Treatment of Congestive Heart Failure

To the Editor: In their Scientific Review article about treatment of advanced heart failure, Dr Nohria and colleagues do not discuss relief of dyspnea by administration of low-dose narcotics.2

The literature in hospice and palliative care has numerous citations about the usefulness of narcotics for palliation of symptoms.2-4 I have found that some patients have dramatic relief of their symptoms and commonly ask why previous physicians did not offer this simple treatment with its dramatic results. Patient and family education about disease management along with successful advance planning allows patients with advanced heart failure to be treated effectively at home.

As a final note, since advanced heart disease is a fatal illness, I also encourage physicians to initiate discussions about advance care planning to ensure that patients receive care that is consistent with their wishes.

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To the Editor: In their Scientific Review article about the management of advanced heart failure, Dr Nohria and colleagues suggested that angiotensin II receptor blockers (ARBs) are a reasonable alternative for patients who cannot tolerate angiotensin converting enzyme (ACE) inhibitors because of severe cough or angioedema. Although we agree that ARBs, or a combination of hydralazine and a nitrate, constitute a reasonable alternative in patients experiencing persistent cough associated with receiving ACE inhibitors, we believe that ARBs in patients with a history of an ACE inhibitor–associated angioedema should only be used with extreme caution, if at all.

ACE inhibitor–associated angioedema can occur hours to years following drug initiation.2 The mechanism of ACE inhibitor–associated angioedema has not been completely elucidated. Some have suggested that this adverse drug reaction is secondary to the inhibition of bradykinin metabolism and accumulation, resulting from ACE inhibition, although other proposed mechanisms include release of histamine, substance P, and prostaglandin.1,3-5 Black patients are at particular risk for developing angioedema. Although others have also recommended ARBs in patients previously experiencing ACE inhibitor–associated angioedema,6,7 recent data have questioned the safety of this practice.8,9 Moreover, an analysis of published cases indicated that in 32% of patients with ARB-associated angioedema had a history of ACE inhibitor–associated angioedema.2 Of even more concern is that in some cases, ARBs were not identified as the responsible agent; thus, continuation of the drug following the first episode resulted in further episodes of angioedema.

We believe that a combination of hydralazine and a nitrate represents a safer and more appropriate alternative for treatment of left ventricular dysfunction in patients with a history of ACE inhibitor induced angioedema.

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To the Editor: Dr Nohria and colleagues provide no evidence for their conclusion that heart failure hospitalization rates are reliably decreased by experienced heart failure physician-nurse teams making decisions but not by centralized nursing services providing patient contact but no intervention except

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through multiple primary providers." We believe that the meta-analysis1 they cited in support of this conclusion is flawed. One2 of the 2 studies in the meta-analysis that was categorized as evaluating telephonic “centralized nursing services” to enhance primary care follow-up did not even focus on a heart failure disease management program. Instead, patients in the Veterans Affairs (VA) health care system with a variety of chronic illnesses received global primary care clinician and nursing support. Second, the patients in the VA study had higher comorbidity and lower baseline quality of life scores than patients in the other studies included in the meta-analysis. Third, the authors of the VA study acknowledged that many factors unique to the VA system may have influenced their findings and thus would limit their generalizability to other health care systems. The appropriateness of quantitatively combining data from this study with the others is questionable, regardless of the results of heterogeneity testing.

In contrast to the conclusions of Nohria et al, we recently reported on the results of a 1-year randomized trial3 of a video-based home telecare intervention in which we found that the mean charges for heart failure–related readmission were 86% lower for the telecare group and 84% lower for the telephone group than the mean charges for the patients who received usual care. The large difference in readmission charges between the usual care and intervention groups did not reach statistical significance, probably due to the small sample size. However, both interventions resulted in significantly fewer congestive heart failure–emergency department visits and charges.

Although specialist expertise may sometimes be required for optimal management of heart failure, the majority of patients with heart failure are managed principally by primary care physicians.4 Generalists and specialists alike should strive to develop collaborative approaches to heart failure management.

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In Reply: We appreciate these perspectives. As Dr Brumley suggests, the increasing population of patients with truly end-stage disease mandates more thoughtful approach to their suffering, which can certainly be alleviated by oral opiates. Drs de Denus and Spinler note that recent information regarding ACE inhibitors does raise considerable concern that these agents may not be indicated for patients with a history of angioedema from ACE inhibitors. Dr Jerant describes the success of his program for managing heart failure. The majority of patients with heart failure are indeed followed up in primary care practices. The clinicians in these settings have by far the most challenging responsibility to provide comprehensive ongoing care for heart failure while managing multiple other complex chronic illnesses.

