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ORIGINAL ARTICLE

Background and episodic breathlessness in advanced cancer patients followed at home

Sebastiano Mercadante^a, Flavio Fusco^b, Amanda Caruselli^c, Claudio Cartoni^d, Francesco Masedu^e, Marco Valenti^e and Federica Aielli^e

^aLa Maddalena Cancer Center, Palermo, Italy; ^bPalliative Home Care Unit, ASL 3, Genova, Italy; ^cHome palliative care program SAMO, Palermo, Italy; ^dHome Care Service of the Rome Section of the Italian Association Against Leukemias, Rome, Italy; ^eUniversity of L'Aquila, L'Aquila, Italy

ABSTRACT

Background: The aim of this study was to assess the phenomenon of episodic breathlessness in advanced cancer patients followed by palliative care services at home.

Methods: A consecutive sample of patients with advanced cancer, admitted to home care for a period of six months, was surveyed. The presence of background breathlessness and episodic breathlessness, their intensity, and drugs used for their treatment were collected. Factors inducing episodic breathlessness, and its influence on daily activities were investigated.

Results: Three hundred forty-seven advanced cancer patients admitted to home palliative care were surveyed. The prevalence of breathlessness was 35.3%. The mean intensity of breathlessness was 3.8 (SD 1.96), out of a maximum score of 10 for worst imaginable. Sixty patients (49.2%) were receiving drugs for background breathlessness. In the multivariate analysis the risk of breathlessness increased with cardiovascular disease, chronic obstructive pulmonary disease, and lung cancer while it decreased in patients with a better performance status. The prevalence of episodic breathlessness in patients with background breathlessness was 79.5% and its mean intensity was 7.1 (SD 1.5, range 2–10). The mean duration of episodic breathlessness was 28.6 minutes (SD 47.1, range 1–300 minutes). Forty-three patients (44.3%) were receiving one or more drugs as needed. The majority of episodic breathlessness events were triggered by activity. Episodic breathlessness was interfering with daily activities in 65 patients (67%). Episodic breathlessness wasn't associated with any variable taken into consideration.

Conclusion: This study showed that episodic breathlessness frequently occurs in advanced cancer patients admitted to home care, is severe in intensity, is triggered in most cases by activity, and is characterized by a short duration which requires rapid measures.

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Introduction

Breathlessness has been described as an unpleasant sensation of breathing, also known as dyspnea, and is characterized by qualitatively distinct sensations presenting with variable intensity¹. Breathlessness is produced by different and complex mechanisms. It may be caused by cancer itself, and pre-existing or concomitant comorbid conditions². Although patients with lung cancer are at higher risk of developing breathlessness³, this phenomenon largely occurs in the general cancer population, particularly in the advanced stage of disease⁴. From a clinical perspective, breathlessness is a very distressing symptom often reported in advanced cancer patients, particularly in the last three months of life. Breathlessness is associated with significant suffering both for cancer patients and for caregivers. This symptom is the most common chief complaint for admission to hospital in patients with lung cancer⁵.

Other than being present as a continuous phenomenon for most hours of the day, Breathlessness may aggravate the

background condition with peaks of intensity that are distinct from the background breathlessness (episodic breathlessness). The temporal characteristics of this symptom resemble those of background pain and breakthrough pain⁶. As breathlessness is a complex entity with difficult management, more information is necessary to understand this phenomenon to provide appropriate therapeutic options.

Breathlessness often becomes more severe and refractory to traditional medical management in the last weeks of life³. At this stage, most patients are commonly followed at home. Several studies performed in advanced cancer patients followed at home have underscored the importance of breathlessness, although episodic breathlessness has not been characterized in this context. Breathlessness tended to further increase at the lowest levels of functional status, particularly in the last week of life⁷. Breathlessness was the most frequent reason for emergency admission of patients who were assisted by a home care program⁸. A substantial proportion of patients presenting with acute breathlessness to an emergency center survive less than two weeks⁹. Indeed, dyspnea

was the most frequent reason for hospital admission of patients who died after being admitted to hospital through the emergency center while being assisted at home. In the last two hours of life of patients followed at home, dyspnea was one of the most important clinical issues¹⁰. Finally, breathlessness is one of the most frequent indications for palliative sedation at home^{11,12}. In a previous paper, the prevalence and characteristics of breathlessness and episodic breathlessness were evaluated in advanced cancer patients recruited in different settings¹³. The aim of this secondary analysis was to assess the characteristics of episodic breathlessness in the subgroup of patients followed at home.

