Limited Generalizability of Registration Trials in Hepatitis C: A Nationwide Cohort Study

Floor A. C. Berden, Robert J. de Knegt, Hans Blokzijl, Sjoerd D. Kuiken, Karel J. L. van Erpecum, Sophie B. Willems, Jan den Hollander, Marit G. A. van Vonderen, Pieter Friederich, Bart van Hoek, Carin M. J. van Nieuwkerk, Joost P. H. Drenth, Wietske Kievit

1 Department of Gastroenterology and Hepatology, Radboud university medical center, Nijmegen, the Netherlands,
2 Department of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands,
3 Department of Gastroenterology and Hepatology, University medical center Groningen, Groningen, the Netherlands,
4 Department of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, location West, Amsterdam, the Netherlands,
5 Department of Gastroenterology and Hepatology, University medical center Utrecht, Utrecht, the Netherlands,
6 Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands,
7 Department of Internal Medicine, Maasstad hospital, Rotterdam, the Netherlands,
8 Department of Internal Medicine, Medical center Leeuwarden, Leeuwarden, the Netherlands,
9 Department of Gastroenterology and Hepatology, Catharina hospital, Eindhoven, the Netherlands,
10 Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands,
11 Department of Gastroenterology and Hepatology, VU university medical center, Amsterdam, the Netherlands,
12 Department for Health Evidence, Radboud university medical center, Nijmegen, the Netherlands

Abstract

Background

Approval of drugs in chronic hepatitis C is supported by registration trials. These trials might have limited generalizability through use of strict eligibility criteria. We compared effectiveness and safety of real world hepatitis C patients eligible and ineligible for registration trials.

Methods

We performed a nationwide, multicenter, retrospective cohort study of chronic hepatitis C patients treated in the real world. We applied a combined set of inclusion and exclusion criteria of registration trials to our cohort to determine eligibility. We compared effectiveness and safety in eligible vs. ineligible patients, and performed sensitivity analyses with strict criteria. Further, we used log binomial regression to assess relative risks of criteria on outcomes.

Results

In this cohort (n = 467) 47% of patients would have been ineligible for registration trials. Main exclusion criteria were related to hepatic decompensation and co-morbidity (cardiac disease, anemia, malignancy and neutropenia), and were associated with an increased risk for serious adverse events (RR 1.45–2.31). Ineligible patients developed significantly more serious adverse events than eligible patients (27% vs. 11%, p< 0.001). Effectiveness was decreased if strict criteria were used.
Conclusions

Nearly half of real world hepatitis C patients would have been excluded from registration trials, and these patients are at increased risk to develop serious adverse events. Hepatic decompensation and co-morbidity were important exclusion criteria, and were related to toxicity. Therefore, new drugs should also be studied in these patients, to genuinely assess benefits and risk of therapy in the real world population.

Introduction

Regulatory approval of drugs and the development of guidelines are supported by evidence generated by registration trials. These trials aim for high internal validity through use of strict eligibility criteria, although this may jeopardize generalizability. [1, 2] Some studies suggest that many real world patients would be excluded from registration trials and that drugs tested through these trials are less effective or less well tolerated in these patients.[3–5]

The treatment arsenal for chronic hepatitis C patients (CHC) has increased enormously with the introduction of Direct Acting Antivirals (DAAs). DAAs were approved by regulatory authorities for use in clinical practice, with evidence coming from registration trials having strict criteria.[6] Indeed, real world cohorts contain large number of treated CHC patients who would be excluded from registration trials.[7–10] A lack of generalizability is only an issue when ineligible patients have worse outcomes, but this is not known for CHC. We hypothesize that CHC patients ineligible for trials, but who are treated in clinical practice have characteristics that are risk factors for treatment failure and toxicity.

Therefore, we aim to compare effectiveness and safety in real world CHC patients who are eligible or ineligible for registration trials. Our secondary aim is to identify criteria that impact trial eligibility and assess the risk of these criteria on outcomes.