Few practicing physicians now can set aside sufficient time for patient education and regular telephone calls to monitor daily fluctuations in clinical status. Whether the supervising physician is a heart failure specialist or primary care physician, a team approach is critical to optimize outcome for these patients. Dedication and experience is required for the nurse specialist to help patients establish an optimal medical regimen, particularly for the initiation and titration of β-blockers. Our emphasis was not on the credentials of nurse-physician teams, but rather on their familiarity with these patients and the flexibility to intervene rapidly to avert decompensation. These functions are limited for national call-in systems that are isolated from the direct providers.

Our article focused on patients with advanced heart failure in whom severe symptoms persist after the usual therapies have been attempted. Many of the newer therapies for these patients are available only in specialized heart failure centers, where this team approach evolved through heart transplantation and clinical trials. For the broader heart failure population, many different approaches have effectively reduced rehospitalization.1–3 These should be adapted to the patient populations, practice patterns, and available resources for each community. As the number of patients with heart failure continues to increase, more nurses trained in heart failure management will be needed to enhance primary care of heart failure in all communities.

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Postmenopausal Hormone Replacement, Body Mass Index, and Quality of Life

To the Editor: Dr Hlatky and colleagues1 reported that postmenopausal hormone therapy improved quality of life only among women who reported flushing at baseline. We suspect that the women in this study who reported flushing were generally thinner than those who did not; thus, we suggest that the results should be reported stratified by body mass index (BMI). Menopausal symptoms, including flushing, are related to the dramatic decrease of estrogen levels due to depletion of


ovarian function. After menopause, peripheral aromatization of androgens in adipose tissue is the primary source of endogenous estrogen, and circulating levels of estrogen in postmenopausal women increase with increasing body mass.2 Significantly lower levels of estradiol and estrone are found in women thinner women.2

Several observational studies have suggested that both risks and benefits of hormone therapy are observed only in thin women.3,4 Breast cancer rates are generally lower among thin postmenopausal women and increase with hormone therapy, while there appears to be no such increase among women with higher BMI.3 Similarly, we have reported that the inverse association between hormone use and coronary heart disease was strongest for thin women.4 These results suggest that there may be a threshold level of estrogen beyond which additional exogenous estrogen has negligible effects.

Women included in the HERS trial, upon which Hlatky et al based their analysis, have higher BMI than average US women: 57% of the women in the treatment group5 had a BMI of greater than 27 kg/m2 compared with 43% of US women in the same age group.3 If there is indeed a threshold in the level of biologically important doses of estrogens, an improvement in mental health and depression associated with hormone use among women in the HERS trial would only be expected in thinner women.

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In Reply: In response to Drs Rodriguez and Calle, only 28% of the women enrolled in HERS had a BMI of 25 kg/m2 or less, and only 5% had a BMI of 20.9 kg/m2 or less. We examined the quality-of-life measures in 3 strata of BMI: 25 kg/m2 or less, more than 25 through 30 kg/m2, and more than 30 kg/m2. Overall quality of life scores declined significantly with increasing BMI. None of the tests for interaction between treatment assigned, follow-up time, and BMI were statistically significant, however, and there were no consistent trends between BMI and an effect of hormone therapy on quality of life.

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Varicella Vaccine and Shingles

To the Editor: Dr Seward and colleagues1 report that the incidence of varicella in the United States decreased following the introduction of vaccination. It is unclear, however, how varicella vaccination will affect the incidence of herpes zoster (HZ). It has been suggested that exposure to varicella can boost specific immunity to varicella zoster virus (VZV) and thus reduce the risk of reactivation.2 If this is the case, reduction of circulating VZV due to varicella vaccination would increase the overall incidence of HZ; unvaccinated adults would be most at risk. This potential danger was recognized by the Food and Drug Administration at the time the varicella vaccine was licensed,3 and the Centers for Disease Control and Prevention (CDC) were recommended to conduct surveillance of both chickenpox and HZ cases after widespread use of the vaccine.4

Mathematical models have suggested that the greater the reduction in the incidence of varicella, the greater the ensuing increase in HZ.1 Thus, the dramatic decline in incidence observed by Seward et al might lead to a significantly increased incidence of HZ over the next 50 years. The incidence of HZ should eventually decline once the vaccinated cohorts reach old age because the varicella vaccine strain is less likely to reactivate than the wild type strain.5 Introduction of booster doses of varicella vaccine to prevent HZ may be an interim option. Thus, Seward et al report only half the story: trends in the annual age-specific incidence of HZ should be presented alongside the varicella data to show the full impact of the vaccination program on VZV disease.

