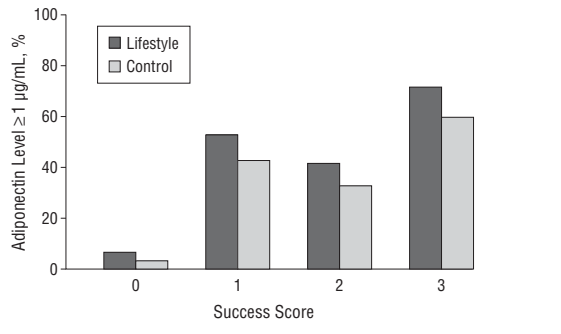

					Total
Lifestyle*	1/13	21/39	15/35	13/18	50/105
Control*	6/120	3/7	3/8	3/5	15/140

Figure. Subjects achieving adiponectin levels of 1 µg/mL or more above the median at the end of follow-up, according to the success score. *Data are given as number at goal/number not at goal in each category.

At 4 years, 155 subjects in both groups were still in the program. The median (interquartile range) of plasma adiponectin concentration was 6.1 (3.5-9.1) µg/mL. The **Figure** shows the numbers of subjects who achieved the goals in each group, as well as the percentage of subjects in each category with adiponectin concentrations of 1 µg/mL or more above the median. The figures were adjusted for weight changes. Absolute numbers of people at goals were significantly lower in the control group; however, percentage values did not show any difference between groups, suggesting that achievement of the goal resulted in raised adiponectin levels independent of the group assignment.

Comment. This study provides evidence that circulating adiponectin levels, in the range of those suggested to offer protection from type 2 diabetes, can be obtained by successful lifestyle changes. Our estimate of the effect of the intervention can be considered conservative, since all subjects in the control group also had benefits from the general health advice. The recent results of the long-term Women's Antioxidant Cardiovascular Study,[6] which showed no effect from generous doses supplement intake of vitamins A and C and beta carotene on primary prevention of type 2 diabetes, further stress the importance of lifestyle changes for diabetes prevention. Successful lifestyle changes are associated with increased circulating levels of adiponectin in overweight subjects.

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Physicians' and Nurses' Experiences With Continuous Palliative Sedation in the Netherlands

Continuous palliative sedation is regarded as an indispensable treatment for alleviating intolerable refractory symptoms in dying patients.[1] This far-reaching treatment requires a multidisciplinary approach, at least involving physicians and nurses.[2,3] As this practice has, to our knowledge, not been studied from both these perspectives at the same time, we describe physicians' and nurses' experiences with continuous sedation until death, focusing on patients' characteristics, decision making, and the effects of sedation.

Methods. In 2008, a structured questionnaire was sent to a random sample of 1580 physicians and a nonrandom sample of 576 nurses working in the northern and western Netherlands in home care, nursing homes, hospices, and hospitals. Nurses who were likely to be involved in the practice of continuous sedation received a questionnaire through contact persons in their setting. The questionnaire contained questions on the patient the respondents had most recently treated with continuous sedation until death. The questionnaire had been pretested among physicians and nurses.[4]

The statistical significance of differences between physicians and nurses was assessed with χ^2 and Kruskal-Wallis tests. Logistic or linear regression analysis was performed to adjust for setting and working experience. For all tests, $P < .05$ was considered statistically significant.

Results. The questionnaire was completed by 606 physicians (response rate, 38%) and 278 nurses (response rate, 48%). Cases were reported by 370 physicians (61%), mainly in general practice, and 185 nurses (67%), mainly hospital nurses. Most patients had cancer (**Table**). The severe symptoms that were most commonly reported before the start of continuous sedation by physicians and nurses were fatigue, pain, and longing for death. Nurses

Table. Respondents, Patient Characteristics, Decision Making, and Effect of Continuous Sedation[a]

