient was investigated with the Wald test based on a  $p < 0.05$ . The quantity of the  $\beta$ -coefficient, with a 95% CI, gives the difference between the two treatment modalities over the study period adjusted for baseline differences.

With the use of a standard deviation (SD) of 0.9%, estimated from a previous randomised study, and a non-inferiority margin of -5.5 mmol/mol [-0.5%], we calculated that we would need to enrol 175 patients (35 CIPII, 140 SC insulin therapy) to show non-inferiority of CIPII therapy at a one-sided alpha level of 0.025.<sup>2</sup> In order to compensate for loss to follow-up, intended group sample sizes were 40 and 150, respectively.

Analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.) and STATA (Stata Corp., College Station, TX: version 12). Results were expressed as mean (SD) or median (interquartile range [IQR]) for normally distributed and non-normally distributed data, respectively. A significance level of 5% was used.

### Ethical considerations

The study protocol was registered prior to the start at the appropriate local (NL41037.075.12) and international (NCT01621308) registers. The study protocol was approved



by the local medical ethics committee and all patients gave informed consent.

## RESULTS

### Patients

From December 2012 to August 2013, a total of 335 patients were screened and received information about the study, of which 190 (57%) agreed to participate (*appendix 1*). After baseline laboratory measurements, two patients were excluded due to impaired renal function and four due to C-peptide concentrations of > 0.2 nmol/l. Consequently, 184 T1DM patients commenced the 26-week study period. After the first visit, one patient withdrew informed consent

due to lack of interest. Therefore, 183 patients were analysed. Baseline characteristics are presented in *table 1*.

### Glycaemic control

Within the group of CIPII-treated patients, HbA1c did not significantly change during the study period while it decreased by -1.0 mmol/mol (95% CI -1.9, -0.1 mmol/mol) [-0.09%, 95% CI -0.17, -0.01] among patients using SC insulin therapy (*table 2*). Taking baseline differences into account, the difference between treatment groups was -3.0 mmol/mol (95% CI -5.0, -1.0 mmol/mol) [-0.27%, 95% CI -0.46, -0.09] and met the non-inferiority criterion of -5.5 mmol/mol [-0.5%]. The results of the intention-to-treat analyses did not differ from the per-protocol analysis

**Table 1. Baseline characteristics**

Characteristic	All (n = 184)	CIPII (n = 39)	SC (n = 145)
Male sex (%)	67 (36)	14 (36)	53 (37)
Age (years)	50 (12)	50 (12)	50 (12)
Current smokers (%)	78 (43)	20 (51)	58 (40)
BMI (kg/m <sup>2</sup> )	26.4 (4.5)	25.9 (4.4)	26.5 (4.6)
Systolic blood pressure (mmHg)	137 (19)	138 (17)	136 (19)
Diastolic blood pressure (mmHg)	80 (11)	83 (10)	79 (11)*
Diabetes duration (years)	26 (13)	29 (10)	26 (13)
Microvascular complication present (%)	87 (47)	25 (64)	62 (43)*
- Retinopathy (%)	64 (35)	17 (44)	47 (32)
- Neuropathy (%)	53 (29)	20 (51)	33 (23)*
- Nephropathy (%)	5 (3)	2 (5)	3 (2)
Macrovascular complication present (%)	26 (14)	7 (18)	19 (13)
Creatinine (µmol/l)	69 (13)	70 (12)	69 (13)
ALAT (U/l)	18 [14, 24]	20 [15, 24]	18 [14, 25]
Total cholesterol (mmol/l)	4.8 (0.9)	4.9 (1.0)	4.8 (0.8)
Urine albuminuria:creatinine ratio (mg/mmol)	0.9 [0.5, 1.8]	1.2 [0.5, 1.8]	0.9 [0.4, 1.7]
Total insulin dose (IU/day)	46 [36, 64]	55 [42, 73]	45 [35, 62]*
Fasting glucose (mmol/l) <sup>a</sup>	8.6 (3.7)	8.4 (3.8)	8.6 (3.7)
HbA1c (mmol/mol)	64 (11)	67 (14)	63 (9)
HbA1c (%)	8.0 (1.0)	8.3 (1.3)	7.9 (0.8)
Hypoglycaemia grade 1 <sup>b</sup>	1 [0, 4]	2 [0, 4]	1 [0, 4]
Hypoglycaemia grade 2 <sup>c</sup>	2 [0, 4]	1 [0, 2]	2 [1, 4]

Data are presented as n (%), mean (SD) or median [IQR]. Variables may not add up because of rounding off. \*p < 0.05 as compared with CIPII, p-values are based on appropriate parametric and non-parametric tests. <sup>a</sup>Based on n = 32 (CIPII) and n = 116 (SC), <sup>b</sup>defined as the number of blood glucose values < 4.0 mmol/l during the last 2 weeks, <sup>c</sup>defined as the number of blood glucose values < 3.5 mmol/l during the last 2 weeks. ALAT = alanine aminotransferase; BMI = body mass index; CIPII = continuous intraperitoneal infusion; SC = subcutaneous.

**Table 2.** Outcomes of glycaemic control during baseline visit, changes within and differences between the CIPII and SC insulin therapy groups

	CIPII Start	Change within CIPII group	SC Start	Change within SC group	Difference between SC and CIPII (adjusted for baseline)
HbA <sub>1c</sub> (mmol/mol)	67 (14.2)	1.4 (-0.7, 3.6)	63 (8.7)	-1.0 (-1.9, -0.1)	-3.0 (-5.0, -1.0)*
HbA <sub>1c</sub> (%)	8.3 (1.3)	0.13 (-0.06, 0.33)	7.9 (0.8)	-0.09 (-0.17, -0.01)	-0.27 (-0.46, -0.09)*
Fasting glucose (mmol/l) <sup>a</sup>	8.4 (3.8)	0.2 (-1.8, 2.3)	8.6 (3.7)	1.0 (0.1, 1.9)	1.0 (-0.6, 2.6)
Total insulin dose (IU/day)	55 [42, 73]	-4.1 (-12.0, 3.8)	45 [35, 62] <sup>†</sup>	-1.3 (-3.2, 0.6)	-0.1 (-5.1, 5.0)
Hypoglycaemia grade 1 <sup>b</sup>	2 [0, 4]	-1.6 (-2.8, 0.4)	1 [0, 4]	-1.2 (-1.7, -0.7)*	0.2 (-0.5, 0.9)
Hypoglycaemia grade 2 <sup>c</sup>	1 [0, 2]	0.8 (-0.2, 1.8)	2 [1, 4]	0.1 (-0.6, 0.7)	0.2 (-1.0, 1.3)
Time spent in hypoglycaemia (%)	2 [0, 7]	0.3 (-1.8, 2.4)	6 [2, 11] <sup>†</sup>	1.0 (-1.2, 3.3)	3.2 (-1.0, 7.4)
Time spent in hyperglycaemia (%)	46 [36, 67]	1.4 (-5.6, 8.5)	39 [29, 50] <sup>†</sup>	-1.3 (-4.5, 1.9)	-9.3 (-15.8, -2.8)*
Time spent in euglycaemia (%)	49 [30, 59]	-1.7 (-8.3, 4.8)	54 [44, 62]	0.2 (-2.7, 3.2)	6.9 (1.2, 12.5)*

Baseline data are presented as mean (SD) or median [IQR]. Data of changes within groups and differences between the (SC vs CIPII insulin therapy) groups adjusted for baseline differences are means (95% CI). <sup>†</sup>p < 0.05 as compared with CIPII at baseline. \*p < 0.05. <sup>a</sup>Based on n = 36 (CIPII) and n = 137 (SC), <sup>b</sup>defined as the number of blood glucose values < 4.0 mmol/l during the last 2 weeks, <sup>c</sup>defined as the number of blood glucose values < 3.5 mmol/l during the last 2 weeks. CIPII = continuous intraperitoneal infusion; SC = subcutaneous.

(*appendix 2*). The number of grade 1 hypoglycaemic episodes during the last two weeks decreased by -1.2 (95% CI -1.7, -0.7) among patients with SC insulin. Patients using SC insulin therapy spent -9.3% (95% CI -15.8, -2.8) less percentage of time in hyperglycaemia and 6.9% (95% CI 1.2, 12.5) more in euglycaemia as compared with CIPII-treated patients.

#### Clinical and biochemical measurements

During follow-up, a new macrovascular complication was diagnosed in three patients: one patient treated with CIPII had angina pectoris, one patient using MDI had a transient ischaemic attack and one patient using CSII had a myocardial infarction. Two patients had a new microvascular complication: nephropathy in one patient using MDI and retinopathy in one patient using CSII. Taking baseline differences into account, CIPII-treated patients had 3.6 U/l (95% CI 1.2, 6.0) lower alanine-aminotransferase (ALAT) concentrations as compared with patients treated with SC insulin therapy.

#### Perceived health status, emotional well-being, diabetes-related QoL, diabetes-specific distress and treatment satisfaction

No differences within groups were observed during the study regarding perceived health status, emotional well-being, diabetes-related QoL, diabetes-specific distress and treatment satisfaction (*table 3*). After adjustment for baseline differences, the SF-36 subscales for social

functioning, role limitations due to physical functioning, vitality, bodily pain and general health were lower among patients treated with CIPII as compared with patients treated with SC insulin. In addition, both component scores were lower. After correction for baseline differences, there were no differences in the WHO-5, DQOL and PAID scores. The percentage of patients with a WHO-5 score indicative of depression was higher among CIPII-treated patients as compared with the SC treatment group: 37% vs. 28% at visit 1 and 47% vs. 24% at visit 2 (p < 0.05 for both). Based on the DTSQ questionnaires, subjects on CIPII reported to perceive less hypoglycaemic events than subjects on SC insulin therapy: 0.7 (95% CI 0.1, 1.2).

#### CIPII versus MDI and CSII

Subgroup analysis comparing patients using MDI (n = 70) and CSII (n = 74) as SC mode of insulin therapy versus CIPII-treated patients are presented in *appendix 3*. In comparison with the CIPII group, MDI and CSII users had a lower HbA<sub>1c</sub> (-3.2 mmol/mol, 95% CI -5.9, -0.4 mmol/mol [-0.29%, 95% CI -0.54, -0.04] for MDI users and -2.8 mmol/mol, 95% CI -5.5, -0.1 mmol/mol [-0.26%, 95% CI -0.5, -0.01] for CSII users, respectively) and spent less time in hyperglycaemia (-10.3%, (95% CI -17.6, -3.0) for MDI users and -8.6% (95% CI -15.5, -1.7) for CSII users, respectively) after adjustment for baseline differences. In addition, MDI users spent 8.2% (95% CI 2.0, 14.5) more time in the euglycaemic range than CIPII-treated patients. Perceived health status scores were lower for CIPII-treated

**Table 3.** Outcomes of QoL and treatment satisfaction during baseline visit, changes within and differences between the CIPII and SC insulin therapy groups

	CIPII Start	Change within CIPII group	SC Start	Change within SC group	Difference between SC and CIPII (adjusted for baseline)
<b>SF-36 Subscales</b>					
Physical functioning	71 (23)	-1.9 (-8.3, 4.4)	86 (18) <sup>†</sup>	-0.2 (-2.5, 2.1)	4.8 (-0.8, 10.4)
Social functioning	70 (25)	-2.3 (-10.5, 4.4)	82 (20) <sup>†</sup>	1.2 (-2.2, 4.6)	9.6 (2.6, 16.6)*
Role limitations-physical	42 (42)	-2.3 (-20.1, 15.4)	77 (35) <sup>†</sup>	1.0 (-5.2, 7.2)	23.8 (10.0, 37.6)*
Role limitations-emotional	76 (40)	-2.1 (-17.9, 13.8)	87 (30)	-0.8 (-5.8, 4.2)	5.7 (-5.1, 16.5)
Mental health	79 (17)	-1.9 (-6.3, 2.4)	77 (15)	-0.4 (-2.7, 1.9)	0.5 (-3.7, 4.7)
Vitality	52 (19)	-3.2 (-11.3, 4.9)	63 (19) <sup>†</sup>	0.8 (-2.1, 3.5)	9.7 (3.7, 15.6)*
Bodily pain	65 (23)	-8.6 (-17.0, -0.3)	78 (23) <sup>†</sup>	1.5 (-2.3, 5.2)	15.2 (7.7, 22.7)*
General health	48 (19)	-2.6 (-7.6, 2.4)	62 (19) <sup>†</sup>	0.3 (-2.3, 2.9)	7.3 (2.1, 12.6)*
<b>SF-36 Component scores</b>					
MCS	65 (18)	-2.6 (-8.6, 3.4)	74 (17) <sup>†</sup>	1.0 (-1.1, 3.2)	6.9 (2.4, 11.3)*
PCS	58 (19)	-3.6 (-10.1, 2.9)	75 (17) <sup>†</sup>	1.1 (-1.1, 3.4)	9.6 (4.2, 15.0)*
<b>WHO-5</b>					
Total score	54 (22)	1.9 (-3.1, 6.9)	63 (19) <sup>†</sup>	64 (18)	2.9 (-2.6, 8.5)
<b>DQOL</b>					
Satisfaction	53 (14)	4.2 (-0.8, 9.2)	58 (10) <sup>†</sup>	-0.4 (1.8, 1.1)	-2.6 (-5.8, 0.7)
Impact of diabetes	51 (8)	0.5 (-1.4, 2.5)	54 (8) <sup>†</sup>	0.1 (-0.8, 1.0)	0.2 (-1.8, 2.1)
Diabetes worry	69 (21)	0.6 (-6.9, 8.1)	73 (16)	0.1 (-3.9, 2.3)	3.5 (-7.5, 14.6)
Social worry	47 (30)	2.2 (-10, 14)	52 (28)	2.9 (-2.8, 8.7)	0.8 (-5.4, 7.1)
<b>DTSQ</b>					
Perceived hyperglycaemia score	4.0 (1.6)	0.0 (-0.7, 0.7)	3.8 (1.5)	-0.2 (-0.4, 0.1)	-0.2 (-0.7, 0.4)
Perceived hypoglycaemia score	2.5 (1.4)	-0.3 (-0.9, 0.3)	2.9 (1.5)	0.2 (-0.1, 0.5)	0.7 (0.1, 1.2)*
Total score	31.1 (3.5)	0.4 (-1.0, 1.8)	29.3 (4.5) <sup>†</sup>	-0.1 (-0.8, 0.7)	-1.1 (-2.5, 0.4)
<b>PAID</b>					
Total score	24 (14)	-3.1 (-6.9, 0.7)	21 (14)	-0.1 (-2.1, 2.0)	2.4 (-1.7, 6.5)
Baseline data are presented as mean (SD) or median [IQR]. Data of changes within groups and differences between the (SC vs CIPII insulin therapy) groups adjusted for baseline differences are means (95% CI). Missing data: SF-36 data incomplete for 18 (CIPII n = 4, SC n = 14) patients, DQOL data incomplete for 18 (CIPII n = 4 and SC n = 14) patients, DTSQ data incomplete for 25 (CIPII n = 5, SC n = 5) patients and PAID data incomplete for 29 (CIPII n = 8, SC n = 21) patients. <sup>†</sup> p < 0.05 as compared with CIPII at baseline. *p < 0.05. CIPII = continuous intraperitoneal insulin infusion; DQOL = Diabetes Quality of life; DTSQ = Diabetes Treatment Satisfaction questionnaire; PAID = Problem Areas in Diabetes; MCS = Mental Component Score; PCS = Physical Component Score; SC = subcutaneous; SF-36 = 36-item short-form health survey; PAID = Problem Areas In Diabetes.					

patients as compared with both MDI and CSII users. In addition, CIPII-treated patients had a lower score on the perceived hypoglycaemia score, as compared with both MDI and CSII users.

## DISCUSSION

The aim of the present study was to compare glycaemic control and QoL data from T1DM patients treated with

long-term CIPII therapy relative to a control group of patients treated with SC insulin therapy during usual care. According to the study protocol, the HbA1c difference between the two treatment groups was assessed using a non-inferiority method. Although the HbA1c difference of -3.0 mmol/mol (95% CI -5.0, -1.0) [-0.27%, 95% CI -0.46, -0.09] between the groups was negative, implying a lower HbA1c for subcutaneously treated patients, the 95% CI remained above the predefined margin of -5.5 mmol/mol [-0.5%]. Therefore, it should be concluded that CIPII is

non-inferior to SC insulin therapy with respect to HbA<sub>1c</sub> in the treatment of T1DM during usual care circumstances. The effects of CIPII versus SC insulin therapy on glycaemia have been described previously in three randomised studies. After six months of cross-over treatment with CIPII and SC insulin, Haardt et al. reported a difference of 14 mmol/mol [1.28%] in favour of CIPII, with a reduction of glycaemic fluctuations and hypoglycaemic episodes.<sup>4</sup> A previous cross-over study in our centre among 24 T1DM patients found an HbA<sub>1c</sub> decrease of 8 mmol/mol [0.76%], with 11% more time spent in euglycaemia without a change in hypoglycaemic events, in favour of CIPII.<sup>2</sup> Subsequent observational studies among CIPII-treated patients found stabilisation of the HbA<sub>1c</sub> during long-term follow-up at an equal or lower level than before initiation of CIPII.<sup>7-9,18</sup> The results of the present study extend the literature by providing a sufficiently powered assessment of the glycaemic status during real-life circumstances among T1DM patients treated long-term with CIPII, relative to a SC insulin therapy control group. Although the difference in HbA<sub>1c</sub> was non-inferior, it should be noted that patients treated with CIPII had a higher glycaemic profile compared with patients treated with SC insulin therapy.