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In Reply: We agree with Dr Brisson and colleagues that surveillance for HZ is essential for evaluating the impact of the

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varicella vaccination program. Because the population sizes in
the varicella active surveillance sites are not sufficient to moni-
tor age-specific HZ incidence, the CDC has funded 2 other
sites—Massachusetts Department of Public Health and Group
Health Cooperative (GHC) in Seattle—to conduct population-
based varicella and HZ surveillance and monitor age-specific
incidence rates. Massachusetts has monitored incidence through
a statewide telephone survey since 1998,1 while GHC is exam-
ing its automated medical records since 1992. To date, no
increase in HZ is evident in any age group in either site (CDC,
unpublished data, 2001). However, continued surveillance is
needed to detect any changes in HZ incidence.

A decline in VZV transmission resulting from widespread
vaccination may affect persons with prior varicella, but is un-
likely to affect vaccinated persons whose risk of HZ is much
lower.3 The trigger for reactivation is poorly understood but
appears to depend on a decline in cell-mediated immunity. Pro-
tection against reactivation may be the result of external boost-
ing (contact with infectious cases), internal boosting (reacti-
vation of the latent virus), or other factors. Brisson et al4 have
modeled the changes in HZ epidemiology following vaccine in-
troduction under different assumptions. Assuming that exter-
nal boosting is the sole determinant of immunity, there could
be an increase in HZ (range, 0%-30%) over the next 5 to 40
years followed by a decrease as immunized individuals re-
place those infected with wild type VZV. Another theory sug-
gests that VZV reactsivates subclinically5 with resultant boost-
ing of immunity6 with unknown effect on HZ incidence. Finally,
if boosting does not affect the risk of HZ, the disease will de-
cline progressively as the population of vaccinated persons in-
creases.

Given the morbidity of HZ, an increase in incidence is of great
concern. We are monitoring HZ incidence and will report more
detailed findings as soon as they are available. In the mean-
time, we also await the results of a multicenter trial of a higher-
titre formulation of the Oka/Merck vaccine strain virus among
persons older than 55 years that may prevent or modify HZ
and provide the scientific basis to address vaccination for HZ.
Although we hope that varicella vaccination will result in de-
clines in both varicella and HZ over time, protecting the large
population of persons already at risk for HZ is a public health
priority.

Chocolate Consumption and Platelet Function

To the Editor: Flavonoid-rich foods and beverages have pu-
tative vascular health benefits, including protection against is-
chemic stroke and reductions in platelet reactivity.1-3 Tea, grapes,
apples, and cocoa contain a class of flavonoids known as the
flavanols, which includes epicatechin and catechin. Flavanols
can polymerize, producing theaflavins and thearubigins (found
in tea) and procyanidins (found in grapes, apples, and cocoa).
We previously reported reductions in platelet primary hemo-
stasis and glycoprotein IIb/IIIa expression 2 and 6 hours after
subjects consumed 300 mL of cocoa containing a total of 897
mg of flavanols and procyanidins.3 We examined whether
smaller amounts of chocolate could affect platelet function.