Materials and Methods

Population and design

We conducted a nationwide, multicenter, retrospective real world cohort study of CHC patients in the Netherlands. We chose genotype 1 patients treated between 2011 and 2015 with telaprevir or boceprevir with peg-interferon and ribavirin as an example cohort. We identified CHC patients using up-to-date local databases. Treatment indication, choice of therapy, drug dosing and duration were at the discretion of the physician, following national guidelines. [11] Patients co-infected with HIV or hepatitis B virus (HBV) were excluded.

Formal evaluation was waived by the institute review board Committee on Research Involving Human Subjects Arnhem-Nijmegen given the retrospective character of our study. However, approval in participating centers was obtained according to local regulations. The study was conducted in accordance with good clinical practice guidelines and the code of conduct for medical research (www.federa.org). We obtained oral informed consent or collected data anonymously in accordance with the code of conduct for medical research. No identifying patient data was collected, and all patient data was anonymously entered in the database.

Identification of registration trials and general set of eligibility criteria

We identified registration trials of telaprevir and boceprevir in CHC patients through a systematic search (S1 Table). We extracted eligibility criteria from published protocols, and used the least stringent criteria of all studies to develop a general criteria set (Table 1). We applied the

Competing Interests: I have read the journal’s policy and the authors of this manuscript have the following competing interests: F. Berden: no conflict; R. de Knecht has served as an advisory board member for Gilead, Janssen, BMS, AbbVie, Roche and Norgine, and has received research funding from Janssen, BMS, AbbVie, and Roche; H. Blokzijl: no conflict; S. Kuiken: no conflict; K. van Erpecum has served as an HCV advisory board member for AbbVie, BMS, Gilead and Janssen Cilag, and as a consultant for AbbVie, and has received research funding from Janssen Cilag, Gilead, and AbbVie; S. Willemse has served as a speaker and an advisory board member for AbbVie, Gilead, BMS, Merck, Roche, Janssen, and has received research funding from AbbVie, Gilead, Merck/MSD, and Roche; J. den Hollander: no conflict; M. van Vonderen: no conflict; P. Friederich: no conflict; B. van Heek has served as an advisor board member for Gilead, Merck, AbbVie, Norgine, Falk, and Janssen; C. van Nieuwkerk: no conflict; J. Drenth has served as an advisory board member for Gilead, Janssen, BMS, and AbbVie, and has received research funding from Janssen, AbbVie (this study), dr. Falk, Ipsen, Novartis, Zambon, and Merck; Dr. Kievit: no conflict. This does not alter our study, dr. Falk, Ipsen, Novartis, Zambon, and Merck; J. den Hollander: no conflict; M. van Vonderen: no conflict; P. Friederich: no conflict; B. van Heek has served as an advisor board member for Gilead, Merck, AbbVie, Norgine, Falk, and Janssen; C. van Nieuwkerk: no conflict; J. Drenth has served as an advisory board member for Gilead, Janssen, BMS, and AbbVie, and has received research funding from Janssen, AbbVie (this study), dr. Falk, Ipsen, Novartis, Zambon, and Merck; Dr. Kievit: no conflict. This does not alter our

Abbreviations: AE, Adverse Event; CHC, Chronic Hepatitis C; CNS, Central Nervous System; CTCAE, Common Terminology Criteria for Adverse Events; DAA, Direct-Acting Antiviral; EMA, European Medicines Agency; FDA, Food and Drug Administration; HBV, Hepatitis B Virus; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; INR, International Normalized Ratio; RNA, Ribonucleic Acid; RR, Relative Risk; SAE, Serious Adverse Event; SVR, Sustained Virological Response; TSH, Thyroid Stimulating Hormone.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>18 years</td>
<td>Hepatitis C virus (HCV) RNA detectable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight between 40–125 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound with no signs of HCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contra-indication to peginterferon or ribavirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Auto-immune disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Current or history of decompensated liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatric comorbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Central nervous system (CNS) disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malabsorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indwelling catheter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comedication</td>
</tr>
</tbody>
</table>