During the aforementioned cross-over study in our centre, perceived health status and general QoL improved during six months of CIPII as compared with SC insulin therapy.<sup>6</sup> During the subsequent six years of follow-up, the perceived health status among these CIPII-treated patients was stable.<sup>7</sup> The present study adds to these observations by demonstrating that the perceived health status among patients treated with CIPII is stable, but remains poor as compared with matched subjects treated with SC insulin therapy. In contrast to the perceived health status, we found no differences in general and diabetes-related aspects of QoL and the total treatment satisfaction scores between CIPII and SC insulin therapy, after adjustment for baseline differences. This discrepancy may suggest that, although the presence of microvascular complications may be of influence, the poorly perceived health status among these patients is not due to their diabetes *per se* but that probably other factors also have an important influence. Possible factors may include poor social functioning, limited support or more (perceived) physical limitations and pain. Additionally, the presence of the personality traits and psychiatric symptoms, identified previously by De Vries et al. and emphasised in the present study by the high number of CIPII patients with a WHO-5 score indicative for depression, may explain this discrepancy.<sup>19</sup>

The presence of frequent hypoglycaemic episodes (often combined with hypoglycaemia unawareness) is an indication for initiation of CIPII and intraperitoneal insulin administration results in more predictable glucose profiles

and a restoration of the hepatic response to hypoglycaemia. A reduction in perceived hypoglycaemia threat may, therefore, be an important determinant of diabetes-related QoL and treatment satisfaction among CIPII-treated patients.<sup>20-22</sup> This is also reflected by the hyperglycaemic profiles and lower perceived hypoglycaemia score even though there was no actual decrease in the number of self-reported hypoglycaemic events among CIPII-treated subjects. In addition to a lower frequency of hypoglycaemic episodes, a reduction in the number of days spent in hospital during CIPII therapy has been suggested to have a positive influence on diabetes-related QoL and treatment satisfaction.<sup>2,7,19</sup>

Besides lower ALAT concentrations among CIPII-treated patients, there were no other differences in clinical and biochemical parameters between groups. Although ALAT concentrations were still within the normal range and the other liver enzymes were stable, this finding is remarkable. It might be hypothesised that, since intraperitoneal insulin administration results in higher hepatic insulin concentrations than SC insulin, this leads to altered hepatic metabolism secondary to higher insulinisation.<sup>23-25</sup>

This is the first study to compare the effects of CIPII and SC insulin administration in a large population of poorly regulated T1DM patients receiving usual care during real-life circumstances. The non-randomised design remains the major limitation of the present study. However, the complexity of the CIPII-treated group necessitated pragmatic measures in the study design. Although patients were on the same therapy for more than four years, measurements were performed with a 26-week interval, outcomes were adjusted for baseline differences and groups were well matched on age, gender, HbA<sub>1c</sub> and hypoglycaemic episodes at baseline, differences between groups that are known to influence glycaemic control could still be present.<sup>26,5</sup> Although hypothetical, the presence of such unmeasured differences between groups may have caused a slight underestimation of the effect of CIPII on glycaemic control. While fully acknowledging these limitations, we feel that the current design is the best available for the present study objective given the real-life, clinical restrictions.

At present, the costs of CIPII, estimated to be approximately € 6000 higher on an annual basis than CSII, seem to outweigh the advantages of CIPII for the majority of patients and health care systems.<sup>27</sup> Nevertheless, based on the short-term positive effects found in previous studies, including HbA<sub>1c</sub> improvements, less hypoglycaemic episodes and improved QoL, and the findings of the present study among CIPII-treated patients relative to SC insulin therapy during usual care, we advocate that CIPII using an implantable pump should still be seen as a feasible last-resort treatment option for

selected patients with T1DM who are unable to reach glycaemic control with SC insulin therapy.<sup>2,4,7,5</sup>

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## DISCLOSURES

The authors have no financial or other relationships that might lead to a conflict of interest.

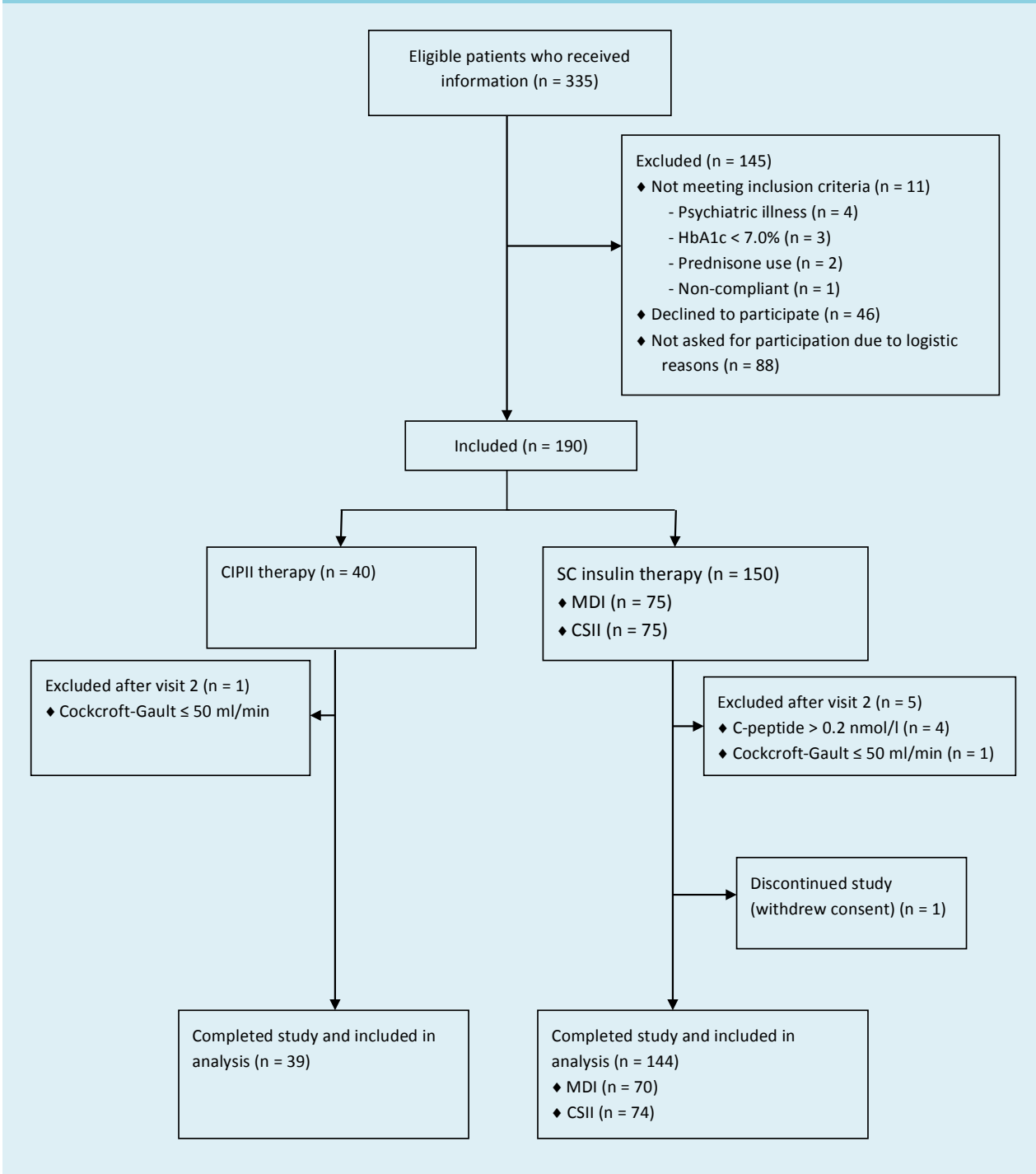
PRvD is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The iPro2 glucose monitoring systems and Enlite sensors for the continuous glucose measurements were sponsored by Medtronic International Trading Sarl (Switzerland). The Contour XT blood glucose meters were sponsored by Bayer Diabetes. Neither of the sponsors had a role in the study design, data collection, analysis, interpretation, or in the writing the report.

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Appendix 1. Patient flowchart



**Appendix 2. Results of the per protocol and intention-to-treat analysis for the primary outcome****Intention to treat analysis (n = 184)**

	CIPII	SC	Difference between means (95% CI)
Baseline (mmol/mol)	66.9 (14.4)	62.8 (8.9)	-4.3 (-9.1, -0.6)
Baseline (%)	8.3 (1.32)	7.9 (0.81)	-0.39 (-0.83, -0.05)
Follow-up (mmol/mol)	68.4 (14.1)	61.8 (9.4)	-6.5 (-11.4, -1.7)
Follow-up (%)	8.4 (1.29)	7.8 (0.86)	-0.59 (1.04, -0.16)
Difference between CIPII and SC adjusted for baseline differences (mmol/mol)			-3.0 (-5.0, -1.0)
Difference between CIPII and SC adjusted for baseline differences (%)			-0.27 (-0.46, 0.09)

Data are means (SD) and difference between means (95% CI).

**Per protocol analysis (n = 183)**

	CIPII	SC	Difference between means (95% CI)
Baseline (mmol/mol)	66.9 (14.4)	62.6 (9.1)	-4.3 (-9.2, -0.6)
Baseline (%)	8.3 (1.32)	7.9 (0.83)	-0.39 (-0.84, -0.05)
Follow-up (mmol/mol)	68.4 (14.1)	61.8 (9.4)	-6.5 (-11.4, -1.7)
Baseline (%)	8.4 (1.29)	7.8 (0.86)	-0.59 (1.04, -0.16)
Difference between CIPII and SC adjusted for baseline differences (mmol/mol)			-3.0 (-5.0, -1.0)
Difference between CIPII and SC adjusted for baseline differences (%)			-0.27 (-0.46, -0.09)

Data are means (SD) and difference between means (95% CI).

**Appendix 3. Outcomes of glycaemic control, QoL and treatment satisfaction during baseline visit, changes within the MDI and CSII groups and differences with the CIPII group**

Characteristic	MDI Start	Change within MDI group	Difference between MDI and CIPII (adjusted for baseline)	CSII Start	Change within CSII group	Difference between CSII and CIPII (adjusted for baseline)
<b>Glycaemic</b>						
HbA1c (mmol/mol)	62.2 (9.1)	-1.1 (-2.3, 0.2)	-3.2 (-5.9, -0.4)*	63.4 (8.8)	-0.9 (-2.1, 0.5)	-2.8 (-5.5, -0.1)*
(%)	7.8 (0.83)	-0.10 (-0.21, 0.02)	-0.29 (-0.54, -0.04)*	8.0 (0.81)	-0.08 (-0.19, 0.05)	-0.26 (-0.5, -0.01)*
Fasting glucose (mmol/l) <sup>a</sup>	8.6 (3.8)	1.4 (-0.2, 3.0)	1.4 (-0.8, 3.7)	8.6 (3.7)	0.7 (-0.4, 1.7)	0.7 (-1.4, 2.8)
Total insulin dose (IU/day)	48.0 [38.0, 65.0]	-1.7 (-4.1, 0.7)	0.6 (-6.2, 7.4)	42.0 [33.1, 59.7]	-0.1 (-3.9, 2.1)	-0.8 (-7.7, 6.1)
Hypoglycaemia grade 1 <sup>†</sup>	0.0 [0.0, 3.0]	-1.0 (-1.6, -0.3)*	-0.1 (-0.9, 1.0)	1.5 [0.0, 5.0]	-1.4 (-2.1, -0.7)*	0.4 (-0.6, 1.3)
Hypoglycaemia grade 2 <sup>‡</sup>	1.0 [0.0, 3.0]	0.1 (-0.7, 0.9)	-0.2 (-1.8, 1.3)	3.0 [1.0, 5.0]	0.1 (-0.9, 1.1)	0.6 (-1.0, 2.2)
Time spent in hypoglycaemia (%)	10 [3, 15]	-1.3 (4.0, 1.3)	2.9 (-2.0, 7.8)	4 [1, 7]	0.3 (-1.8, 2.4)	3.4 (-1.1, 7.9)
Time spent in hyperglycaemia (%)	35 [23, 44]	0.0 (-4.2, 4.2)	-10.3 (-17.6, -3.0)*	41 [32, 51]	1.4 (-5.6, 8.5)	-8.6 (-15.5, -1.7)*
Time spent in euglycaemia (%)	56 [43, 62]	1.3 (-2.3, 5.0)	8.2 (2.0, 14.5)*	52 [45, 62]	-1.7 (-8.3, 4.9)	5.7 (-0.5, 11.8)

SF-36 subscales						
Physical functioning	85 (20)	-0.4 (-4.4, 3.7)	4.3 (-1.7, 10.5)	88 (17)	-0.1 (-2.5, 2.4)	5.3 (-0.9, 11.5)
Social functioning	82 (21)	3.0 (-1.3, 7.3)	11.1 (3.5, 18.8)*	82 (19)	-0.6 (-6.0, 4.8)	-3.1 (-9.3, 3.0)
Role limitations-physical	80 (34)	1.2 (-7.5, 9.9)	25.4 (10.3, 40.6)*	74 (37)	0.8 (-8.3, 9.8)	22.3 (7.4, 37.1)*
Role limitations-emotional	84 (32)	2.2 (-5.6, 9.9)	7.1 (-4.7, 18.9)	89 (29)	-3.7 (-10.1, 2.7)	4.3 (-7.6, 16.1)
Mental health	78 (15)	-0.7 (-3.7, 2.2)	0.6 (-4.1, 5.2)	76 (23)	0.0 (-3.5, 3.5)	0.5 (-4.2, 5.1)
Vitality	65 (19)	2.3 (-1.7, 6.2)	11.8 (5.3, 18.2)*	61 (20)	-0.9 (-4.0, 3.2)	7.7 (1.3, 14.1)*
Bodily pain	81 (23)	-0.2 (-5.4, 5.0)	14.4 (6.1, 22.6)*	77 (23)	3.1 (-2.5, 8.7)	15.6 (7.8, 24.2)*
General health	63 (19)	1.1 (-2.5, 4.8)	8.9 (3.1, 14.7)*	60 (18)	-0.5 (-4.3, 3.3)	5.9 (0.2, 11.6)*
SF-36 component scores						
Mental component score	75 (17)	2.0 (-1.1, 5.2)	10.1 (4.1, 16.0)*	73 (16)	0.0 (-3.0, 3.0)	9.1 (3.3, 15.0)*
Physical component score	76 (17)	1.3 (-2.5, 4.8)	8.0 (3.1, 12.9)*	73 (17)	1.0 (-1.9, 3.9)	5.7 (0.9, 10.6)*
WHO-5						
Total score	64 (18)	1.9 (-1.6, 5.5)	3.9 (-2.1, 10.1)	62 (18)	0.8 (-4.0, 5.4)	1.9 (-4.1, 8.0)
DQOL						
Satisfaction	61 (11)	-0.5 (-2.6, 1.5)	-1.4 (-5.4, 2.5)	56 (10)	-0.2 (-2.3, 1.8)	-3.1 (-6.7, 0.5)
Impact	54 (9)	0.1 (-1.1, 1.4)	0.2 (-1.9, 2.4)	54 (7)	0.2 (-1.1, 1.5)	0.1 (-2.1, 2.4)
Worry: diabetes related	74 (17)	-0.1 (-4.6, 4.2)	1.9 (-5.2, 9.1)	73 (14)	-1.4 (-5.8, 2.8)	-0.1 (-4.0, 6.8)
Worry: social/vocational	49 (26)	5.9 (-2.7, 14.6)	5.0 (-7.7, 17.8)	55 (29)	0.2 (-7.6, 8.1)	2.2 (-9.8, 14.2)
DTSQ						
Perceived hyperglycaemia score	3.6 (1.6)	-0.1 (-0.5, 0.4)	-0.2 (-0.8, 0.4)	4.0 (1.3)	-0.2 (-0.6, 0.1)	-0.1 (-0.7, 0.4)
Perceived hypoglycaemia score	3.6 (1.6)	-0.1 (-0.4, 0.3)	0.6 (0.03, 1.2)*	2.7 (1.4)	0.4 (-0.01, 0.9)	0.7 (0.2, 1.3)*
Total score	29.1 (5.6)	0.1 (-1.0, 1.2)	-0.7 (-2.3, 0.8)	28.8 (5.1)	-0.2 (-1.2, 0.7)	-1.3 (-2.9, 0.2)
PAID						
Total score	19 (14)	-1.1 (-3.7, 1.6)	1.0 (-3.6, 5.6)	22 (14)	0.9 (-2.4, 4.1)	3.6 (-0.9, 8.1)

Data are presented as mean (SD), median [IQR] or mean difference (95% confidence interval). <sup>a</sup>based on n = 116 and n = 32, <sup>b</sup>based on n = 137 and n = 36. SF-36 data incomplete for 14 (MDI n = 6, CSII n = 8) patients, WHO-5 data incomplete for 14 (MDI n = 6, CSII n = 8) patients, DQOL data incomplete for 14 (MDI n = 7, CSII n = 7) patients, DTSQ data incomplete for 20 (MDI n = 10, CSII n = 10) patients and PAID data incomplete for 31 (MDI n = 21, CSII n = 8) patients. \*p < 0.05. <sup>†</sup>Defined as the number of blood glucose value <4.0 mmol/l during the last two weeks. <sup>‡</sup>Defined as the number of blood glucose value <3.5 mmol/l during the last two 2 weeks. <sup>§</sup>Defined as the number of hypoglycaemic episodes requiring third party help or losing consciousness during the last two weeks. CSII = continuous subcutaneous insulin infusion; CIPII = continuous intraperitoneal infusion; DQOL = Diabetes Quality of life; DTSQ = Diabetes Treatment Satisfaction Questionnaire, MDI = multiple daily injections; MCS = Mental Component Score; PAID = Problem Areas in Diabetes; SF-36 = 36-item short-form health survey, WHO-5 = World Health Organisation-Five Well-Being Index.

# Modified Bova score for risk stratification and short-term outcome in acute pulmonary embolism

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## ABSTRACT

**Introduction:** Risk stratification in acute pulmonary embolism (PE) is crucial to identify those patients with a poorer prognosis. We aimed to investigate a modified Bova score for risk stratification in acute PE.

**Materials and methods:** We performed a retrospective analysis of PE patients treated in the internal medicine department. Both haemodynamically stable and unstable PE patients,  $\geq 18$  years with measurements of cardiac troponin I (cTnI) and existing echocardiography were included in the analysis.

