provide some data on patients presented between 3 and 6 h following the onset of symptoms.

Wouter E.M. Kok, MD
Victor A. Umans, MD, FACC
Alfred E. Arnold, MD
Department of Cardiology
Medisch Centrum Alkmaar
The Netherlands

REPLY
We thank Kok, Umans, and Arnold for their statistical calculations. Indeed, a large sample size would be required to prove that there is equivalence in clinical outcome between patients directly admitted compared to transferred patients. To demonstrate that the six-month mortality rate would not exceed more than 1% (6.6% vs. 7%) would require a sample size of even more than 25,000 patients! However, it was not our objective to prove that transferred patients have an identical clinical outcome compared to directly admitted patients. The "primary endpoints" of this analysis were variables such as ejection fraction, enzymatic infarct size and patency rate. For completeness, six-month mortality and reinfarct rates were reported, demonstrating that the delay was indeed not associated with a strong increase of adverse events. However, we emphasize the importance of the patency rate achieved in the referred patients for longterm survival (1,2), and therefore, our data are compatible with equivalence in clinical outcome, albeit without the statistical proof.

The second question regards data on the subgroup of patients admitted between 3 h and 6 h following onset of symptoms. As described in our article, one of the characteristics of referral patients is the short delay between onset of symptoms and admission. This is probably caused by the criteria used by referral cardiologists for the decision to transport the patient for primary angioplasty. In the study group, therefore, only 43 patients presented between 3 h to 6 h following onset of symptoms. This subset of patients is too small to be separately evaluated.

Aylee Liem, MD
Felix Zijlstra, MD
Hospital de Weeenlanden
Groot Weenland 20
8011 JW Zwolle
The Netherlands

REFERENCES

Seasonal Distribution of Myocardial Infarction and Seasonal Mood Changes
I read with interest the article by Spencer et al. on the seasonal distribution of acute myocardial infarction (1). I would like to offer some comments on this article.

Since ancient times, people have known about the seasonal changes in mood and behavior (2). Seasonal changes in mood were later described by Esquirol in 1845 (3) and by Kraepelin in 1921 (4). In 1984, the syndrome of "seasonal affective disorder," a condition where depressions in fall and winter alternate with nondepressed periods in the spring and summer, was described (5). Sadness, anxiety, irritability, decreased activity, difficulties at work, social withdrawal, changes in appetite, decreased libido and changes in sleep are characteristic symptoms of winter depression. The degree to which seasonal changes influence mood, energy, sleep, appetite, food preference or the wish to socialize with other people has been called "seasonality" (6). Seasonality can manifest itself to a different degree in different individuals. Some people experience only very mild seasonal changes, and others are severely influenced. Surveys have shown that 25% of the general population in New York City and 27% of the general population in Montgomery County, Maryland, noted that seasonal changes were a problem in their lives (6,7). Recent studies have demonstrated that seasonal mood changes are related to the genetic factors (8). It means that people may have genetically determined sensitivity to seasons.

Psychological factors have a very considerable effect on the cardiovascular system (9–12). Many studies have documented increased cardiovascular morbidity and mortality in patients with depressive disorders. Depression has been implicated as an independent risk factor in the pathophysiologic progression of cardiovascular disease. Depression, stress, anger, anxiety and social isolation have been shown to substantially increase risk for myocardial infarction in patients diagnosed with coronary artery disease. Therefore, I suggest that seasonal mood changes may play a part in the observed seasonal differences in the incidence of myocardial infarction.

Leo Sher, MD
Section on Biological Rhythms
National Institute of Mental Health
Bethesda, Maryland

REFERENCES
Left Ventricular Hypertrophy and Sudden Death

Haider et al. (1) and the editorial by Frohlich (2) remind us of the poor prognosis conferred by left ventricular hypertrophy (LVH) in hypertensive subjects. They accurately point out that much work still remains to be done to elucidate the mechanisms by which LVH leads to sudden cardiac death and other adverse consequences. Although considerable research has been directed at cardiac ultrastructure, electrophysiology and the coronary microcirculation in LVH, the relationship between hemorheology and hypercoagulability in hypertension, especially if LVH is present, has been relatively neglected. Although the blood vessels are exposed to high pressures in hypertension, the main complications of hypertension and LVH (that is, stroke and myocardial infarction) are paradoxically thrombotic rather than hemorrhagic (3). Indeed, the hypothesis that hypertension and LVH may confer a hypercoagulable state can be examined by careful reference to Virchow’s triad (3).

In a high proportion of patients suffering sudden death, postmortem examination demonstrates the immediate cause to be thrombotic occlusion of a major epicardial coronary artery (4). Indeed, a number of hemorheologic and thrombotic markers have been shown to be significantly related to, and predictive of, thrombotic cardiovascular events in hypertension (3,5). In keeping with Virchow’s triad for thrombus formation (thrombogenesis), patients with hypertension demonstrate abnormalities of vessel wall (endothelial dysfunction or damage), blood constituents (abnormal levels of hemostatic factors, platelet activation and fibrinolysis) and blood flow (rheology and flow reserve), suggesting that hypertension does confer a prothrombotic or hypercoagulable state (3). These components appear to be related to target organ damage and long-term prognosis, and are altered by treatment.

In the Leigh general practice study, for example, hypertensive subjects with plasma fibrinogen levels >3.5 g/l had a 12-fold higher cardiovascular risk than those with plasma fibrinogen levels <2.9 g/l (5). We recently reported that hypertensive patients with LVH had higher plasma fibrinogen levels compared with those without LVH; fibrinogen levels were also significantly correlated with left ventricular mass, left ventricular mass index and left atrial size (6). Hemorheologic abnormalities, such as increases in whole blood viscosity or fibrinogen, may account for the reduced coronary flow noted in LVH.

We believe that further study of hemorheology and hypercoagulability in hypertension and of the relationship to LVH would increase our understanding of the mechanisms by which LVH leads to sudden death. The main mechanisms for sudden death in LVH are unlikely to be simply electrophysiologic or arrhythmogenic, as suggested by Frolich (2), but are also very likely to be thrombotic in origin.

Charles G. C. Spencer, MBBS, MRCP

Gregory Y. H. Lip, MD, FRCP(Edin), FESC, FACC

Hemostasis, Thrombosis and Vascular Biology Unit
University Department of Medicine
City Hospital
Birmingham B18 7QH
United Kingdom

REFERENCES


To Trust or Not To Trust

I am writing in response to two articles recently published by Watanabe et al. (1,2) in the Journal. The accompanying editorial (3) highlights the fact that there is debate within the scientific community concerning the results published by this group of investigators.

These articles are the latest in a series examining pharmacologic interventions aimed at preventing nitrates tolerance. The interventions range from angiotensin-converting-enzyme inhibition to vitamin C, vitamin E and now, carvedilol (1,2,4–9). Measures of nitrate effects include platelet cyclic GMP responses along with vascular effects documented by blood pressure and forearm plethysmography. The results in each case have been striking, with definitive prevention of tolerance across experimental groups that include normal volunteers, patients with coronary disease and those with congestive heart failure. The experimental results are enviable, with closely matched treatment groups (despite small sample sizes) and highly consistent results in response to the

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