The extent and clinical impact of treatment adjustments in hospitalised (morbidly) obese patients through the use of digital clinical decision support. A prospective intervention study.

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Date:	03/02/2023
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Abstract [NED]

Introductie - Overgewicht en obesitas zijn wereldwijd een groeiend probleem. De wereldwijde prevalentie is de afgelopen 40 jaar bijna verdrievoudigd: in 2016 was 13% van de volwassenen obees. Fysiologische veranderingen treden op bij obese patiënten om de overmatige hoeveelheid vetweefsel te ondersteunen. Als gevolg hiervan kunnen de farmacokinetiek en -dynamiek van geneesmiddelen veranderen. Daarom zijn hogere doseringen of alternatieve geneesmiddelen gewenst voor deze patiënten, maar vaak worden standaarddoseringen voorgeschreven waardoor de behandeling suboptimaal is. Om de behandeling van obese patiënten te optimaliseren kan digitale clinical decision support (CDS) nuttig zijn. CDS is een systeem geïntegreerd in het elektronisch patiëntendossier van een ziekenhuis, dat gebruikt wordt om zorgverleners bij hun besluitvorming te ondersteunen met gerichte klinische kennis en patiëntinformatie. Het doel van deze studie was om te onderzoeken in hoeverre digitaal CDS leidt tot farmacotherapeutische interventies en -aanpassingen in de behandeling van gehospitaliseerde (morbide) obese patiënten.

Methode - De studie is een prospectieve interventie studie waarbij ook een retrospectieve nulmeting is gedaan. De studiepopulatie bestond uit patiënten ≥ 18 jaar met een BMI ≥ 30 kg/m² en/of gewicht ≥ 90 kg die een geneesmiddel ontvingen waarop de CDS zou triggeren en die gehospitaliseerd waren in het ETZ in Tilburg tussen 1/1/2022 en 30/9/2022 (pre-CDS groep) of tussen 10/10/2022 en 25/11/2022 (post-CDS groep). De interventie bestond uit 1. het detecteren van patiënten waarvan de medicatieorder aangepast moest worden en 2. het adviseren van de arts met als doel de behandeling van de patiënt te optimaliseren. Farmacotherapeutische adviezen aan de arts bestonden uit aanbevelingen voor ophoging van de dosering of voor een alternatief geneesmiddel. De primaire studieparameters waren het aantal patiënten met een of meer medicatieorders (patiëntperspectief) en het aantal medicatieorders (medicatieorderperspectief) met een CDS-trigger, met een interventie als gevolg van een CDS-trigger en met een daadwerkelijke aanpassing. De verandering in het percentage aanpassingen pre-CDS en post-CDS was ook een primaire studieparameter. Secundaire studieparameters waren het aantal CDS-triggers, interventies en geaccepteerde interventies per geneesmiddel, de redenen voor het niet interveniëren ondanks een CDS-trigger, de redenen voor het niet accepteren van een interventie door de arts en het aantal patiënten met therapiefalen of bijwerkingen geassocieerd met de interventie.

Resultaten - Het aantal geïncludeerde patiënten was in de pre-CDS groep 4428 en in de post-CDS 800. In de geëvalueerde post-CDS groep waren 804 patiënten met in totaal 842 medicatieorders met een CDS-trigger. Voor 328 patiënten met in totaal 349 medicatieorders met een trigger zijn interventies gedaan waarvan voor 167 patiënten met in totaal 186 medicatieorders daadwerkelijk een aanpassing is gemaakt. Het percentage patiënten met medicatieorders aangepast aan BMI of gewicht was in de post-CDS groep 2,1 keer hoger dan in de pre-CDS groep (37,4% versus 17,7%) en het percentage medicatieorders aangepast aan BMI of gewicht was in de post-CDS 2,8 keer hoger dan in de pre-CDS groep (38,5% versus 17,7%). Beide verschillen waren statistisch significant (p=0,000). Het overgrote deel van de CDS-triggers, interventies en aanpassingen waren voor nadroparine, maar een trigger leidde niet altijd tot een interventie. De voornaamste redenen voor niet interveniëren waren dat de dosering al was aangepast en dat de normale dosering correct was. Daarnaast leidde een interventie niet altijd tot een aanpassing; de acceptatiegraad was 53,3%. De acceptatiegraad voor aanpassing van nadroparine was relatief laag (50,3%) vergeleken met die van de andere geneesmiddelen (80-100%). De voornaamste reden voor het niet accepteren van een interventie door een arts was dat de patiënt al met ontslag was. Er zijn geen gevallen van therapiefalen gevonden in de 161 patiënten van wie de medicatie niet was aangepast aan BMI of gewicht. Er zijn 4 mogelijke bijwerkingen gevonden in 3 van de 167 patiënten van wie de nadroparine dosering was aangepast aan BMI of gewicht, maar het was onduidelijk of dit het gevolg was van de verhoogde dosering.

Conclusie - Uit dit onderzoek is gebleken dat implementatie van en monitoring met digitaal CDS leidt tot een significante toename in farmacotherapeutische interventies en -aanpassingen in de behandeling van gehospitaliseerde (morbide) obesitas patiënten.

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1 Introduction

Overweight is an increasing problem worldwide. Overweight and obesity are defined as abnormal or excessive fat accumulation that poses a risk to health[1]. More and more people are becoming obese (body mass index (BMI) ≥ 30 kg/m² [2]) or morbidly obese (BMI ≥ 40 kg/m² or ≥ 35 kg/m² with comorbidities[2]). The global prevalence of obesity almost tripled between 1975 and 2016, with 13% of adults that were obese in 2016[3]. This corresponds to the Dutch population, of which 13.9% of adults were obese in 2020[4].

(Morbidly) obese patients (hereafter: obese patients) have an excessive amount of adipose tissue and several physiological changes occur to support this tissue. These changes include increased blood volume, cardiac output, oxygen consumption, muscle mass, liver size and -flow. These patients are also at increased risk of conditions such as type 2 diabetes, hypertension, sleep apnea, osteoarthritis, gastroesophageal reflux, liver and kidney diseases, cancer and depression.[2,4,5] Due to these conditions, these patients tend to consume more health care and drugs.[4]

The aforementioned physiological changes in obese patients may alter the pharmacokinetics and pharmacodynamics of drugs. Obesity may affect the absorption, distribution and elimination of drugs.[6,7,8] Therefore, dose adjustments should be made for certain drugs in obese patients. For example, a study by Rocca et al. found that obese patients probably receive a too low dose when on standard once daily low molecular weight heparin (LMWH) prophylaxis. Higher doses may be more effective in moderately to very obese patients[9]. Another study, by Chung et al. investigated the pharmacokinetics and pharmacodynamics of piperacillin and tazobactam in obese and non-obese patients. It was shown that both volume of distribution and renal clearance were increased in obese patients demanding higher dosing[10]. Nonetheless, standard doses are often prescribed. This is because little is known about how the standard dose should be adjusted in these patients, because they are often excluded from participation in drug trials. A study of Pestine et al. assessed the reporting of information about eligibility and enrolment of obese participants in obesity-related cancer randomised controlled trials (RCTs)[11]. Information on the eligibility of obese participants was available in 7% of the trials and the proportion of obese participants could be estimated in 12% of the trials only. Consequently, obese patients are often treated with standard doses, potentially resulting in suboptimal treatment due to altered exposure and effect of the drugs compared to patients with a normal BMI.[5] Therefore, the Royal Dutch Pharmacists Association (KNMP), among others, recommends to increase the dose of certain drugs in obese patients.[12]

To optimise the treatment of obese patients and to reduce the risk of adverse clinical outcomes, digital clinical decision support (CDS) may be useful. Digital CDS is an electronic system, often integrated in a hospital's electronic health record (EHR) system, used to support healthcare providers in their decision making processes with targeted clinical knowledge, patient information and other health information. CDS is being used increasingly and has been found to assist healthcare providers in a variety of decisions.[13] A study by Polso et al. examined compliance with antibiotic dose recommendations in morbidly obese patients. In this study, dosing was supported with online available recommendations leading to 64% dose compliance of doses dispensed. However, these recommendations were only on the internal website and an integrated automated CDS system was not used.[14] In the Elisabeth-TweeSteden hospital (ETZ) we developed an integrated digital CDS tool that supports pharmacists to give dosing advices in patients with obesity.

The aim of this study was to examine the extent to which digital CDS leads to pharmacotherapeutic interventions and pharmacotherapy adjustments in the treatment of hospitalised (morbidly) obese patients.

2 Method

2.1 Study design

This study was a prospective intervention study. A retrospective baseline measurement was also performed to compare data from before and after the intervention (pre-CDS versus post-CDS). Baseline data were collected from 1/1/2022 to 30/9/2022 (39 weeks) and prospective intervention data were collected from 10/10/2022 to 25/11/2022 (7 weeks). The study took place at the ETZ in Tilburg, The Netherlands. The ETZ is a large, top-clinical, teaching hospital with three locations. These locations have a combined capacity of 792 beds.[15]

2.2 Study population

The baseline study population (pre-CDS) consisted of patients aged ≥ 18 years with BMI ≥ 30 kg/m² and/or weight ≥ 90 kg who were admitted to the ETZ in Tilburg between 1/1/2022 and 30/9/2022 and who received a drug on which the CDS would have triggered during their admission, i.e. who received a drug that needed adjustment (see appendix A). The prospective study population (post-CDS) was similar and consisted of patients aged ≥ 18 years with BMI ≥ 30 kg/m² and/or weight ≥ 90 kg admitted to the ETZ in Tilburg between 10/10/2022 and 25/11/2022 and who received a drug on which the CDS triggered. Patients who were admitted more than once during the study period were considered a new patient at every admission.

BMI was defined as the last documented weight in kilograms in the patient's record divided by the patient's square of height in meters. Weight was defined as last documented weight in kilograms in the patient's record.

2.3 Intervention

The intervention period was from 10/10/2022 till 25/11/2022. The intervention was 1. to detect patients aged ≥ 18 years with a BMI ≥ 30 kg/m² and/or weight ≥ 90 kg who were prescribed one or more drugs that needed an adjustment by using a digital CDS tool, integrated in the EHR, and 2. to give their physician pharmacotherapeutic advice with the aim to optimise their treatment. The digital CDS tool is a homegrown automated rule-based tool that generates a patient list in the EHR. This list shows all patients with a CDS-trigger, i.e. those patients who are prescribed one or more drugs of which the dose needs to be adjusted to that patient's current BMI or weight. See appendix A for a more detailed description of the CDS tool.

The executive researcher monitored the hospital's CDS-based patient list in the EHR daily (Monday-Friday) to detect any doses that needed intervention The potential pharmacotherapeutic adjustments were advised to the patient's attending physician by phone or by a message in the EHR by the executive researcher under the supervision of a clinical pharmacist. The pharmacotherapeutic advices consisted of recommendations for increasing the dose or the dose frequency of the drug or recommendations for an alternative drug in accordance with appendix A.