Patients and methods

This is a secondary analysis of a survey conducted in several centers in a variety of clinical settings, including oncology wards, hospices, acute palliative care units, and home care. From this sample, advanced cancer patients admitted to home palliative care programs were surveyed for a period of six months. All patients who were able to provide information about breathlessness were eligible. Patients who were dying or were unable to collaborate due to cognitive failure or other reasons were excluded. Informed consent and institutional approval of the University of Palermo were obtained.

At home admission, the epidemiological characteristics, stage of disease, concomitant comorbidities, ongoing oncologic treatments, and Karnofsky status were recorded. Karnofsky status is a well validated tool for classifying patients' functional impairment¹⁴. Scores range from 0 (dead) to 100 (full function). Patients were asked about the presence of breathlessness, and its intensity was measured on a numerical scale from 0 to 10 (where 0 = none and 10 = worst imaginable), over the past 24 hours. Drugs used for background breathlessness were recorded. Patients were also asked if they had experienced episodic breathlessness, according to a standard definition: a predictable or unpredictable increase in breathlessness occurring intermittently, clearly distinguishable in intensity from background breathlessness over the past 24 hours. The intensity of episodic breathlessness was similarly measured on a numerical scale from 0 to 10 (where 0 = none and 10 = worst imaginable), and duration of untreated episodes was recorded. Factors triggering breathlessness, including going up the stairs, walking, recumbency, and changes of position were recorded. Patients were also asked whether episodic breathlessness would influence daily activities, and whether they were receiving drugs for relieving such episodes.

Statistical analysis

The statistical analysis accounted for the study design having the twofold aim of describing background breathlessness and episodic breathlessness occurrence alone. Summary statistics for dyspnea, continuous and categorical variables, and the associated frequency distributions are provided. Primary tumors were categorized into 11 categories. The variable age was categorized to improve its interpretability and model

implementation into four categories ranging from age less than 65 years to age more than 85 years. Explorative χ^2 cross-tabulation tests of association among variables, assuming $\alpha = 0.05$, were carried out. A preliminary understanding of the variables' values combinations importance has been surveyed using a χ^2 component wise analysis. Afterwards an odds ratio risk profile was used performing a logistic regression including primitive tumors, cardiovascular diseases, chronic bronchopulmonary disease and Karnofsky score selected with the previous univariate analysis.

Overall model fitting was tested using the Wald statistics (χ^2 (df = 13) = 63.99; $p = .00$). The variable selection procedure as described above was carried out for dyspnea event occurrence alone without getting statistically significant associations. Because we did not select statistically significant eligible variables we did not estimate a corresponding multivariable risk model. The analysis was accomplished using Stata (Version 14) statistical software.

Results

Three hundred forty-seven advanced cancer patients admitted to home palliative care were surveyed in the study period. The mean age was 70.9 years (standard deviation [SD] 12.5), and 174 (50%) patients were males. The primary tumors were in a rank order: lung 80 (23%), gastrointestinal 65 (18.7%), pancreas 38 (10.9%), breast 35 (10.1%), hematological 22 (6.3%), liver 22 (6.3%), urological 18 (5.2%), gynecological 18 (5.2%), head-neck 17 (4.9%), melanoma 6 (1.7%), others 26 (7.5%). One patient was then excluded for inability to provide further data. Eighty-five patients (24.5%) were receiving disease-oriented therapy. The mean Karnofsky status recorded at admission was 45.3 (SD = 13.7).

Background breathlessness

The prevalence of background breathlessness was 35.3% ($n = 122$). In such patients the mean intensity of breathlessness was 3.8 (SD 1.96). Sixty patients (49.2%) were receiving drugs for background breathlessness, in a rank order: corticosteroids ($n = 45$, 36.9%), bronchodilators ($n = 20$, 16.4%), opioids ($n = 17$, 13.9%), benzodiazepines ($n = 4$, 3.3%), and oxygen ($n = 10$, 8.2%).