⁶ Significant cardiac disease was defined as: current or history of unstable cardiac disease (angina, congestive heart failure, recent myocardial infarction, pulmonary hypertension, complex congenital heart disease, cardiomyopathy, and/or significant arrhythmia)  
⁷ Auto-immune disease was defined as: immunologically mediated disease (inflammatory bowel disease, celiac disease, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, sarcoidosis, severe psoriasis, or autoimmune hepatitis)  
⁸ Psychiatric comorbidity was defined as: severe depression or hospitalization for depression, schizophrenia, bipolar illness, severe anxiety or personality disorder, a period of disability or impairment due to a psychiatric disease within the past 5 years  
⁹ CNS disorder was defined as: CNS trauma requiring intubation, intracranial pressure monitoring, brain meningeal/skull surgery, or resulting in seizure, coma, neurologic deficits, abnormal brain imaging, cerebrospinal fluid leak, prior brain hemorrhage and/or intracranial aneurysms, or history of stroke or transient ischemic attack  
† ULN = upper limit of normal; LLN = lower limit of normal  

doi:10.1371/journal.pone.0161821.001
general set to our real world population to determine eligibility. If variables were missing, we assumed the patient would be eligible for that criterion.

Data acquisition and definitions
We extracted demographics, CHC characteristics, and laboratory values from the patients’ medical records on a pre-designed case report form. Baseline variables were collected at the start of treatment not exceeding one year prior to treatment. Baseline concomitant medication was collected prior to possible medication switch for expected interactions. Data was collected until 24 weeks after cessation of treatment. We collected whether patients had a history of or current decompensated liver disease, this was defined as a history or signs of ascites, variceal bleed or hepatic encephalopathy. Effectiveness was defined as sustained virological response (SVR): undetectable hepatitis C virus RNA 12 or 24 weeks after cessation of treatment. Safety data included adverse events (AEs) and serious adverse events (SAEs). AEs were defined as any event that required 1) dose reduction of peg-interferon or ribavirin, 2) prescription of medication or 3) referral. We used the FDA definition for SAEs. We categorized AEs and SAEs by common terminology criteria for adverse events (CTCAE version 4.0). We recorded data anonymously in an Access database (Microsoft Access 2007).

Outcomes and analysis
The primary outcomes were SVR and (S)AE rates, which were compared between patients eligible and ineligible for registration trials. Furthermore, we identified criteria that affected eligibility and were associated with the outcomes. Analyses were performed on an intention to treat population, where telaprevir and boceprevir treated patients were pooled. To check validity of pooling, we compared baseline characteristics and treatment outcomes between telaprevir and boceprevir patients.

SVR rates, and (S)AE rates were analyzed with $\chi^2$ (or Fisher exact if counts <5), and Mann-Whitney U test (median number of (S)AEs). For analyses on SVR, we separated patients into two groups based on expected similar effectiveness: 1) treatment-naive and relapse patients, and 2) patients with a prior non-response, viral breakthrough or early discontinuation; for safety outcomes this distinction was not made. We used frequency counts to identify most important eligibility criteria. To study the association of criteria and outcomes, we performed log binomial regression (relative risk) or poisson regression. To explore the validity of our generated set of the least stringent criteria from the protocols, we performed three sensitivity analyses: a) with most stringent criteria (S2 Table), b) with strictest exclusion of co-morbidity, and c) with the most important factor for exclusion eliminated from the criteria set. All analyses were two-sided with a significance level of $p < 0.05$, and performed in SPSS (IBM SPSS Statistics 20).

Results
Population
We identified 489 treated patients from 45 centers, and we excluded 22 patients (Fig 1). Centers treated a median of 8 patients (range 1–53). Overall, the majority of patients (60%) was treatment naive, 52% had advanced fibrosis or cirrhosis and 5% had a history of decompensated liver disease. Baseline characteristics are shown in Table 2. We pooled telaprevir ($n = 265$) and boceprevir ($n = 202$) data, as there were no significant differences in characteristics and treatment outcomes between patients (S3 and S4 Tables).
Our search yielded eight trials of telaprevir and boceprevir [17–24], and five registration trials were included. (S1 Table). On the basis of the general criteria (Table 1), 47% of patients treated in real world practice would be excluded from registration trials. We than compared the eligible to ineligible population with respect to safety parameters. We found that ineligible patients had significantly more SAEs compared to eligible patients (27% vs. 11%, p < 0.001) (Fig 2). A total of 37 SAEs occurred in 28 eligible patients (1 patient died due to an accident), compared to 103 SAEs which occurred in 60 ineligible patients (7 patients died) (S5 Table).

