SEI MESI DI SUPPLEMENTAZIONE DI VITAMINA D MIGLIORANO SIGNIFICATIVAMENTE LA FE NEI PAZIENTI ANZIANI CON SCOMPENSO CARDIACO E DEFICIT DI VITAMINA D

Nutr Metab Cardiovasc Dis. 2014: S0939-4753(14)00086-6.

Queste sono le conclusioni a cui sono giunti i i ricercatori coordinati da Dalbeni A dell'Università di Verona. Essendo noto che bassi livelli plasmatici di vitamina D sono associati con scompenso cardiaco (HF) i ricercatori hanno voluto valutare il ruolo della supplementazione di vitamina D sulla funzione miocardica inpazienti anziani con HF. Ventitre pazienti con HF con un'età media di 74 anni e livelli di vitamina D < 30 ng / mL, hanno RICEVUTO 800.000 UI (4000 UI / die) di colecalciferolo o placebo per 6 mesi. I risultati valutati al basale e dopo 6 mesi erano la frazione di eiezione (FE) ed altri parametri ecocardiografici, il propeptide carbossiterminale di procollagene di tipo I (PIP), i peptidi natriuretici, il profilo lipidico, la renina, l'ormone paratiroideo, la pressione arteriosa e l'indice di massa corporea (BMI). Nei 13 pazienti in trattamento attivo per 6 mesi, le concentrazioni medie di 25-idrossi vitamina D plasmatiche (15,51 vs -1,40 ng / mL, p < 0.001) e di calcio plasma (9,3-9,6 mmol / L, p < 0.05) sono aumentate in modo significativo. Tuttavia, altri biomarcatori del metabolismo osseo non differivano tra il gruppo di trattamento e il gruppo placebo. La FE è aumentata significativamente nel gruppo di intervento (6,71 vs -4,3%, p < 0,001) e la concentrazionesierica di PIP è aumentata solo nel gruppo placebo dopo 6 mesi (1.140,98 vs -145 mcg / L, p < 0,05). La pressione arteriosa sistolica era più bassa dopo 6 mesi di trattamento (129,6-122,7 mm Hg, p < 0.05). Nessuna variazione significativa è stata osservata per altri parametri.

Le polmoniti possono essere peggiorate dalla terapia con inibitori di pompa protonica

CLINICAL CONTEXT

Proton pump inhibitors (PPIs) are effective and generally safe medications for patients with acid-related disorders. However, this drug class has come under scrutiny in recent years because of potential adverse effects associated with long-term use. Corleto and colleagues addressed the potential dangers of PPIs in a review published in the February 2014 issue of *Current Opinion in Endocrinology, Diabetes, and Obesity*. They found that PPIs were certainly associated with hypomagnesemia. However, they noted that the evidence that PPIs may increase the risk for fracture was fairly weak. Moreover, only limited evidence suggests that PPIs may promote a higher risk for infection with *Clostridium difficile*. However, the risk for microscopic colitis appears elevated among patients who use PPIs, even for a short amount of time.

This review was largely dismissive of the potential for serious risks associated with the use of PPIs, but there is little doubt that PPIs remain one of the most overused of all prescribed medications. In a study of PPI prescriptions by hospitalists, Eid and colleagues found that only 39% of these prescriptions followed published guidelines for PPI use among inpatients. This research, which was published in *Internal Medicine* in 2010, found that the most common erroneous indication for providing PPIs was prophylaxis against gastrointestinal tract bleeding. Physicians in academic centers were more likely to adhere to PPI-prescribing guidelines, and an inappropriate PPI prescription in the hospital was associated with a higher chance of being prescribed a PPI, probably inappropriately as well, as an outpatient.

The current study by Bhattarai and colleagues, results which were presented at the 2014 American College of Chest Physicians Meeting, evaluates another potential risk associated with gastric acid suppression: community-acquired pneumonia.

STUDY SYNOPSIS AND PERSPECTIVE

Acid suppressors are associated with more severe community-acquired pneumonia, according to a study performed at an inner-city hospital. However, comorbidities such as diabetes and chronic obstructive pulmonary disease (COPD) could have played a role in the results.