**Results:** Data from 130 patients were included for this retrospective analysis. Three patients (2.3%) died in hospital; 84 patients had a Bova score of  $< 4$  points and  $46 \geq 4$  points. PE patients with a score  $\geq 4$  points were older ( $71.2 \pm 13.8$  vs.  $66.3 \pm 15.5$  years,  $p = 0.0733$ ), died more frequently during the in-hospital course (6.5% vs. 0.0%,  $p = 0.0183$ ), had a more prevalent high-risk PE status (10.9% vs. 1.2%,  $p = 0.0122$ ), more often had right ventricular dysfunction (100.0% vs. 35.7%,  $p < 0.000001$ ), presented more frequently with syncope/collapse (21.7% vs. 3.6%,  $p = 0.00101$ ) and had a higher heart rate ( $104.6 \pm 23.5$  vs.  $90.0 \pm 20.6$ /min,  $p = 0.000143$ ), shock index ( $0.91 \pm 0.59$  vs.  $0.62 \pm 0.18$ ,  $p = 0.000232$ ), cTnI ( $0.36 \pm 0.42$  vs.  $0.03 \pm 0.10$ ng/ml,  $p < 0.000001$ ) and creatinine ( $1.32 \pm 0.50$  vs.  $1.03 \pm 0.27$  mg/dl,  $p = 0.000170$ ). Adjusted multivariate logistic regressions revealed significant associations between the Bova score and in-hospital death

(OR 4.172, 95% CI 1.125-15.464,  $p = 0.0326$ ) as well as pneumonia based on PE-related lung infarction (OR 1.207, 95% CI 1.005-1.449,  $p = 0.0442$ ). ROC analysis for Bova score predicting in-hospital death and pneumonia based on PE-related lung infarction showed area under the curve values of 0.908 and 0.606 with Bova score cut-off values of 3.5 points and 1.5 points, respectively.

**Conclusions:** The modified Bova score is highly effective to predict poorer outcome in acute PE.

## KEYWORDS

Lung, troponin, risk stratification, pulmonary embolism, right ventricular dysfunction

## INTRODUCTION

Pulmonary embolism (PE) is connected with high morbidity and mortality.<sup>1-3</sup> Rapid risk stratification in acute PE is crucial to identify those PE patients with a poorer prognosis and in deciding the appropriate therapy.<sup>14-16</sup> The recommended risk stratification in patients with acute PE according to the current European and American guidelines is based on assessment of haemodynamic status, evaluation of right ventricular (RV) dysfunction, cardiac injury markers and outcome scores, such as the Pulmonary Embolism Severity Index (PESI).<sup>17,18</sup> Guideline

recommendations are based on study results that have emphasised that adverse events and mortality in acute PE are closely related to the initial haemodynamic status of the patients and typical cardiac adaptations.<sup>1-4,6,19-25</sup> Haemodynamic instability is associated with the highest mortality rates.<sup>2,4,6,13,18,26-28</sup>

The Bova score is another simple grading system for stratifying the risk of short-term complications in normotensive PE patients.<sup>29,30</sup> The score consists of four variables, which are assessed at the time of PE diagnosis.<sup>30</sup> The four variables comprise heart rate, systolic blood pressure, cardiac troponin (cTn) and RV dysfunction.<sup>30</sup>

We modified the Bova score and, in this study, aimed to test the effectiveness of this modified Bova score to predict in-hospital death in haemodynamically stable and unstable PE patients. The modification of the Bova score was based on the objective to investigate the Bova score not only in normotensive PE patients but also haemodynamically unstable PE patients.

## METHODS AND PATIENTS

We performed a retrospective analysis of patients with a confirmed diagnosis of acute PE. Consecutive patients treated in the internal medicine department between May 2006 and June 2011 were included. The patients were identified by a search in the hospital information system database for the diagnostic code of PE (ICD Code: I26).

Studies in Germany involving retrospective analysis of diagnostic standard data do not require an ethics statement.

### Enrolled subjects

Patients were eligible for this study based on the following:

1. If the diagnosis of acute PE was confirmed by an identified filling defect in the pulmonary artery system on a computed tomography (CT) pulmonary angiogram of the chest, a scintigraphic ventilation-perfusion (V/Q) scan read as high probability for PE or positive venous ultrasound/phlebography of an extremity consistent with deep venous thrombosis (DVT) in patients with typical symptoms of PE (chest pain or dyspnoea) and positive D-dimer;
2. If patients were treated in the internal medicine department of the hospital;
3. If patients were at least 18 years old and
4. If patients had undergone a transthoracic echocardiography (TTE) and a cardiac troponin I (cTnI) value was available, both performed in the acute phase.

All CT, scintigraphy and phlebography images were analysed by experienced radiologists.

### Routine diagnostic strategy

The routine diagnostic strategy followed the recommendations of the European Society of Cardiology (ESC) guidelines from 2008.<sup>6</sup> In haemodynamically stable patients with suspected PE, CT was the primary diagnostic tool to confirm the PE diagnosis. In cases of impaired renal function a V/Q scan was used to make the diagnosis. A confirmed DVT with additional typical symptoms of PE and a positive D-dimer value were considered adequate to diagnose PE in only a minority of patients, especially multi-morbid patients with suspected PE. Transthoracic echocardiography and laboratory testing of cTnI were intended for all patients with suspected and confirmed PE, but were not done in all patients.

### Definitions

#### *Cardiac injury*

According to the American Heart Association (AHA) scientific statement from 2011, myocardial necrosis was defined as a cardiac cTnI elevation higher than 0.4 ng/ml.<sup>18</sup>

#### *Right ventricular dysfunction*

RV dysfunction was defined according to the AHA scientific statement<sup>18</sup> as a quotient of RV septal-lateral diameter/ left ventricular (LV) septal-lateral diameter > 0.9 in the four-chamber view on transthoracic echocardiography.<sup>18</sup> Moreover, RV dysfunction was defined as RV hypokinesia and tricuspid regurgitation by echocardiography.<sup>18</sup>

#### *High-risk pulmonary embolism*

PE patients with a systolic blood pressure < 90 mmHg at admission were classified as high-risk PE according to the definition from the ESC guidelines<sup>6,17</sup> and AHA scientific statement.<sup>18</sup>

#### *Modified Bova score*

Patient characteristics at the time of PE diagnosis determined the Bova score.<sup>29,30</sup> In order to use the original Bova score in both haemodynamically stable and unstable PE patients, we modified the criterion of systolic blood pressure 90-100 mmHg of the original Bova score to systolic blood pressure < 100 mmHg in our modified Bova score. The modified Bova score is shown in *table 1*; it was calculated for haemodynamically stable and unstable PE patients. The sum of the points for each of the four predictor variables produced the total score for each patient.<sup>30</sup>

### Study parameters

The retrospective analysis of PE patients focused on echocardiographic and CT results, cTnI, systolic blood pressure and heart rate values.



**Table 1.** Modified Bova score

Predictor variable	Points
Systolic blood pressure < 100 mmHg	2
Cardiac troponin I > 0.04 ng/ml	2
Right ventricular dysfunction	2
Heart rate $\geq$ 110 beats/min	1

### Study outcome measures

Endpoints of this analysis were in-hospital death and the complication of pneumonia based on PE-related lung infarction. In-hospital death comprised all causes of death during the hospital course. Pneumonia based on PE-related lung infarction consisted of existing lung infarction with infiltration of lung tissue with elevated inflammatory markers (C-reactive protein) and following treatment with antibiotics.

### Statistics

PE patients with a Bova score  $\geq$  4 points and those with a Bova score < 4 points were compared using the Wilcoxon-Mann-Whitney U test.

We used multivariate logistic regression models to investigate the associations between the Bova score and the study endpoints in-hospital death and pneumonia based on PE-related lung infarction, each of which was adjusted for age and gender.

Receiver operating characteristic (ROC) curves with areas under the curves (AUC) and Youden indices were calculated to test the effectiveness of the Bova score to predict in-hospital death and pneumonia based on PE-related lung infarction in an acute PE event. The Wilcoxon-Mann-Whitney test was used to test the deviation of the ROC curve from the angle bisector.

The commercially available software BIAS® (version 10.04) was used for the computerised analysis. P values of < 0.05 were considered to be statistically significant. We used the Bonferroni method to adjust the significance level for multiple testing.

## RESULTS

From May 2006 to June 2011, 182 patients with confirmed acute PE were found by a search of the hospital information system database for the diagnostic code of PE. From these identified patients, 52 patients were excluded because they had no cTnI measurement or had not undergone transthoracic echocardiography. Therefore, we included 130 patients in this analysis.

In 86.2% of the patients, the PE diagnosis was confirmed by CT, in 8.4% by V/Q scan and in 5.4% by positive venous ultrasound/phlebography of an extremity consistent with

DVT in patients with typical symptoms of PE (chest pain or dyspnoea) and positive D-dimer.

In the study sample, three patients (2.3%) died in hospital after the PE, and six patients (4.6%) presented with haemodynamically unstable PE (high-risk PE patients). Moreover 43.1% (56 patients) presented with pneumonia based on PE-related lung infarction and 70% (91 patients) had a concomitantly detected DVT. The recommended Bova risk staging showed 79 patients in stage I (0-2 points), 33 in stage II (3-4 points) and 18 in stage III (> 4 points).

### Comparison between the groups

The total study sample comprised 84 PE patients (64.6%) with a Bova score of < 4 points and 46 PE patients (35.4%) with a Bova score  $\geq$  4 points. The patient characteristics stratified for point sum of  $\geq$  4 or < 4 points are shown in table 2. PE patients with a Bova score  $\geq$  4 points were older ( $71.2 \pm 13.8$  vs.  $66.3 \pm 15.5$  years,  $p = 0.0733$ ), died more frequently during the in-hospital course (6.5% vs. 0.0%,  $p = 0.0183$ ), had a more prevalent high-risk PE status (10.9% vs. 1.2%,  $p = 0.0122$ ), more often had RV dysfunction (100.0% vs. 35.7%,  $p < 0.000001$ ) and presented more frequently with syncope or collapse (21.7% vs. 3.6%,  $p = 0.00101$ ).

Moreover PE patients with a Bova score  $\geq$  4 had higher levels of heart rate ( $104.6 \pm 23.5$  vs.  $90.0 \pm 20.6$ /min,  $p = 0.000143$ ), shock index ( $0.91 \pm 0.59$  vs.  $0.62 \pm 0.18$ ,  $p = 0.000232$ ), cTnI ( $0.36 \pm 0.42$  vs.  $0.03 \pm 0.10$  ng/ml,  $p < 0.000001$ ), creatinine ( $1.32 \pm 0.50$  vs.  $1.03 \pm 0.27$  mg/dl,  $p = 0.000170$ ) and lower levels of creatinine kinase ( $98.0 \pm 70.1$  vs.  $100.3 \pm 237.3$ ,  $p = 0.00761$ ) (table 2).

After Bonferroni adjustment of the significance level for multiple testing, the adjusted significance level was computed at 0.00238. After this adjustment the parameters syncope or collapse, heart rate, shock index, creatinine, creatinine kinase and RV dysfunction still remained significantly higher in those PE patients with a Bova score  $\geq$  4 than in those with a Bova score < 4.

### Association between Bova score and outcome parameters

The multivariate logistic regression models revealed a significant association between the Bova score and in-hospital death (OR 4.172, 95% CI 1.125-15.464,  $p = 0.0326$ ) and between the Bova score and pneumonia based on PE-related lung infarction (OR 1.207, 95% CI 1.005-1.449,  $p = 0.0442$ ); each model was adjusted for age and gender respectively.

### Effectiveness and optimal cut-off of outcome prediction

The calculated ROC analysis for the Bova score predicting in-hospital death showed an AUC of 0.908 with a Bova score cut-off value of 3.5 points and a  $p = 0.0160$  for differentiation. The percentages of misclassification, sensitivity, specificity, and positive and negative predictive values were 16.9%, 100.0%, 74.7%, 66.1% and 100.0%, respectively (figure 1).

**Table 2.** Characteristics of patients with pulmonary embolism

Parameter	PE patients with Bova score < 4	PE patients with Bova score ≥ 4	P-value for difference
Number of patients	84 (64.6%)	46 (35.4%)	
Age at event (years)	66.3 ± 15.4	71.2 ± 13.8	0.0733
Female gender	50 (59.5%)	26 (56.5%)	0.681
<b>Comorbidities</b>			
Surgery or trauma in last 3 months before PE event	19 (22.6%)	7 (15.2%)	0.315
DVT or PE in patient's history	25 (29.8%)	9 (19.6%)	0.194
Current DVT	62 (73.8%)	29 (63.0%)	0.202
Cancer currently or in patient's history	16 (19.0%)	10 (21.7%)	0.201
Lung infarction with pneumonia	33 (39.3%)	23 (50.0%)	0.240
In-hospital death	0 (0.0%)	3 (6.5%)	<b>0.0183</b>
High-risk PE stage	1 (1.2%)	5 (10.9%)	<b>0.0122</b>
<b>Symptoms</b>			
Chest pain	28 (33.3%)	18 (39.1%)	0.510
Dyspnoea	70 (83.3%)	42 (91.3%)	0.210
Haemoptysis	1 (1.2%)	3 (6.5%)	0.0884
Syncope or collapse	3 (3.6%)	10 (21.7%)	<b>0.00101</b>
<b>Physical examination</b>			
Systolic BP (mmHg)	148.3 ± 24.0	133.5 ± 38.5	0.0817
Diastolic BP (mmHg)	78.6 ± 19.8	75.8 ± 22.1	0.977
Heart rate (beats/min)	90.0 ± 20.6	104.6 ± 23.5	<b>0.000143</b>
Shock index	0.62 ± 0.18	0.91 ± 0.59	<b>0.000232</b>
<b>Laboratory markers</b>			
Cardiac troponin I (ng/ml)	0.03 ± 0.10	0.36 ± 0.42	<b>&lt; 0.000001</b>
Creatinine kinase (U/l)	100.3 ± 237.3	98.0 ± 70.1	<b>0.00761</b>
Creatinine (mg/dl)	1.03 ± 0.27	1.32 ± 0.50	<b>0.000170</b>
<b>Echocardiography</b>			
RV dysfunction	30 (35.7%)	46 (100.0%)	<b>&lt; 0.000001</b>

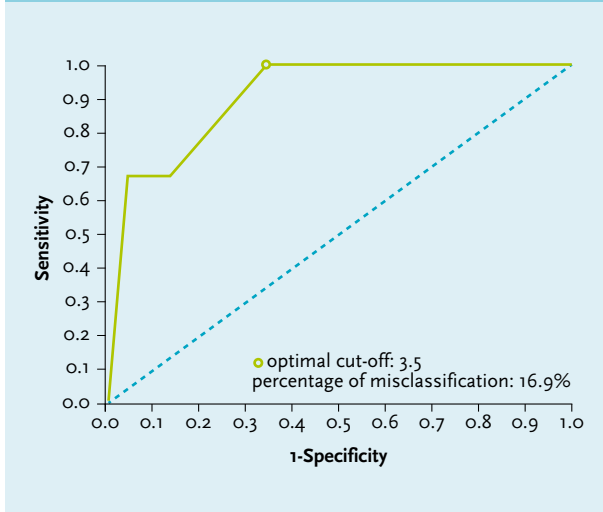
PE patients were stratified by Bova score < 4 or ≥ 4 points. Results were described as mean values with standard deviation or relative percentages. Groups were compared with the Wilcoxon-Mann-Whitney-U test. BP = blood pressure; DVT = deep venous thrombosis; PE = pulmonary embolism; RV = right ventricular.

The ROC analysis for the Bova score predicting pneumonia based on PE-related lung infarction revealed an AUC of 0.606 with Bova score cut-off level of 1.5 points and a  $p = 0.0383$  for differentiation. The percentage of misclassification, sensitivity, specificity, and positive and negative predictive values were 40.9%, 63.4%, 56.9%, 43.2% and 75.0%, respectively (figure 2).

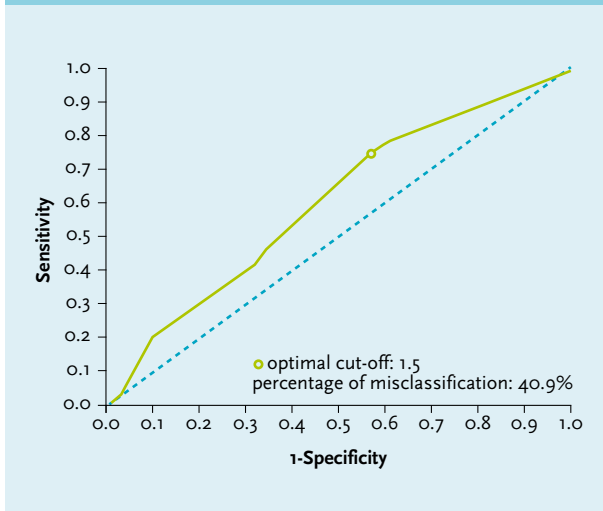
## DISCUSSION

Rapid risk and accurate stratification in acute PE is crucial for evaluation of the patient's prognosis and for the determination of the appropriate therapy.<sup>14-16,31,32</sup> Several study results in acute PE have found that presence of RV dysfunction or myocardial necrosis is associated

**Figure 1.** Receiver operating characteristic (ROC) curve with area under the curve (AUC) and Youden Index were calculated to test the effectiveness of the Bova score to predict in-hospital death in acute PE



**Figure 2.** Receiver operating characteristic (ROC) curve with area under the curve (AUC) and Youden Index were calculated to test the effectiveness of the Bova score to predict pneumonia based on the lung infarction of acute PE



with increased mortality.<sup>2-4,6,9,11,17-22,24,27,33-40</sup> PE patients with an elevated cTn showed a 3.5- to 5.3-fold increase of mortality in the first three months after an acute PE.<sup>3,6,10,19</sup> Additionally, heart rate and systolic blood pressure are rapidly available and reliable parameters for the risk stratification process. Heart rate elevations in settings of acute PE are connected with a more severe PE stage and poorer outcome.<sup>6,41-43</sup> Therefore, elevated heart rate values have been included in outcome scores, such as the PESI, as a risk stratification parameter.<sup>41</sup> Tachycardia was associated with sevenfold higher risk of in-hospital death in one of

our analyses that has already been published.<sup>44</sup> Systolic blood pressure values of < 90 mmHg were identified as an important prognostic factor in the International Cooperative Pulmonary Embolism Registry (ICOPER).<sup>45</sup> In the PESI and the simplified PESI, a systolic BP of < 100 mmHg is one of the parameters to predict poorer prognosis.<sup>17,41,46</sup>

The Bova score is another new, simple grading system for stratifying the risk of short-term complications in normotensive PE patients.<sup>29,30</sup> The Bova score condenses the important risk stratification markers of RV dysfunction, cTn, heart rate elevation and hypotension.<sup>29,30</sup> The Bova score was developed for the risk stratification of normotensive PE patients only. We aimed to analyse the usefulness of the Bova score, without focusing on the haemodynamic status, for all PE patients in the internal medical section of our hospital. Therefore, we modified this Bova score for the use in PE risk stratification of both haemodynamically stable and unstable PE patients. We aimed to underline the usefulness and the helpfulness of this score. Although the Bova score was created for better risk stratification, especially in normotensive PE patients, our investigation showed that the Bova score is highly effective to identify those patients with a higher complication and in-hospital death rate in both haemodynamically stable and unstable PE patients. A Bova score of  $\geq 4$  points identified the patients with a higher risk of short-term mortality with high specificity and specificity and low misclassification rate. All PE patients who died in hospital had a Bova score  $\geq 4$  points. Bova score was strongly associated with in-hospital death.