Intervention-related information was recorded: the drug that triggered CDS with the associated dose, whether action was undertaken or not, including the reason for not taking action (e.g. dose already adjusted by physician) and whether the physician accepted the intervention or not, including reason if not (e.g. physician does not see benefit of adjustment). If the same trigger for one patient occurred more than once during a hospital admission, it was only recorded the first time.

Appendix A includes a detailed description of the CDS tool and shows the drugs that cause a CDS-trigger, including the BMI and/or weight cut-off values above which adjustments are required per drug and the recommended adjustment.

2.4 Outcomes

2.4.1 Primary study parameters

The frequency of CDS-triggers and consequent pharmacotherapeutic interventions was used as a measure for the extent to which digital CDS leads to interventions and adjustments in the pharmacotherapeutic treatment of hospitalised obese patients. Consequently, from a patient perspective, primary study parameters were the number of patients with 1 or more CDS-triggers, the number (percentage) of patients for whom interventions were performed as a result of a CDS-trigger, and the number (percentage) of patients for whom interventions were accepted by the physician (acceptance rate).

For one single patient more than one CDS-trigger could occur, as more than one drug with a CDS-trigger could be prescribed. Accordingly, from a CDS perspective, primary study parameters were the number of CDS-triggers, the number (percentage) of interventions performed as a result of a CDS-trigger and the number (percentage) of interventions accepted by the physician.

To assess the effect of the CDS the rate of pharmacotherapeutic adjustments in the pre-CDS and post-CDS were compared. The rate of adjustments was defined as the proportion of adjustments of the total number of medication orders with a CDS-trigger that needed intervention.

2.4.2 Secondary study parameters

The occurrence of treatment failure and adverse events was used as a measure for the clinical effects of CDS-based pharmacotherapeutic interventions. Consequently, the number of treatment failures and the number of adverse events associated with adjustment were secondary study parameters.

Additionally, the drugs involved in the CDS-triggers were used to get insight into the nature of CDS-based pharmacotherapeutic interventions: an overview of the drugs that led to CDS-triggers, the number of CDS-triggers per drug, the number (percentage) of interventions performed as a result of a CDS-trigger per drug and the number (percentage) of interventions actually accepted by the physician per drug were secondary study parameters too.

Finally, to get insight into why part of the triggers did not lead to an intervention, the reasons for not intervening despite a trigger were collected. And additionally, to get insight into why part of the interventions was not accepted by the attending physician, the reasons for not accepting pharmacy's advice were collected as secondary study parameter.

2.5 Data collection

For each study period (pre-CDS group and post-CDS group), the required data, including the data recorded in the I-vents (evaluated post-CDS group), were extracted to a database from the EHR (EPIC®, EPIC Systems, Verona, USA). Patient data from the prospective intervention period were collected until two weeks after the intervention period to obtain information on treatment failure and adverse events after adjustment. For each included patient, the following characteristics were extracted from or manually searched for in the EHR: age, gender, BMI, weight, medication and dose during admission (any of the drugs included in the CDS), treating medical specialty and length of hospital stay. For each CDS-trigger, intervention and accepted intervention post-CDS and for each potential trigger and adjustment pre-CDS, the involved drug was noted.

The patients who were prescribed one or more drugs that would have invoked a CDS-trigger were manually selected from the database. Consequently, per study period, it was determined whether there had actually been an adjustment or not per patient, per drug.

To get an impression of the clinical effects of the pharmacotherapeutic interventions, the occurrences of treatment failure and adverse events were collected, see table 1. These events were manually extracted from the physicians' daily progress reports of a patient in the EHR and recorded in a separate file (Excel®).

For practical reasons we focused on a selection of most important and evident adverse events per drug.[16,17,18,19,20,21]. After a patient's discharge, the progress reports from day 3 after the intervention to the day of discharge were checked for treatment failure and/or adverse events. The adverse event and the drug and dose under which it occurred were recorded. If any of the listed adverse events were present, it was checked and documented whether this was actually an adverse reaction resulting from the adjustment, whether the patient was already suffering from it before the adjustment or whether it was a possible adverse event of another drug.

Table 1: Definitions of treatment failures and adverse events under LMWH, DOAC or antibiotic treatment

Treatment failure	**Definition**
LMWH/DOAC	Thrombotic complications or adjustment of the anticoagulant treatment (e.g. switch to other drug or adjustment)
Antibiotics	Aggravated or relapsed infection or adjustment of the antibiotic treatment
Adverse events	**Definition**
LMWH	Bleeding
DOAC	Bleeding, anemia and/or gastrointestinal complaints (e.g. nausea, dyspepsia, abdominal pain and/or diarrhea)
Antibiotics	Gastrointestinal complaints (e.g. nausea, vomiting and/or abdominal pain) and/or hypersensitivity reactions

LMWH = low molecular weight heparin, DOAC = direct oral anticoagulant

2.6 Data analysis

Descriptive statistics were used to present the patient characteristics. Data are presented as median with minimum, maximum and interquartile range (IQR). Descriptive statistics were also used to analyse data from both pre-CDS and post-CDS separately. With the numbers obtained as primary study parameters post-CDS, different proportions could be calculated: the proportions of patients resp. triggers for which interventions were performed resp. accepted.

The numbers obtained as secondary study parameters post-CDS could be used to determine, per drug, the proportions of patients resp. triggers for which interventions were performed resp. accepted, the proportion of treatment failure or adverse events, the proportion of reasons for not intervening despite a trigger and the proportion of reasons for not accepting pharmacy's advice.

Test statistics were used to compare the rate of adjustments pre-CDS and post-CDS. The chi-squared test is used because of categorical, unpaired and non-normal distributed data.

3 Results

3.1 Study population

In the baseline period, there were a total of 74,022 admissions to ETZ. Of these, 16,520 (22.3%) patients were obese and 1,545 (2.1%) were morbidly obese. These percentages correspond to the intervention period (13,750 admissions) in which 3,195 (23.2%) patients were obese and 268 (1.9%) were morbidly obese. To obtain the pre-CDS study population, the extraction from the EHR with all orders of the included drugs (see appendix A) for patients ≥ 18 years and BMI ≥ 30 and/or weight ≥ 90 kg from 1/1/2022 to 30/9/2022 was cleaned using a flowchart (appendix B, figure B1). Finally, 6,049 medication orders remained that would have produced a CDS-trigger in the pre-CDS group. After removing duplicate admission numbers, 4,428 patients with 6,049 orders with one or more triggers could be included. The same procedure was followed to get the post-CDS study population (appendix B, figure B2). This resulted in the inclusion of 800 patients with a total of 1,173 medication orders that triggered during the intervention period.

Table 2 shows the patient characteristics of the pre-CDS group, the post-CDS group from the extraction and the evaluated post-CDS group from the recorded I-vents (hereafter: evaluated group). The post-CDS group and evaluated post-CDS group slightly differed because the post-CDS group could include patients that were not evaluated, such as patients in the evening and night and on Saturday and Sunday. On the other hand, patients who appeared in the evaluated post-CDS group may not have appeared in the post-CDS group because the BMI or weight was above the threshold at the time of prescription but not at the time of extraction or because the start date of the orders was before the start date of the intervention period but these orders were still active and triggered during the intervention period. The proportion of male and female patients was equally distributed in all groups. The median age in all groups was around 60 years (60.0 years (IQR 46.0-72.0) pre- and post-CDS and 61.0 years (IQR 47.3-7.0) in the evaluated group). The median weight was 95.0 kg (IQR 90.0-105.0), 96.3 (IQR 90.0-106.0) and 97.3 (IQR 90.3-106.0) in the pre-CDS, post-CDS and evaluated group respectively. The median BMI was 32.5 kg/m^2 in each group (IQR 30.4-35.6 pre-CDS, 30.5-36.1 post-CDS and 30.2-36.0 in the evaluated group). In each group, the majority had a BMI between 30 and 35 kg/m^2 (52.8%, 52.8% and 47.0%, respectively). The higher the BMI, the less common it was. The medical specialties represented the most were surgery (20.6%, 19.6% and 29.4%), neurosurgery (9.5%, 8.6% and 13.9%) and urology (6.7%, 9.3% and 10.7%) in the pre-CDS, post-CDS and evaluated group respectively.

Table 2: Patient characteristics of the pre-CDS group, post-CDS group and evaluated post-CDS group

		Pre-CDS group (n= 4,428)	**Post-CDS group (n= 800)**	**Evaluated post-CDS group (n= 804)**
Gender	Males Females	2,196 (49.6%) 2,232 (50.4%)	397 (49.6%) 403 (50.%)	421 (52.4%) 383 (47.6%)
Age (y)	Median Range Interquartile range	60.0 18-97 46.0-72.0	60.0 19-96 46.0-72.0	61.0 18-96 47.3-73.0
Length (cm)	Median Range Interquartile range	172.0 113-202 164.0-180.0	172.0 145-199 164.0-180.0	172.0 146-202 164.0-181.0
	Missing	2 (0.05%)	0	1 (0.1%)

Weight (kg)*	Median Range Interquartile range	95.0 52.0-250.0 90.0-105.0	96.3 65.5-206.0 90.0-106.0	97.3 59.5-206.0 90.3-106.0
BMI (kg/m^2)*	Median Range Interquartile range	32.44 22.79-67.60 30.44-35.60	32.46 23.45-78.49 30.48-36.06	32.50 18.20-78.50 30.20-36.00
	BMI < 30 BMI 30-34.99 BMI 35-39.99 BMI 40-44.99 BMI 45-50 BMI > 50	817 (18.5%) 2,338 (52.8%) 850 (19.2%) 299 (6.8%) 84 (1.9%) 38 (0.9%)	132 (16.5%) 422 (52.8%) 164 (20.5%) 53 (6.6%) 24 (3.0%) 5 (0.6%)	176 (21.9%) 378 (47.0%) 166 (20.6%) 53 (6.6%) 26 (3.2%) 4 (0.5%)
	Missing	2 (0.05%)	0	1 (0.1%)
Length of admission (days)	Median Range Interquartile range	2.81 0.05-103.45 1.20-6.70	2.29 0.13-39.61 1.17-5.65	3.04 0.07- 84.90 1.24-7.28
	Missing	0	34 (4.3%)	7 (0.9%)
Medical specialism	Surgery Neurosurgery Urology Obstetrics and gynaecology Internal medicine Pulmonology Orthopaedics Gastroenterology Neurology Cardiology Geriatrics Plastic surgery Oral and Maxillofacial surgery Ear-Nose-Throat Psychiatry Emergency room	911 (20.6%) 419 (9.5%) 296 (6.7%) 311 (7.0%) 309 (7.0%) 245 (5.5%) 232 (5.2%) 161 (3.6%) 147 (3.3%) 120 (2.7%) 62 (1.4%) 38 (0.9%) 31 (0.7%) 15 (0.3%) 10 (0.2%) 3 (0.1%)	157 (19.6%) 69 (8.6%) 74 (9.3%) 58 (7.3%) 46 (5.8%) 32 (4.0%) 44 (5.5%) 28 (3.5%) 20 (2.5%) 16 (2.0%) 6 (0.8%) 9 (1.1%) 4 (0.5%) 4 (0.5%) 5 (0.6%) 0	236 (29.4%) 112 (13.9%) 86 (10.7%) 70 (8.7%) 68 (8.5%) 51 (6.3%) 55 (6.8%) 41 (5.1%) 23 (2.9%) 24 (3.0%) 10 (1.2%) 16 (2.0%) 4 (0.5%) 5 (0.6%) 3 (0.4%) 0
	Missing	1,118 (25.2%)	228 (28.5%)	0
Number of triggers per patient	Median Range Interquartile range	1.0 1-22 1.0-1.0	1.0 1-9 1.0-2.0	1.0 1-3 1.0-1.0
Number of triggers per admission day	Median Range Interquartile range	0.46 0.01-21.18 0.20-0.87	0.54 0.03-7.46 0.26-0.91	0.34 0.01-15.03 0.14-0.82
	Missing	0	0	7 (0.9%)