"I looked through the literature and found there was a high association between acid suppression and ventilator-associated pneumonia," chief resident Bikash Bhattarai, MD, who is now a pulmonary fellow at the Interfaith Medical Center in Brooklyn, New York, told *Medscape Medical News.*

Previous research has shown that acid suppression can increase susceptibility to community-acquired pneumonia, possibly because reducing gastric acid secretion enhances colonization of the upper gastrointestinal tract with oral bacteria.

However, none of the participants in those studies were black. "We have a huge African American population, so that's what prompted me to do the study," Dr Bhattarai explained here at CHEST 2014.

His team conducted a retrospective analysis to determine whether there was also an association between acid suppression and severity of community-acquired pneumonia.

The researchers analyzed all patients with community-acquired pneumonia admitted to their inner-city hospital from 2010 to 2013. Patients who were suspected of having aspiration pneumonia or who were immunosuppressed in any way were excluded from the analysis.

In the study cohort, 86% of patients were black and 53% smoked. Although there were no fundamental differences in demographic characteristics, there was more use of acid suppression at the time of hospital admission in patients with certain comorbidities.

Table 1. Association Between Acid Suppression and Comorbidities

Comorbidity	Acid Suppression (n = 468), %	No Acid Suppression (n = 398), %
COPD	27.1	22.4
Diabetes mellitus	38.9	28.6
Previous stroke	14.1	8.5
Cancer	12.2	7.3
Chronic kidney disease	28.4	22.6

Physicians are very comfortable prescribing acid suppression. In fact, one meeting attendee said that the proportion of patients with community-acquired pneumonia taking acid suppressors was surprisingly low (46%). However, the results of the study suggest that the agents should be used more judiciously, said Dr Bhattarai.

"Even when the patient comes to the hospital, I'm not very comfortable discontinuing the acid suppressors, and my reflex is to put them on the medication if they're not on it already. But we shouldn't give these medications if they aren't indicated because there are risks," he said.

There was also an association between acid suppression and indicators of the severity of community-acquired pneumonia, some of which fell just short of statistical significance.

Table 2. Link Between Acid Suppression and Severity of Pneumonia

Indication of Severity	Acid Suppression (n = 468)	No Acid Suppression (n = 398)	*P* Value
Positive blood culture result (%)	12	5.5	< .001
Thrombocytopenia (%)	22	17	< .001
Radiologic pneumonia (%)	94	93.7	
Length of hospital stay (days)	10.51	8.96	.057
Mortality (%)	15.1	11.5	.057

Still, not everyone is convinced by the data. The study was observational and relatively small, and confounding factors might explain the results, according to Punginathn Dorasamy, MB ChB,

professor of medicine at McMaster University in Hamilton, Ontario, Canada, who attended the presentation.

He pointed out that previous research has yielded conflicting results and, in one case, the study authors suspected that patients receiving acid suppressors had preexisting conditions that predisposed them to pneumonia.

"It's difficult to say that acid suppression is contributing to the worsening of the pneumonia. But there may be a message that in a small subset of patients, such as those with diabetes or COPD, if we are suppressing the acid, we may increase the risk of severe types of pneumonia," Dr Dorasamy told *Medscape Medical News*.

Dr Bhattarai and Dr Dorasamy have disclosed no relevant financial relationships.

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STUDY HIGHLIGHTS

- The study was conducted as a retrospective analysis of cases in an inner-city community hospital in New York City.
- Researchers collected data regarding patients admitted for community-acquired pneumonia between 2011 and 2013. Patients with suspected aspiration pneumonia and those with HIV infection were excluded from analysis.
- Researchers divided the overall study cohort based on patient treatment with acid suppressive therapy before hospital admission.
- The main study outcomes were the effects of acid suppression on the severity and outcomes of community-acquired pneumonia. Researchers used a regression analysis to account for other variables separating the 2 study groups.
- 866 patients were included in the analysis. An estimated 48% of patients were men, and 86% were African American.
- 54% of the study sample had received acid suppressive therapy.
- Demographic variables were not significantly associated with the use of acid suppressive therapy, but patients with more comorbidity, including COPD, diabetes mellitus, previous stroke, or cancer were more likely to receive acid suppressive treatment.
- Rates of positive blood culture results were higher among patients who received acid suppressive therapy vs those who did not (12% vs 5.5%, respectively). The respective rates of thrombocytopenia were 22% and 17%. Both of these differences were statistically significant.
- However, the rates of radiologic evidence of pneumonia were similar and were above 90% regardless of acid suppressive therapy.
- The average lengths of hospital stay among patients who did and did not receive acid suppressive therapy were 10.51 and 8.96 days, respectively. The respective rates of mortality were 15.1% and 11.5%. Both of these differences just missed statistical significance.

