

The role of nurses in physician-assisted deaths in Belgium

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∞ See related research article by Chambaere and colleagues, page 895

ABSTRACT

Background: Belgium's law on euthanasia allows only physicians to perform the act. We investigated the involvement of nurses in the decision-making and in the preparation and administration of life-ending drugs with a patient's explicit request (euthanasia) or without an explicit request. We also examined factors associated with these deaths.

Methods: In 2007, we surveyed 1678 nurses who, in an earlier survey, had reported caring for one or more patients who received a potential life-ending decision within the year before the survey. Eligible nurses were surveyed about their most recent case.

Results: The response rate was 76%. Overall, 128 nurses reported having cared for a patient who received euthanasia and 120 for a patient who received life-ending drugs without his or her explicit request. Respectively, 64% (75/117) and 69% (81/118) of these nurses were involved in the physician's decision-making process. More often this entailed an exchange of information on the patient's condition or the patient's or relatives' wishes (45% [34/117] and 51% [41/118]) than sharing in the decision-making (24% [18/117] and 31% [25/118]). The life-ending drugs were administered by the nurse in 12% of the cases of euthanasia, as compared with 45% of the cases of assisted death without an explicit request. In both types of assisted death, the nurses acted on the physician's orders but mostly in the physician's absence. Factors significantly associated with a nurse administering the life-ending drugs included being a male nurse working in a hospital (odds ratio [OR] 40.07, 95% confidence interval [CI] 7.37–217.79) and the patient being over 80 years old (OR 5.57, 95% CI 1.98–15.70).

Interpretation: By administering the life-ending drugs in some of the cases of euthanasia, and in almost half of the cases without an explicit request from the patient, the nurses in our study operated beyond the legal margins of their profession.

focuses mainly on the role and responsibilities of the physician.⁶ However, physicians worldwide have reported that nurses are also involved in these medical practices, mostly in the decision-making and sometimes in the administration of the life-ending drugs.^{1–3,7–9} Critical care,¹⁰ oncology¹¹ and palliative care nurses^{12,13} have confirmed this by reporting their own involvement, particularly in cases of euthanasia.^{14,15}

In Belgium, the law permits physicians to perform euthanasia under strict requirements of due care, one of which is that they must discuss the request with the nurses involved.¹⁶ There are no further explicit stipulations determining the role of nurses in euthanasia. Physician-assisted death is legally regulated in some other countries as well (e.g., the Netherlands, Luxemburg and the US states of Oregon and Washington State), without specifying the role of nurses. Reports from nurses in these jurisdictions are scarce, apart from some that are limited to particular settings, or lack details about their involvement.^{13,14}

We conducted this study to investigate the involvement of nurses in Flanders, Belgium, in the decision-making and in the preparation and administration of life-ending drugs with, or without, a patient's explicit request. We also examined patient- and nurse-related factors associated with the involvement of nurses in these deaths. In a related research article, Chambaere and colleagues describe the findings from a survey of physicians in Flanders about the practices of euthanasia and assisted suicide, and the use of life-ending drugs without an explicit request from the patient.¹⁷

Methods

Study design

In 2007, we performed a two-phase large-scale survey exploring the attitude of nurses toward end-of-life decisions with a possible or certain life-shortening effect, and their involvement in these types of decisions.

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Medical end-of-life decisions with a possible or certain life-shortening effect occur often in end-of-life care.^{1–5} The most controversial and ethically debated medical practice is that in which drugs are administered with the intention of ending the patient's life, whether at the patient's explicit request (euthanasia) or not. The debate

Box 1: Three end-of-life decisions with a possible or certain life-shortening effect

- Withholding or withdrawal of a potential life-prolonging treatment (including food and fluid).
- Intensification of medical therapy to alleviate pain or symptoms with a possible life-shortening effect.
- Administration of life-ending drugs with explicit intention of ending the patient's life.

The first phase was conducted between August and November 2007. It involved 6000 nurses in Flanders, Belgium, who were identified from a federal government database and asked about their attitudes toward life-shortening end-of-life decisions. The response rate of this study was 63%. More information about the characteristics of the study population and its findings is reported elsewhere.^{18,19} In that survey, we assessed each nurse's experience in the 12 months before the survey in caring for patients for whom life-shortening end-of-life decisions were made. We presented three types of decisions (Box 1).