The computed effectiveness for the modified Bova score in predicting in-hospital death (AUC 0.908) was thereby distinctly higher than that of cTnI (AUC 0.719)<sup>47</sup> or heart rate (AUC 0.655)<sup>44</sup> separately predicting in-hospital death in our study. In contrast, Janata et al.<sup>48</sup> described a higher effectiveness (AUC 0.92) for cTnT in predicting in-hospital death.<sup>48</sup> In the study by Kucher et al.<sup>25</sup> the reported AUC for prediction of an adverse outcome was 0.89 for cTnI alone and 0.90 for the combination of cTnI and RV dysfunction in echocardiography.<sup>25</sup>

In contrast, effectiveness of the Bova score to predict pneumonia based on PE-related lung infarction as a complication of PE was only moderate.

The selection by the inclusion criteria of existing transthoracic echocardiography and existing cTnI value in this analysis, reducing the number of the included patients from 182 to 130, could lead to a selection bias, but this is a retrospective study and we wanted to have an accurately assessed Bova score in each patient. Therefore, it is hypothetical whether more PE patients with low-risk PE did not undergo transthoracic echocardiography examination or have a cTnI value and were excluded than PE patients with intermediate or high-risk PE, but of course it has

to be expected that transthoracic echocardiography and cTnI were done less often in PE patients with a lower PE severity status than in those with a higher severity status and therefore a bias has to be suggested. The portion of PE patients with pneumonia related to lung infarction seems high in our study sample at > 40%, but in accordance with these results Goldhaber et al.<sup>49</sup> reported in their autopsy study that 54 of 1455 patients showed major pulmonary embolism at autopsy and of these 54 patients 21 (38.9%) had an concomitant pneumonia.<sup>49</sup> Therefore, these percentage values are not very different.

Overall mortality of patients with acute PE remains high despite modern diagnostic and reperfusion strategies.<sup>32</sup> Management options of acute PE include anticoagulation treatment alone, thrombolysis (systemic or localised) plus anticoagulation, insertion of inferior vena cava filter, catheter embolectomy, or surgical embolectomy.<sup>50</sup> The decision-making process to choose the appropriate therapy requires rapid and accurate risk stratification and is crucial to identify those PE patients with a poorer prognosis.<sup>14-16,50</sup> ESC guidelines recommend that thrombolytic therapy is the first-line treatment in PE patients with high-risk PE status, presenting with arterial hypotension or cardiogenic shock, with very few absolute contraindications.<sup>17</sup> The routine use of thrombolytic therapy in normotensive PE patients was not recommended by the ESC guidelines.<sup>17</sup> Randomised trials have shown that thrombolytic therapy resolves the obstruction of the pulmonary artery bed and is connected with beneficial effects on the haemodynamic status of PE patients.<sup>16,17,51-56</sup> The results of the PEITHO study emphasised that intermediate-risk PE patients could also benefit from more aggressive treatment options such as fibrinolytic therapy but with the concomitant higher risk of bleeding.<sup>16</sup> Beside systemic thrombolysis, catheter-directed thrombolysis in combination with or without ultrasound acceleration for thrombolysis are used to perform localised thrombolysis therapy with lower bleeding risk.<sup>57-61</sup>

The Bova score could be helpful to identify those PE patients who are of higher risk to die during the early in-hospital course.

### Limitations

Important study limitations are the small to medium number of included PE patients and the study's single centre and retrospective design.

### CONCLUSIONS

The modified Bova score is highly effective to predict poorer outcome in acute PE.

### DISCLOSURES

The authors declare no conflict of interest. No funding or financial support was received.

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# The estimated future disease burden of hepatitis C virus in the Netherlands with different treatment paradigms

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## ABSTRACT

**Background & Aims:** Prevalence of hepatitis C virus (HCV) infection in the Netherlands is low (anti-HCV prevalence 0.22%). All-oral treatment with direct-acting antivirals (DAAs) is tolerable and effective but expensive. Our analysis projected the future HCV-related disease burden in the Netherlands by applying different treatment scenarios.

**Methods:** Using a modelling approach, the size of the HCV-viraemic population in the Netherlands in 2014 was estimated using available data and expert consensus. The base scenario (based on the current Dutch situation) and different treatment scenarios (with increased efficacy, treatment uptake, and diagnoses) were modelled and the future HCV disease burden was predicted for each scenario.

**Results:** The estimated number of individuals with viraemic HCV infection in the Netherlands in 2014 was 19,200 (prevalence 0.12%). By 2030, this number is projected to decrease by 45% in the base scenario and by 85% if the number of treated patients increases. Furthermore, the number of individuals with hepatocellular carcinoma and liver-related deaths is estimated to decrease by 19% and 27%, respectively, in the base scenario, but may both be further decreased by 68% when focusing on treatment of HCV patients with a fibrosis stage of  $\geq$  F2.

**Conclusions:** A substantial reduction in HCV-related disease burden is possible with increases in treatment uptake as the efficacy of current therapies is high. Further reduction of HCV-related disease burden may be achieved through increases in diagnosis and preventative measures. These results might inform the further development of effective disease management strategies in the Netherlands.

## KEYWORDS

HCV disease burden, HCV epidemiology, HCV treatment, prediction model, the Netherlands

## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major cause of chronic liver disease. It causes liver fibrosis and may ultimately lead to liver cirrhosis, hepatocellular carcinoma and death.<sup>1</sup> It has been estimated that there are around 80 million people worldwide with chronic HCV infection.<sup>2</sup> There is a large geographical variation in prevalence of HCV infection and in many countries the epidemiology of HCV infection is not well known. At the same time, HCV-related mortality continues to increase as the infected population ages<sup>3</sup> and the infected population advances

to late-stage liver disease.<sup>4,6</sup> Recently, the World Health Organisation (WHO) recognised viral hepatitis as a global public health problem,<sup>7</sup> and asked countries to develop comprehensive national viral hepatitis strategies.<sup>8</sup>

In the Netherlands, estimates on antibody prevalence of HCV infection vary from 0.1 to 0.6%.<sup>9-13</sup> The most recent and reliable nationwide estimate was 0.22% (0.07%-0.37%) in Dutch habitants aged 15-79 years in 2009, incorporating prevalence data among different subpopulations,<sup>9</sup> corresponding with about 28,000 adult individuals ever infected with HCV. Assuming a spontaneous clearance rate of 26%,<sup>14</sup> around 20,000 of them are or have been viraemic. This corresponds to a viraemic prevalence of 0.13% in the total Dutch population. The risk groups of individuals with a known viraemic HCV infection (relatively many (ex-)drug users) are different from the groups of individuals currently at risk of a new HCV infection (strikingly almost no drug users, but mainly HIV-positive men who have sex with men). This situation is different in the Netherlands compared with many other countries where HCV transmission among people who inject drugs is ongoing. Importantly, the undiagnosed population might be substantial due to the symptom-free course in approximately 80% of cases.<sup>15</sup> A study from the southern region of the Netherlands indicated that 66% of HCV infections are hidden to current screening practices ('hidden population').<sup>16</sup>

With the availability of new powerful peginterferon-free treatment modalities in sight, treatment of HCV will become more effective and have fewer side effects. As a result, the barriers for starting treatment are expected to be lower and more patients will be treated. Following the recommendations of the WHO, it is important to develop a strategy to diagnose the 'hidden' HCV-infected population in the Netherlands in order to be able to benefit from the treatment advances. However, reliable data on epidemiology and understanding of disease dynamics and barriers to HCV screening and treatment are needed before robust plans can be made.

The aim of this study was twofold:

- The first aim was to estimate the future disease burden for the Netherlands using available data and expert opinion for if the current treatment paradigm and cure rates were to continue.
- The second aim was to show the impact of different intervention strategies on the future disease burden. Extreme strategies were considered to illustrate the potential range of outcomes. The reality may fall within one of these strategies. The focus of this analysis was not prescriptive, stating what should be done to reduce HCV infection disease burden. Instead, the focus was descriptive, showing the impact on disease burden if certain assumptions can be met. Cost-effectiveness analyses were not considered.

This study is part of a larger project to quantify HCV epidemiology in a systematic manner in countries around the world, and for which the same prediction model has been used.<sup>2,6,17</sup> In our report we focus on the situation in the Netherlands.

## METHODS

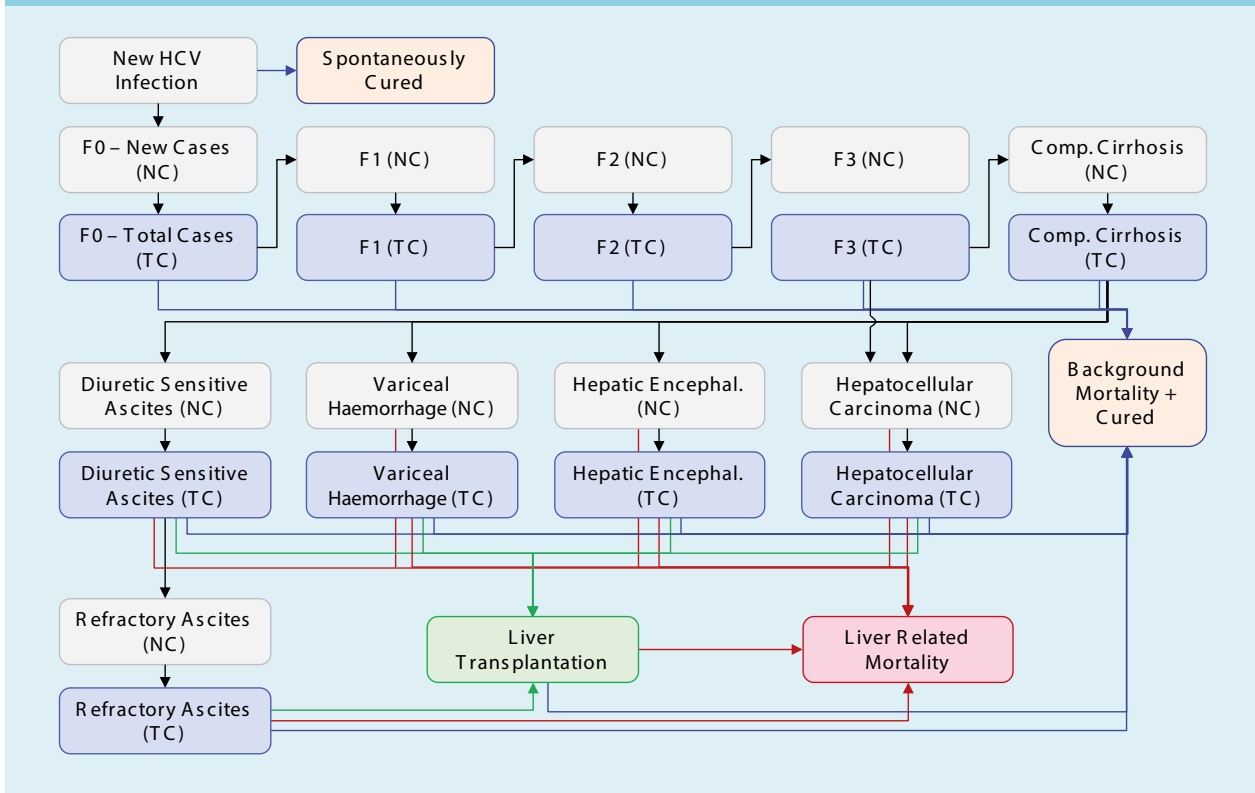
### Baseline population characteristics

#### Inputs

A systematic review of the literature was conducted to identify studies reporting the total number of HCV cases diagnosed, treated and cured in the Netherlands. Indexed articles were found by searching PubMed and Embase. The review encompassed all studies between January 1990 and July 2013. Non-indexed sources were identified through Ministry of Health websites and reports from international agencies. As described in detail in an earlier published study,<sup>18</sup> this literature search was combined with face-to-face discussions with a panel of experts (consisting of epidemiologists, hepatologists, infectious disease specialists, public health professionals and virologists) to gather epidemiological data and consensus estimates. The obtained data were used to estimate the historical number of new HCV infections per calendar year.

#### Model

A disease progression model was constructed in Microsoft Excel® (Microsoft Corp., Redmond, WA) to quantify the size of the HCV-infected population by liver disease stages (METAVIR score F0-F4), from 1950-2030. The model was set up for sensitivity and Monte Carlo analysis using Crystal Ball®, an Excel® add-in by Oracle®. Beta-PERT distributions were used for all uncertain inputs. The Excel® optimisation add-in, Frontline Systems' Solver, was used to calculate the number, age and gender distribution of the annual acute HCV infections which progressed to chronic HCV infection after accounting for spontaneous clearance of the virus (*figure 1*).<sup>6</sup> The model was validated in countries where annual hepatocellular carcinoma incidence and liver-related deaths were reported.<sup>6,17</sup> The progression of these new cases was followed along with all chronic infections from prior years. Unless specified, the scope of the model was limited to HCV-viraemic (ribonucleic acid (RNA) positive) cases. Non-HCV-viraemic cases (those patients who spontaneously cleared the virus or were treated and cured) were not considered even though they would test positive to HCV antibodies and may still progress to more advanced stages of liver disease despite viral clearance.<sup>19</sup> In addition, re-infections following spontaneously or treatment-induced clearance were not considered as it was not possible to add this factor to the prediction model we used. The total number

**Figure 1.** The flow of the HCV disease progression model

of cases, at each stage of the disease, was tracked by age and gender. Five-year age cohorts were used up to age 84; those aged 85 and older were treated as one cohort. Each year, one fifth of the population in each age group, except for those 85 and older, was moved to the next age cohort to simulate ageing.

### Estimation of chronic and new HCV infections

#### Prevalence of HCV infections

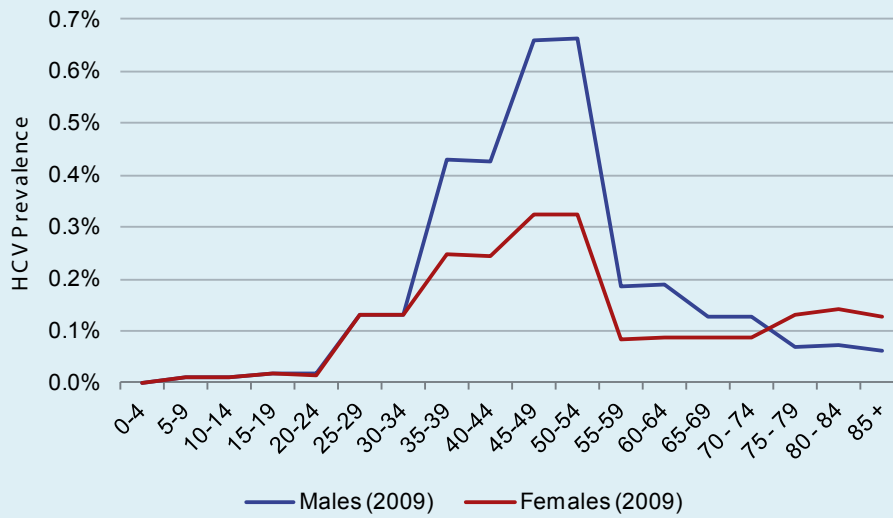
Available data were used to estimate the number of adults living with an HCV-RNA positive infection in the Netherlands. The paper we used for estimating anti-HCV-antibody prevalence was chosen because it was the most recent estimate and had the best representation of the overall population in the Netherlands.<sup>9</sup> There were no reliable age and gender distributions available for the Netherlands but the median age was reported at 54 years in 2006-2007,<sup>10</sup> slightly younger than in the United States.<sup>20</sup> In addition, United States and Dutch gender ratios were considered comparable, as well as the timing of the peak infections,<sup>9,20,21</sup> so the Dutch age and gender distributions were established using the United States as an analogue (figure 2). Dutch population data were obtained by five-year age and gender cohorts from the United Nations population database, which uses the data registered at the Dutch central bureau for statistics (Statnet).<sup>22</sup> The genotype

distribution (table 1) was established using data from an analysis of patient data collected between 2002 and 2005 from 53 hospitals in 11 of the 12 Dutch provinces.<sup>23</sup>

#### Diagnosed HCV infections

The annual number of newly diagnosed HCV cases ranged from 400 to 800 according to the expert panel. This range was based on different recent and less recent reports. One of these data sources is the compulsory reporting system for new HCV infections from 1999 to 2003, in which 600 to 700 new infections were reported per year (3.9-4.1 per 100,000 inhabitants).<sup>24</sup> Another data source is the information system of Dutch microbiology laboratories reporting the number of positive HCV tests per year. Not all laboratories participate, giving an underestimation, but there are also patients tested more than once per year, which may compensate for this underestimation. From 2005 to 2010 there were 700 to 900 diagnoses per year, and from 2011 to 2014 the number declined to 380 diagnoses per year.<sup>25</sup> By 2013, it was estimated that 12,000 individuals were diagnosed (an average of 600 newly diagnosed cases per year over 20 years). In 2013, based on estimations of the expert panel in combination with data in the literature, it was estimated that 650 individuals were newly diagnosed with HCV viraemia.