CLINICAL IMPLICATIONS

- **Good evidence exists that PPIs are widely overused among inpatients**. However, a review found weak evidence that PPIs may adversely affect bone health or increase the risk for infection with *C difficile*. PPIs do promote hypomagnesemia.
- **The current study by Bhattarai and colleagues suggests that adults using acid suppressive therapy are more likely to have severe community-acquired pneumonia and experience longer lengths of hospital stay and higher rates of mortality**.

Il Donepezil può rallentare l'atrofia ippocampale in pazienti con AD prodromico

Laird Harrison

February 04, 2015

Donepezil (*Aricept*, Esai) slows atrophy of the hippocampus in patients with prodromal Alzheimer's disease, a new randomized study shows.

"After 1 year we were surprised to see a 42% reduction of hippocampal atrophy in prodromal Alzheimer's patients," lead researcher Bruno Dubois, MD, told *Medscape Medical News*. "This is a very strong result."

Dr Dubois, a neurology professor at Hôpital La Salpêtrière, Paris, France, and his colleagues at 15 French institutions published their findings online January 14 in *Alzheimer's & Dementia*.

However, the study did not show any effects on cognition, disappointing researchers who had hoped to identify a subgroup of patients who might especially benefit from the medication.

Early Intervention

Researchers have been working to identify patients with prodromal Alzheimer's disease: mild cognitive impairment that foreshadows progression to full-blown disease. They hope that by intervening early enough they might prevent the disease from progressing.

Earlier studies showed that the hippocampus shrinks rapidly in patients with mild cognitive impairment as that condition progresses to Alzheimer's disease. Donepezil slows atrophy of the hippocampus in patients with mild to moderate Alzheimer's disease, as well as slowing the patients' cognitive decline, but few researchers have looked at donepezil in patients with mild cognitive impairment.

To fill that gap, Dr Dubois and colleagues used a memory test, the Free and Cued Selective Reminding Test (FCSRT), to identify patients most likely to have prodromal Alzheimer's disease. The test has been correlated with hippocampal volume and changes in cerebrospinal fluid characteristic of Alzheimer's disease.

They recruited 216 people over age 50 who had no dementia but scored low on the FCSRT. They randomly assigned 103 to take a placebo and 113 to take donepezil, 10 mg/day.

They used brain MRI to measure the volume of the patients' hippocampus at baseline, 6 months, and 1 year.

Adverse reactions occurred more frequently in the donepezil group and included muscle spasms, nightmares, diarrhea, headache, nausea, sleep disorder, abdominal pain, and vertigo.

Partly because of the adverse reactions, several patients dropped out. After a year, 81 remained in the placebo group and 75 remained in the donepezil group.

In these remaining patients, the donepezil group lost 1.89% of hippocampal volume over the year, while the placebo group lost 3.47%. The difference was statistically significant ($P < .001$).

Although apolipoprotein has been linked to the decline in hippocampal volume in people with Alzheimer's disease, hippocampal volume did not differ between *APOE4* carriers in the 2 groups.

The researchers gave their patients a battery of neuropsychological tests but didn't find any significant differences between the two groups.

This last finding means this study has no implications for current clinical practice, Dr Dubois said.

Direction for Future Research

Keith Fargo, PhD, director of scientific programs and outreach at the Alzheimer's Association, agreed.

"At this point it's more about giving direction to additional research," said Dr Fargo, who was not associated with this study. "The literature in this area has been somewhat mixed, and this paper answers a question. But all research has to be followed up on."

One possibility for future researchers is to look further for neuropsychological benefits from donepezil in this category of patients.

"If you follow people longer, if you had more people in the study, would you see benefits to cognition, would you see benefits to daily living, for example?" Dr Fargo asked.

Dr Dubois said he and his colleagues are planning to continue analyzing their current data, looking further at the effect of donepezil on other brain structures.