Also, after excluding patients with a history of decompensated liver disease (n = 24) from the analysis, ineligible patients had significantly higher SAE rates (24% vs. 11%, p < 0.001). Further, ineligible patients had a higher median number of AEs and SAEs (p = 0.039 and p < 0.001 respectively, S6 Table). The incidence of some typical hepatic or therapy related (S)AEs (anemia, thrombopenia and hepatobiliary events) were significantly higher in the ineligible patients (Fig 3).

We found (non-significant) lower SVR rates in ineligible patients. Two sensitivity analyses detected lower SVR rates in ineligible patients (treatment naive–relapse group): when applying most strict criteria (81% vs. 67%, p = 0.01) or when most stringent exclusion of patients with co-morbidity was done (76% vs. 65%, p = 0.02). We observed no difference in SVR in the third
sensitivity analysis, where we excluded concomitant medication from the criteria set (Fig 4).
No significant differences in effectiveness were found in the non-responder group (S1 Fig).

Criteria for ineligibility

Most important criteria for ineligibility were related to co-morbidity and signs or history of hepatic decompensation. In 220 ineligible patients, main reason for exclusion was the use of prohibited concomitant medication (n = 65), followed by anemia (n = 25), psychiatric co-morbidity (n = 24), and current or history of decompensated liver disease (n = 24). Median number of exclusion criteria within a patient was 1 (range 1–6). Univariable analysis showed most important criteria associated with lack of SVR, i.e. current or history of decompensated liver disease (RR 0.66), platelet count (RR 0.58), albumin (RR 0.49), bilirubin (RR 0.58) and neutrophil count (RR 0.55). Similar criteria were associated with a higher risk on an SAE: a history of decompensated liver disease (RR 1.81), platelet count (RR 1.45), albumin (RR 2.03), bilirubin (RR1.89), hemoglobin (RR 1.72), malignancy (RR 2.31) and presence of cardiac disease (RR 1.97). Outcomes of these analyses are depicted in Table 3.
Discussion

This study sheds doubt on the generalizability of registration trials to the real world CHC population. In our study, one of the key findings is that nearly half of treated CHC patients would be ineligible for registration trials. Most important exclusion criteria relate to signs or history of hepatic decompensation and co-morbidity (cardiac disease, anemia, malignancy and neutropenia). Patients meeting those exclusion criteria developed more SAEs (RR between 1.45 and 2.31) and were less likely to reach SVR (RR between 0.49 and 0.66), especially when strict criteria were used. Vice versa, eligible patients had SVR and SAE rates comparable to published trials.[17–21] Altogether, this indicates that results from registration trials are only generalizable to the real world patients who fulfill the eligibility criteria. Translating results originating from registration trials to patients that would be ineligible should be done with caution.

Fig 2. Safety in real world patients who would be eligible and ineligible for registration trials. The bars represent the proportion of patients who experienced a serious adverse event or adverse event in patients eligible or ineligible for registration trials.

Fig 3. Incidence of specific (serious) adverse events in eligible and ineligible patients. The bars represent the incidence of various categories of (serious) adverse events between patients eligible and ineligible for registration trials. The asterix (*) marks significant differences between eligible and ineligible patients.

doi:10.1371/journal.pone.0161821.g002

doi:10.1371/journal.pone.0161821.g003
The difference between registration trials and real world reflects a ‘development paradox’. Drugs are developed through a phase II-III program that targets easy-to-treat patients, while in the real world difficult-to-treat patients are prioritized for treatment.[1, 25, 26] The sequence of drug development starting with easy-to-treat patients seems appropriate, but the final hurdle to perform trials that specifically target difficult-to-treat patients is often sidestepped or delayed until after market authorization. As a result, this population who has a clear treatment indication is exposed to DAAs in the real world, without proper data on efficacy and toxicity.[27] This results in an increased proportion of adverse events, dropouts and hence lower effectiveness.[28] Our results support the ‘development paradox’ and provide reasons why real world outcomes do differ from registration trials.