A total of 1678 nurses met the inclusion criterion for the second phase of the study (see Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.091881/DC1). In the second phase, conducted between November 2007 and February 2008, we mailed a questionnaire to these 1678 nurses with a supporting letter from two major professional nursing organizations. If necessary, a reminder letter was sent, followed by a second mailing of the questionnaire, followed by a final reminder as needed. Confidentiality of data was ensured, and all data were processed anonymously. The Ethics Committee of the University Hospital of the Vrije Universiteit Brussel granted ethical approval of the study design.

Questionnaire

The questionnaire (see Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.091881/DC1), including the classification of the end-of-life decisions in Box 1, was based on the instrument used in incidence studies (performed among physicians) that had been proven to be valid and reliable.¹⁻⁵ To translate this to nursing practice, we made adaptations to the questionnaire on the basis of one used in a Dutch study about the involvement of nurses in euthanasia¹⁴ and by testing the questionnaire extensively. Content validity was established through expert review and through an in-depth discussion by a focus group. Cognitive testing²⁰ was conducted with 20 nurses to assess comprehension of the questions and categories of answers as well as comprehension of the wording of questions with particular emphasis placed on the classification of the life-shortening end-of-life decisions.

We asked the nurses to recall the most recent patient they had cared for whose treatment involved one or more life-shortening end-of-life decisions (Box 1). We selected only those cases in which the nurses reported that the patient had had life-ending drugs administered with the explicit intention of ending the patient's life. We further classified a case as "euthanasia" if the patient had made an explicit request for this act to be performed and as "the use of life-ending drugs without explicit request" if the patient had not.

Statistical analysis

Nurse and patient characteristics, and the nurse's involvement in decision-making and in administering life-ending drugs, are presented as frequencies and proportions. We used the Fisher exact test to compare differences in distributions between cases of euthanasia and cases involving the use of life-ending drugs without explicit request. We performed logistic regression analysis to study the relation between nurse and patient characteristics and the nurse's involvement in decision-making and in administering the drugs.

Results

Ten of the 1678 questionnaires were returned as undeliverable. Of the remaining 1668 questionnaires, 1265 were returned completed, for a response rate of 76%. Overall, 128 nurses reported that the last patient in their care for whom a life-shortening end-of-life decision was made received euthanasia; 120 nurses reported that the last patient in their care for whom a life-shortening end-of-life decision was made received life-ending drugs without his or her explicit request (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.091881/DC1). The characteristics of these 248 nurses are presented in Table 1. Among the nurses working in home care settings, more were involved in cases of euthanasia (25%) than in cases

Table 1: Characteristics of 248 nurses involved in cases of assisted death in Flanders, Belgium

| Characteristic | Type of assisted death; no. (%) of nurses | |
|-------------------------------------|--|---|
| | With patient's explicit request <i>n</i> = 128 | Without patient's explicit request <i>n</i> = 120 |
| Sex, male | 11 (9) | 15 (12) |
| Age, yr | <i>n</i> = 127 | <i>n</i> = 117 |
| 22–35 | 26 (20) | 33 (28) |
| 36–45 | 57 (45) | 43 (37) |
| 46–55 | 44 (35) | 41 (35) |
| Education | <i>n</i> = 126 | <i>n</i> = 120 |
| Diploma or associate degree | 57 (45) | 68 (57) |
| Baccalaureate degree | 64 (51) | 52 (43) |
| Master's degree | 5 (4) | 0 |
| Position | <i>n</i> = 128 | <i>n</i> = 120 |
| Bedside nurse | 118 (92) | 106 (88) |
| Head nurse | 7 (5) | 10 (8) |
| Other | 3 (2) | 4 (3) |
| Principal workplace* | <i>n</i> = 127 | <i>n</i> = 119 |
| Hospital | 75 (59) | 75 (63) |
| Care home | 20 (16) | 32 (27) |
| Patient's home | 32 (25) | 12 (10) |
| Specialist palliative care function | <i>n</i> = 122 | <i>n</i> = 116 |
| 20 (16) | 13 (11) | |

**p* = 0.003 for comparison between study groups.

of assisted death without the patient's explicit request (10%). The opposite was observed among nurses working in care homes: 16% reported that their patient had received euthanasia and 27% that life-ending drugs had been used without the patient's explicit request. Most of the patients who received euthanasia were less than 80 years old (84% [102/122]), had cancer (78% [99/127]) and died in hospital (53% [68/128]). Most of the patients who received life-ending drugs without their explicit request were over 80 years old (42% [50/118]), had cancer (43% [52/120]) or cardiovascular disease (23% [28/120]) and died in hospital (64% [76/119]).