This study was funded by Eisai, the company that markets donepezil as Aricept. The authors and commenter have disclosed no relevant financial relationships.

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I NAOC nei pazienti con FA naïve: dalla Danimarca arriva il punto della situazione nella real life

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Olesen et al. hanno indagato il ruolo dei NAOC (Non-vitamin K Antagonist Oral AntiCoagulation agents) per la prevenzione di stroke nel 'real-world' danese da quando sono stati introdotti sul mercato (22 agosto 2011- 31 ottobre 2013) nei pazienti con fibrillazione atriale (FA) naïve. Dai registri danesi, usando modelli di regressione lineari sono stati paragonati i dati dei pazienti che iniziavano terapia con warfarin versus quelli che assumevano uno dei 3 NAOC in commercio: dabigratan, apixaban o rivaroxaban. Sono stati identificati 18.611 pazienti con FA naïve dei quali 9.902 (53%) avevano iniziato il trattamento con warfarin, 7.128 (38%) con dabigatran, 1.303 (7%) con rivaroxaban e 278 (1%) con apixaban. Su tutti, il 40% dei nuovi pazienti che assumeva NAOC iniziavano la terapia anticuagulante orale con il dabigatran nei primi 4 mesi da quando la molecola è stata introdotta sul mercato. Da ottobre 2013, il 40% aveva iniziato la terapia anticoagulante orale rispettivamente con warfarin e dabigatran ed un altro 20% aveva assunto rivaroxaban o apixaban. I pazienti in terapia con rivaroxaban e apixaban generalmente avevano un profilo di rischio di stroke e sanguinamenti maggiore rispetto agli utilizzatori di warfarin e dabigatran. L'età avanzata, il sesso femminile e l'anamnesi positiva per precedenti stroke erano i fattori associati all'uso di NOAC versus il warfarin, mentre i fattori contrari risultavono l'insufficienza renale, l'infarto miocardico e lo scompenso cardiaco. In conclusione, in Danimarca dall'introduzione dei NAOC, agosto 2011 per il dabigratan, l'uso del warfarin risulta in declino ed il dabigratan, appunto, risulta essere il principale NOAC prescritto. Nonostante ciò, l'introduzione degli altri due NAOC sta lentamente incrementando ed il loro uso è principalmente indirizzato ai pazienti a maggior rischio di sanguinamento e stroke rispetto ai pazienti che iniziano warfarin e dabigratan.

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AD/PD 2015: International Conference on Alzheimer's and Parkinson's Diseases

Medscape Medical News > Conference News

Finalmente una grande vittoria per gli ab monoclonali nell' Alzheimer

Daniel M. Keller, PhD

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NICE, France — After years of disappointing trials of monoclonal antibodies directed against forms of β-amyloid for the treatment of Alzheimer's disease (AD), one appears to have hit the mark, at least in early stages of the disease. The eagerly awaited trial of aducanumab (formerly BIIB037) did not disappoint, although much work still lies ahead.

Speaking here at AD/PD 2015: International Conference on Alzheimer's and Parkinson's Diseases, Jeff Sevigny, MD, from Biogen Idec reported results of this prespecified interim analysis of the PRIME trial.

"We observed a statistically significant dose- and time-dependent reduction in amyloid plaque by PET [positron emission tomography] imaging, evident as early as 6 months, out to 1 year," Dr Sevigny.

Importantly, the treatment also was associated with significant dose-dependent slowing of cognitive decline at 1 year, as measured by the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Scale-sum of boxes (CDR-sb) scores.

The randomized, double-blind, phase 1b study of aducanumab randomly assigned patients with prodromal or mild AD to 1, 3, 6, or 10 mg/kg of drug or placebo in a 3:1 fashion, with approximately 30 patients per active treatment group. Patients were 50 to 90 years of age (mean age, 70.5 to 73.7 years across the groups), had confirmed β-amyloid deposition as assessed by florbetapir (^{18}F-AV-45) PET scans, and met clinical criteria for prodromal or mild AD by MMSE and CDR-sb. They received the drug or placebo intravenously once every 4 weeks for 52 weeks. Most patients were also taking concomitant AD medications.

A composite Standard Uptake Value Ratio (SUVR) of florbetapir was calculated from a volume of six brain regions of interest, specifically the frontal, parietal, lateral temporal, sensorimotor, anterior cingulate, and posterior cingulate regions, and compared with whole cerebellum as a reference region.