Methods. We measured platelet function in 18 adult sub-
jects, without history of heart disease or other chronic dis-
ease, at baseline and at 2 and 6 hours after they consumed 25
g of semisweet chocolate chips (Mars Inc, Hackettstown, NJ),
which contained 220 mg of flavanols and procyanidins. Plate-
let function was assessed with the PFA-100 (Dade Behring, Deer-
field, Ill), which measures platelet primary hemostasis as the
time it takes for adenosine diphosphate (ADP)–stimulated or
epinephrine-stimulated whole blood to occlude an aperture in
a collagen membrane under high shear conditions. Congeni-
tal platelet defects, glycoprotein IIb/IIIa inhibition, and aspi-
rin will prolong closure times with the epinephrine/collagen
PFA-100 cartridge, while the ADP/collagen cartridge is insen-
itive to the effects of aspirin. Plasma epicatechin, the predomi-
nant flavanol found in chocolate, was measured by reversed-
phase high-performance liquid chromatography as a marker
for flavanol absorption. Because platelet quiescence is main-
ained, in part, by nitric oxide and prostacyclin produced from
the intact endothelium,4 we also measured plasma concentra-
tions of the prostacyclin metabolite 6-keto-prostaglandin-F1α,
and the pro-inflammatory eicosanoids leukotriene (LT) C4, D4,
E4. Closure times were compared with repeated-measures (RM)
analysis of variance (ANOVA). Plasma metabolites were ana-
yzed by ANOVA or by Kruskal-Wallis ANOVA, depending on
whether the data were normally distributed. The Tukey all-
pairwise comparison test (which only indicates whether a P
value for a comparison is <.05) was performed if the P value for
the overall test was <.05.

Results. Relative to baseline, a significant increase in clo-
sure time was observed in both ADP/collagen-induced (P = .006;
Friedman repeated measure analysis of variance [RM ANOVA],

REFERENCES

shingles in Massachusetts using the BRFSS. Paper presented at: 34th National Im-
2. Seward JF. Update on varicella and varicella vaccine, United States. Paper pre-

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and Tukey all-pairwise comparison test; Figure, A) and epi-
epinephrine/collagen-induced ($P_{/H1021}=.05$; RM ANOVA on ranks, and
Tukey all-pairwise comparison test; Figure, B) primary hemo-
stasis 2 hours after chocolate consumption. Six hours after con-
suming chocolate, the closure times were significantly in-
creased with ADP/collagen ($P_{/H1021}=.01$; Figure, A), but not
epinephrine/collagen (Figure, B). We note that there were 2
outlying closure times in the epinephrine/collagen test at the
6-hour time point, although the cause is unknown.

Two hours after chocolate consumption we observed sig-
nificant increases ($P_{/H1021}<.05$; Kruskal-Wallis ANOVA on ranks,
Dunn all-pairwise comparison test) in mean (SD) plasma epi-
catechin concentrations (427 [249] nmoL/L) relative to base-
line (39 [62] nmoL/L). This increase in plasma flavanol was
transient in nature ($P<.05$), with epicatechin concentrations
decreasing to 114 (79) nmoL/L by 6 hours. Plasma concentra-
tions of 6-keto-prostaglandin-$F_{/H1021}$ were significantly increased
at the 2-hour ($P<.001$) and 6-hour ($P<.001$) time points (169.8
[71.3] pg/mL and 163.1 [74.0] pg/mL, respectively) relative to
baseline (88.5 [69.0] pg/mL). In contrast, leukotriene concentra-
tions were unchanged ($P=.995$) from baseline 2 hours after
chocolate consumption (163 [311] pg/mL and 39 [42] pg/mL,
respectively). Overall, an antithrombotic eicosanoid response
was observed at 2 hours, with the ratio of 6-keto-prostaglandin-
$F_{/H1021}$ to LT $C_4$, D$_4$, and E$_4$ significantly increased ($P<.05$) over
baseline (14 [35] and 23 [39], respectively).

Comment. We observed significant increases in plasma fla-
vanol concentrations, with a concurrent increase in the ratio
of prostacyclin to leukotriene shortly after consumption of a
small amount of chocolate. We also observed reductions in both
ADP/collagen-stimulated and epinephrine/collagen-stimulated
platelet-related primary hemostasis. These results support the concept that small amounts of foods rich in flavo-
noids, such as chocolate, can transiently affect platelet func-
tion.

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1. Freedman JE, Parker CI, Li L, et al. Select flavonoids and whole juice from purple
grapes inhibit platelet function and enhance nitric oxide release. *Circulation.*
2001;103:2792-2798.

2. Duffy SJ, Keaney JF Jr, Holbrook M, et al. Short- and long-term black tea con-
sumption reverses endothelial dysfunction in patients with coronary artery dis-

3. Rein D, Paglieroni TG, Wun T, et al. Cocoa inhibits platelet activation and func-


5. Kris-Etherton P, Keen CL. Evidence that the antioxidant flavonoids in tea and

factors and converting enzyme inhibition. *Am J Cardiol.* 1995;76:3E-12E.