*BMI and weight may change during admission. Table 2 shows the last known weight and BMI. The weight or BMI at which an intervention was done may differ from the weight or BMI shown in table 2.
Note: BMI = Body Mass Index; CDS = Clinical Decision Support

3.2 Primary study parameters

The primary study parameters are presented from both a patient perspective and a medication order perspective. Figure 1 shows the primary study parameters from the patient perspective, i.e. the number of patients with one or more medication orders with a CDS-trigger, the number of patients with one or more medication orders with a CDS-trigger that needed intervention and the number of patients with one or more medication orders adjusted to body weight (BW) or BMI, in the pre-CDS group, the post-CDS group and the evaluated post-CDS group, respectively. In the pre-CDS group, the total number of patients with one or more medication orders with a CDS-trigger was 4,428. For 2,176 of these patients (49.1%), one or more medication orders with a CDS-trigger needed intervention. For 385 of these 2,176 patients (17.7%), one or more medication orders were adjusted to BW or BMI. In the post-CDS group, the total number of patients with one or more medication orders with a CDS-trigger was 800. For 388 of these patients (48.5%), one or more medication orders with a CDS-trigger needed intervention. For 145 of these 388 patients (37.4%), one or more medication orders were adjusted to BW or BMI. In the evaluated post-CDS group, the total number of patients with one or more medication orders with a CDS-trigger was 804. For 328 of these patients (40.8%), one or more medication orders with a CDS-trigger needed intervention. For 167 of these 328 patients (50.9%), one or more medication orders were adjusted to BW or BMI.

Figure 2 shows the primary study parameters from the medication order perspective, i.e. the number of medication orders with a CDS-trigger, the number of medication orders with a CDS-trigger that needed intervention and the number of medication orders adjusted to BW or BMI, in the pre-CDS group, the post-CDS group and the evaluated post-CDS group. In the pre-CDS group, the number of medication orders with a CDS-trigger was 6,049. For 2,530 of these medication orders (41.8%) an intervention was needed. 447 of these 2,530 medication orders (17.7%) were adjusted to BW or BMI. In the post-CDS group, the number of medication orders with a CDS-trigger was 1,173. For 447 of these medication orders (38.1%) an intervention was needed. 172 of these 447 medication orders (38.5%) were adjusted to BW or BMI. In the evaluated post-CDS group, the number of medication orders with a CDS-trigger was 842. For 349 of these medication orders (41.5%) an intervention was performed: a pharmacotherapeutic adjustment was advised to the patient's attending physician. The acceptance rate was 53.3%, i.e. the attending physician accepted the advice for 186 of the 349 medication orders. The corresponding tables C1 (for the primary study parameters from the patient perspective) and C2 (for the primary study parameters from the medication order perspective) are shown in appendix C.

To compare the rate of patients with medication orders adjusted to BW resp. BMI and the rate of medication orders adjusted to BW resp. BMI between the pre-CDS period and the post-CDS period, a chi-squared test was used (appendix D). The proportion of patients with medication orders adjusted to BW resp. BMI in the post-CDS group was 2.1 times higher than in the pre-CDS group: 37.4% versus 17.7% resp. The proportion of medication orders adjusted to BW resp. BMI in the post-CDS group was 2.2 times higher than in the pre-CDS group: 38.5% versus 17.7% resp. Both differences were statistically significant (p=0.000).

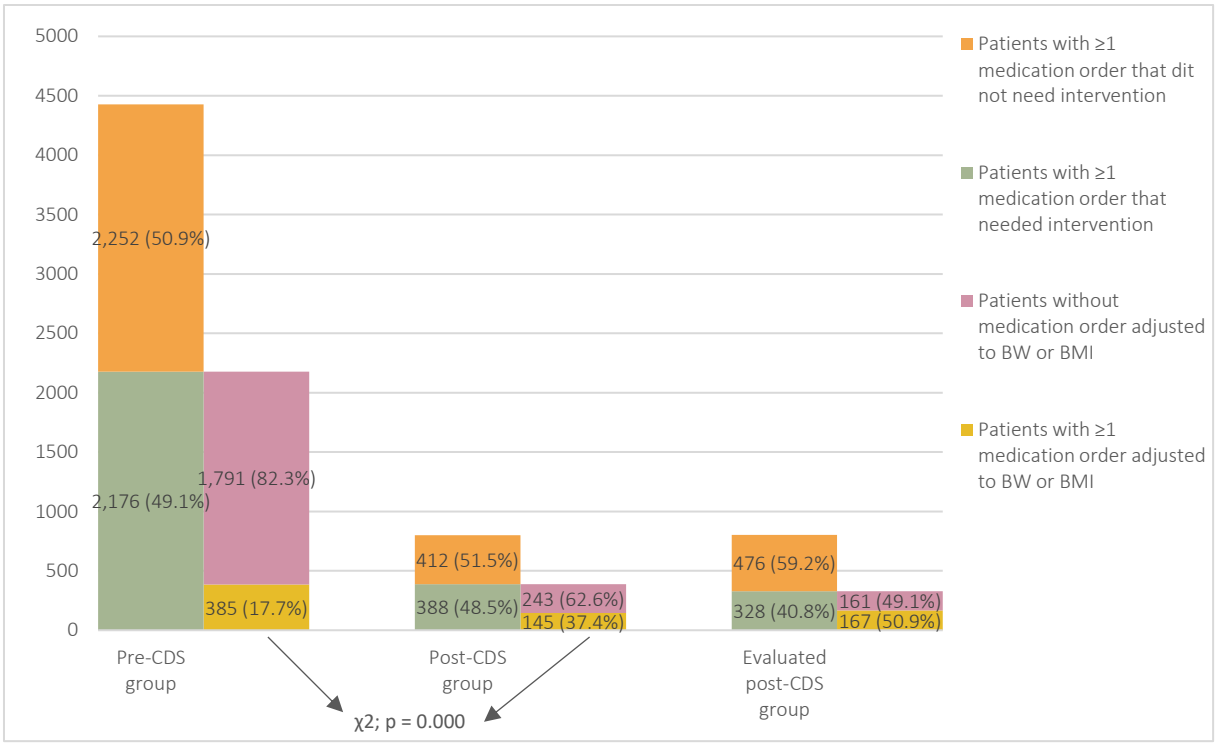


Figure 1: Number and percentage of patients with one or more medication orders with a CDS-trigger, that did or did not need intervention, including whether the medication order was adjusted according to BW resp. BMI or not, in the pre-CDS group, post-CDS group and evaluated post-CDS group (patient-perspective)