Our data on limited generalizability of registration trials accords with the literature. An increased likelihood for SAEs in patients with a history of decompensated cirrhosis who would have been excluded from registration trials was reported in a large CHC cohort (n = 2084). [9] Some 30–47% of compensated cirrhotic patients treated with first-generation protease inhibitors would be ineligible for registration trials, and this study showed unexpected high SAE rates in that population.[7] In addition, a study on ledipasvir/sofosbuvir in advanced liver disease patients, published after FDA and EMA approval, reported much higher SAE rates (23%) compared to registration trials (3%). [29] For another CHC regimen, paritaprevir/ritonavir, ombitasvir and dasabuvir, the FDA label changed within one year following approval based on review of adverse events. This regime is now contra-indicated in patients with Child-Pugh B cirrhosis. [30] It is likely that this could have been prevented if these patients had been trialed prior to approval of the regimen. There is literature that suggests that serious adverse events might be related to disease course instead of therapy.[31] Nonetheless, timely controlled

---

**Fig 4. Effectiveness in real world treatment naive and relapse patients who would be eligible and ineligible for registration trials.** Primary and sensitivity analyses on effectiveness of therapy in eligible vs. ineligible naive and relapse patients (n = 348). The bars represent the proportion of patients who reached a sustained virological response (SVR) within the groups. For sensitivity analyses different criteria sets are used to determine eligibility of patients, hence different numbers of patients in both groups.

doi:10.1371/journal.pone.0161821.g004
studies in CHC patients with decompensated liver disease are necessary to accurately gauge risk-benefit balance for these individual patients.

Here, we used the first-generation protease inhibitor treated patients as an example cohort. We believe that our results are also applicable to new generation DAAs, because eligibility criteria of registration trials are comparable to the set used in the current study (S7 Table). [31–37] Indeed, a Canadian HIV/HCV cohort, found that up to 94% of patients from that cohort would be ineligible for registration trials with new generation DAAs. [10] Furthermore a real world cohort showed that liver decompensation and SAEs during sofosbuvir containing regimens were associated with lower baseline albumin and higher total bilirubin, which are general exclusion criteria. [38] As toxicity of new generation DAAs decreases, the difference between trials and real world might become smaller, however with the high ineligibility rate of real world patients, generalization of results remains difficult.

Limited generalizability of registration trials is also seen in other liver diseases such as hepatocellular carcinoma (HCC) and HBV infection. For example, sorafenib was approved for HCC treatment, on the basis of studies that excluded Child-Pugh B and C cirrhotic patients. [39, 40] A real world cohort reported significantly decreased overall survival with sorafenib in Child-Pugh B compared to Child-Pugh A cirrhotics. [41] Likewise, post-marketing studies in entecavir for chronic HBV infection show lower proportions of ALT normalization than was shown in registration trials. [42]

Our study comes with strengths and limitations. Strengths of this study are the nationwide and multicenter character, resulting in a large and representative real world cohort. Limitations of this study are the retrospective character that resulted in (some) missing values. We handled this conservatively, by classifying the missing value as eligible for that criterion. Furthermore,
chart review may result in reporting bias, but we used strict definitions to reduce this. Another limitation is that patients received first-generation protease inhibitors, peginterferon and ribavirin, which may increase the potential for toxicity. However, we think that our results are also valid for new generation DAAs.

In conclusion, nearly half of CHC patients treated in real world practice would be ineligible for registration trials. In these patients we found impaired safety and effectiveness related to specific eligibility criteria (hepatic decompensation, co-morbidity). Prior to regulatory approval, new drugs should also be studied in the difficult-to-treat population, including patients with hepatic decompensation and co-morbidity, to genuinely assess the benefits and risks of treatment in the real world population.

Supporting Information

S1 Fig. Effectiveness in real world treatment nonresponder and other patients who would be eligible and ineligible for registration trials. Primary and sensitivity analyses on effectiveness of therapy in eligible vs. ineligible nonresponder or other patients (n = 118). For sensitivity analyses different criteria sets are used to determine eligibility of patients, hence different numbers of patients in groups.

S1 Table. Search strategy. This is the flowchart of the systematic search for registration trials with telaprevir and boceprevir.