Variable	Physicians (n=370)	Nurses (n=185)	*P* Value, χ^2 Test	*P* Value Adjusted[b]
Respondents				
Age, mean (SD), y	49 (8)	40 (11)	.001	NA
Work experience, mean (SD), y	19 (9)	17 (11)	.03	NA
Setting				
Home	250 (68)	50 (27)	<.001	NA
Nursing home/hospice	64 (17)	58 (26)		
Hospital	56 (15)	87 (47)		
Patients				
Age, mean (SD), y	70 (14)	65 (16)	<.001	NA
Diagnosis: cancer[c]	265 (75)	144 (80)	.21	NA
Severe symptoms before start of continuous sedation[d]				
Fatigue	258 (73)	119 (69)	.66	.46
Pain	212 (58)	115 (67)[e]	.07	.07
Longing for death	207 (58)	90 (54)[e]	.64	.11
Loss of dignity	172 (48)	63 (37)[e]	.11	.07
Hopelessness	170 (48)	72 (43)[e]	.66	.51
Loss of control	143 (40)	67 (40)[e]	.53	.85
Dyspnea	138 (38)	82 (47)[e]	.13	.84
Motor restlessness	111 (31)	62 (36)[e]	.16	.26
Anxiety	111 (31)	74 (42)[e]	.001	.03
Delirium	96 (27)	40 (24)[e]	.49	.54
Nausea/vomiting	95 (27)[e]	33 (20)[e]	.11	.73
Loss of interest	88 (25)[e]	35 (21)[e]	.77	.56
Burden to environment	57 (16)	26 (16)[e]	.67	.15
Depression	28 (8)[e]	14 (9)[e]	.52	.72
Decision making				
Life expectancy at start of continuous sedation				
<2 d	130 (36)	63 (34)	.49	NA
2 d to 2 wk	223 (61)	101 (55)		
>2 wk	10 (3)	18 (10)		
Decision to use continuous sedation discussed with competent patient	(n=255)	(n=124)		
Yes, patient was informed	46 (18)	9 (7)	<.001	NA
Yes, patient was involved	208 (81)	110 (88)		
Decision to use continuous sedation discussed with relatives				
Relatives were informed	68 (19)	17 (10)	.009	NA
Relatives were involved	296 (81)	160 (90)		
Physicians' intention when using continuous sedation				
No intention to hasten death	312 (85)	131 (75)	.002	NA
Partial intention to hasten death	50 (14)	35 (20)		
Explicit intention to hasten death	4 (1)	9 (5)		
Effect of continuous sedation				
Symptoms were properly relieved[f]	340 (95)	162 (90)	.52	.36
Relatives were satisfied with the course of continuous sedation[g]	343 (93)	156 (86)	.44	.33
Estimated shortening of life[h]				
No shortening	148 (41)	66 (36)	.18[i]	NA
<2 d	82 (25)	34 (19)		
2 d to 2 wk	54 (15)	15 (9)		
>2 wk	5 (1)	0		
Quality of dying[j]	299 (83)	126 (74)	.03	.85

Abbreviation: NA, not applicable.

[a] Data are given as number (percentage) unless otherwise indicated. Missing data per question ranged from 0.6% to 15.1%. Valid percentages are used; variables with more than 5% missing values are indicated.

[b] Corrected for experience and setting using logistic regression analysis.

[c] The most-common other diagnoses were heart failure, chronic obstructive pulmonary disorder, dementia, and neurologic disease.

[d] Number (percentage) of patients who were given a score of 4 or 5 on a Likert scale of 1 to 5.

[e] Percentage missing values was greater than 5%.

[f] Answer "don't know" was given by 2% of the physicians and 6% of the nurses ($P = .01$).

[g] Answer "don't know" was given by 1% of the physicians and 7% of the nurses ($P < .001$).

[h] Answer "don't know" was given by 18% of the physicians and 36% of the nurses ($P < .001$).

[i] Tested as no shortening vs shortening of life.

[j] Number (percentage) of patients who were given a score of 1 or 2 on a Likert scale of 1 to 5.

reported anxiety significantly more often than physicians. The decisive indications for starting continuous sedation that were most reported by both physicians and nurses were dyspnea and pain (data not shown). Nurses specified pain as the decisive indication more often than physicians, who reported physical exhaustion and de-

lirium more often than nurses. Psychological exhaustion and existential suffering were reported mainly when there was more than 1 decisive indication.

In most cases, life expectancy at the start of continuous sedation was estimated to be less than 2 weeks. In nurses' cases, competent patients and relatives had been involved in the decision making significantly more often. While physicians reported more often than nurses that they felt they were put under pressure to start continuous sedation, mostly by patients and relatives, they less often reported that continuous sedation had been provided with the full or partial intention of hastening the patient's death. In most cases, respondents reported that symptoms had been properly relieved, that relatives had seemed satisfied with the course of continuous sedation, and that the quality of dying had been good.