The researchers had learned lessons from past trials of monoclonal antibodies in AD that largely failed or had equivocal results, and they designed this one to be able to see a positive signal if at all possible. First, they started with patients with prodromal or mild disease. Second, they confirmed that the patients actually had AD and amyloid accumulation, thereby minimizing any "noise" from inclusion of inappropriate participants. Estimates are that up to 30% of patients in some previous trials did not have sufficient amyloid and therefore could in no way show reductions or be helped cognitively by an antiamyloid therapy.

Amyloid Plaque Reduction

At week 26, aducanumab treatment was associated with a reduction in amyloid plaque in all brain regions of interest, with even greater reductions seen at week 54.

Reductions occurred in the frontal, parietal, lateral temporal, sensorimotor, anterior cingulate, posterior cingulate, medial temporal, and occipital cortex, as well as in the striatum. In each area, plaque reduction was greater with the 10 mg/kg compared with the 3 mg/kg dose.

Table. Adjusted Mean Change in Composite SUVR From Baseline

Dose	Patients (n)	Change in SUVR	*P* Value
At 26 weeks			
Placebo	34	<–0.01	NS
1 mg/kg	26	–.030	NS
3 mg/kg	27	–0.087	<.01
6 mg/kg	23	–0.143	<.001
10 mg/kg	27	–0.205	<.001
At 54 weeks			
Placebo	21	0	NS
1 mg/kg	21	–0.056	NS
3 mg/kg	26	–0.139	<.001
6 mg/kg	Ongoing	Ongoing	Ongoing
10 mg/kg	21	–0.266	<.001

NS, not significant.

The mean SUVR starting values were between 1.40 and 1.50. In healthy persons, the cut-point for florbetapir is less than 1.13. By week 54, the mean composite SUVR for the 10 mg/kg dose was about 1.15.

Aducanumab slowed the rate of decline in MMSE scores at the 3 mg/kg and 10 mg/kg doses by week 54. Whereas the placebo group had an adjusted mean decline in MMSE score compared with a baseline of 3.1, the difference from placebo was 2.39 points higher for the 3 mg/kg dose and 2.55 higher for the 10 mg/kg dose (both $P < .05$ vs placebo). The CDR-sb adjusted mean score at 10 mg/kg was significantly lower (ie, better) than for placebo (0.50 vs 2.00; $P < .05$).

Good Safety and Tolerability

Three percent of aducanumab-treated patients developed antibodies against the drug, but titers were minimal and had no effect on pharmacokinetics or safety, the researchers report.

Almost all patients had some adverse event. Serious adverse events occurred in 10% to 13% of patients at lower doses, in 38% of those in the highest dose group, and, curiously, in 38% in the placebo group. Six percent to 10% discontinued the study in the placebo and lower dose groups, but 31% stopped in the 10 mg/kg group. Three patients died — two in placebo group and one in the 10 mg/kg group — but no deaths were considered treatment related.

Amyloid-related imaging abnormalities with edema and effusion (ARIA-E) on MRI were the main safety and tolerability signal. ARIA-E occurred in a dose-dependent manner, affecting 33% and 41% of patients at the 6 mg/kg and 10 mg/kg doses, respectively. It was more prevalent in ApoE ε4 carriers.

Most cases occurred within the first five doses; 65% of cases were asymptomatic, and the rest were generally mild. Signs of ARIA-E resolved within 4 to 12 weeks after the drug was stopped. Patients could resume dosing at the next lower dose once ARIA resolved.

Headache occurred in 22% of patients receiving aducanumab compared with 5% in the placebo groups and appeared to be dose-dependent, a company statement noted.

On the basis of these encouraging phase 1b results, Dr Sevigny said the plan is to go directly into a phase 3 trial.

"Compelling" Approach

In the days leading up to the aducanumab presentation, some attendees expressed pessimism about how the trial would come out, based on certainly less than stellar earlier results with other monoclonal antibodies against forms of β-amyloid. However, just before the session, John Trojanowski, MD, PhD, professor of geriatric medicine and director of the Institute on Aging at the University of Pennsylvania in Philadelphia, told *Medscape Medical News* that he thought the trial would be a success, and he was right, calling the approach "very compelling" after seeing the data.