S2 Table. Set of least and most stringent combined inclusion and exclusion criteria of registration trials. This table shows the least stringent and most stringent criteria of different registration trials per variable. The least stringent criteria set was used for primary analyses and the most stringent criteria set for a sensitivity analysis.

S3 Table. Baseline characteristics telaprevir and boceprevir treated patients. Table including baseline characteristics of patients treated with telaprevir and boceprevir, these patients are pooled in the primary analysis.

S4 Table. Effectiveness and safety of telaprevir compared to boceprevir. Table showing effectiveness and safety results of telaprevir vs. boceprevir, these patients are pooled in the primary analysis.

S5 Table. Serious adverse events categories. Table with categories of serious adverse events in eligible vs. ineligible patients.

S6 Table. Sensitivity analyses. Table showing outcomes of sensitivity analyses: analysis with most stringent criteria, analysis with strict exclusion of patients with co-morbidity, analysis without prohibited comedication as exclusion criterion.

S7 Table. Exclusion criteria of registration trials in new generation DAAs. Table with exclusion criteria of new generation DAAs in comparison to our general criteria set.
Acknowledgments
The authors thank the following physicians, nurses and participating centers for their contribution and collaboration in this study: J. Vrolijk and C. Richter, Rijnstate Hospital, Arnhem; J. Kamphuis and B. Blank, Maxima Medical Centre Eindhoven; T. Römkens and M. van Ijzendoom, Jeroen Bosch Hospital, ’s Hertogenbosch; T. Dofferhoff and K. Kok, Canisius Wilhelmina Hospital, Nijmegen; I. Gisbertz, Hospital Bernhoven, Uden; M. Verhagen, Diakonessen Hospital, Utrecht; R. Adang, VieCurie Medical Center, Venlo; M. Klemt-Kropp, Medical Center Alkmaar, Alkmaar; A. Vrij, ZGT Twente, Almelo; H. Tellemans, Flevoziekenhuis, Almere; P. Friederich, Meander Medical Centre, Amersfoort; B. Baak, Onze Lieve Vrouwe Gasthuis, Amsterdam; A. Depla, Slotervaart Hospital, Amsterdam; W. Erkelens, Gelre Hospital, Apeldoorn; M. Wagtmans, Rode Kruis Hospital, Beverwijk; P. van Wijngaarden, Amphia Hospital, Breda; J. Brouwer, Reinier de Graaf Gasthuis, Delft; H. van Soest, Medical Center Haaglanden, Den Haag; F. ter Borg, Deventer Hospital, Deventer; P. Honkoop, Albert Schweitzer Hospital, Dordrecht; M. Kerbert-Dreter, Medisch Spectrum Twente, Enschede; J. Kuyvenhoven, Kennemer Gasthuis, Haarlem; C. Bakker, Atrium Medical Centre Heerlen, Heerlen; J. Tjie-Wensing, Elkerliek Hospital, Helmond; R. Lieverse, Bethesda Hospital, Hoogeveen; S. Abraham, Rijnland Hospital and Diaconessenhuis, Leiderdorp; G. Koek, Maastricht University Medical Center, Maastricht; P. Stadhouders, Sint Antonius Hospital, Nieuwegein; P. Bus, Laurentius Hospital, Roermond; L. Berk, Sint Franciscus Gasthuis, Rotterdam; J. Otte, Hospital Zeeuws Vlaanderen, Terneuzen; M. van Kasteren, Sint Elisabeth Hospital, Tilburg; M. van den Berge, Admiraal de Ruyter Hospital, Vlissingen; P. Groeneveld, Isala Klinieken, Zwolle.

Author Contributions
Conceptualization: FACB JPHD WK.
Data curation: FACB WK.
Formal analysis: FACB WK.
Funding acquisition: JPHD.
Investigation: FACB.
Methodology: FACB JPHD WK.
Project administration: FACB.
Resources: FACB RjdK HB SDK KJLvE SBW JdH MGAvV PF BvH CMJvN JPHD.
Supervision: JPHD WK.
Validation: FACB WK.
Writing – original draft: FACB WK JPHD.
Writing – review & editing: FACB RjdK HB SDK KJLvE SBW JdH MGAvV PF BvH CMJvN JPHD WK.

References