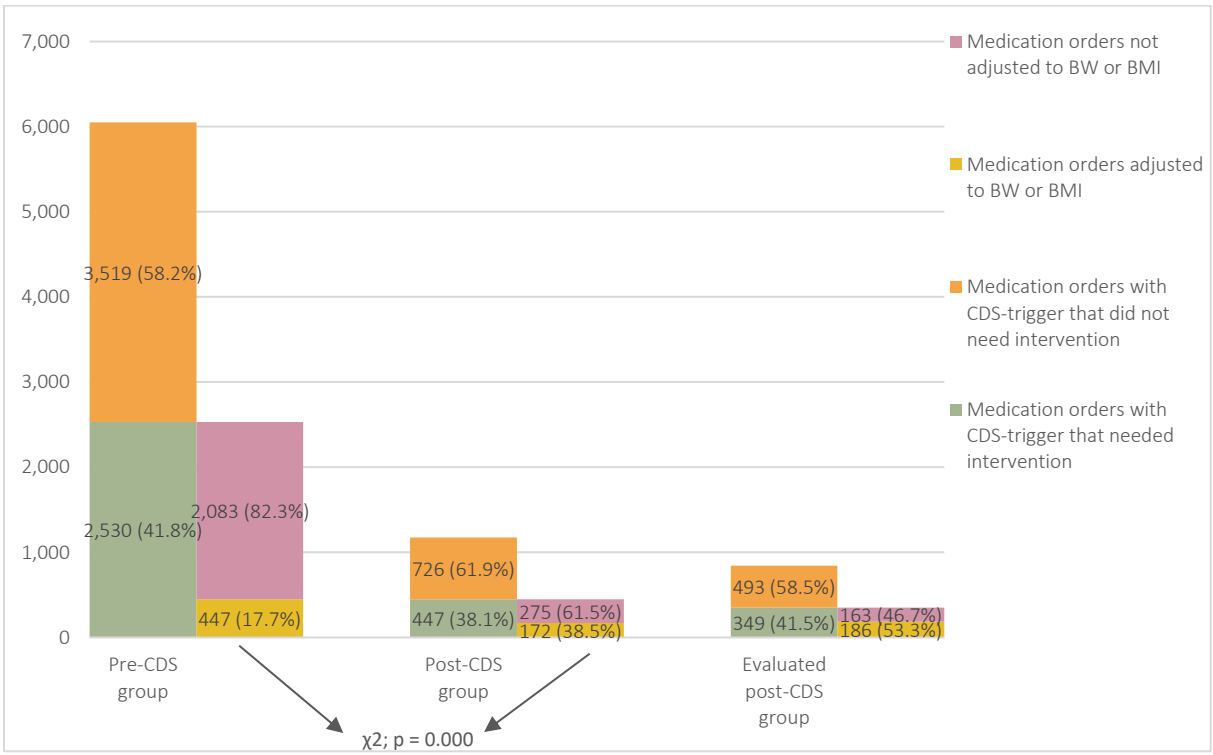


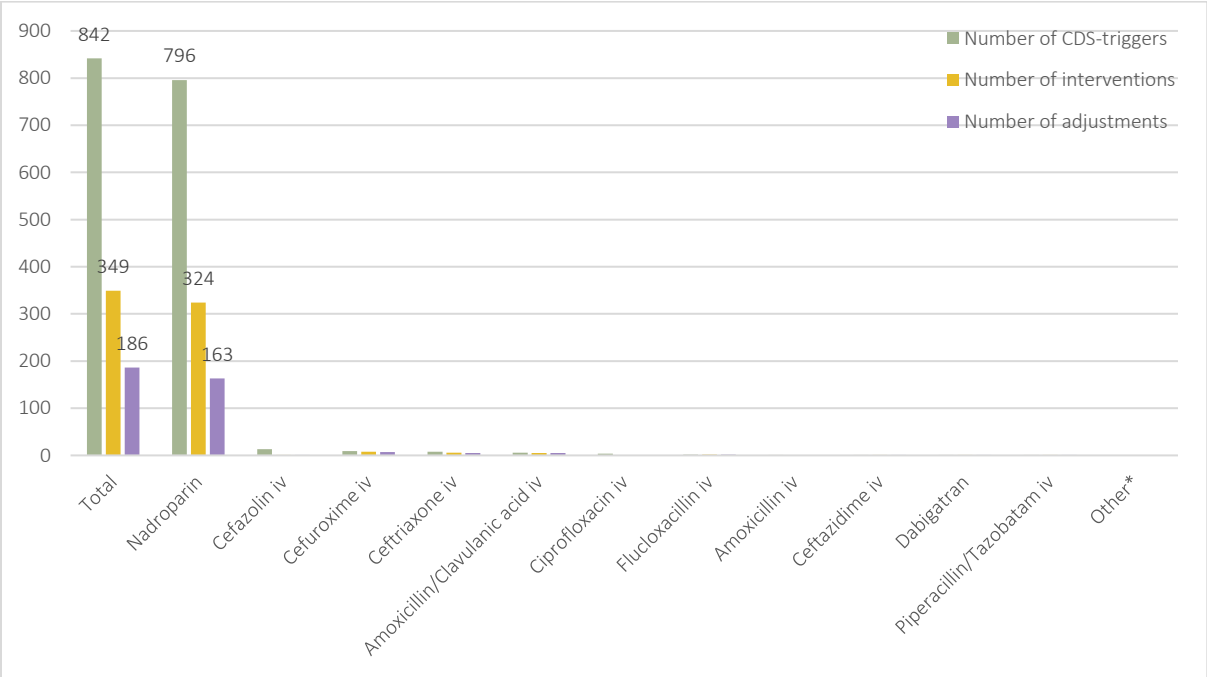
Figure 2: Number and percentage of medication orders with a CDS-trigger, that did or did not need intervention, including whether the medication order was adjusted according to BW resp. BMI or not, in the pre-CDS group, post-CDS group and evaluated post-CDS group (medication order-perspective)

3.2 Secondary study parameters

3.2.1 CDS-triggers, interventions and adjustments per drug

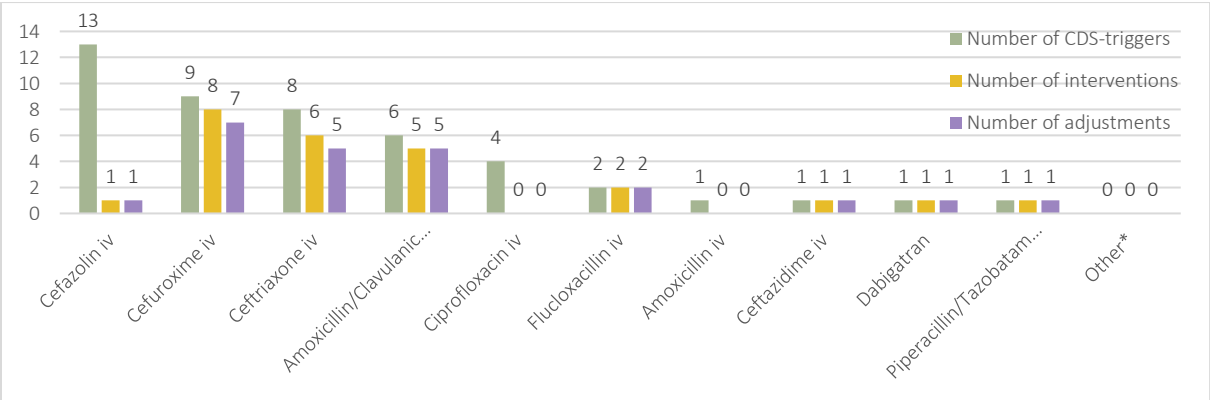
The distribution of CDS-triggers, interventions and consequent adjustments in the evaluated post-CDS group are shown in figure 3. Figure 3b is a subset of figure 3a with a zoom in on the drugs with lower counts. The vast majority of triggers and interventions were for nadroparin (796 triggers (94.5%)), but a trigger did not always lead to an intervention (324/796=40.7%). For the other drugs, an intervention almost always followed a trigger, except for cefazolin (7.7%). Looking at the acceptance rate per drug, nadroparin has a relatively low acceptance rate (50.3%) compared to all other drugs that have acceptance rates of about 80-100%, see appendix E. Table E1 in appendix E further illustrates the frequencies and percentages of triggers, interventions and accepted interventions for each drug.

The frequencies and percentages of the number of CDS-triggers, interventions needed and adjustments to BW or BMI per drug were also determined for the pre-CDS group and the post-CDS group. In appendix E, see figure E1 and table E2 for the pre-CDS group and figure E2 and table E3 for the post-CDS group.



*Other = dalteparin, enoxaparin, apixaban, edoxaban, rivaroxaban and clindamycin iv/po

Figure 3a: Frequency of CDS-triggers, interventions and adjustments in the evaluated post-CDS group, per drug



*Other = dalteparin, enoxaparin, apixaban, edoxaban, rivaroxaban and clindamycin iv/po

Figure 3b: Frequency of CDS-triggers, interventions and adjustments in the evaluated post-CDS group, per drug, zoomed in on the drugs with low counts of figure 3a

3.2.2 Reasons for interventions not made or not accepted

Previously, figure 2 showed that there were 842 medication orders with a CDS-trigger in the evaluated group and 349 (41.5%) of these actually led to a pharmacotherapeutic advice. Consequently, 493 (58.5%) medication orders were not intervened. Figure 4 shows the various reasons why not. For 265 (53.8%) medication orders the dose had already been adjusted to BW/BMI and for 211 (42.8%) medication orders the 'normal dose' was correct. 'Normal dose' relates to doses for certain indications, for which higher doses are already given as standard, regardless of BMI or weight. In those cases, this standard higher dose, i.e. the normal dose for that indication, was correct. Other reasons were discharge, temporarily discontinued pharmacotherapy and near discontinuation of the drug.

Of the 349 medication orders that were intervened, 163 (46.7%) interventions were not accepted. Figure 5 shows the various reasons why not. In almost all cases (n=148 (90.8%)) the patient had been discharged and in 10 (6.1%) of the cases, therapy would end soon. In 2 cases (1.2%) the attending physician responded to consider accepting the advice, but ultimately did not execute the adjustment. Other reasons occurred only once each: physician did not see the benefit, adjustment would lead to risks for the patient and the patient was doing well, resp.

The frequencies of the reasons why interventions were not made or accepted are also shown in the corresponding table F1 in appendix F.

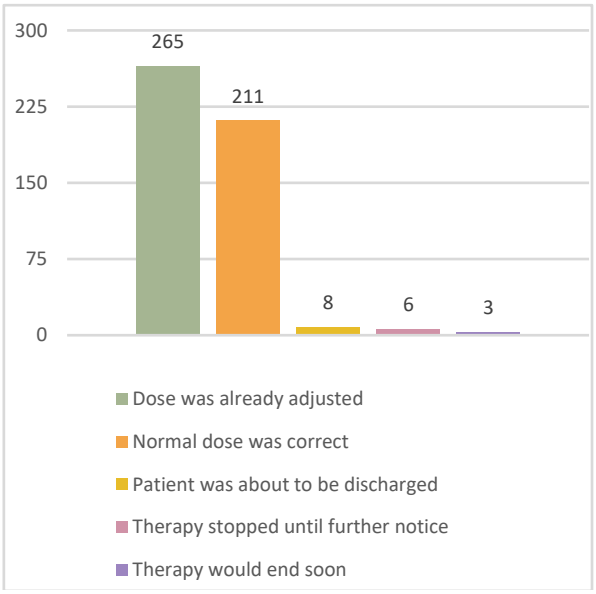


Figure 4: Frequency of reasons for interventions not made

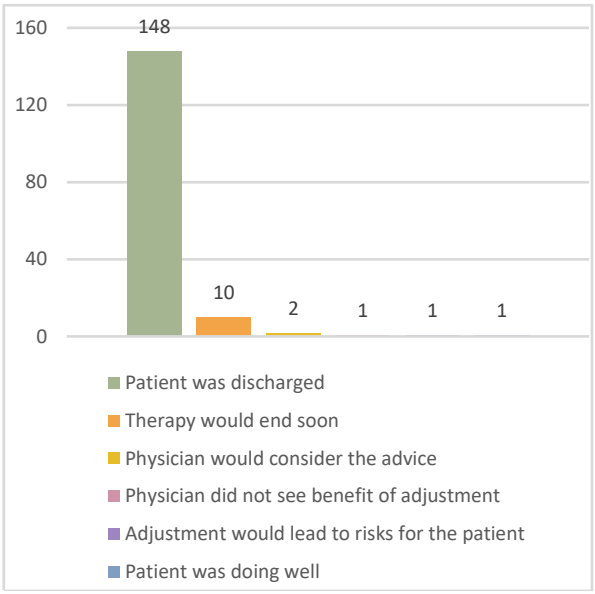


Figure 5: Frequency of reasons for interventions not accepted

3.2.2.1 Reasons for interventions not made or not accepted per drug

Figure 6 illustrates per drug why an intervention was not made despite a CDS-trigger. Of the medication orders that were not intervened, the vast majority were for nadroparin (472/493=95.7%). For nadroparin, in 265 (56.1%) of the cases the dose had already been adjusted and for 196 (41.5%) the normal dose was correct. For cefazolin, in 11 of 12 (91.7%) of the medication orders for which there was no intervention, the normal dose was correct. Not intervening barely occurred for other drugs, see Figure 6. Other reasons for not intervening were discharge, temporary discontinuation of therapy and near discontinuation of the drug.

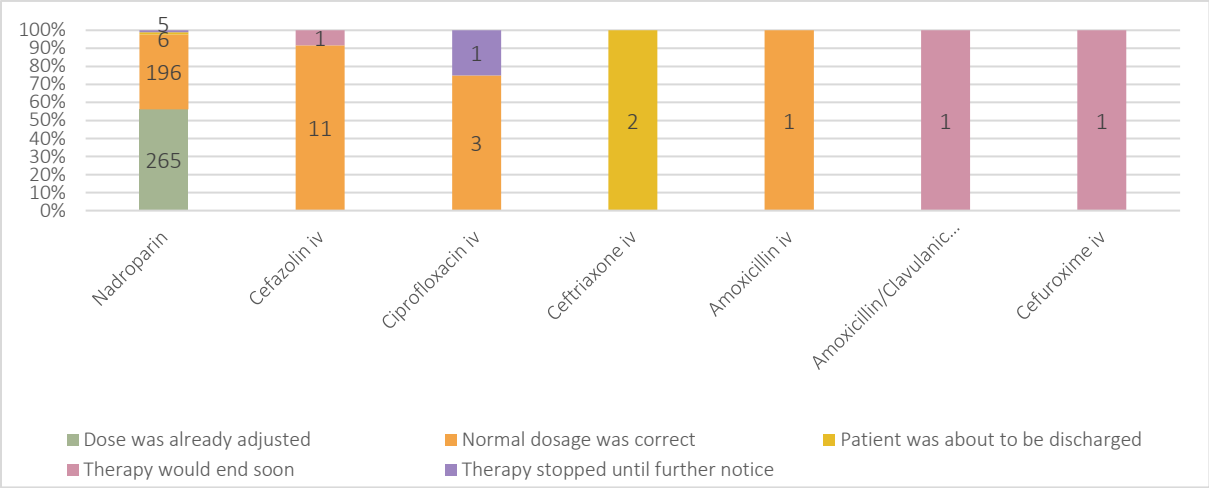


Figure 6: Frequency of reasons for interventions not made, per drug

Figure 7 illustrates per drug why an intervention was not accepted. Of the interventions not accepted, the vast majority were for nadroparin (161/163=98.8%). For nadroparin, in 148 (91.9%) of the cases, the patient was about to be discharged and in 9 (5.6%) cases the therapy was about to end. For both ceftriaxone and cefuroxime, only one intervention was not accepted. Other reasons for not accepting an intervention were: physician responded to consider accepting the advice but did not execute the adjustment, physician did not see the benefit, adjustment would lead to risks for the patient and the patient was doing well.