Associated comorbidities were in a rank order: cardiovascular disease (42.4%), chronic obstructive pulmonary disease (14.4%), renal failure (7.2%), liver dysfunction (2.3%), others (5.5%). Breathlessness was significantly associated with cancer diagnosis and comorbidities (Table 1). In the multivariate analysis the risk of breathlessness increased with cardiovascular disease, chronic obstructive pulmonary disease, and diagnosis of lung cancer, while it decreased in patients with a better Karnofsky level (Table 2).

Episodic breathlessness

The prevalence of episodic breathlessness among patients with continuous breathlessness was 79.5% ($n = 97$) and its mean intensity was 7.1 (SD 1.5, range 2–10). The mean

Table 1. Number (%) of patients with breathlessness according to the variables taken into consideration (all patients =346).

	No breathlessness	Breathlessness	
Age			<i>p</i> = .3
≤65 years	65 (62.5)	39 (37.5)	
66–75 years	55 (58.5)	39 (41.5)	
76–85 years	69 (71.1)	28 (28.9)	
≥85 years	35 (68.6)	16 (31.4)	
Gender			<i>p</i> = .4
Male	116 (66.7)	58 (33.3)	
Female	108 (62.8)	64 (37.2)	
Cancer			<i>p</i> = .00
Lung	31 (38.75)	49 (61.2)	
Breast	29 (82.9)	6 (17.1)	
Gastrointestinal	48 (75)	16 (25)	
Liver	15 (68.2)	7 (31.8)	
Gynecological	11 (61.1)	7 (38.9)	
Head–Neck	12 (70.6)	5 (29.4)	
Hematological	14 (63.6)	8 (36.4)	
Melanoma	5 (83.3)	1 (16.7)	
Pancreas	31 (81.6)	7 (18.4)	
Urological	10 (55.6)	8 (44.4)	
Other	18 (69.2)	8 (30.8)	
Comorbidity			<i>p</i> = .04
Cardiovascular			
Yes	86 (58.5)	61 (41.5)	
No	138 (69.3)	61 (30.6)	
Bronchopulmonary			<i>p</i> = .00
Yes	21 (42.0)	29 (58.0)	
No	203 (68.8)	92 (31.2)	
Kidney disease			<i>p</i> = .61
Yes	15 (60.0)	10 (40.0)	
No	209 (65.1)	112 (34.9)	
Liver disease			<i>p</i> = .10
Yes	3 (37.5)	5 (62.5)	
No	221 (65.4)	117 (34.6)	
Treatment			<i>p</i> = .10
Disease-oriented	58 (68.3)	27 (31.7)	
Palliative Care	166 (63.6)	95 (36.4)	

Table 2. Multivariate analysis for breathlessness.

	OR	SD	<i>p</i>	95% CI	
Cancer					
Lung	2.35	1.01	.04	1.02	5.43
Breast	0.36	0.21	.08	0.12	1.13
Gastrointestinal	0.50	0.23	.14	0.21	1.25
Liver	0.77	0.44	.65	0.25	2.38
Gynecological	1.31	0.87	.68	0.36	4.83
Head–Neck	0.71	0.47	.61	0.19	2.59
Hematological	0.89	0.53	.84	0.28	2.86
Melanoma	0.27	0.32	.27	0.03	2.72
Pancreas	0.39	0.21	.08	0.13	1.13
Urological	0.81	0.45	.70	0.27	2.42
Comorbidity					
Cardiovascular	1.63	0.41	.04	1.01	2.64
Bronchopulmonary	2.07	0.69	.02	1.08	3.99
Performance Status					
Karnofsky	0.98	0.01	.02	0.97	0.99

OR: odds ratio; SD: standard deviation.

duration of untreated episodes was 28.6 minutes (SD 47.1, range 1–300 minutes). The majority of episodic breathlessness events were triggered by activity, including going up the stairs (7.3%), walking (30.5%), recumbency (8.4%), changes of position (10.5%), going up the stairs and walking (21.0%), all of these (12.6%). In 9.5% of cases (9 patients), no precipitant factors were reported. In 65 patients (67.0%), episodic breathlessness interfered with daily activities: going up the stairs (10.1%), walking (36.3%), recumbency (8.6%), changes of position (10.2%), going up the stairs and walking (24.6%), all of

Table 3. Number (%) of patients with episodic breathlessness among patients with continuous breathlessness (*N* = 122) according to the variables taken into consideration.