Of the nurses whose patient received euthanasia, 69% (84/122) reported that the patient had expressed his or her wishes about euthanasia to them. Of the nurses whose patient received euthanasia, 64% (75/117) reported having been involved in the decision-making process, but with different experiences (Table 2). Of the nurses whose patient received life-ending drugs without his or her explicit request, 4% (5/119) reported that the patient had expressed his or her wishes about the decision to them. Involvement in the decision-making process was reported by 69% (81/118) of nurses (Table 2). In both groups, the physician and nurse deciding together occurred less often (24% in euthanasia group and 31% in group without explicit patient request) than did the exchanging information between physician and nurse about the patient's or relatives' wishes and the patient's condition (45% in euthanasia group and 51% in group without explicit patient request).

In the cases of euthanasia, 40% of the nurses were involved in some way in the preparation of the life-ending drugs (Table 3). During the administration of the drugs, 34% of the nurses reported that they were present and 31% that they gave support to the patient, the relatives, the physician or colleague nurses. The drugs were administered by the nurse in 14 (12%) of the cases of euthanasia. The physician was not a co-administrator in 12 of the 14 cases, but the drug was always given on his or her orders. The nurse administered a neuromuscular relaxant in four cases, a barbiturate in one case and opioids in nine cases. In nine cases of euthanasia (64%), the physician was not present during the administration of the drugs.

In the cases involving the use of life-ending drugs without the patient's explicit request, 48% of the nurses reported that they had some part in the preparation of the drugs (Table 3). During the administration of the drugs, 56% reported that they were present and 51% that they gave support to the patient, the relatives, the physician or colleague nurses. The drugs were administered by the nurse in 45 (45%) of the cases. The physician was not a co-administrator in 37 of these cases; however, the drug was given on his or her orders in almost all cases (42 of 43 in which this information was reported). The nurse administered a neuromuscular relaxant in 6 (13%) of the 45 cases, a barbiturate in 3 (7%) and opioids in 34 (76%). The physician was not present in 58% of the

cases in which the nurse administered the life-ending drugs.

Compared with nurses in the euthanasia group, those involved in the cases without an explicit request from the patient more often were present during the administration of the life-ending drugs ($p = 0.001$), gave support ($p = 0.002$) and administered the life-ending drugs ($p < 0.001$) (Table 3).

In the multivariable logistic regression analysis, factors significantly associated with a decreased involvement in decision-making were the nurse working in a home care setting (odds ratio [OR] 0.30, 95% confidence interval [CI] 0.13–0.74) and older age of the nurse (OR 0.92, 95% CI 0.88–0.97) (Table 4). Factors significantly associated with the nurse administering the life-ending drugs were the absence of an explicit request from the patient (OR 4.52, 95% CI 1.75–11.65), the patient being more than 80 years old (OR 5.57, 95% CI 1.98–15.70) and the nurse having had a recent experience with life-shortening end-of-life decisions (OR 2.55, 95% CI 1.00–6.51). Other factors were the sex and principal workplace of the nurses: female nurses working in hospitals were nearly six times (OR 5.92, 95% CI 1.97–17.81) and male nurses working in hospitals were 40 times (OR 40.07, 95% CI 7.37–217.79) more likely than their male and female counterparts working in other settings to administer the life-ending drugs.

Interpretation

In our study, more than half of the nurses surveyed in Flanders, Belgium, reported that they were involved in the physician's decision-making about the use of life-ending drugs. In most cases, the involvement was merely an exchange of information about the patient's or relatives' wishes and about the patient's condition. The nurse administered the life-ending drugs at the physician's request in many cases, most of which were cases without an explicit request from the patient.