The frequencies of the reasons why interventions were not made or accepted per drug are also shown in the corresponding table F2 in appendix F.

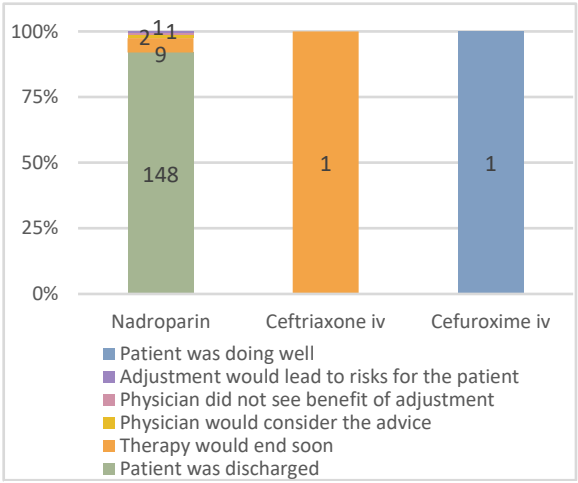


Figure 7: Frequency of reasons for interventions not accepted, per drug

3.2.3 Therapy failure and adverse events

The occurrence of therapy failure and adverse events was examined in the evaluated post-CDS group (n=328 patients). We evaluated therapy failure in those patients whose medication was not adjusted to BW or BMI (n=161) and we evaluated adverse events in those patients whose treatment was adjusted based on BW or BMI (n=167). We did not find any cases of therapy failure. Switching between antibiotics did take place, but this was on the basis of microbiological cultures, not due to insufficient efficacy. Four possible adverse events occurred in patients whose nadroparin dose was increased. These events included two haematoma, one bloody wound leakage and one rectal bleeding due to a diverticular haemorrhage. These events occurred in 3 of 167 patients. For the latter adverse event, nadroparin was stopped and restarted in a lower dose.

4 Discussion

The aim of this study was to investigate the extent to which digital CDS leads to pharmacotherapeutic interventions and pharmacotherapy adjustments in the treatment of hospitalised (morbidly) obese patients. In the evaluated post-CDS group, 804 patients had one or more medication orders with a CDS-trigger of which over 40% needed intervention for dose adjustment based on BW or BMI. Additionally, this study showed that implementation of digital CDS led to a significant increase in the proportion of patients with correct doses: 37.4% post-CDS vs. 17.7% pre-CDS (p=0.000).

The rate of accepted interventions (adjustments) was 53.3% in the evaluated post-CDS group. This seems low, but is mainly due to the acceptance rate of nadroparin (50.3%). The acceptance rate for the other drugs is much higher (80-100%). In addition, it can be seen that interventions not made, despite a CDS-trigger, occurred mainly for nadroparin and cefazolin. For the other drugs, an intervention almost always followed a trigger. The reasons for not intervening were by far (in 96.6% of cases) that the dose had already been adjusted or that the normal dose was correct. The main reason (in 90.8% of cases) for not accepting an intervention was that the patient was discharged, followed by the reason that therapy would end soon (6.1%). Thus, it barely occurred that the physician did not accept the intervention because of other reasons which indicates that the will to go along with interventions is high among physicians. The reason that the patient was discharged occurred only for nadroparin, which also explains the low acceptance rate for nadroparin. The explanation why this occurred only for nadroparin is that for an intervention for nadroparin, a note for the physician was first made in the patient record with the instruction to adjust the dose. If the next day no adjustment was made, the physician was called. But often it turned out that the patient had been discharged or was going to be discharged that day and nadroparin prophylactic dose was discontinued at discharge. For the other drugs, the physician was called directly, so this reason never came up here. It is expected that the acceptance rate for nadroparin, and therefore the overall acceptance rate, would be higher if the physician was called directly for nadroparin as well.

Studies that have investigated CDS in morbidly obese patients are scarce which makes it difficult to compare this study. The study by Polso et al.[14] examined compliance with antibiotic dosing recommendations in morbidly obese patients. Compliance occurred in 64% of doses dispensed. In our study, the mean acceptance rate for the antibiotic interventions was 95.8%. The acceptance rate is higher in this study, probably due to the fact that the study by Polso et al. did not use CDS but used recommendations available online. Therefore, the studies are not easily comparable. But this does indicate that by using CDS, the acceptance rate may be higher. Recently, Brand et al.[22] published a study on CDS in the treatment of hospitalised morbidly obese patients. The study has similarities with our study (such as the use of CDS, similar advices and inclusion of the patient population) but included fewer drugs than our study. The mean acceptance rate in that study was not reported, with exception of that for ciprofloxacin (64%). This cannot be compared with our study, as no interventions for ciprofloxacin were done in our study. At last, a study by Zaal et al.[23] examined physicians' acceptance of pharmacists' interventions in daily hospital practice in The Netherlands. Focus was not on morbidly obese patients, but on the general population. This study found an acceptance rate of 71.2%. This acceptance rate is higher than that in our study, probably because here the physician was always called directly.

What makes this study strong is that it is one of the first to give promising results for the application of CDS to optimise the treatment of (morbidly) obese patients. The study is relevant because obesity is a growing problem worldwide. Little information is available on CDS in the treatment of (morbidly) obese patients, so this study contributes greatly with information on the use of CDS and therapy adjustments in these patients. The promising results give reason to implement CDS to optimise the treatment of patients with (morbid) obesity in practice and to conduct more research on therapy adjustments in (morbid) obesity to further

increase the percentage of correctly dosed drugs. In addition to CDS, this could be addressed in other ways, such as education for physicians and pharmacists. Another strength of the study is that a lot of drugs were included in the study, compared to the study by Brand et al.[22] At last, strengths were a large number of patients included, a large number of triggers occurred and a large number of interventions made. This makes the results robust and reliable. Because of the prospective study design and because of the standardised interventions by digital CDS, the data are considered valid.

Besides the strengths, there are also some limitations to this study. First, BMI and/or weight is not always measured and updated immediately upon admission, leaving the old values in the patient record when a drug is prescribed. Because the CDS is based on the last known BMI and/or weight, patients may be missed or may cause a trigger unfairly because the old BMI or weight is lower or higher than the current one, respectively. After a few days, the patient does appear in the CDS list if the BMI and weight are updated and above the limits. However, it is also possible that a patient is discharged and BMI and weight are not updated at all. Thus, these patients were not included.

The second limitation is that the CDS patient list was not maintained on weekends and nights so patients and CDS-triggers from these days and nights were not included in the evaluated post-CDS group unless they were still in the CDS patient list on Monday or in the morning, respectively. The percentage of missing patients was 6.1% and the percentage of missing CDS-triggers was 21.8% (data not shown). Thus, if interventions had been performed in these missed patients the number of interventions would have been higher. Nonetheless in practice, this would also be the case, so our results adequately reflect clinical practice.

The third limitation is that there may be discrepancies in the I-vent documentation of the reason "dose was already adjusted" for nadroparin 5700 IU. It was sometimes difficult to determine whether the dose of 5700 IU was a normal dose for a particular indication or whether this dose had already been adjusted for BMI and/or weight. This may have led to an overestimation of the number of “doses already adjusted to BMI and/or weight”. This does not negatively affect the results of the study though, because in both cases the therapy did not require adjustment.

The fourth limitation is that physicians may have learned from the advice given by the pharmacy during the intervention period. As a result, they possibly already adjusted doses themselves to BW/BMI, thus reducing the need for interventions. We did not investigate this further, but see it as positive if physicians proactively adjusted doses.

The fifth limitation is that mainly interventions for nadroparin were not accepted. It is explained earlier that this is because a note for the physician was first made in the EHR with instruction to adjust the nadroparin dose and if the dose was not adjusted by the next day, a call was made to the physician. It frequently occurred that the patient was discharged the next day so no further call was made and thus causing it to be noted that the intervention was not accepted. It is expected that the interventions would be accepted if a call to the physician had been immediately on the first day. Thus, this may overestimate the number of nadroparin interventions not accepted.

The last limitation is that therapy failure and adverse events due to treatment adjustment or not in patients with (morbid) obesity were not examined in the pre-CDS group. Consequently, the number of patients with therapy failure or adverse events post-CDS cannot be compared, leaving it unclear whether there is an increase or decrease in therapy failure or adverse events after implementation of digital CDS. As a result, no conclusion can be drawn about the clinical relevance of using digital CDS.

It can be stated that digital CDS contributes significantly to pharmacotherapeutic interventions and pharmacotherapy adjustments in the treatment of hospitalised (morbidly) obese patients. However, there

are still some aspects that can be improved. It can be noted that CDS-triggers occurred mainly for nadroparin. This is because many patients receive nadroparin as thrombosis prophylaxis and because the dose should already be increased from a weight of 90 kg and/or from a BMI of 30 kg/m^2. It was also noticed that many medication orders with a CDS-trigger did not require intervention. To reduce this number of CDS-triggers, the digital CDS could be altered. Now, all medication orders of the included drugs in obese patients appear in the CDS list, regardless of the dose. The results also showed that the main reasons for not intervening were that the dose was already adjusted or correct. An improvement would be to modify the CDS so that only those orders with a dose that needs an adjustment appear in the list. Another way to have less triggers is for the physician to receive, for example, a pop-up at the time of prescribing a drug indicating that higher doses or an alternative drug should be given at the current weight and/or BMI. Another advantage of such a pop-up, is that single-dose administrations would also be included in the CDS. Now these are missed because these administrations have already been given. By using such a pop-up for example, adjustments could also be made immediately for single-dose administrations. In addition, an improvement is the modification of the CDS so that it takes into account the estimated discharge date and does not trigger for prophylactic nadroparin if the estimated discharge date is within 24 hours. This will reduce triggers for medication orders that require intervention but are unlikely to be accepted because the patient would be discharged soon. Moreover, the results showed that the acceptance rate is higher when the physician is called directly for an intervention. Therefore, in the future, interventions that need to be made will require direct calls to the physician. It was also noted that occasionally an increased antibiotic dose was reduced again after several days. It is unknown why this happened. One explanation could be that the reason for the increase was not documented so the next attending physician was unaware why a higher dose was prescribed. It is therefore important to make recording the reason for adjustment in the patient record obligatory and to make this reason visible in the future.