**Figure 2.** Prevalence of viraemic HCV infections by age and gender (2009)



*New HCV infections*

The annual number of new cases (i.e. acute HCV infections and new chronic HCV infections due to immigration) has not remained stable since 1950. Thus, an annual relative incidence value was used to describe the change in the number of new infections over time. Relative incidence was set to 1 in 1950 and based on discussion with the expert panel, taking into account the risk factors common in the Netherlands over time (nosocomial infections before 1992, injection drug use, etc.), it was estimated that the number of new infections peaked in 1989 and gradually declined thereafter. In 2013, 62 new cases of acute HCV infection were notified to the National Institute of Public Health and the Environment (RIVM). Of these cases only two were reported to be due to injecting drug use<sup>26</sup> and an earlier study performed in 1999 to 2001 showed that 6% of all new HCV cases were attributable to injecting drug use.<sup>24</sup> In line with these findings, cohort studies show a very low incidence.<sup>27</sup> Therefore, in the model the annual number of new cases due to injecting drug use was considered low. In the Netherlands, as in many other countries, transfusion of blood products has not been considered a risk factor for new HCV infections since 1992, as donor blood screening started in 1991. A linear declining rate was applied to get the percentage of total infections attributed to transfusion to zero by 2030. The annual number of new cases due to immigration was calculated by gathering net annual immigration, by country of origin and the corresponding anti-HCV prevalence in the country of origin. Based on the immigration data the numbers increase from 1995 until 2011, and then stay constant from 2011 onwards (see notes in *table 2* for more details).<sup>2</sup> Another group with a high risk

**Table 1.** HCV genotype distribution in the Netherlands, 2002-2005<sup>19</sup>

Genotype	%
1a	14.8
1b	15.7
1 Other/NA	18.8
2	9.7
3	19.1
4	10.5
5	0.0
6	0.0
Other	1.1

of a new HCV infection is the group of HIV-positive men who have sex with men (MSM). Of the 362 newly reported HCV infections in 2013, 155 were among HIV-positive MSM.<sup>28</sup> The risk of re-infection is considered low among people who inject drugs<sup>29</sup> but substantial among MSM<sup>30</sup> in the Netherlands. However, in the model we used, it was not possible to consider re-infections.

The model calculated the annual number of all-cause and liver-related deaths and the cured cases as described below.

*Progression rates*

Disease progression by age and sex was simulated by multiplying the total number of cases at a particular stage of the disease by a progression rate to the next stage. The rates were gathered from previous studies<sup>5,12,31-37</sup> or

**Table 2. Model inputs and 2014 estimations**

	Historical (min-max uncertainty interval)	Year (Reference)	2014 (95% uncertainty interval)
<b>HCV-infected cases</b>			
Number of anti-HCV cases	29,450 (9400-49,530) <sup>1</sup>	2009	26,010 <sup>2</sup> (7,140-45,820)
Anti-HCV prevalence	0.2% (0.1%-0.3%) <sup>1</sup>		0.2% (0.0%-0.3%)
Number of viraemic cases	21,800 (6370-36,650) <sup>1</sup>	2009	19,200 (4740-35,480) <sup>2</sup>
Viraemic prevalence	0.13% (0.0%-0.2%) <sup>1</sup>		0.12% (0.0%-0.2%)
Viraemic rate	74.0% <sup>3</sup>		74.0%
<b>HCV diagnosed (viraemic)</b>			
Viraemic diagnosed	10,470 <sup>4</sup>	2013	10,200
Viraemic diagnosis rate			51.1%
Annual newly diagnosed	650 <sup>5</sup>	2013	650
<b>New infections</b>			
New infections			510 <sup>6</sup>
New infection rate (per 100K)			3.0
<b>Treated</b>			
Number treated			880 <sup>7</sup>
Annual treatment rate			4.5%
<b>Risk factors</b>			
Infected via injecting drug use (%)			4090 (21.3%) <sup>8</sup>
Infected via blood transfusion (%)	6.0% <sup>9</sup>	2000	614 (3.2%)

<sup>1</sup>The reported prevalence of anti-HCV antibodies was 0.22% (28,100) in 15-79 year olds.<sup>9</sup> Prevalence in older and younger individuals was extrapolated resulting in an overall prevalence of 0.18% or 29,450 for all ages. The viraemic rate was applied to both the viraemic prevalence as well as the number of viraemic cases. <sup>2</sup>Model estimate after considering new infections and cured. <sup>3</sup>Thomas et al.<sup>15</sup> <sup>4</sup>Panel expert estimate – over the last 20 years, on average 600 individuals were newly diagnosed per year, the panel estimated 650 in 2013. <sup>5</sup>According to laboratory reports, 679 cases were newly diagnosed in 2011 and 500 cases in 2012. In 2013, it was estimated that 650 HCV infections were newly diagnosed (expert panel together with literature findings). <sup>6</sup>New viraemic infections estimated using the following data: 6 among IDU, 354 among immigrants (used Statistics Netherlands to calculate net immigrants in 2011 (n = 35,131) with an average prevalence of 1.01%; the average prevalence included an adjustment for a lower HCV prevalence among younger immigrants), 155 among HIV+ MSM (incidence rate of 12/1000 (from Van den Berg et al.<sup>27</sup>) applied to 12,880 HIV+ MSM who are HCV negative of a total of 14,000 HIV+ MSM of whom 8% is already HIV/HCV co-infected), 6 nosocomial infections (range 4-8). This adds up to a total of 521 new infections. <sup>7</sup>GIPdatabank<sup>41,42</sup>. <sup>8</sup>EMCDDA – European Drug Report 2013.<sup>9</sup> Chaves et al.<sup>24</sup>

calculated using known numbers from Dutch national reports. Liver transplant data were available through the Eurotransplant Statistics Report Library and from the individual transplant centres in the Netherlands. In 2013, there were 142 liver transplants performed in the Netherlands.<sup>38</sup> Of all liver transplants 12% are attributable to HCV infection each year (a frequency of 11-13% over the past 12 years, based on personal communication with the three transplant centres in the Netherlands). The total number of cases was adjusted for ageing, all-cause mortality and proportion of cured HCV infections in any given year.

#### All-cause mortality

The all-cause mortality rates by age and gender were gathered from the Human Mortality Database.<sup>39</sup> Mortality rates were adjusted using standard mortality ratios among

people who inject drugs and individuals who have received blood products.<sup>40</sup>

#### Treated and cured

Analysis of ribavirin units sold (for chronic or acute HCV infection) was used to estimate the total number of treated HCV patients in the Netherlands.<sup>41,42</sup> In 2013, this number was 880. It was assumed that the number of treated patients stayed constant after this last reported year (2013). It was also assumed that the number of treated patients for each genotype was proportional to the genotype distribution of the HCV-infected population.

The annual number of cured patients was estimated using the average sustained viral response (SVR) rate of the different treatments in a given year (SVR rates were based on available literature).<sup>43-45</sup> A separate SVR was used for the major genotypes, as shown in *figure 3*. A weighted

average of different treatment options in a given year was considered (dual therapy with peginterferon and ribavirin or triple therapy with peginterferon, ribavirin and a direct-acting antiviral (DAA)).

The number of cured patients from all genotypes was summed by stage of the disease and we assumed that the numbers were equally distributed among eligible age cohorts.

*Treatment protocols and strategies*

The model interface allowed for changing assumptions for the number of patients treated, the proportion of cases eligible for treatment, the reduction in treatment restrictions, the average SVR rate by genotype, the number of newly diagnosed individuals and the number of new infections at five different points in time. The year in which these changes were observed was also an input field. The different new therapies considered were: DAA + peginterferon + ribavirin, DAA + ribavirin (interferon-free) and all-oral DAA combinations with or without ribavirin. For the model, we assumed that all changes took effect immediately. The co-existence of multiple therapies was handled by modifying the average SVR.

The pool of patients who could be treated was impacted by explicit or implicit treatment protocols. According to the literature, approximately 40-60% of HCV patients are eligible for peginterferon /ribavirin.<sup>43-45</sup> The definition of eligibility includes contraindications to the drugs as well as patient preference. In this analysis, 60% of the patients were considered eligible for standard-of-care treatment (figure 3), being peginterferon + ribavirin for genotype 2 to 6 and peginterferon + ribavirin + DAA for genotype 1.

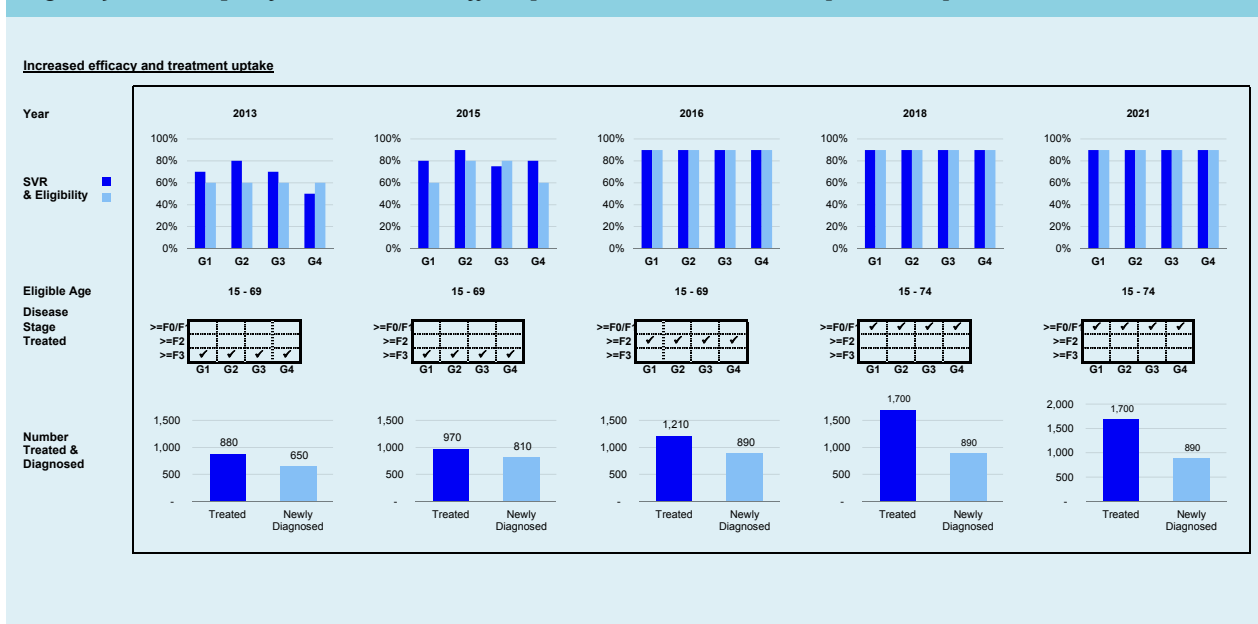
When peginterferon could be eliminated, the eligibility was increased. We assumed that the increase in eligibility would not directly increase the number of patients treated in the future. However, we assumed that it did increase the pool of diagnosed and eligible patients who could be drawn upon. Any changes in treatment were implemented using a separate input.

The future number of treated patients was capped by (I) the number already diagnosed, (II) number eligible, and (III) unrestricted cases, related to implicit (defined by physicians' practice) and/or explicit (defined by treatment guidelines) restrictions. These restrictions could be modified by changing the upper and lower end of patient age and their stage of fibrosis (F4 (Child-Pugh A, B or C), F3, F2, or F1/F0). Review of the treatment guidelines and interviews with the expert panel were used to identify both of these factors. Decompensated cirrhotic patients were considered ineligible for peginterferon-containing therapies (irrespective of genotype). The fibrosis stages eligible for treatment are shown in figure 3. When the number of treated patients was greater than those diagnosed, eligible and unrestricted, the number of newly diagnosed cases was increased or the treatment restrictions were loosened. The focus of the analysis was to highlight how many cases have to be diagnosed to achieve a treatment strategy rather than to forecast the screening capacity.

**Scenarios**

Multiple treatment strategies were considered and are described below: base scenario, increased efficacy only, increased efficacy and treatment uptake, screening and

**Figure 3. Model inputs for the 'Increased efficacy and treatment scenario', by calendar year**





elimination, and focused treatment of individuals with different fibrosis stages. Scenario inputs, including SVR, fibrosis stage and medical eligibility, divided by genotype and year, are shown in *figure 3*. The numbers of treated and diagnosed patients necessary to achieve the desired scenario outputs are also shown.

In all instances, HCV-viraemic infections represented all current HCV infections (acute and chronic HCV infections). The term viraemic was used throughout this study to highlight the presence of HCV-RNA. The term incidence was used for new HCV infections per calendar year and not newly diagnosed. Hepatocellular carcinoma referred to the total number of viraemic HCV-related hepatocellular carcinoma cases, rather than new cases. Additionally, all reductions by disease stage were assumed to occur among the viraemic HCV-infected population. The effects of non-HCV-related liver disease were not considered in this analysis.

#### *Base scenario*

The base scenario was defined as the scenario where all assumptions (the number of acute cases, treated patients, percentage of patients eligible for treatment, treatment restrictions, the number of newly diagnosed and the average SVR by genotype) remained the same as in 2013-2014. The base scenario was previously described in detail, together with other countries,<sup>17,46</sup> and was assumed to be the most conservative scenario. Even more conservative scenarios are possible (e.g., stop treating HCV-infected patients completely), but those were deemed to be unlikely.

As described above, in this scenario we assumed 650 newly diagnosed HCV infections annually and treatment of 880 HCV infections annually in the Netherlands. Treatment in this scenario was focused on patients aged 15-69 years and with a METAVIR score of  $\geq F_3$  assessed using FibroScan. In the light of a future high treatment rate, we considered patients with a fibrosis stage of  $\geq F_2$  (according to METAVIR, measured using FibroScan) eligible for treatment in 2018, and patients with a fibrosis stage of  $\geq F_0/F_1$  eligible for treatment in 2021. We assumed SVR rates of 70% for genotype (G) 1 and G3, 80% for genotype 2 (G2) and 50% for genotype 4 (G4). We used fibrosis scores obtained using FibroScans because that is the most common mode of fibrosis assessment at the moment.

#### *Increased efficacy only*

A second scenario was developed to assess the impact of improved treatment efficacy without changes in the number of treated or diagnosed patients. Treatment age and fibrosis staging eligible for treatment, as presented in the base scenario, was held constant. In 2015, it was projected that SVR could increase to 80% for G1 and G4, 90% for G2 and 75% for G3. In 2016, SVR was estimated

at 90% across all genotypes. These rates were held constant through to 2030.

#### *Increased efficacy and treatment uptake*

A third scenario was created to assess the actions necessary to eliminate chronic HCV infection by 2030. Beginning in 2015, treatment uptake was increased by 10% across all genotypes to 970 individuals and the number of diagnoses was increased by 25% to 810 individuals annually. Treatment was open to individuals aged 15 to 69 years. In 2016, treatment uptake was increased to 1210 individuals annually and diagnosis was increased to 890 individuals annually. Patients with fibrosis  $\geq F_2$  were considered eligible for treatment. In 2018, treatment uptake was increased to 1700 individuals annually. Treatment was now also open for patients with fibrosis  $> F_0/F_1$  and the eligible age range was increased up to 74 years. Treatment and diagnosis uptake were held constant from 2018 through to 2030. In 2021, all patients, regardless of fibrosis staging, were eligible for treatment.

#### *Screening and elimination*

A fourth scenario was created to assess the response of increased treatment and the corresponding required increase in screening (and diagnoses) to keep up with treatment. In addition, it was assumed that preventive measures will be taken to reduce the number of new infections by 40% over six years.

#### *Focused treatment: $\geq F_3$ , $\geq F_2$ , $\geq F_0/F_1$*

A fifth, sixth and seventh scenario were created to assess the impact of focused treatment of individuals with fibrosis  $\geq F_3$ ,  $\geq F_2$  and  $\geq F_0/F_1$ . Starting in 2015 treatment uptake was increased by 10% across all genotypes to 970 individuals and the number of diagnoses was increased by 25% to 810 individuals. In 2016, the treatment uptake increased by 25% to 1210 individuals and the diagnosis rate increased 10% to 890 individuals annually. By 2018, the eligible age range was increased to 74 years while treatment was increased by 40% to 700 individuals, as in this year treatment exceeded eligible individuals. For the  $\geq F_2$  and  $\geq F_0/F_1$  scenarios treatment uptake was increased by 40% to 1700 individuals. In 2021, the number of diagnoses was kept constant at 890 individuals. For the  $\geq F_3$  scenario 400 individuals were treated annually. For the  $\geq F_2$  scenario 530 individuals were treated as the treatment outpaced eligibility in 2020. For the  $\geq F_0/F_1$  scenario 1700 individuals were treated annually.

#### *Birth cohort effect*

The age distribution was determined as described above.<sup>10,17</sup> The disease progression model was used to age the HCV-infected population after taking into account mortality and SVR.<sup>24</sup> For this analysis, the median age

in each five-year age cohort was selected and converted to a birth year. A range of birth years were selected which accounted for approximately 75% (or more) of the total HCV-infected population using the 2014 HCV population distribution.<sup>4</sup> The number of people that need to be screened to identify one viraemic case was calculated by taking the inverse of the viraemic HCV prevalence. The number needed to screen to identify one new case was calculated as follows:

$$\frac{1}{(\text{HCV viraemic prevalence} * (1 - \% \text{ of HCV population already diagnosed}))}$$

**RESULTS**

The results of the literature review and expert opinion, including estimates of HCV antibody and HCV viraemia prevalence, diagnosis, as well as annual treatment and liver transplants are summarised in *table 2*.