Table 2: Nurses' involvement in decision-making in assisted deaths

| Involvement | Type of assisted death; no. (%) of nurses | |
|--|--|---|
| | With patient's explicit request <i>n</i> = 117 | Without patient's explicit request <i>n</i> = 118 |
| Involved in decision-making* | 75 (64) | 81 (69) |
| Physician and nurse decided together | 18 (24) | 25 (31) |
| Nurse's personal opinion was asked or given | 15 (20) | 6 (7) |
| Nurse advocated for patient's or relatives' wishes | 8 (11) | 9 (11) |
| Physician and nurse exchanged information about patient's or relatives' wishes and about patient's condition | 34 (45) | 41 (51) |
| Not involved in decision-making | 42 (36) | 37 (31) |
| Only physician communicated decision after it was made | 6 (14) | 8 (22) |
| No communication with physician about the decision | 36 (86) | 29 (78) |

*The categories are exclusive; although nurses could have answered affirmatively in more than one category, the category with the most explicit level of involvement was used to classify their involvement.

The euthanasia law in Belgium states that the physician must discuss requests for euthanasia with the nurses involved.¹⁶ From the completed questionnaires we received, this did not always occur. In a survey of physicians in Belgium, only half of those who had had cases of euthanasia reported that they had involved nurses in their decision-making.⁹ In the study by Chambaere and colleagues, physicians reported having discussed the decision with the nurses in 54% of the cases of euthanasia or assisted suicide and in 40% of the cases of assisted death without the patient's explicit request.¹⁷ In our

study, the involvement of nurses was restricted mainly to informing the physician about the patient's condition or the patient's and relatives' wishes. It appears that the physicians who did consult nurses recognized their value as providers of information, acknowledging their function as intermediaries between the physician and the patient or relatives, but that the shared decision-making between physician and nurse was less common. We observed a similar level of involvement in the cases of life-ending drugs given without the patient's explicit request. In such cases, the patient is usually no longer able to

make a request because of exacerbation of symptoms or the progression of disease.²¹ From our findings, it seems that physicians were no more likely to involve nurses in their decision-making when the patient was unable to communicate his or her wishes than when they were able to.

In previous surveys, physicians reported that nurses sometimes administered drugs explicitly intended to hasten death.^{7,9,17,22} Nevertheless, uncertainty remained about the understanding by the nurses of the act that they performed. In our study, nurses did administer life-ending drugs with the recognition that the death of the patient was intended. In the cases of euthanasia, 12% of the nurses administered the drugs. In the United States, where no legal framework for euthanasia is provided, 16% of critical care nurses¹⁰ and 5% of oncology nurses¹¹ reported engaging in euthanasia. Similar findings have been reported in other countries.^{14,15} In our study, administration of the life-ending drugs by the nurse occurred more frequently in the cases without an explicit request from the patient than in the cases of euthanasia. Previous studies have shown that nurses believe an explicit request from the patient is required when accepting an assisting role in dying.²³⁻²⁵ However, a recent study showed that nurses were not necessarily averse to the possibility of administering life-ending drugs without an explicit request from the patient, to the point of accepting an active role in it.¹⁸

Different points about our findings deserve further attention. First, we wonder whether nurses overestimated the actual life-shortening effect of the drug administration, especially when opioids were used,^{26,27} and whether the physician had intended to end the patient's life when he or she ordered the nurse to administer the drugs. Nurses may have thought that they were ending the patient's life, when in fact the drugs were intended to relieve symptoms in an aggressive, but necessary manner. However, incidence studies worldwide have shown that physicians reported administering opioids with the explicit intention of ending the patient's life.^{4,28,29}

Table 3: Nurses' involvement in administration of life-ending drugs in assisted deaths