An idea for a follow-up study would be to examine the effect of implementing the aforementioned pop-up during the prescription of a drug in an obese patient. For example, that study could examine the number of interventions still to be made by the pharmacist. Another idea for a follow-up study would be to examine therapy failure and adverse events due to interventions made or not made. In this current study, there have been a few of such observations, but with no clear correlation, mainly due to too low numbers. It would be interesting to set up a multicenter study that mainly focuses on therapy failure and adverse events.

5 Conclusion

It can be concluded that implementation of digital CDS led to pharmacotherapeutic interventions and consequent adjustments in the treatment of hospitalised (morbidly) obese patients: the proportion of (patients with) doses adjusted to BW/BMI doubled (p=0.000). We observed significantly more correctly dosed orders post-CDS, but there is still room for improvement in the percentage of false triggers (those that do not require action) and there is room for improvement in the acceptance rate, or in other words, in the percentage of interventions that actually result in pharmacotherapy adjustment. No cases of therapy failure and only a few possible adverse events were found. These are all leads for follow-up research to further optimise the treatment of (morbidly) obese patients.

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Appendix A

The CDS is a homegrown automated rule-based tool that generates a patient list in the EHR. This list has been built to show patients who are prescribed a drug of which the dose needs to be adjusted to that patient's current BMI or weight. These patients are displayed in the list with relevant associated patient characteristics, such as age, gender, BMI and weight, together with the drug prescriptions that cause the CDS-trigger. A CDS-trigger is defined as an event that causes a decision support rule to be invoked. In this study the event concerned a drug that was prescribed by a physician in the EHR of an admitted patient. For one patient more than one trigger could occur, as more than one drug with a CDS-trigger could be prescribed. The drugs that cause a CDS-trigger are in accordance with the Royal Dutch Pharmacists Association (KNMP) dose recommendations for obese patients and with the local hospital protocol. The KNMP recommendations include all drug groups for which scientific evidence exists that the dose of these drugs should be adjusted in obese patients for optimal treatment.[12] Not all KNMP's drug groups are adopted in the CDS, because either no action is required, or a concrete action is missing to actually support clinical decision making, or therapeutic drug monitoring (TDM) is used to determine the correct patient dose. Also, not all advice from the KNMP is literally adopted because the local hospital protocol gives different, more specific, advice for some drugs and this protocol is leading in our clinical decision making. Moreover, several drugs (cefuroxime and ceftazidime) are included in the CDS that are not in the KNMP's recommendations, but are in the local hospital protocol, because these drugs should also be dosed higher in obese patients, based on pharmacists' experience and on protocols from other hospitals.

Table A1: drugs that cause a CDS-trigger, including the BMI and/or weight cut-off values above which adjustments are required per drug and the recommended adjustment

Drug group	Drug	Normal dose	Adjustment criteria	Recommendation
LMWH	Nadroparin	2850 IE or 5700 IE	Weight > 90 kg and/or BMI > 30 Weight > 160 kg	→ 5700 IE → 7600 IE
	Dalteparin		BMI > 40	Prophylactic dosing, low thrombosis risk: 5000IE 1x daily or alternative Prophylactic dosing, high thrombotic risk: 7500IE 1x per day or alternative Therapeutic dose: dose on total body weight without cut-off value
	Enoxaparin		BMI > 40	Prophylactic dose: → dose at normal weight 1x per day 20 mg: increase to 1x per day 40 mg → dose at normal weight 1x per day 40 mg: increase to 1x per day 60 mg Therapeutic dose: dose on total body weight without cut-off value
DOAC	Apixaban		Weight > 175 kg	Avoid use of apixaban. Prophylactic: LMWH Therapeutic: VKA
	Dabigatran		BMI > 40	Avoid use of dabigatran Prophylactic: LMWH Therapeutic: VKA, or apixaban or rivaroxaban in patients up to 175 and 173kg, respectively

	Edoxaban		Weight > 140 kg	Avoid use of edoxaban Prophylactic: LMWH Therapeutic: VKA, or apixaban or rivaroxaban in patients up to 175 and 173kg, respectively
	Rivaroxaban		Weight > 173 kg	Avoid use of rivaroxaban. Prophylactic: LMWH Therapeutic: VKA
Antibiotics	Amoxicillin iv	4dd1000mg	BMI > 40 BMI > 50	→ 6dd1g → 8-12g/day *Dose at upper limit of normal dose range. See relevant indications for dose range.*
	Amoxicillin/ Clavulanic acid iv	4dd1200mg	BMI >40 BMI > 40 + GFR < 30ml/min	→ amox/clav 4dd1200mg + amox 2dd1g → amox/clav 2dd1200mg + amox 4dd1g *Dose at upper limit of normal dose range. See relevant indications for dose range*
	Cefazolin iv	2dd1000mg	BMI > 40	→ 2dd2g *Dose at upper limit of normal dose range.*
	Ceftazidime iv	3dd2000mg	BMI > 40	→ 3dd2,5-3g *Dose at upper limit of normal dose range.*
	Ceftriaxone iv	1dd2000mg	BMI > 40	→ 1dd3g *Dose at upper limit of normal dose range.*
	Cefuroxime iv	3dd1500mg	BMI > 40	→ 3dd2g *Dose at upper limit of normal dose range.*
	Ciprofloxacin iv	2dd400mg	BMI > 30	→ adults 10 mg/kg/day in 2-4 doses, max. 400 mg at a time, max. 1.6 g/day
	Clindamycin iv and po	3dd600mg	Weight > 180kg	→ 900 mg at a time
	Flucloxacillin iv	6dd1000mg	BMI > 40 and GFR ≥ 50ml/min BMI > 50 and GFR ≥ 50ml/min	→ 8dd1g → 10-12g/day
	Piperacillin and tazobactam iv	3dd4500mg	BMI > 40	→ 4dd4500mg *Dose at upper limit of normal dose range.*

Note: BMI = body mass index; DOAC = direct oral anticoagulant; GFR = glomerular filtration rate ; IE = international units; iv = intravenous; LMWH = low molecular weight heparin; po = per os; VKA = vitamin K antagonist

Appendix B

First, orders of oral antibiotics (except oral clindamycin) and orders of skin tests for antibiotics were removed. This was done because the CDS only triggers on intravenous administrations of antibiotics (for clindamycin also on oral administrations). Next, orders for single administrations advanced and administered in the OR (operating room) or ED (emergency room) were removed, because we do not get these orders in the list of the CDS. Then the orders were removed using the defined criteria (see appendix A). The patients with these orders did not have a BMI or weight at which the CDS would trigger with the prescribed drug. At last, duplicate orders were removed. These orders consisted of the same drug with the same dose and were prescribed at the same time. In practice, we see this as one trigger.