	No episodic breathlessness	Episodic breathlessness	
Age			<i>p</i> = .65
≤65 years	10 (26.3)	28 (73.7)	
66–75 years	7 (17.9)	32 (82.1)	
76–85 years	4 (14.3)	24 (85.7)	
≥85 years	3 (18.7)	13 (81.3)	
Gender			<i>p</i> = .89
Male	11 (19.3)	46 (80.7)	
vFemale	13 (20.3)	51 (79.7)	
Cancer			<i>p</i> = .55
Lung	8 (16.3)	41 (83.7)	
Breast	0 (0)	6 (100.0)	
Gastrointestinal	3 (18.7)	13 (81.5)	
Liver	3 (42.9)	4 (57.1)	
Gynecological	2 (28.6)	5 (71.4)	
Head–Neck	2 (40.0)	3 (60.0)	
Hematological	2 (25.0)	6 (75.0)	
Melanoma	0 (0)	1 (100.0)	
Pancreas	2 (28.6)	5 (71.4)	
Urological	0 (0)	8 (100.0)	
Other	2 (28.6)	5 (71.4)	
Comorbidity			<i>p</i> = .06
Cardiovascular			
Yes	8 (13.1)	53 (86.9)	
No	16 (26.7)	44 (73.3)	
Bronchopulmonary			<i>p</i> = .43
Yes	7 (24.1)	22 (75.9)	
No	16 (17.6)	75 (82.4)	
Kidney disease			<i>p</i> = .99
Yes	2 (20.0)	8 (80.0)	
No	22 (19.8)	89 (80.2)	
Liver disease			<i>p</i> = .25
Yes	2 (40)	3 (60)	
No	22 (19.0)	94 (81)	
Treatment			<i>p</i> = .89
Disease-oriented	5 (18.5)	22 (81.5)	
Palliative Care	19 (20.2)	75 (79.8)	

these (10.1%). Episodic breathlessness was not associated with any variable taken into consideration (Table 3). Forty-three patients (44.3%) were receiving one or more drugs for episodic breathlessness, in a rank order: morphine (*n* = 24, 55.8%), corticosteroids (*n* = 14, 32.5%), bronchodilators (*n* = 10, 9.3%), benzodiazepines (*n* = 4, 9.3%), oxygen (*n* = 4, 9.3%), fentanyl (*n* = 1, 2.3%).

Discussion

This study assessed the characteristics of background and episodic breathlessness in a specific subgroup of the advanced cancer population admitted to home care, revealing interesting findings.

Background breathlessness

About one third of home care cancer patients had breathlessness. Only about half of them were receiving drugs for this symptom, principally represented by corticosteroids. In the original study performed in different settings¹³ the prevalence was 30%, with a mean intensity of about 4/10 on a numerical scale, confirming the findings of previous studies¹⁵. Background breathlessness in advanced cancer patients followed at home had a statistically higher prevalence in

comparison with other settings (35.3% versus 25.9%, $p = .003$), but with a lower intensity (3.8 versus 4.6, $p = .0008$). This could be related to the worsening condition, including the presence of symptoms such as fatigue.

The care setting and stage of disease seems to influence the prevalence⁴. In previous studies, lung involvement and anxiety were independently correlated with intensity of breathlessness¹⁶. Psychological distress has been found to be correlated with breathlessness¹⁷. In ambulatory advanced lung cancer patients breathlessness interfering with daily life activities had a prevalence of 55%¹⁸. It is worthwhile to note that in studies of breathlessness the concept of episodic breathlessness was not still recognized, and it is likely that the evaluation was overlapping background breathlessness and episodic breathlessness. The level of breathlessness considered to be of mild, moderate, and severe intensity has not been analyzed in appropriate studies, in contrast to pain, in which some cut-off points have been established¹⁹. It is reasonable that similar cut-off points could be applied for breathlessness, although no specific study assessed this aspect.