"The biomarker changes that were shown — abeta [β-amyloid] clearance coupled with the improvement in MMSE and CDR sum of boxes… there was a dose-dependent improvement in the biomarkers and improvement of cognition, so I think the…study looks very promising," he said. He added that replication will be needed, and many candidate drugs fail after initial encouraging results.

Dr Trojanowski mentioned that it may be good that the antibody does not recognize amyloid monomers, which may help to clear aggregates through the action of microglia. And in line with much of the opinion

at the conference, he believes a multitargeted approach that attacks plaques, tangles, and Lewy bodies will be needed.

Even with these reservations, "I want to end on an upbeat note by saying that this is really amazing, really exciting, it's what the field needs, a signal as robust as this that progresses on to an FDA [US Food and Drug Administration] approval," he said, "but at the end of the day, we're going to need combination therapy as well."

Nonetheless, "this is just so far beyond where the field has been with earlier immune therapy efforts. It was a very exciting morning," he stated with a smile.

Session moderator Colin Masters, MD, senior deputy director of the Florey Institute of Neuroscience and Mental Health in Victoria and a laureate professor at the University of Melbourne, Australia, commented to *Medscape Medical News* that what distinguishes this antibody from previous ones, according to Biogen, is that it recognizes aggregated β-amyloid.

"Because it is derived from a human [B cell] clone, it's recognizing an epitope which is there in real life, whereas all the other antibodies are being created against artificial constructs," he explained, with the implication that those epitopes may not be as relevant.

Furthermore, he called it a "reasonable supposition" to think that if monomeric amyloid has a beneficial function in the body, as Dr Trojanowski alluded to, in terms of clearance of amyloid aggregates through microglia, aducanumab should allow those functions to continue.

On the downside, Dr Masters said, "there are a lot of ARIA in the Biogen study, and that's a big problem, but it can be managed…it needs to be investigated much more, and obviously they can't push the dose too high."

Aducanumab is a human recombinant monoclonal antibody that selectively binds aggregated forms of β-amyloid, including soluble oligomers and insoluble fibrils, but does not bind β-amyloid monomers, according to its developers. It was developed by a novel method of reverse translational medicine, taking memory B cells from healthy elderly and cognitively stable patients and screening for ones that produced antibody against aggregated β-amyloid.

PPI ed insufficienza renale nell'anziano

I pazienti anziani che assumono inibitori della pompa protonica (PPI), un comune rimedio per il bruciore precordiale ed il reflusso acido, vanno incontro ad un rischio raddoppiato di essere ricoverati in ospedale per insufficienza renale rispetto alle loro controparti che non assumono questi farmaci. Benché l'effetto collaterale in questione sia estremamente raro, e non sia stato provato che l'insufficienza renale venga provocata direttamente dai farmaci, l'associazione è comunque preoccupante, in quanto i PPI vengono assunti ogni anno da decine di milioni di persone ed, in alcune zone, vengono venduti anche come medicinali da banco. Il dato deriva da uno studio su 290.000 soggetti di Tony Antoniou, del *St. Michael's Hospital* di Toronto, che afferma che "in genere si tratta di farmaci molto ben tollerati e la vasta maggioranza dei pazienti che li assumono non sviluppa insufficienza renale o altri problemi gravi, ma si tratta comunque di farmaci che andrebbero assunti per il più breve periodo possibile".

L'effetto collaterale più preoccupante dei PPI rimane comunque l'osteoporosi, in quanto in conseguenza della loro assunzione potrebbe verificarsi una riduzione dell'assorbimento di alcuni nutrienti, fra cui magnesio, ferro, vitamina B12 e calcio. Benchè alcuni pazienti possano sfruttare gli antiacidi per alleviare i sintomi di bruciore precordiale, i PPI svolgono un ruolo importante nel trattamento dei soggetti con problemi medici più gravi: nei pazienti con reflusso gastroesofageo essi possono prevenire lo sviluppo di tumori esofagei, ma la loro necessità andrebbe revisionata spesso e, in molti casi, la modifica dello stile di vita potrebbe essere sufficiente ad ottenere l'effetto desiderato. (*CMAJ Open* online 2015, pubblicato il 16/4)