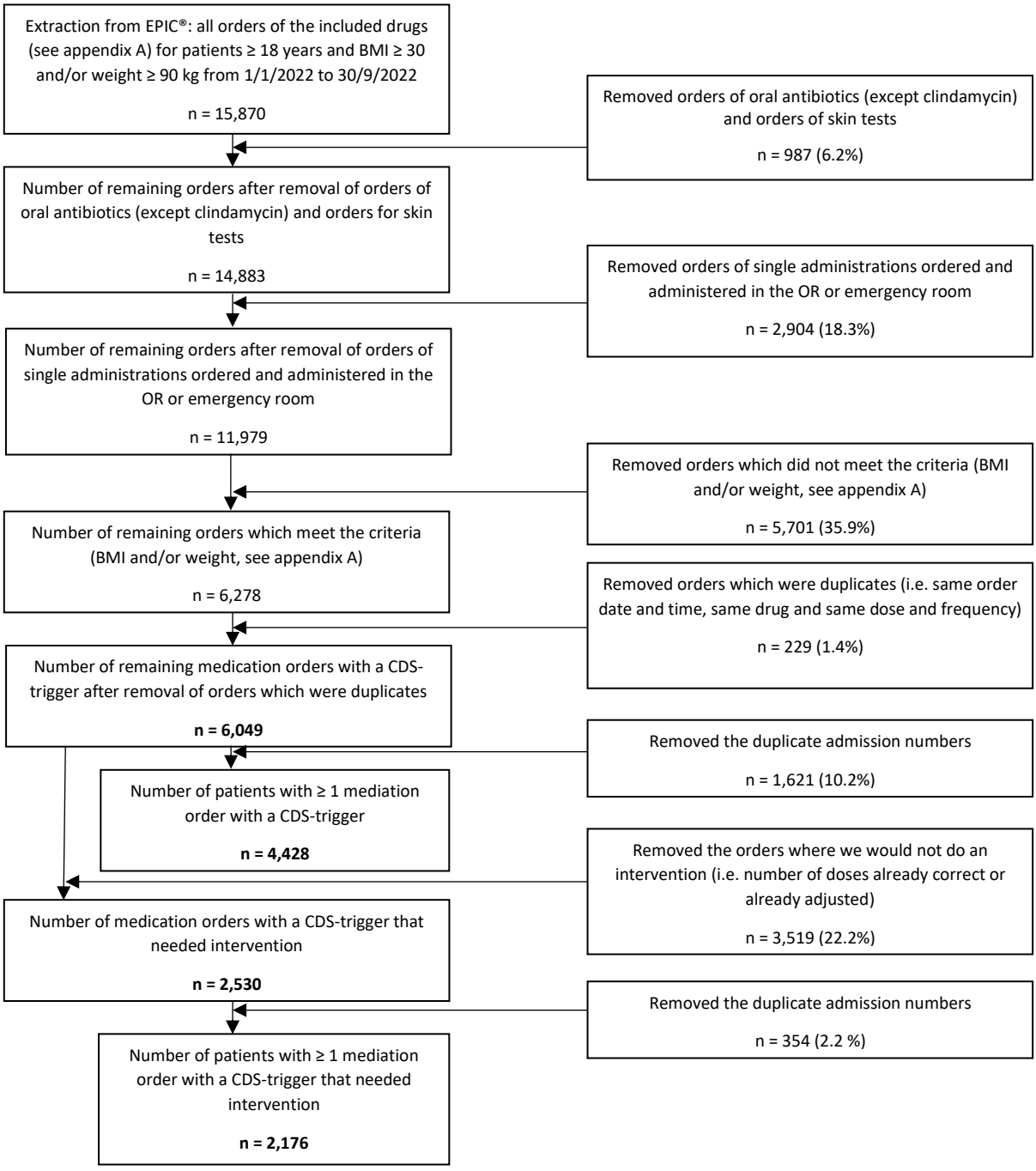


Figure B1: Flowchart for cleaning up the extraction of the pre-CDS group

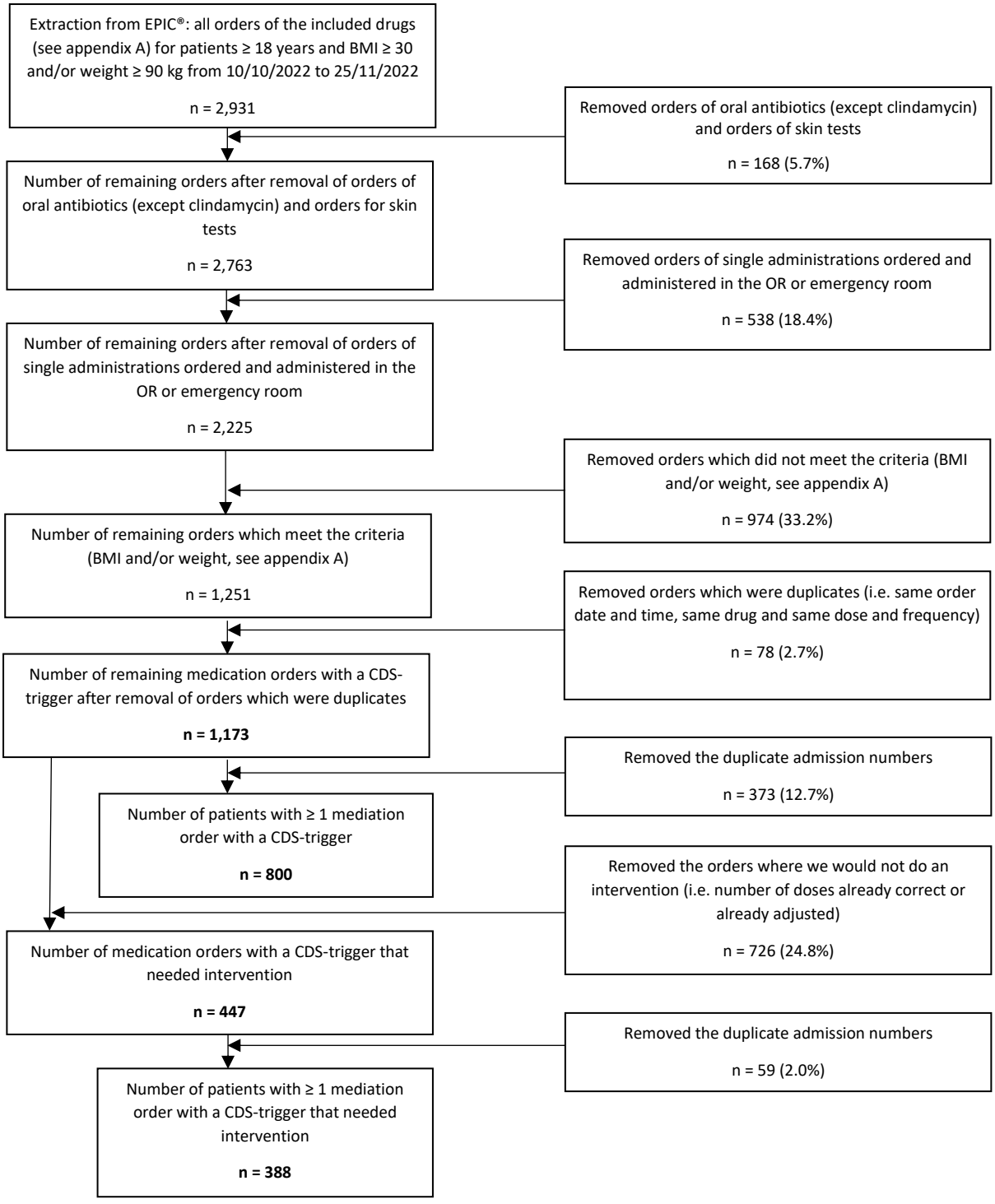


Figure B2: Flowchart for cleaning up the extraction of the post-CDS group

Appendix C

Table C1 : Patient-perspective; number of patients with ≥ 1 mediation order with a CDS- trigger, number of patients with ≥ 1 mediation order that needed intervention and number of patients with ≥ 1 mediation order adjusted tot BW or BMI

	Pre-CDS group (39 weeks)	**Post-CDS group (7 weeks)**	**Evaluated post-CDS group (7 weeks)**
Total number of hospitalised patients ≥ 18 years, BMI ≥ 30 kg/m² and/or weight ≥ 90 kg	12,170	3,055	3,055
Total number of patients with ≥ 1 mediation order with a CDS-trigger	4,428	800	804
Total number of patients with ≥ 1 mediation order that needed intervention	2,176 (49.14%)	388 (48.50%)	328 (40.80%)
Total number of patients with ≥ 1 medication order adjusted to BW or BMI	385 (17.69%)	145 (37.37%)	167 (50.91%)

Note: BMI = body mass index; BW = body weight; CDS = clinical decision support

Table C2: Medication order-perspective; number of medication orders with a CDS-trigger, number of medication orders that needed intervention and number of medication orders adjusted to BW or BMI

	Pre-CDS group (39 weeks)	**Post-CDS group (7 weeks)**	**Evaluated post-CDS group (7 weeks)**
Total number of hospitalised patients ≥ 18 years, BMI ≥ 30 kg/m² and/or weight ≥ 90 kg	12,170	3,055	3,055
Total number of medication orders with a CDS-trigger	6,049	1,173	842
Total number of medication orders that needed intervention	2,530 (41.83%)	447 (38.11%)	349 (41.45%)
Total number medication orders adjusted to BW or BMI	447 (17.67%)	172 (38.48%)	186 (53.30%)

Note: BMI = body mass index; BW = body weight; CDS = clinical decision support

Appendix D

*Table D1: Cross table adjusted dose * group for Chi-Square Tests (patient-perspective)*

		Group		
		Pre-CDS	Post-CDS	Total
Adjusted	yes	414	156	570
	no	1877	253	2130
Total		2291	409	2700

Table D2: Chi-Square Tests (patient-perspective)

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	83,946[a]	1	,000		
Continuity Correction[b]	82,745	1	,000		
Likelihood Ratio	74,696	1	,000		
Fisher's Exact Test				,000	,000
N of Valid Cases	2700				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 86,34.

b. Computed only for a 2x2 table

*Table D3: Cross table adjusted dose * group for Chi-Square Tests (medication order-perspective)*

		Group		
		Pre-CDS	Post-CDS	Total
Adjusted	yes	447	172	619
	no	2083	275	2358
Total		2530	447	2977

Table D4: Chi-Square Tests (medication order-perspective)

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	99,896[a]	1	,000		
Continuity Correction[b]	98,636	1	,000		
Likelihood Ratio	88,359	1	,000		
Fisher's Exact Test				,000	,000
N of Valid Cases	2977				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 92,94.

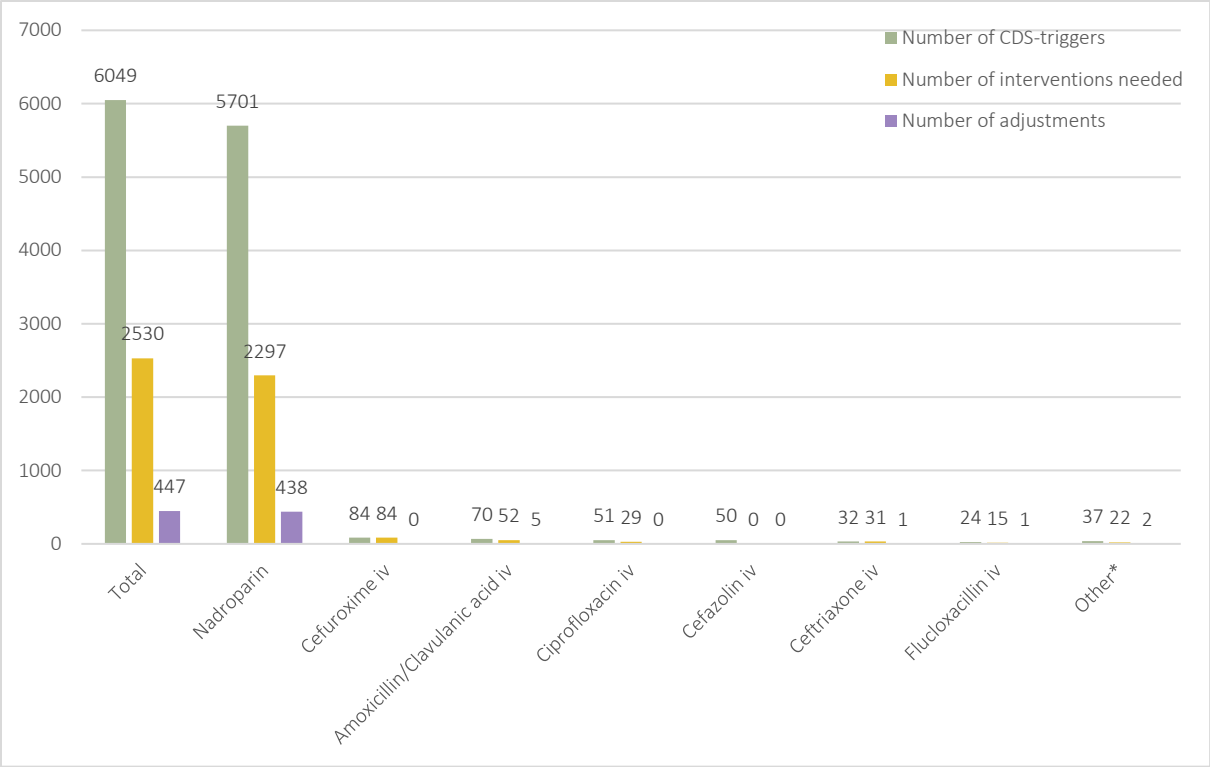
b. Computed only for a 2x2 table

Appendix E

Table E1: Frequency of CDS-triggers, interventions and adjustments in the evaluated post-CDS group, per drug

Drug group	Drug	Number of medication orders with a CDS-trigger (n = 842)	Number of medication orders that needed intervention (n = 349)	Number of medication orders adjusted to BW or BMI (n = 186)	Number of medication orders that needed intervention / Number of medication orders with a CDS-trigger (%)	Number of medication orders adjusted to BW or BMI / Number of medication orders that needed intervention (acceptance rate) (%)	Number of medication orders adjusted to BW or BMI / Number of medication orders with a CDS-trigger (%)
LMWH	Dalteparin	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Enoxaparin	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Nadroparin	796 (94.54%)	324 (92.84%)	163 (87.63%)	40.65%	50.31%	20.45%
DOAC	Apixaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Dabigatran	1 (0.12%)	1 (0.29%)	1 (0.54%)	100%	100%	100%
	Edoxaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Rivaroxaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
Antibiotics	Amoxicillin iv	1 (0.12%)	0 (0.00%)	0 (0.00%)	0.00%	/	/
	Amoxicillin/ Clavulanic acid iv	6 (0.71%)	5 (1.43%)	5 (2.69%)	83.33%	100%	83.33%
	Cefazolin iv	13 (1.54%)	1 (0.29%)	1 (0.54%)	7.70%	100%	7.70%
	Ceftazidime iv	1 (0.12%)	1 (0.29%)	1 (0.54%)	100%	100%	100%
	Ceftriaxone iv	8 (0.95%)	6 (1.72%)	5 (2.69%)	75.00%	83.33%	62.50%
	Cefuroxime iv	9 (1.07%)	8 (2.29%)	7 (3.76%)	88.89%	87.5%	77.78%
	Ciprofloxacin iv	4 (0.48%)	0 (0.00%)	0 (0.00%)	0.00%	/	/
	Clindamycin iv/po	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Flucloxacillin iv	2 (0.24%)	2 (0.57%)	2 (1.08%)	100%	100%	100%
	Piperacillin/ Tazobactam iv	1 (0.12%)	1 (0.29%)	1 (0.54%)	100%	100%	100%