The risk of breathlessness was increased in patients with comorbidities, such as cardiovascular diseases and chronic bronchopulmonary diseases, a diagnosis of lung cancer, and a lower Karnofsky level, differently from data recorded in lung cancer patients, where the risk of breathlessness increased only with bronchopulmonary disease²⁰, or advanced cancer patients followed in different settings in which the prevalence decreased in patients receiving disease-oriented therapy, and patients with gastrointestinal tumors¹³. It is likely that the different numbers of patients may explain such differences. These aspects deserve further study to gather information about the relationship between an oncological treatment and symptom intensity. Finally, for continuous breathlessness less than 50% of patients were regularly receiving drugs commonly considered to alleviate the symptom. Corticosteroids have been found to be the drugs most frequently administered, while opioids were used in a minority of patients. Indeed, the use of corticosteroids for other purposes cannot be excluded, as frequently it occurs in palliative care.

As mentioned above, the level of patients' acceptability of breathlessness intensity has not been well established, as it has been for background pain. Could optimization of background treatment, such as with opioids, be helpful in decreasing background breathlessness and potentially reducing the occurrence of episodic breathlessness? This question is an important issue to be developed in future research. For instance, it has been suggested that opioid-naïve patients could be slowly titrated starting with low doses, since inadequate doses may generate no response²¹.

Characteristics of episodic breathlessness

In this subgroup of patients followed at home, the prevalence of episodic breathlessness in patients with continuous breathlessness was high (almost 80%), was most often severe in intensity and lasted on average close to 30 minutes.

In 67% of patients episodic breathlessness was interfering with daily activities. The intensity of episodic breathlessness was clearly distinguished by the intensity of background breathlessness. The need to distinguish background and episodic breathlessness resembles recent observations on breakthrough pain²². The definition used in this study is similar to previous operational definitions^{16,23–27}, based on strict criteria.

Episodic breathlessness was considered as a high intensity episode distinguished from usual fluctuations of breathlessness²⁵. In some studies the overlapping intensities of breathlessness and episodic breathlessness were confounding factors^{23,24}. In the literature, the mean number of episodic breathlessness events has been reported to be 1–5 per day²⁶. This aspect was not included in the present study. However, the number of episodic breathlessness events will strongly depend on the will or the need to start an activity, as it occurs with predictable breakthrough pain due to movement (see triggering factors).

In other studies the relationship and coexistence of breathlessness and episodic breathlessness have been variably examined. In a mixed population of cancer and non-cancer patients, a clear relationship between breathlessness and episodic breathlessness was found²⁸, although a minority of patients, about 20%, had episodic breathlessness without background breathlessness. In another clinical study of advanced cancer patients episodic breathlessness was recorded in patients without background breathlessness in a high percentage of cases (61%), while a large number of patients with background breathlessness did not have superimposed episodic breathlessness²³. Misinterpretation of the questionnaires, as confirmed by the high levels of intensity of continuous breathlessness in comparison with episodic breathlessness, as well as the exclusion of patients with the most frequent causes of breathlessness, may explain such findings²⁴. A broad definition of episodic breathlessness may confound the data. For example, an episodic breathlessness duration of less than 24 hours cannot be distinguished from background breathlessness that is longer than 24 hours.

As reported in more recent studies, the duration of episodic breathlessness is relatively short, ranging from 5 to 15 minutes^{20,23,24}. In the previous study performed in variable settings, duration was slightly longer (about 20 minutes)¹⁴. In this analysis of a subgroup of patients followed at home the mean duration of episodic breathlessness was even longer, being approximately 30 minutes. This finding could be explained by the intense weakness of respiratory muscles in patients with a shorter survival. Regardless of the duration range (10–30 minutes), the temporal pattern and the peak of intensity should circumscribe patients having episodic breathlessness. A duration of hours should be interpreted as continuous breathlessness. For a similar phenomenon, like breakthrough pain, the majority of episodes last less than one hour^{6,29}. Indeed, in all the studies a risk of recall bias should be considered, when interpreting this data. Unfortunately, existing data regarding episodic breathlessness in home care setting is lacking.

The majority of episodic breathlessness events were predictable, that is triggered by an identifiable factor.

Any activity, including minimal movements in the bed, could induce episodic breathlessness. However, in about 10% of patients no known precipitant factor was found, similar to data reported in the original study performed in different settings¹³. It is likely that psychological factors, that were not specifically explored in this study, could be involved. As reported for background breathlessness¹⁵, psychological distress has often been reported as a possible cause of episodic breathlessness²⁶. The relationship between breathlessness and anxiety is complex and could be inverse or reinforcing, as in turn episodic breathlessness may contribute to the development of anxiety. A vicious cycle with somatization should also be considered²⁴. In other studies other triggers have been identified, including emotions or environmental factors. Indeed, raw measurements at time of admission, patients' selection, and clear definition may explain the more stringent data found in this study.