**Base scenario**

Using historical data,<sup>9</sup> it was estimated that there were around 19,200 individuals in the Netherlands with a viraemic HCV infection in 2014. This was forecasted

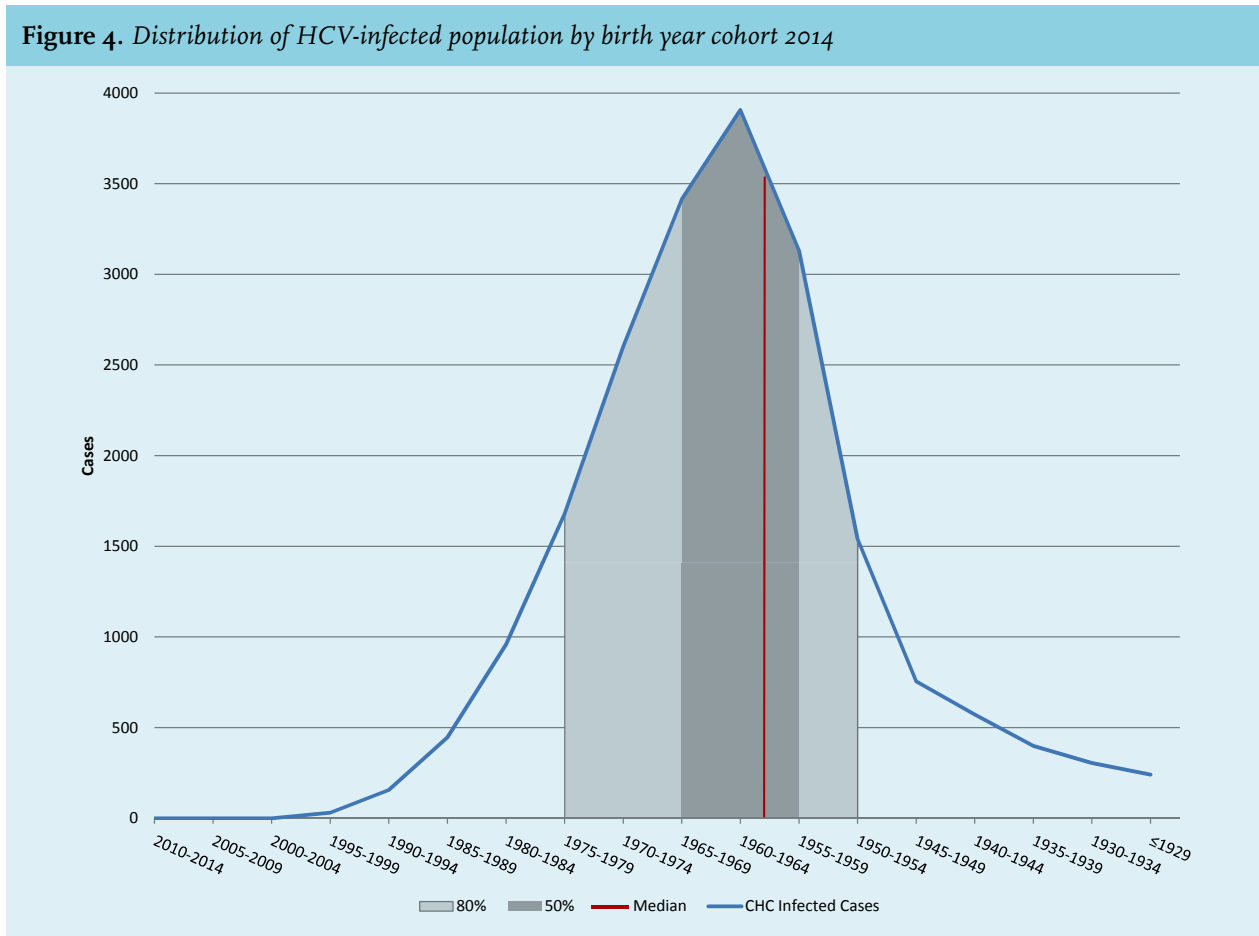
to decrease to 10,599 (45%) in 2030. The number of HCV-related hepatocellular carcinoma cases in 2014 was estimated at 110, and it was forecasted to decrease by 19% by 2030. The number of liver-related deaths in chronic HCV patients was forecasted to decrease 27% from a base of 102. *Figure 2* shows the age and gender distribution of the HCV-infected population in 2009 while *figure 4* shows the projected age distribution in 2014. *Figure 5* shows the number of viraemic HCV infections over time in the Netherlands from 1950 to 2030 and *figure 6* shows the projected HCV disease burden for this period.

**Other scenarios**

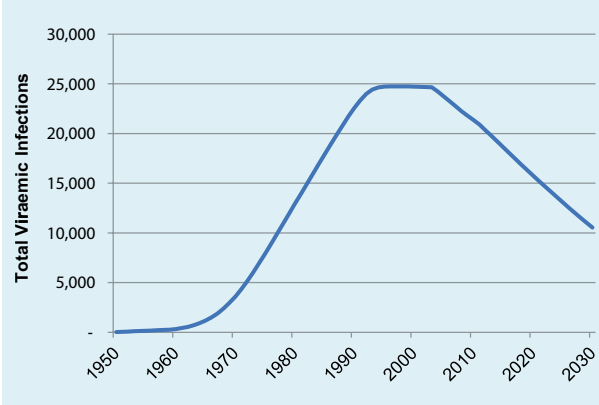
The results of the analyses for HCV morbidity and mortality, by scenario, are summarised in *figure 7* and the percent change from the base scenario can be found in *figure 8*. *Table 3* compares the change in HCV disease burden in 2014-2030 by scenario.

*Increased efficacy only*

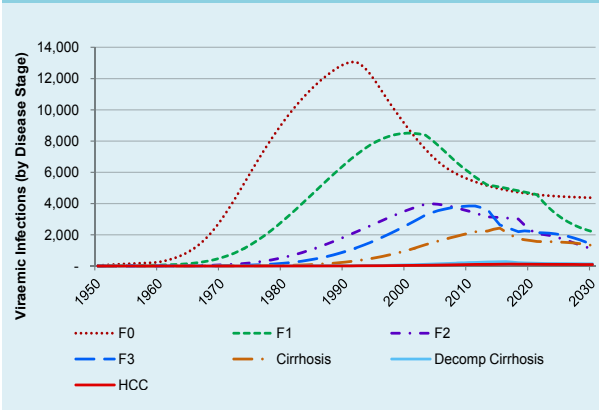
There will be 2413 fewer HCV-viraemic individuals in 2030, a 23% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths both decrease by 25% from the base scenario. This scenario would result in 463 cirrhosis cases being averted.



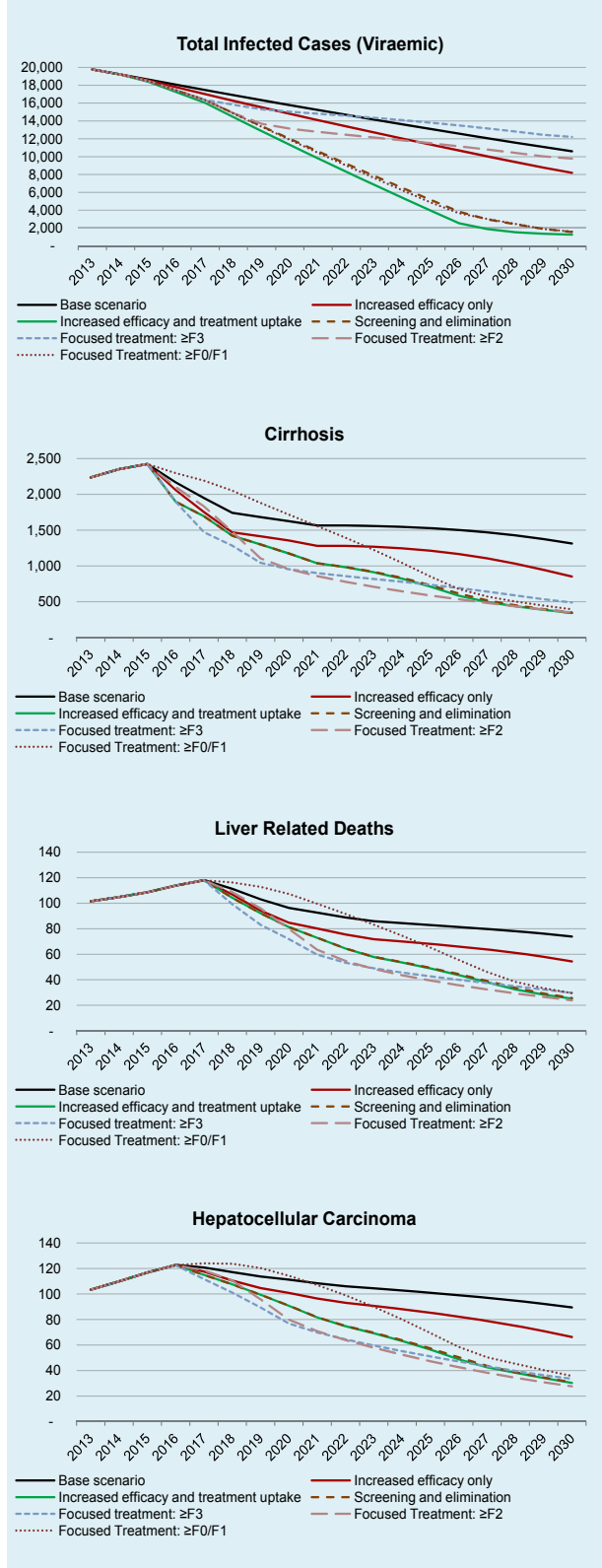
**Figure 5.** The number of viraemic HCV infections over time, the Netherlands 1950-2030 (base scenario)



**Figure 6.** HCV disease burden over time, the Netherlands 1950-2030 (base scenario)



**Figure 7.** HCV characteristics, by scenario, the Netherlands 2013-2030



*Increased efficacy and treatment uptake*

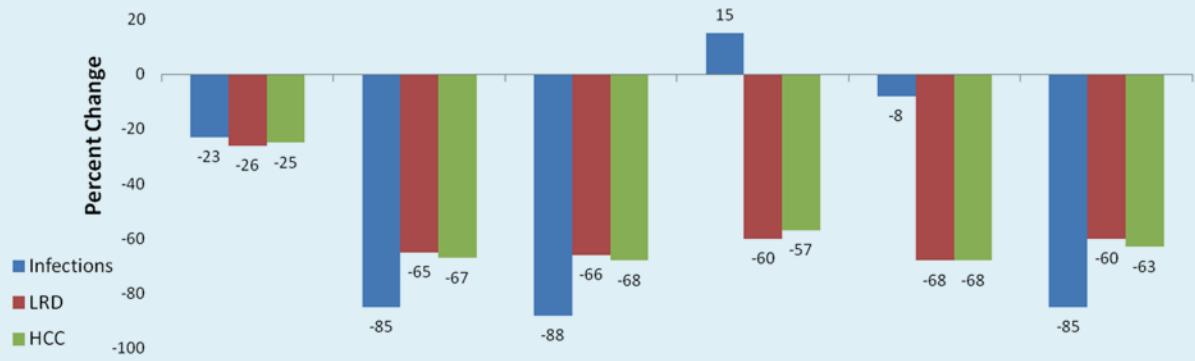
With an aggressive treatment and diagnosis strategy, there will be 9043 fewer HCV-viraemic individuals in 2030, an 85% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths in 2030 decrease by 67% and 65%, respectively, from the base scenario. This scenario would result in 964 cirrhotic cases being averted.

*Screening and elimination*

With a screening and elimination strategy, there will be 9334 fewer HCV-viraemic individuals in 2030, an 88% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths in 2030 decrease by 68%

**Figure 8.** Percent change from the base scenario to 2030 with treatment by scenario

Scenario	Increased efficacy only	Increased efficacy and treatment uptake	Screening and elimination	Focused treatment: $\geq F_3$	Focused treatment: $\geq F_2$	Focused treatment: $\geq F_0/F_1$
Maximum Treated	880	1700	1700	1210	1700	1700
Max Year	-	2018-2027	2018-2026	2016-2017	2018-2019	2018-2026
2030 Treated	880	410	270	370	390	420



HCC =hepatocellular carcinoma; LRD = liver-related death.

**Table 3.** Predicted number of viraemic HCV infections, cases with hepatocellular carcinoma and liver-related deaths according to scenario from 2014 to 2030

Scenario	HCV infections N	HCC N	LRD N
2014 (base)	19,200	110	102
Base scenario N (% decrease*)	10,599 (45)	89 (19)	74 (27)
Increased efficacy only N (% decrease*) Compared with base scenario	8187 (57) - 23%	66 (40) - 25%	54 (47) - 25%
Increased efficacy and treatment uptake N (% decrease*) Compared with base scenario	1556 (92) - 85%	30 (73) - 67%	25 (75) - 65%
Screening and elimination N (% decrease*) Compared with base scenario	1265 (93) -88%	31 (72) - 68%	26 (75) - 66%
Focused treatment: $\geq F_3$ N (% decrease*) Compared with base scenario	12,210 (36) +15%	33 (79) - 57%	30 (71) - 60%
Focused treatment: $\geq F_2$ N (% decrease*) Compared with base scenario	9788 (49) - 8%	28 (75) - 68%	24 (76) - 68%
Focused treatment: $\geq F_0/F_1$ N (% decrease*) Compared with base scenario	1600 (92) - 85%	36 (76) - 63%	30 (71) - 60%

\*Decrease compared with base (from 2014 to 2030). HCC = hepatocellular carcinoma; LRD = liver-related deaths.

and 66% respectively from the base scenario. This scenario would result in 972 cirrhotic cases being averted.

*Focused treatment:  $\geq F_3$*

There will be 1610 more HCV-viraemic individuals in 2030, a 15% increase as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths

in 2030 decrease by 57% and 60%, respectively, from the base scenario. This scenario would result in 825 cirrhotic cases being averted.

*Focused treatment:  $\geq F_2$*

There will be 811 fewer HCV-viraemic individuals in 2030, an 8% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma

**Table 4.** HCV viraemic prevalence according to screening by birth cohort

	General	1955-1969	1950-1979	1960-1964
HCV prevalence	0.12%	0.28%	0.23%	0.31%
Tests required to identify 1 viraemic case	833	354	430	322
Tests required to identify 1 new case	1706	725	880	659

cases and the number of liver-related deaths in 2030 both decrease by 68% from the base scenario. This scenario would result in 965 cirrhotic cases being averted.

#### *Focused treatment: $\geq F_0/F_1$*

There will be 8999 fewer HCV-viraemic individuals in 2030, an 85% reduction as compared with the base scenario. The number of HCV-related hepatocellular carcinoma cases and the number of liver-related deaths in 2030 decrease by 63% and 60% respectively from the base scenario. This scenario would result in 921 cirrhotic cases being averted.

#### *Birth cohort*

The median age of the viraemic HCV-infected population in 2014 was 51 years (birth year 1963). More than 50% of the viraemic HCV-infected population was born between 1955 and 1969; over 80% were born between 1950 and 1979 (*figure 4*). The highest prevalence of HCV viraemia is in the population born between 1960 and 1964 (0.31%). By focusing screening on this birth cohort it is estimated that one case can be newly diagnosed for every 659 screened (after taking into consideration those already diagnosed), if participation rates are equal among HCV-infected and uninfected individuals within this age cohort (*table 4*). It was assumed that 51% of the total HCV-viraemic population have been diagnosed for all age groups.

#### **Sensitivity analysis**

A sensitivity analysis was conducted to assess the effect of variations in different input and outcome parameters (new infections 2014, treatment 2014, fibrosis stage, progression to hepatocellular carcinoma and/or liver-related death) on the key driver of uncertainty in HCV prevalence (range 0.05-0.27%).<sup>9</sup> Since the model is based on the incidence of HCV, the number of new HCV infections required to match the reported prevalence was calculated in the model. The top driver reflecting the uncertainty in HCV prevalence is new HCV infections. This has a direct impact on the forecasted population by disease stage, mortality and disease progression. The impact of all other assumptions was small.

## **DISCUSSION**

Under the current treatment structure, the base scenario, the prevalence of viraemic HCV infection is projected to decrease by 45% over the next 15 years. This sharp decline is likely attributed to successful treatment of HCV infection and lower mortality among the ageing population, in combination with low incidence of new HCV infections. Although transmission of HCV in the Netherlands is low, HCV-related mortality and occurrence of hepatocellular carcinoma is substantial. Treatment of HCV infection in an early stage might prevent the occurrence of HCV-related mortality and hepatocellular carcinoma.

Of all scenarios, the 'screening and elimination' scenario predicts the largest reduction of 88% in viraemic HCV infection prevalence in the Netherlands. This scenario is probably not the most feasible scenario as it requires screening and prevention programs to achieve the inputs required. A more realistic scenario would be the 'increased efficacy and treatment uptake' scenario, in which a phased increase of treatment uptake is calculated based upon genotype and fibrosis stage. This scenario predicts only a slightly smaller reduction in viraemic HCV infection prevalence compared with the base scenario of 85%.

If we focus on liver-related deaths and hepatocellular carcinoma, the ' $\geq F_2$  only model' provides the greatest decrease from the base scenario (both liver-related deaths and hepatocellular carcinoma 68%). However, the decrease in this model is only slightly greater than the decrease predicted by the 'screening and elimination model', the 'increased efficacy and treatment uptake model' and the '>  $F_0/F_1$  model' (68% for the ' $\geq F_2$  only model' versus 60 to 67% for the other three models). Besides this, the ' $F_2$  only model' predicts only a slight reduction in viraemic HCV infection prevalence (8%) whereas the other three models predict a reduction of 85 to 88% compared with the base scenario.

Taken together, it seems that the 'increased efficacy and treatment uptake' scenario is the most feasible scenario in the current Dutch situation, which also predicts substantial reductions in viraemic HCV infection prevalence, hepatocellular carcinoma and liver-related

deaths. However, due to the current high costs of treatment with DAAs it is very unlikely that this scenario will be adopted in the near future. Lower prices of DAAs are necessary to make this scenario, in which a substantial decrease of prevalent HCV infections can be achieved, more realistic.

Most of the described models require an increase in treatment uptake to 1700 individuals annually and allowing treatment access to individuals regardless of fibrosis stage. Over the last years there have been about 1000 (range: 880-1130) treatments with peginterferon and ribavirin (with or without DAAs) annually.<sup>41,42</sup> Assuming that this number is representative of the number of treatments for HCV, an increase from 1000 to 1700 treatments annually may be feasible with the current capacity in the Netherlands as new therapies have a shorter duration and less side effects. Next to this, it should be noted that the increase in treatment uptake per year is only required for the first eight years. After this initial investment, the yearly treatment drops significantly to 270 patients treated yearly by 2030.

Increases in SVR have the potential to result in favourable improvements in end-stage liver disease, with maybe few changes in the ultimate treatment rates. With the new treatment regimens with low side effects, treatment uptake is likely to increase, and with the high SVR rates, the need for retreatment will be low. It is known that curing HCV infection in liver cirrhosis patients reduces complications of cirrhosis and risk of hepatocellular carcinoma.<sup>47</sup> However, although reduced, these patients are still at risk of decompensation of liver cirrhosis and/or hepatocellular carcinoma. They are therefore advised to remain in long-term clinical care for monitoring progression of liver disease and/or development of hepatocellular carcinoma. In the current model these patients were not considered as a continued burden of HCV infection after SVR. From this point of view, it might be worthwhile to treat patients before the stage of cirrhosis, as the risk of hepatocellular carcinoma following SVR among patients with Fo-I-2-3 is negligible.<sup>48</sup> This higher treatment rate (with high SVR rates) for patients with a lower fibrosis stage may have favourable improvements in end-stage liver disease with no changes in the eventual treatment rates and could prevent ongoing transmission.<sup>47,49</sup> This might save future costs for follow-up of chronic liver disease (cirrhosis) and long-term hepatocellular carcinoma monitoring. Next to this, achievement of SVR after treatment of chronic HCV reduces non-liver related mortality and hepatic and extra-hepatic manifestations of HCV infection, and improves quality of life. These are all factors in reducing healthcare costs related to HCV infection.<sup>50</sup>

Achievement of our described strategy to treat more HCV patients is dependent upon the detection of people with

HCV infection, thus reinforcing the need for increased awareness and intensified screening among risk groups and professionals.