Note: BMI = body mass index; BW = body weight; CDS = clinical decision support; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin



* Other = Clindamycin iv/po, edoxaban, enoxaparin, rivaroxaban, apixaban, dalteparin, amoxicillin iv, ceftazidime iv, piperacillin/tazobactam iv and dabigatran

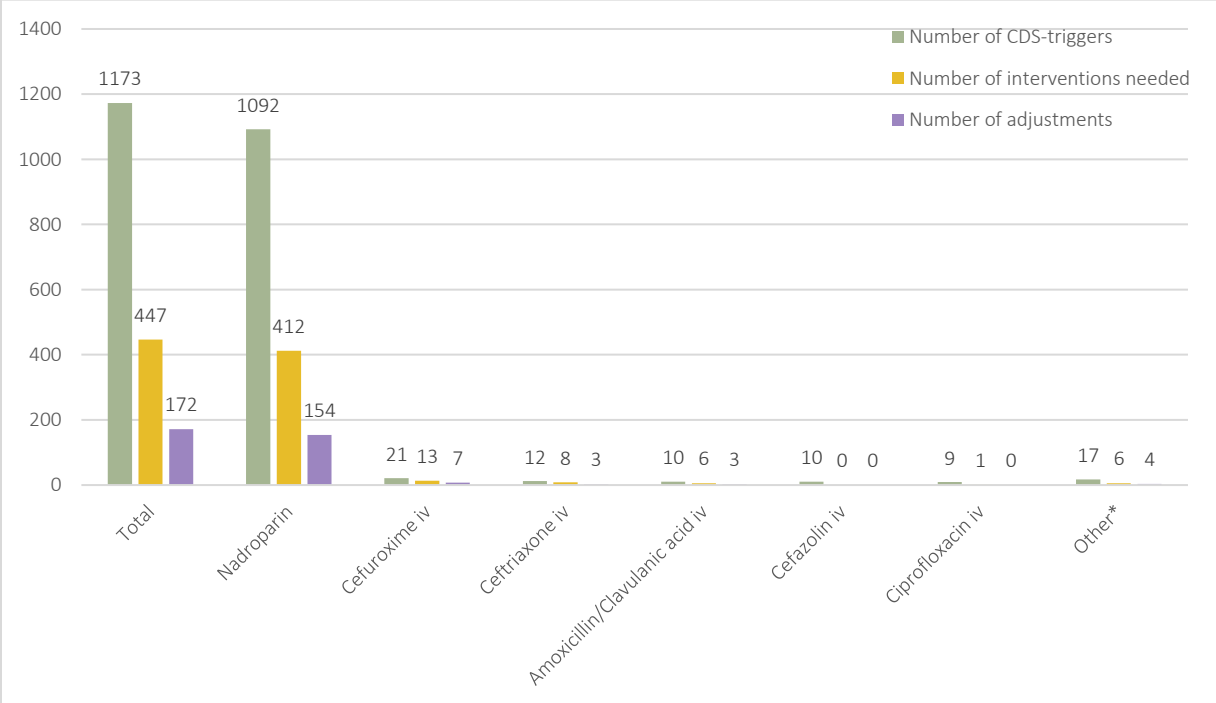
Figure E1: Frequency of CDS-triggers, interventions needed and adjustments to BW or BMI in the pre-CDS group, per drug

Table E2: Frequency of CDS-triggers, interventions needed and adjustments to BW or BMI in the pre-CDS group, per drug

Drug group	**Drug**	**Number of medication orders with a CDS-trigger (n = 6,049)**	**Number of medication orders that needed intervention (n =2,530)**	**Number of medication orders adjusted to BW or BMI (n= 447)**	**Number of medication orders that needed intervention / Number of medication orders with a CDS-trigger (%)**	**Number of medication orders adjusted to BW or BMI / Number of medication orders that needed intervention (%)**	**Number of medication orders adjusted to BW or BMI / Number of medication orders with a CDS-trigger (%)**
LMWH	Dalteparin	3 (0.05%)	0 (0.00%)	0 (0.00%)	0.00%	/	0.00%
	Enoxaparin	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Nadroparin	5,701 (94.25%)	2,297 (90.79%)	438 (97.99%)	40.29%	19.07%	7.68%
DOAC	Apixaban	2 (0.03%)	2 (0.08%)	0 (0.00%)	100%	0.00%	0.00%
	Dabigatran	6 (0.10%)	6 (0.24%)	0 (0.00%)	100%	0.00%	0.00%
	Edoxaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Rivaroxaban	1 (0.02%)	1 (0.04%)	0 (0.00%)	100%	0.00%	0.00%

Antibiotics	Amoxicillin iv	12 (0.20%)	3 (0.12%)	0 (0.00%)	25.00%	0.00%	0.00%
	Amoxicillin/ Clavulanic acid iv	70 (1.16%)	52 (2.06%)	5 (1.12%)	74.29%	9.62%	7.14%
	Cefazolin iv	50 (0.83%)	0 (0.00%)	0 (0.00%)	0.00%	/	0.00%
	Ceftazidime iv	4 (0.07%)	4 (0.16%)	0 (0.00%)	100%	0.00%	0.00%
	Ceftriaxone iv	32 (0.53%)	31 (1.23)	1 (0.22%)	96.88%	3.23%	3.13%
	Cefuroxime iv	84 (1.39%)	84 (3.32%)	0 (0.00%)	100%	0.00%	0.00%
	Ciprofloxacin iv	51 (0.84%)	29 (1.15%)	0 (0.00%)	56.86%	0.00%	0.00%
	Clindamycin iv/po	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Flucloxacillin iv	24 (0.40%)	15 (0.60%)	1 (0.22%)	62.50%	6.67%	4.17%
	Piperacillin/ Tazobactam iv	9 (0.15%)	6 (0.24%)	2 (0.45%)	66.67%	33.33%	22.22%

Note: BMI = body mass index; BW = body weight; CDS = clinical decision support; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin



*Other = dabigatran, dalteparin, enoxaparin, apixaban, edoxaban, rivaroxaban, clindamycin iv/po, amoxicillin iv, Flucloxacillin iv and piperacillin/tazobactam iv

Figure E2: Frequency of CDS- triggers, interventions needed and adjustment to BW or BMI in the post-CDS group, per drug

Table E3: Frequency of CDS-triggers, interventions needed and adjustments to BW or BMI in the post-CDS group, per drug

Drug group	Drug	Number of medication orders with a CDS-trigger (n = 1,173)	Number of medication orders that needed intervention (n = 447)	Number of medication orders adjusted to BW or BMI (n = 172)	Number of medication orders that needed intervention / Number of medication orders with a CDS-trigger (%)	Number of medication orders adjusted to BW or BMI / Number of medication orders that needed intervention (%)	Number of medication orders adjusted to BW or BMI / Number of medication orders with a CDS-trigger (%)
LMWH	Dalteparin	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Enoxaparin	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Nadroparin	1,092 (93.09%)	412 (92.17%)	154 (89.53%)	37.73%	37.38%	14.10%
DOAC	Apixaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Dabigatran	2 (0.17%)	2 (0.45%)	0 (0.00%)	100%	0.00%	0.00%
	Edoxaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Rivaroxaban	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
Antibiotics	Amoxicillin iv	6 (0.51%)	0 (0.00%)	0 (0.00%)	0.00%	/	0.00%
	Amoxicillin/ Clavulanic acid iv	10 (0.85%)	6 (1.34%)	3 (1.74%)	60.00%	50.00%	30.00%
	Cefazolin iv	10 (0.85%)	0 (0.00%)	0 (0.00%)	0.00%	/	0.00%
	Ceftazidime iv	2 (0.17%)	1 (0.22%)	1 (0.58%)	50.00%	100%	50.00%
	Ceftriaxone iv	12 (1.02%)	8 (1.79%)	3 (1.74%)	66.67%	37.50%	25.00%
	Cefuroxime iv	21 (1.79%)	13 (2.91%)	7 (4.07%)	61.90%	53.85%	33.33%
	Ciprofloxacin iv	9 (0.77%)	1 (0.22%)	0 (0.00%)	11.11%	0.00%	0.00%
	Clindamycin iv/po	0 (0.00%)	0 (0.00%)	0 (0.00%)	/	/	/
	Flucloxacillin iv	5 (0.43%)	2 (0.45%)	2 (1.17%)	40.00%	100%	40.00%
	Piperacillin/ Tazobactam iv	4 (0.34%)	2 (0.45%)	2 (1.17%)	50.00%	100%	50.00%

Note: BMI = body mass index; BW = body weight; CDS = clinical decision support; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin

Appendix F

Table F1: Frequencies of the reasons for interventions not made or not accepted

Triggers	842	
Intervention?	Yes: 349 (41.45%)	
	No: 493 (58.55%)	Dose was already adjusted: 265 (53.75%) Normal dose was correct: 211 (42.80%) Patient was about to be discharged: 8 (1.62%) Therapy stopped until further notice: 6 (1.22%) Therapy would end soon: 3 (0.61%)
Accepted intervention?	Yes: 186 (53.30%)	
	No: 163 (46.70%)	Patient was discharged: 148 (90.80%) Therapy would end soon: 10 (6.13%) Physician would consider the advice: 2 (1.23%) Physician did not see benefit of adjustment: 1 (0.61%) Adjustment would lead to risks for the patient: 1 (0.61%) Patient was doing well: 1 (0.61%)

Table F2: Frequencies of the reasons for interventions not made or not accepted, per drug

		Intervention?						Accepted intervention?						
		Yes	No					Yes	No					
			Dose was already adjusted	Normal dose was correct	Patient was about to be discharged	Therapy stopped until further notice	Therapy would end soon		Patient was discharged	Therapy would end soon	Physician would consider the advice	Physician did not see benefit of adjustment	Adjustment would lead to risks for the patient	Patient was doing well
Drug group	Drug													
LMWH	Dalteparin													
	Enoxaparin													
	Nadroparin	324	265	196	6	5		163	148	9	2	1	1	
DOAC	Apixaban													
	Dabigatran	1						1						
	Edoxaban													
	Rivaroxaban													
Antibiotic	Amoxicillin iv			1										
	Amoxicillin/ Clavulanic acid iv	5					1	5						
	Cefazolin iv	1		11			1	1						
	Ceftazidime iv	1						1						
	Ceftriaxone iv	6			2			5		1				
	Cefuroxime iv	8					1	7						1
	Ciprofloxacin iv			3		1								
	Clindamycin iv/po													
	Flucloxacillin iv	2						2						
	Piperacillin/ Tazobactam iv	1						1						