The interference of episodic breathlessness with activities confirmed previous data^{13,24}. Interestingly, exercise has been used as a model for inducing episodic breathlessness³⁰.

Survival was not assessed. However, in patients followed in home care services in Italy, the mean survival has been reported to be approximately two months³¹. Episodic breathlessness may be the expression of extreme fatigue, possibly triggered by psychological and physical factors. Fatigue and dyspnea have been found to be correlated, particularly in the last weeks of life^{13,16,24} and both have obvious influence on daily life activities¹⁸, independent of a pulmonary problem¹⁷. In the previous study performed in different settings, episodic breathlessness was particularly prevalent in patients with a higher Karnofsky level, possibly because they were more physically active and had more possibilities to develop episodic breathlessness with exertion. In patients followed at home no factor associated with episodic breathlessness was found. This could be related to worsening condition, including fatigue, that may balance with the other factors. Fatigue is a very common symptom in advanced cancer patients and has been reported to be correlated with high intensity breathlessness^{16,24}.

From a clinical perspective, the temporal characteristics and duration of episodic breathlessness suggest a medication with a short onset, independently from the treatment of background breathlessness. Data gathered from this subgroup of patients admitted to home care are slightly different from those reported in the global population of different settings¹³. More patients, about 44%, were receiving a medication as needed, but opioids were less frequently used, with morphine being used in about 50% of patients who were using some breathlessness medication. The reasons to explain why in the home palliative care setting there is lower opioid use for episodic breathlessness should be further explored. It is worthwhile to remember that oral morphine pharmacokinetics should not allow a proper effect within the expected duration of episodic breathlessness³².

Potentially, fentanyl products could better fit the temporal pattern of episodic breathlessness, as with breakthrough pain. The lowest strength of fentanyl preparations, however, are designed for patients tolerant to 60 mg/day of oral morphine equivalents, posing a relevant problem of dosing

fentanyl for episodic breathlessness. It is likely that fentanyl dose could be slowly titrated in opioid-naïve patients. However, it is also likely that opioid-tolerant patients receiving opioids for their background pain or breathlessness require higher doses, possibly proportional to their daily opioid doses. This aspect has never been examined and deserves particular attention. For instance, parenteral fentanyl given prophylactically in doses proportional (15–25%) to the basal opioid regimen were safe and effective³⁰. These preliminary studies suggest that fentanyl products could be given before an expected trigger, similar to their use for preventing predictable breakthrough pain^{33,34}.

In this study there are some limitations. This is a secondary analysis of a bigger study performed in different settings. The role of emotional triggers for breathlessness was not explored, although this relationship is difficult to demonstrate, given the vicious cycle of dyspnea–anxiety. In addition, patients were selected on the basis of the presence of background dyspnea. As for breakthrough pain³⁵, episodic breathlessness could occur without significant background intensity of breathlessness. Moreover, non-pharmacological approaches were not assessed. Recall bias could have influenced the data recorded for breathlessness evaluation. Furthermore, drugs prescribed for dyspnea could also be used for other indications, as it often occurs in palliative care. Finally, the role of fatigue was not assessed and could have a determinant role in triggering the episodes.

Conclusion

In conclusion, this secondary analysis has shown that breathlessness and episodic breathlessness are common in patients with advanced cancer when they are admitted to a home palliative care program. Breathlessness prevalence was higher in patients with cardiovascular or respiratory disease, and lung cancer, and lower in patients with higher Karnofsky level. The prevalence of episodic breathlessness was high and was interfering with daily activities. No specific factor was found to be associated with episodic breathlessness. Episodic breathlessness was severe in intensity, of short duration, and induced by activity. The treatment of background breathlessness and episodic breathlessness should be better elucidated balancing the bi-level intensities. Future studies with appropriate designs should clarify these aspects that have obvious therapeutic consequences.

Transparency

Declaration of funding

This study was not funded.

Declaration of financial/other relationships

S.M., F.F., A.C., C.C., F.M., M.V., and F.A. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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