Comment. Pain, dyspnea, and delirium are commonly reported indications for palliative sedation.[5,6] Our study confirmed these findings and pointed to physical exhaustion as another decisive indication. This is consistent with fatigue being the most common severe symptom before the start of the sedation, apparently to the extent that it can become refractory to treatment and thus become an indication for continuous sedation until death. Psychological exhaustion and existential suffering were also mentioned as indications, mostly in combination with physical symptoms. The use of continuous sedation until death, therefore, often follows from a clinical picture in which a combination of physical and nonphysical symptoms results in a refractory state.

Nurses more often than physicians reported that patients and relatives were involved in decision making, they less often felt pressure from patients or relatives to start continuous sedation, and they more often thought that the physicians' intention for using sedation was to hasten the patient's death.

Although these physicians and nurses did not report on the same cases, we think we can interpret these differences because the practice on which they reported seems to be comparable. First, virtually all these respondents' cases involved both a physician and a nurse. Second, our respondents were selected in the same regions of the Netherlands and in the same period. Lastly, the patients' characteristics did not differ notably, and physicians and nurses assessed the frequency of severe symptoms similarly.

We therefore think that the differences in decision making, feelings of pressure, and intention might at least be partly related to the different roles of physicians and nurses in continuous sedation practice.

First, nurses usually have more frequent contacts with patients. Such frequent contacts might explain why more nurses indicated that patients and relatives were actively involved in the decision making. Nurses' greater involvement in patient handling might explain why more nurses mentioned pain as a decisive indication for starting continuous sedation and why they also reported more feelings of anxiety. Both pain and anxiety might be more easily recognized during daily care and nursing activities.

Second, the differences might also reflect the physicians' and nurses' different responsibilities. Because physicians are responsible for the decision making on the use of continuous palliative sedation, patients and relatives might put particular pressure on them to start sedation.[7] In studies of euthanasia, physicians have also reported to feel subjected to pressure.[8] Thus, taking account of the varying perspectives and emotions of all those involved in end-of-life decision making may be complex.

Finally, it has been shown elsewhere that nurses sometimes worry about the potential use of continuous sedation for accelerating death.[9] Taken together with our finding that more nurses than physicians think that continuous sedation was used with the intention to hasten death, this may reflect that physicians are not always clear about their intentions. This stresses the paramount importance of proper communication between physicians and nurses.[10]

In conclusion, while continuous sedation until death is usually provided because of severe and refractory physical symptoms, nonphysical symptoms may also contribute to the clinical picture. At several points, physicians and nurses experience the decision-making process differently. End-of-life care would benefit from fuller communication between physicians and nurses about all relevant aspects of the patients' situation and the care provided.

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COMMENTS AND OPINIONS

Analytical Performance vs Clinical Use of Natriuretic Peptide Measurements

In their elegant meta-analyses, Porapakkham and colleagues[1] conclude that B-type natriuretic peptide (BNP)-guided therapy reduces all-cause mortality in patients with chronic heart failure (HF) compared with usual clinical care.

It is not our purpose to inquire into the methods of statistical or data analysis. However, we would like to call attention to analytical performance of natriuretic peptide measurements. Specific literature is extensive. It is reported that intraindividual biological variation of BNP and *N*-terminal pro-BNP (NT-pro-BNP) can induce misinterpretation on disease progression or treatment optimization.[2,3] Moreover, results from testing for imprecision showed systematically high total coefficients of variation. In our clinical laboratory, using Clinical and Laboratory Standards Institute–standardized protocol to verify method performance,[4] data ranged from 0.9% to 50.8%, depending on sample storage and analyte (BNP or NT-pro-BNP). These uncomfortable numbers motivated a recent guidelines document addressing the clinical use of BNP and NT-pro-BNP testing in the context of HF.[5]

Taking this into consideration, it is risky when the authors do not discuss these important limitations. The words "laboratory," "variation," or "coefficient" were not even mentioned in the article's text. Actually, these words were not cited in most of randomized controlled trials selected in the meta-analysis.

As clinical pathologists, we want to express our apprehension about the scarcity of reflection about the limitations of laboratory testing by clinicians and clinical scientific community.

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The Challenges of Properly Identifying the Cause of Heart Failure Hospitalization

I read with interest the meta-analysis by Porapakkham et al[1] concerning BNP-guided heart failure therapy. The authors correctly point out the need to assess the impact of this approach on HF hospitalization with the expectation of improvement in this outcome. However, considering the high prevalence of co-