| Involvement | Type of assisted death; no. (%) of nurses | | p value† |
|--|--|---|----------|
| | With patient's explicit request* n = 128 | Without patient's explicit request† n = 120 | |
| Before administration | | | |
| Had a role in preparing the life-ending drugs§ | 47 (40) | 53 (48) | 0.23 |
| Received the drugs from the pharmacist | 24 (21) | 19 (17) | 0.61 |
| Prepared and controlled the drugs | 35 (30) | 46 (42) | 0.07 |
| Set out the drugs/equipment for the physician | 21 (18) | 15 (14) | 0.47 |
| Passed the drugs/equipment to the physician | 15 (13) | 8 (7) | 0.19 |
| During administration | | | |
| Was present | 43 (34) | 65 (56) | 0.001 |
| Gave support§ | 39 (31) | 59 (51) | 0.002 |
| To patient | 29 (23) | 15 (13) | 0.05 |
| To relatives | 33 (26) | 46 (40) | 0.028 |
| To physician | 10 (8) | 10 (9) | 1.00 |
| To colleague nurses | 10 (8) | 24 (21) | 0.005 |
| Administered the drugs | 14 (12) | 45 (45) | < 0.001 |
| With physician as co-administrator | 2 (14) | 8 (18) | 1.00 |
| By physician's orders | 14 (100) | 42 (98) | 1.00 |
| With physician present | n = 14 | n = 40 | 0.36 |
| Yes, continuously | 3 (21) | 4 (10) | |
| Yes, intermittently | 2 (14) | 13 (32) | |
| No | 9 (64) | 23 (58) | |
| Type of drugs administered** | n = 14 | n = 45 | 0.53 |
| Neuromuscular relaxants | 4 (29) | 6 (13) | |
| Barbiturates | 1 (7) | 3 (7) | |
| Opioids | 9 (64) | 34 (76) | |
| Other | 0 | 2 (4) | |
| No involvement | 56 (48) | 30 (28) | 0.002 |

*Missing cases: 11 for "had a role in preparing the life-ending drugs," 1 for "was present during administration," 3 for "gave support," 12 for "administered the drugs" and 12 for "no involvement."

†Missing cases: 10 for "had a role in preparing the life-ending drugs," 4 for "was present during administration," 5 for "gave support," 20 for "administered the drugs," 2 for "by physician's orders" and 12 for "no involvement."

‡Calculated using Fisher exact test, for comparison between assisted death with and without explicit request from the patient.

§Multiple answers were possible.

**Drugs could have been neuromuscular relaxants, in any combination; barbiturates, alone or in combination with other drugs except neuromuscular relaxants; opioids, alone or in combination with other drugs except neuromuscular relaxants and barbiturates; benzodiazepines, alone or in combination with other drugs except neuromuscular relaxants, barbiturates and opioids; or other drugs, in any combination.

Second, we wonder why nurses more often administered the life-ending drugs in cases without an explicit patient request than in cases of euthanasia. Perhaps nurses took a more active role out of concern for frailer patients who could no longer communicate, or for very old patients because physicians are more reluctant to give assistance in dying when dealing with these patients.³⁰ Further, in cases of euthanasia, communication between the physician and the patient is common. When the patient can no longer communicate, nurses are, by the nature of their work, more directly confronted with the patient's suffering and may therefore wish to take a more active role in life-ending acts.¹⁸ We also have to consider that the administration of life-ending drugs without the patient's explicit request may have included situations of terminal sedation or an increase in pain alleviation, in which the delegation by physicians to nurses to administer the drugs is considered common practice.^{21,31} Finally, although about half of the nurses' reports indicated that there was no explicit request from the patient, it should be stated that the physicians and nurses probably acted according to the patient's wishes.^{4,21}

Third, the nurses we surveyed who administered the life-ending drugs did not do so on their own initiative. Although the act was often performed without the physician being present, it was predominantly carried out on the physician's

orders and under his or her responsibility. However, the administration of life-ending drugs by nurses, whether or not under the physician's responsibility, is not regulated under Belgium's euthanasia law and therefore not acceptable. In particular, when criteria for due care are not fulfilled, such as in cases where the patient has not made an explicit request, nurses, next to the physician, risk legal prosecution. Nurses may get caught in a vulnerable position between following a physician's orders and performing an illegal act. Further, physicians who perform euthanasia are required to report their case to a review committee after the act. In a study of all cases of euthanasia in Belgium, Smets and colleagues found that physicians did not always report their cases and that unreported cases often involved the use of opioids and the administration of them by nurses.³² It seems that the current law (which does not allow nurses to administer the life-ending drugs) and a control system do not prevent nurses from administering life-ending drugs. Therefore, professional guidelines are needed to help clarify their involvement in these practices.