One might consider a risk-group approach. Alternatively, focusing on a birth cohort of 1960-to 1964 without prior assessment of HCV risk might be effective as our model suggests that one newly diagnosed viraemic case may be found per 659 tests, compared with 1 out of 1706 for the general population. This approach was chosen in the USA and was described in 2012.<sup>51</sup> However, the effectiveness and cost-effectiveness of a birth cohort screening strategy or a modified birth cohort screening strategy in which additional risk-based screening criteria are used, need to be determined. Also, it is difficult to suggest specific recommendations on birth cohort screening as the age and gender distribution of the viraemic HCV-infected population in the Netherlands is not well known.

For first-generation migrants born in countries where HCV infection is endemic, and other difficult-to-reach risk groups for HCV, various pilot screening projects have been performed in recent years, using different screening strategies.<sup>52-57</sup> However, the costs and effectiveness of these strategies relative to each other has not been studied yet, hampering efficient targeting of screening programs. Moreover, there is no structural screening program for migrant groups in place and combining HCV screening with screening for other infections might be considered. We suggest that cost-effectiveness analyses of screening strategies targeted at first-generation migrants should be performed and awareness among risk groups as well as healthcare professionals should be increased. Increasing knowledge of HCV infection among healthcare professionals and the general population may also lower the barriers of testing and referring.<sup>58</sup>

Besides migrants, two other groups require attention. The first group consists of people who have already been diagnosed with a viraemic infection in the past (e.g. HCV-infected blood donors) but have been lost to follow-up in clinical care. The feasibility to retrieve these individuals should be investigated. The second group is more difficult to find because it is hidden in society: individuals that have injected drugs in the past, acquired a tattoo in an endemic region, or received a blood transfusion before 1992. For this group, again, awareness should be increased for both the individuals themselves and the healthcare professionals, in particular general practitioners and public health workers. Innovative approaches such as internet-mediated blood screening services<sup>58</sup> might be considered. There are some factors that limit the value of the described outcomes of the prediction models. First, many parameters that were used as input are based on assumptions or data of less recent years. These data include the current and future number of diagnosed and treated viraemic HCV



infections, and the distribution of genotype, fibrosis stage, age and gender of treated and untreated patients. Retrieving actual figures on the different parameters in the Netherlands is very difficult, as there is no national registry of HCV patients in place. The sensitivity analysis that was conducted with the key driver of uncertainty in HCV prevalence was in turn driven by uncertainty in the number of new HCV infections. The impact of all other assumptions was small. Second, parameters were not specified per risk group. These groups, however, have different characteristics, including the proportion diagnosed, genotypes, treatment rates and treatment outcome, influencing the outcome of the models. Third, factors such as sex differences and HIV infection, and their impact on clearance and HCV disease progression, have not been taken into account. Fourth, in this analysis it was assumed that the number of new infections and re-infections remained constant in all scenarios described. While disease progression models can predict disease burden, they are less accurate for estimating future prevalence as they do not explicitly model HCV transmission nor include the possibility of re-infection following successful therapy.<sup>39</sup> Finally, FibroScan was used for assessing the fibrosis score as a selection criterion for treatment and defining the different groups for the models. This might not be the most accurate method as FibroScan scores are only reliable in low (F0) and high (F4) ranges, but are not between METAVIR scores F1 to F3. Also, FibroScan does not differentiate between METAVIR scores F2 and F3. Fibrosis staging in this range should be done using a liver biopsy. These limitations may lead to incorrect inputs and estimations, leading in turn to incorrect predictions. Over time, the input of the models may have to be adjusted and updated, and linked with transmission models to achieve correct predictions. In conclusion, the largest decrease in viraemic HCV infections in the Netherlands may be achieved by applying the ‘elimination’ strategy. Preventing progression of HCV-related liver disease leading to HCV-related death and hepatocellular carcinoma is best achieved when using the ‘ $\geq$  F2 fibrosis’ strategy. The most realistic scenario with reasonable reductions in HCV prevalence, HCV-related death and hepatocellular carcinoma would be the ‘increased efficacy and treatment uptake’ strategy with a phased increase of treatment uptake. To be able to achieve these future goals, diagnosis of people with HCV infections in the Netherlands who may benefit from treatment should be increased. Prevalence data and knowledge regarding facilitating and impeding factors for HCV screening are needed for the largest risk groups separately (including the different migrant groups). Awareness among risk groups and professionals as well as the general population should be increased whereas

barriers on different levels (practical, psychological) should be lowered.

A coordinated national strategy and sufficient financial means to support it are needed to achieve these goals. The presented models on the future disease burden might inform our national strategy.

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## DISCLOSURES

S.B. Willemse: AbbVie (C), BMS (C,R), Gilead Sciences (C,R), Roche (C).

D. Razavi-Shearer: AbbVie (R), Boehringer Ingelheim (R), Gilead Sciences (R), Intercept (R).

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M. Prins: Gilead Sciences (C,R), MSD (C,R), Roche (C,R).

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# Epstein-Barr virus mimicking lymphoma – A case report

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## ABSTRACT

A 50-year-old male without a relevant medical history came to the emergency department with fever, muscle pain and fatigue without any localising symptoms. Blood and urine cultures remained negative. Laboratory work-up showed elevated liver enzymes and lactate dehydrogenase; Epstein-Barr virus (EBV) serology was negative. Additional imaging showed a splenomegaly and cervical, axillary, mediastinal and hilar lymphadenopathy. Pathological examination of one of the lymph nodes and bone marrow biopsy revealed a peripheral T-cell non-Hodgkin's lymphoma not otherwise specified. Before the start of treatment he was asymptomatic, the laboratory results had normalised and the EBV polymerase chain reaction was strongly positive. Computed tomography scan was repeated and showed complete remission of the lymphadenopathy and normalised spleen volume. Follow-up bone marrow analysis including clonal rearrangement of the T-cell receptor after three months and one year revealed a decreasing clonal T-cell population (41%, 39% and 11% respectively). In conclusion, this was an extreme course of an EBV infection. The clinical relevance of the remaining small monoclonal T-cell population detectable in the bone marrow is unclear.

## KEYWORDS

Epstein-Barr virus (EBV), mimicking lymphoma, T-cell non-Hodgkin's lymphoma NOS

## INTRODUCTION

Non-Hodgkin's lymphoma is rarely associated with a previous Epstein-Barr virus (EBV) infection; however, EBV

infection may also mimic non-Hodgkin's lymphoma. We present a patient with an unusual course of EBV infection which was initially diagnosed as a T-cell non-Hodgkin's lymphoma.

## CASE REPORT

A 50-year-old male, without relevant medical history, presented to the emergency department with intermittent fever, muscle pain and fatigue for four weeks. Localising symptoms or other B-symptoms, except for fever, were absent. At presentation he was afebrile and physical examination was unremarkable and negative for lymphadenopathy or organomegaly. Laboratory investigations revealed the following: C-reactive protein 3 mg/l (< 10), leukocytes  $19.4 \times 10^9/l$  (4.5-11), leukocyte differential count showed bands 2% (0-5), segments 7% (45-75), lymphocytes 85% (20-50), monocytes 4% (2-10), basophils 2% (0-2) and many atypical lymphocytes, direct bilirubin 12  $\mu\text{mol/l}$  (< 17), alkaline phosphatase 256 U/l (< 90), gamma-GT 665 U/l (< 50), aspartate aminotransferase 78 U/l (< 35), alanine aminotransferase 102 U/l (< 45), and lactate dehydrogenase 1241 U/l (< 248). Electrolytes and creatinine were normal. Urinalysis was normal and the chest X-ray showed no infiltrative abnormalities. Virus serology was negative for an acute infection with EBV (VIDAS Biomerieux: EBV IgM negative, EBV nuclear antigen (EBNA) negative, viral capsid antigen (VCA) IgG indeterminate), cytomegalovirus, hepatitis B, C and human immunodeficiency virus. Blood and urine cultures remained negative. Additional imaging was performed, computed tomography of the neck/ thorax/ abdomen showed cervical (7 and 12 mm), axillary (8 and 11 mm), mediastinal and hilar (12 mm) lymphadenopathy and splenomegaly (15 cm). Additional diagnostic lymph node extirpation and bone marrow biopsy were performed.



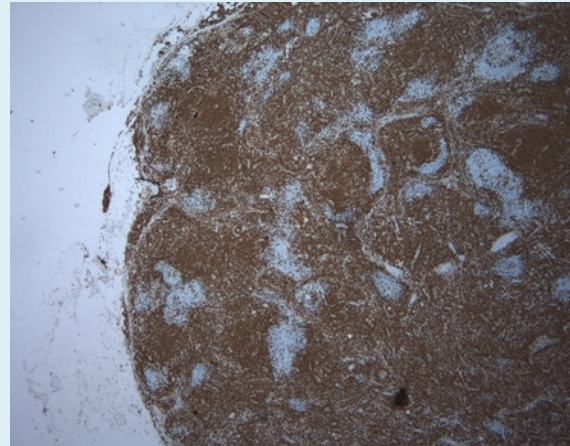
The lymph node revealed disturbed architecture and expansion into the adjacent tissue. The paracortical expansion is caused by an increase in T-lymphocytes (*figure 1*), resulting in a strong suspicion of a peripheral T-cell non-Hodgkin's lymphoma not otherwise specified (NOS). Clonality analysis confirmed monoclonality of the T-cell population. Immunohistochemistry revealed a T-cell fraction which shows a uniform and strong immunoreactivity with antibodies against Ki67 and in the background Epstein-Barr virus-encoded small RNA (EBER) positive blasts (*figure 2*). Bone marrow biopsy also revealed a peripheral T-cell non-Hodgkin's lymphoma NOS. Morphological analysis showed a strongly increased lymphopoiesis of 54% and at immunophenotyping 47% were lymphocytes of which 41% T-lymphocytes, especially CD8+. Clonality analysis of the lymph node and bone marrow showed an identical clonal T-cell population.

In conclusion, our patient was diagnosed with a stage IV T-cell non-Hodgkin's lymphoma NOS. Suggested treatment was two weekly cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy followed by autologous stem cell transplantation. At presentation to the outpatient clinic he was asymptomatic and the laboratory results had normalised. Virus serology was repeated on serum drawn seven days after the first serology was performed, as a biomarker of a T-cell non-Hodgkin's lymphoma; this test was positive for EBV with VCA IgG and IgM and the EBNA test was positive (Diasorin LIAISON® EBV). The first serum sample was tested for EBV DNA by polymerase chain reaction (PCR), the result was positive  $3.9 \times 10^4$  copies/ml. Chemotherapy was cancelled. CT scan was repeated and showed no lymphadenopathy and a normalised spleen volume. EBV PCR was dubiously positive after one month and one year of follow-up. Follow-up bone marrow analysis after three months and one year revealed an unchanged identical clonality analysis but a decreasing abnormal T-cell population (41%, 39% and 11% respectively). Eventually this was diagnosed as an unusual course of EBV infection, after the initial diagnosis of T-cell non-Hodgkin's lymphoma. The clinical relevance of the remaining small monoclonal T-cell population detectable in the bone marrow is unclear.

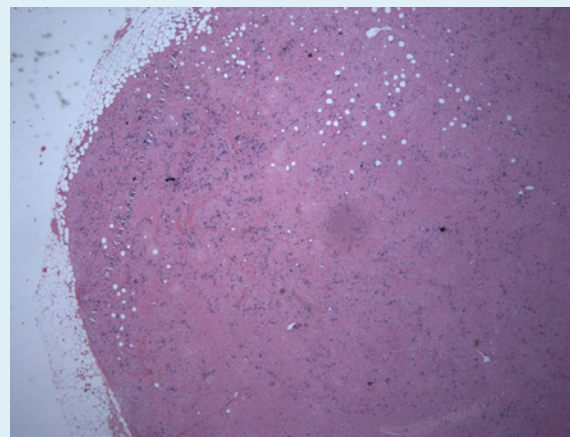
## DISCUSSION

Epstein-Barr virus is a widespread herpesvirus and the primary agent of mononucleosis infectiosa. An IgM class antibody directed against the viral capsid antigen (anti-VCA IgM) is the first humoral response. In one article Odumade et al. reported that 90% of the anti-VCA IgM became positive within seven days of onset of symptoms, in six patients they became positive during the second

**Figure 1.** Lymph node, x20 magnification, CD3 staining positive



**Figure 2.** Lymph node, x20 magnification, diffuse EBER positive B-blasts



week of illness and one did not become positive until 49 days after onset of illness. Anti-VCA IgG antibodies were developed in all patients, which peak during the first two to four months and then persist during life. Those antibodies may present in acute infection but in smaller quantities than anti-VCA IgM.<sup>1</sup> Circulating cell-free EBV DNA has been detected in plasma/ serum from patients with EBV-associated tumours.<sup>2</sup> In approximately 40% of peripheral T-cell lymphomas NOS EBV is detected. There is an association between EBV infection and the development of Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma and in very rare cases of natural killer cell T-cell lymphomas. The exact mechanism is as yet unclear.<sup>3</sup> Additionally, it has been described in the literature that morphological characteristics of an EBV-infected lymph node can imitate a lymphoma. One case series was published which describes 18 cases with

acute EBV infection, all of which were suspicious for or initially diagnosed as a malignant lymphoma.<sup>4</sup>

## CONCLUSION

Acute EBV infection may present in different ways and can mimic malignant lymphoma at presentation. Negative EBV serology can be misleading. We advise an EBV PCR in case of a clinical suspicion of EBV infection or confirmation by a different serological test. When a spontaneous clinical improvement occurs in a patient diagnosed with a lymphoma, an extreme course of EBV infection must be considered.

## DISCLOSURES

No conflict of interest.

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# Non-articular Felty's syndrome: An uncommon diagnosis

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## ABSTRACT

Felty's syndrome is a triad of rheumatoid arthritis, neutropenia, and splenomegaly. We hereby report an unusual case of non-articular Felty's syndrome and its management along with discussing the importance of appropriately ruling out alternate causes of neutropenia with splenomegaly.

## KEYWORDS

Felty's syndrome, rheumatoid arthritis, neutropenia

## INTRODUCTION

Felty's syndrome is a triad of rheumatoid arthritis, neutropenia, and splenomegaly. We report an unusual case of moderately severe asymptomatic neutropenia and splenomegaly with positive serologies (rheumatoid factor and anti-citrullinated protein antibody) but no joint involvement, i.e. non-articular Felty's syndrome.

## CASE REPORT

A 73-year-old Caucasian female sought medical attention because of an incidental finding of leukopenia and neutropenia. She had a past medical history of essential hypertension, ischaemic cardiomyopathy with an ejection fraction of 45-50% (status post-implantable cardioverter defibrillator) and ventricular tachycardia on amiodarone. She was found to have leukopenia (1800 cells/ $\mu$ l, normal = 3800-10,600 cells/ $\mu$ l) and neutropenia (700 cells/ $\mu$ l, normal = 1800-7700 cells/ $\mu$ l) on routine blood testing

### What was known on this topic?

Felty's syndrome is a triad of rheumatoid arthritis, neutropenia, and splenomegaly.

### What does this case add?

We present a case of severe neutropenia and mild splenomegaly in a patient with high titres of rheumatoid factor and anti-CCP with no signs of synovitis. After ruling out alternate causes of neutropenia and splenomegaly, a diagnosis of non-articular Felty's syndrome was made.

which persisted despite discontinuation of the amiodarone for three to four months. Review of the systems was negative for morning stiffness, joint pain, joint swelling, oral-nasal or genital ulcers, rash or any family history of autoimmune diseases. She was a non-smoker with no alcohol or recreational drug use.

Physical examination was unremarkable except for splenomegaly. There was no obvious synovitis or limited range of motion in any of her joints.

Imaging confirmed splenomegaly (18 cm) with no hepatomegaly or adenopathy and was otherwise unremarkable. She subsequently underwent bone marrow biopsy and multiple peripheral smears which were negative for alternate causes of neutropenia. There was no immunophenotypic evidence of either a mature T or B lymphoid neoplasm in the flow cytometry analysis.

Autoimmune work-up revealed a normal direct anti-globin test, anti-nuclear antibodies, anti-dsDNA antibody, anti-SSA, anti-SSB, C<sub>3</sub>, C<sub>4</sub>, c-ANCA, p-ANCA, extractable nuclear antigen antibodies and monoclonal protein evaluation. Serology for syphilis, brucellosis,

infectious mononucleosis and viral hepatitis was negative. Tuberculosis skin test, quantiFERON-TB gold test, human immunodeficiency virus testing and cytomegalovirus polymerase chain reaction were negative. However, rheumatoid factor (180 IU/ml, normal < 15 IU/ml), cyclic citrullinated peptide (CCP) (45 IU/ml, normal < 7 IU/ml) and erythrocyte sedimentation rate (65 mm/h, normal 0-20 mm/h) were significantly elevated. Imaging of wrists, hands, knees, ankles and feet showed no evidence of erosions or joint space narrowing.

A final diagnosis of non-articular Felty's syndrome was proposed. She was started on daily prednisone 40 mg daily with subsequent improvement in the leukocyte (4100 cells/ $\mu$ l) and neutrophil (1700/ $\mu$ l) counts within ten weeks, at which time it was tapered down to 20 mg daily and subsequently to 10 mg daily and finally discontinued.

## DISCUSSION

The differential diagnosis in our case vignette included myeloproliferative syndromes, systemic lupus erythematosus, large granular lymphocyte syndrome, tuberculosis and sarcoidosis, all of which were ruled out by appropriate testing.