Strengths and limitations

The large random sample of nurses, the high response rate, the comprehensive testing of the questionnaire with attention

Table 4: Factors associated with nurses' involvement in decision-making and administration of life-ending drugs

| Factor | Decision-making | | Administration of drugs | |
|---|-----------------|----------------------|-------------------------|----------------------|
| | p value | Adjusted OR (95%CI)* | p value | Adjusted OR (95%CI)* |
| Patient-related factor | | | | |
| No explicit request | 0.71 | 0.87 (0.40–1.86) | 0.002 | 4.52 (1.75–11.65) |
| Female sex | 0.53 | 0.80 (0.40–1.61) | 0.16 | 0.56 (0.25–1.26) |
| Age > 80 years | 0.32 | 1.50 (0.67–3.35) | 0.001 | 5.57 (1.98–15.70) |
| Cause of death | | | | |
| Malignant disease (ref) | – | 1.00 | – | 1.00 |
| Cardiovascular disease | 0.86 | 1.11 (0.36–3.39) | 0.67 | 0.76 (0.22–2.63) |
| Other | 0.33 | 0.65 (0.27–1.55) | 0.10 | 0.40 (0.13–1.21) |
| Nurse-related factor | | | | |
| Age | 0.001 | 0.92 (0.88–0.97) | 0.54 | 0.98 (0.93–1.04) |
| Male sex | 0.39 | 1.75 (0.48–6.36) | – | |
| Education level† | 0.13 | 1.76 (0.85–3.64) | 0.51 | 0.73 (0.28–1.88) |
| Home care setting as principal workplace | 0.008 | 0.30 (0.13–0.74) | – | |
| Recent experience with end-of-life decision | 0.27 | 1.48 (0.74–2.96) | 0.05 | 2.55 (1.00–6.51) |
| Bedside nurse (v. other position) | 0.30 | 0.48 (0.12–1.96) | 0.75 | 0.78 (0.18–3.48) |
| Specialist palliative care function | 0.11 | 2.50 (0.81–7.71) | 0.51 | 1.47 (0.47–4.62) |
| Religious (v. not) | 0.81 | 0.90 (0.38–2.15) | 0.76 | 1.19 (0.40–3.57) |
| Religion considered important‡ (v. not) | 0.66 | 0.85 (0.41–1.75) | 0.78 | 0.88 (0.36–2.17) |
| Workplace × sex of nurse§ | | | | |
| Male nurse in hospital setting | | | < 0.001 | 40.07 (7.37–217.79) |
| Female nurse in hospital setting | | | 0.002 | 5.92 (1.97–17.81) |
| Workplace setting other than hospital (ref) | | | – | 1.00 |

Note: CI = confidence interval, OR = odds ratio, ref = reference group.

*Each odds ratio was adjusted for the other variables in the table.

†Diploma or associate degree (ref) v. baccalaureate or master's degree.

‡In professional attitudes toward end-of-life decisions.

§In this model, interaction occurred between the nurse's sex and work setting. Because there was an empty cell (no male nurses who administered life-ending drugs worked at a setting other than hospital), the two variables were transformed into a combined variable.

given to the interpretation of the life-shortening end-of-life decisions, the fact that recall was limited to the 12 months before the survey, and the endorsement of the study by professional nursing organizations contributed to the reliability of our results. However, the administration of drugs with the explicit intention of ending a patient's life is a sensitive, complex issue. Our study is possibly limited by selection bias, a reluctance of respondents to report illegal acts, the self-reported nature of the data and the lack of information from the attending physician or about the doses of drugs used. It is also unknown whether our findings are generalizable to practices elsewhere in the world, although the studied practices and legal prohibition of nurses' involvement in administering life-ending drugs exists worldwide.^{1-5,10,11,14,15,22,33,34}

Conclusion

By administering life-ending drugs at the physician's request in some cases of euthanasia, and even more so in cases without an explicit request from the patient, the nurses in our study operated beyond the legal margins of their profession. Future research should closely monitor and examine the involvement of nurses in these practices nationally and internationally to allow comparisons between countries with and without euthanasia legislation.

This article has been peer reviewed.

Competing interests: None declared.

Contributors: Els Inghelbrecht was the primary investigator of the study. All authors were involved in the conception and design of the study protocol. Els Inghelbrecht was involved in the acquisition of data. All of the authors were involved in the analysis and interpretation of the data. Els Inghelbrecht and Johan Bilsen were involved in the drafting of the manuscript. All of the authors were involved in the critical revision of the manuscript and approved the final version submitted for publication. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

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