Rheumatoid arthritis is a chronic inflammatory arthritis with significant extra-articular manifestations. Felty's syndrome is a severe extra-articular feature of rheumatoid arthritis. Felty's syndrome is characterised by the triad of rheumatoid arthritis, neutropenia, and splenomegaly.<sup>1</sup> The lifetime risk of Felty's syndrome for a rheumatoid arthritis patient is less than 1%.<sup>1</sup>

Felty's syndrome usually develops late in rheumatoid arthritis. Arthritis almost always appears first and has typically been present for ten years or more before neutropenia is recognised. In very rare cases, neutropenia appears before or without arthritis.<sup>1</sup>

The articular disease in rheumatoid arthritis associated with Felty's syndrome is usually severe in terms of both erosions and deformity. In some affected individuals, Felty's syndrome may develop during a period when the symptoms and physical findings associated with rheumatoid arthritis have subsided or are not present. In such cases, it may remain undiagnosed. Also, as a result of neutropenia, affected people are increasingly susceptible to certain infections such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Herpes zoster* and fungi.<sup>2</sup>

Anti-CCP has a very high specificity for rheumatoid arthritis. The combination of rheumatoid factor and anti-CCP has a specificity of 99.5% for rheumatoid arthritis.<sup>3</sup> There is no specific diagnostic test for Felty's syndrome. It is a clinical diagnosis in rheumatoid arthritis with unexplained neutropenia and splenomegaly.

The treatment of neutropenia in Felty's syndrome is mainly comprised of disease-modifying anti-rheumatic drugs including methotrexate, hydroxychloroquine, cyclophosphamide, azathioprine, glucocorticoids, and G-CSF.<sup>4</sup>

## CONCLUSION

Manifestations of Felty's syndrome without clinical but only with laboratory features of rheumatoid arthritis are extremely rare. We present a case of severe neutropenia and mild splenomegaly in a patient with high titres of rheumatoid factor and anti-CCP with no signs of synovitis. The current vignette highlights the importance of appropriately ruling out alternate causes of neutropenia with splenomegaly and to recognise an uncommon presentation of Felty's syndrome.

## DISCLOSURES

There are no disclosures and no author had any relationship with the industry. The authors declare no conflicts of interest.

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# Girl with conjunctival nodule

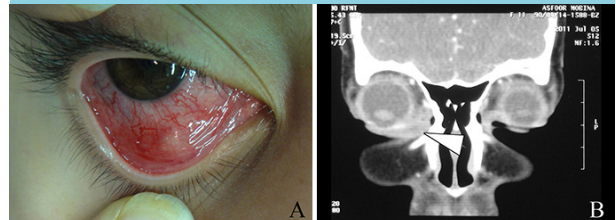
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## CASE REPORT

A 7-year-old Iranian girl from the coastal margin of the Persian Gulf presented with a nodule in her right lower conjunctiva (*figure A and B*). It had been present for two months with no changes and there were no complaints of visual impairment. On physical examination of the right eye, the nodule measured 1 × 1 cm in the bulbar conjunctiva, superior to the inferior fornix. There was conjunctival redness and chemosis but no anterior or posterior chamber inflammation. Examination of the left eye was unremarkable. The systemic physical examination was unremarkable, in particular she had no cutaneous lesions. The haematological profile was normal and there was no eosinophilia. Liver and kidney function tests were within the normal limits. Computed tomography showed a lesion located in the periocular structures (*figure B, arrow*).

**Figure A-B.** A: right eye redness and chemosis with a nodule in the inferior fornix. B: Sagittal section in CT scan shows lesion located in periocular structures



## WHAT IS YOUR DIAGNOSIS?

See page 438 for the answer to this photo quiz.

## ANSWER TO PHOTO QUIZ (PAGE 437)

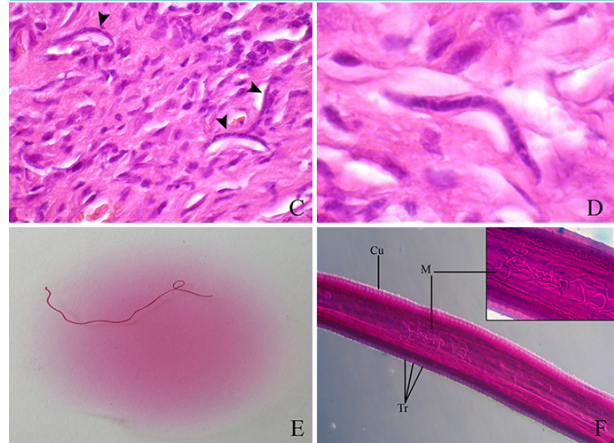
## GIRL WITH CONJUNCTIVAL NODULE

## DIAGNOSIS

The nodule was first excised under local anaesthesia. Microscopic examination showed severe chronic granulomatous inflammation, many eosinophils and, interestingly, many microfilaria (figure C and D) together with a cross section of a mature fertile worm (with evidence of incomplete removal of the mature worm). A second attempt to extract the mature worm was undertaken during a slitlamp examination when a coiled live worm, approximately 20 cm long with a maximal diameter of 450 µm, was removed from the subconjunctiva with no difficulty (figure E). The worm was examined microscopically. An adult worm with a thick multi-layered cuticle, prominent transverse cuticular ridges (Tr) and microfilariae (M) was clearly visible (figure F). The worm and the nodule were sent in alcohol and glycerine medium to the Center for Disease Control (CDC). Considering these features, along with the report from the CDC, the worm was identified as *Onchocerca volvulus*. Onchocerciasis, also known as river blindness, affects about 18 million people in endemic areas, resulting in severe visual impairment or blindness for approximately 2 million. The disease is transmitted through the bite of the black fly, which breeds in fast-moving rivers and streams. The fly injects larvae of the parasite worm into human skin, whose microfilaria migrate to superficial tissues, and may invade any part of the eye. Eye involvement (e.g. anterior segment involvement due to microfilaria, optic neuritis, choroidoretinal scarring, glaucoma, intraocular inflammation, visual field loss) is well-known in endemic areas.<sup>1</sup>

For onchocerciasis affecting people in endemic areas or moving outside endemic areas, ivermectin may be given annually for the lifetime of the adult worm (15 years).<sup>2,3</sup> Although our patient was not from an endemic area and had no travel history to those regions, she was managed with this treatment after removal of the worm and had an uneventful follow-up. It is worth mentioning that due to paucity of data, there is no conclusive recommendation on treatment of the patient in non-endemic areas.

**Figure C-F.** C and D: Microscopic examination showed severe chronic granulomatous inflammation, many eosinophils, and many microfilariae with cross section of mature fertile worm. E and F: An adult worm with thick multilayered cuticle (Cu), transverse cuticular ridges (Tr) and microfilaria (M) was clearly visible



## ACKNOWLEDGEMENTS

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# A painful blue foot

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## CASE REPORT

A 66-year-old Caucasian male patient presented to our emergency department with severe pain and bluish discoloration of his left foot that began acutely the day of his presentation (*figures 1 and 2*). Opioids had no effect on the patient's pain. A week before his presentation the patient had been diagnosed with a deep vein thrombosis (DVT) of the left leg. He had been anticoagulated with fraxiparin in a therapeutic dose and acenocoumarol. Three days after his DVT was diagnosed – and while taking anticoagulants – pulmonary emboli were diagnosed.

Physical examination revealed a man in obvious distress due to pain with a heart rate of 84 beats/min, a blood pressure of 165/97 mmHg and an oxygen saturation of 97%. The patient's left leg was slightly oedematous distal to the knee and his left foot was cool in comparison to

the right. A bluish mottling of the left foot and ankle was noted. Arterial pulsations were palpable in the left groin but were not palpable in the left popliteal fossa or foot. Arterial pulsations were normally present in these locations in the right leg. Doppler examination revealed biphasic pulsations of the left posterior tibial and dorsalis pedis arteries. Sensitivity to light touch and motor function were diminished in the left foot and were normal elsewhere. Laboratory values included a lactate level of 0.9 mmol/l and a creatinine kinase level of 20 U/l which are within the normal range. The INR value was 1.71.

## WHAT IS YOUR DIAGNOSIS?

See page 440 for the answer to this photo quiz.

**Figure 1.** Cyanosis and oedema of the heel and toes of the left foot



**Figure 2.** Cyanosis and oedema of the sole of the left foot





**DIAGNOSIS**

Our differential diagnosis comprised: phlegmasia cerulea dolens (PCD), arterial insufficiency and compartment syndrome. The factors which led to our final diagnosis of PCD included: the recently diagnosed DVT and pulmonary emboli, a sub-therapeutic INR, the low creatinine kinase level (usually markedly elevated in compartment syndrome), and the absence of recent leg trauma. The patient's clinical presentation of a cool, blue, intensely painful and swollen leg with absent distal pulses also supported our PCD diagnosis. We did not measure compartment pressures.

Our patient was immediately transferred to a tertiary care hospital where he underwent catheter-guided venous urokinase thrombolytic therapy and ultrasound-accelerated thrombolysis. This resulted in a dramatic symptomatic and clinical improvement, although subsequently the patient's first, third and fourth toes on the left foot became necrotic necessitating partial amputations. The underlying cause of the patient's PCD was also investigated and no evidence of malignancy or other disease was found on computed tomographic scans of the thorax and abdomen.

PCD is a severe form of venous thrombosis with clotting of the deep and superficial veins. Venous pressure can increase to such an extent that arterial perfusion may be impaired, as was the case in our patient. The elevated venous pressure coupled with oedema and compromised arterial flow may lead to gangrene which may in turn produce shock and death. PCD is a highly morbid condition and amputation rates of 12 to 50% have been described. Mortality rates range from 20 to 40%. Modern treatment may result in better outcomes.

PCD patients usually present with sudden severe limb (usually leg) pain, cyanosis (cerulea) and oedema. Prompt diagnosis and treatment is necessary to save the patient's limb and life. Many cases are preceded by the less severe phlegmasia alba dolens, characterised by pain, oedema and blanching (rather than cyanosis).

PCD treatment consists of: systemic anticoagulation, thrombectomy and/or intravenous thrombolysis. Immediate referral to an interventional radiologist and a vascular surgeon with expertise in PCD treatment is necessary. Once the patient is stabilised, further analysis should be performed to elucidate the aetiology of the PCD. Malignancy is the most common cause of PCD (20 to 40%).

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# Two siblings with hepatosplenomegaly and pulmonary reticulation

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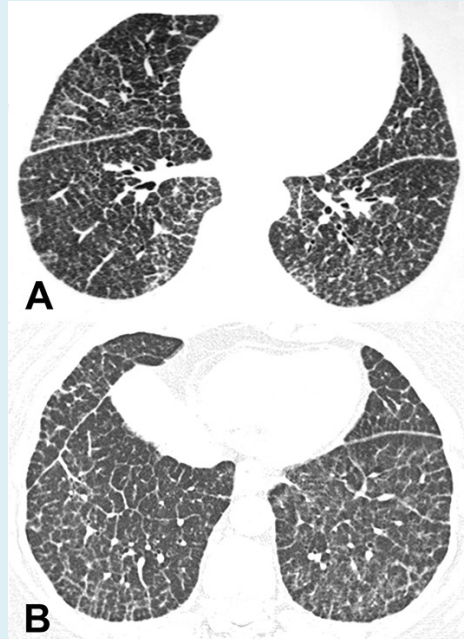
## CASE REPORT

A 28-year-old woman with stable hepatosplenomegaly (diagnosed at the age of 2-3 years) presented with a one-year history of progressive dyspnoea. She denied other pulmonary symptoms. The patient had a younger sister, aged 25 years, who had also had hepatosplenomegaly since early childhood and complained of mild dyspnoea. Physical examination in both sisters confirmed hepatosplenomegaly. High-resolution computed tomography performed in both sisters (*figure 1*) showed the same aspects, characterised by thickening of the interlobular septa and intralobular interstitium in association with small foci of ground-glass opacity.

## WHAT IS YOUR DIAGNOSIS?

See page 442 for the answer to this photo quiz.

**Figure 1.** High-resolution computed tomography images from two sisters aged 28 (A) and 25 (B) years. The images show similar aspects, with thickening of the interlobular septa and intralobular interstitium. Note also small foci of ground-glass opacities



**DIAGNOSIS**

The results of the hepatic biopsy of the older patient were consistent with lysosomal storage disease and suggested Niemann-Pick disease. Neurological examination and respiratory function test results were normal. White blood cell sphingomyelinase activity was reduced, confirming the diagnosis of Niemann-Pick disease type B.

Niemann-Pick disease is a rare recessive and autosomal hereditary lysosomal storage disease caused primarily by an absence or deficiency of the enzyme acid sphingomyelinase. It is characterised by the intracellular accumulation of sphingomyelin in the liver, spleen, lungs, bone marrow, and/or brain, resulting in the presence of lipid-laden 'foamy' macrophages (Niemann-Pick cells) in these organs.<sup>1,4</sup>

Niemann-Pick disease presents with three subtypes. Type A is a severe neurodegenerative disorder that results in death in early childhood.<sup>1,4,5</sup> Type B is less severe, with little or no neurological involvement.<sup>1,5</sup> Type C is caused by a different genetic mutation.<sup>4</sup> Niemann-Pick disease type B is characterised by hepatosplenomegaly and pulmonary and bone marrow involvement, with an insidious course and a more benign prognosis.<sup>1,2,4</sup> Pulmonary involvement ranges from a lack of symptoms to respiratory failure with oxygen dependence.<sup>1,2</sup> High-resolution computed tomography (HRCT) findings consist of smooth thickening of the interlobular septa mainly involving the lower lung zones, intralobular lines, and patchy ground-glass opacities throughout both lungs, sometimes with a crazy-paving pattern.<sup>2,5</sup>

The diagnosis of Niemann-Pick disease is made by bone marrow biopsy or sphingomyelinase enzyme assays in leukocytes, lymphocytes, or fibroblast skin cultures.<sup>3,5</sup> On histopathological examination, the lungs show alveolar filling by lipid-laden macrophages, which causes a type of endogenous lipoid pneumonia. Macrophages also infiltrate the alveolar walls and interstitium, but the lung architecture is generally preserved. Fibrosis is generally absent or mild.<sup>1,3,5</sup>

In conclusion, Niemann-Pick disease type B must be considered in patients presenting with dyspnoea and HRCT findings of interlobular and intralobular septal thickening in association with small foci of ground-glass opacity, especially when associated with a long-term history of hepatosplenomegaly or when a patient has family members with comparable problems.

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# Gentamicin is frequently underdosed in patients with sepsis in the emergency department

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To the Editor,

Dosing of antibiotics can be challenging, as was demonstrated in your journal for vancomycin and intensive care patients by Brinkman et al.<sup>1</sup> We would like to warn colleagues for potential underdosing of gentamicin in patients with sepsis, as we recently found in our emergency department.

Aminoglycosides are frequently used in the empirical treatment of sepsis in the emergency department. In our hospital, we aim to prescribe gentamicin 5 mg/kg once daily, to broaden the antibiotic spectrum of amoxicillin/clavulanic acid.<sup>2</sup> Gentamicin is a concentration dependent bactericidal antibiotic. Underdosing will lead to a lower gentamicin peak concentration and consequently to potential treatment failure and increased morbidity and mortality.<sup>3,4</sup> Therefore, we investigated actual gentamicin dosing in patients with sepsis in our emergency department.

All patients who received gentamicin at our emergency department (Maastricht University Medical Centre, the Netherlands) from April 2011 to April 2012 were included. We retrospectively retrieved data on body weight, height, gentamicin dose and clinical characteristics from the electronic patient files and electronic prescribing system. To calculate the correct dose of gentamicin (5 mg/kg), actual body weight was used for patients with a body mass index (BMI) < 30 kg/m<sup>2</sup>, and adjusted body weight for patients with BMI > 30 kg/m<sup>2</sup>.<sup>5</sup> Underdosing of gentamicin was defined as at least 10% under the advised dose, i.e. < 4.5 mg/kg.

We included 173 patients, of whom 34 (20%) were underdosed. The mean gentamicin dose was 3.8 ± 0.5 mg/

**Table 1.** Patient characteristics comparing underdosed patients with adequately dosed patients

Mean ± SD or n (%) n = 173	Underdosed n = 34	Adequately dosed n = 139	p-value
Age (years)	70.0 ± 15.6	66.7 ± 17.1	0.31
(Calculated) Weight (kg)	74.6 ± 14.5	68.9 ± 10.6	0.01
Body mass index (kg/m <sup>2</sup> )	26.7 ± 5.1	25.0 ± 5.8	0.12
Dose (mg/kg)	3.8 ± 0.5	5.1 ± 0.5	<0.001
Sepsis	10 (29.4)	62 (44.6)	0.12
Severe sepsis	17 (50.0)	57 (41.0)	0.44
Septic shock	7 (20.6)	20 (14.4)	0.43
ICU admission directly from ED	7 (20.6)	10 (7.2)	0.047
Creatinine at ED (µmol/l)	203 ± 171	132 ± 91	0.001
28-day mortality	7 (20.6)	16 (11.5)	0.17

(Calculated) Weight = actual body weight for patients with BMI < 30 mg/kg<sup>2</sup> and adjusted body weight for patients with BMI > 30 mg/kg<sup>2</sup>; ICU = intensive care unit; ED = emergency department.

kg in the underdosed group, and 5.1 ± 0.5 mg/kg in the adequately dosed group (table 1). There was no difference in severity of sepsis according to the SIRS criteria (i.e. sepsis, severe sepsis, or septic shock) in both groups.<sup>6</sup> Mean serum creatinine was higher in underdosed patients (203 ± 171 vs. 132 ± 91 µmol/l, p = 0.001) and underdosed patients were more often directly admitted to the ICU (21%

vs. 7% of patients,  $p = 0.047$ ), which may indicate a worse condition of these patients.

In conclusion, gentamicin is frequently underdosed in patients with sepsis in our emergency department. This leads to lower peak concentrations, which may negatively influence clinical outcome. The higher serum creatinine in gentamicin underdosed patients might suggest that fear of nephrotoxic side effects is an important reason for underdosing. Other reasons might be an incorrect estimation of body weight, which was also seen in patients receiving thrombolysis,<sup>7</sup> or rounding down of the gentamicin dose, based on whole ampules (i.e. 80 mg/2 ml).

Given the frequent occurrence of underdosing of gentamicin in our hospital, this could be a concern in other hospitals as well. We suggest that other emergency departments check the doses of aminoglycosides actually given. To improve dosing, standardised weighing before administering gentamicin might be considered. Alternatively, plasma peak concentrations could be useful in the adequate dosing of gentamicin.

## DISCLOSURES

The authors declare no conflicts of interest.

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