SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

The Therapeutic Role of Vasopeptidase Inhibition in Hypertension – Results of the OCTAVE Study

A Report on a Satellite Symposium at the American College of Cardiology 51st Annual Scientific Sessions

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March 17-20, 2002 Atlanta, Georgia

and

The Late-breaking Trials Session of the 17th Annual Meeting of the American Society of Hypertension

Originally Presented by: John Kostis, MD

May 14-18, 2002 New York, New York

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Hypertension remains an important public health issue, contributing to a major burden of morbidity and mortality worldwide. Control of blood pressure to target levels has been shown to reduce the risk of cardiovascular events. However, despite the availability of multiple treatment regimens, blood pressure remains poorly controlled in many patients with hypertension. Accordingly, new advances in the treatment of hypertension are required. Vasopeptidase inhibition (VPI), by simultaneously blocking angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP), represents a novel approach to the treatment of hypertension. Preliminary data have indicated that omapatrilat, the VPI agent at the most advanced stage of clinical development, produces greater reductions in blood pressure compared to conventional agents. To define the benefit/risk ratio of this novel class of agents, the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) study was designed to compare the efficacy and safety of omapatrilat with an ACE inhibitor in a broad spectrum of patients with hypertension. In this *Cardiology Scientific Update*, the preliminary results of the OCTAVE study will be reviewed and discussed.

Cardiovascular disease (CVD) remains the most important public health issue worldwide. In the United States, 61.8 million people have one or more types of CVD.[1] This includes 50 million people (81%) with hypertension, 12.6 million (20%) with coronary artery disease (CAD), 4.6 million (7%) with stroke, and 4.8 million (8%) with heart failure. Hypertension is an important antecedent factor for the development of CAD, stroke, and heart failure.[2] The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that the relative risk for mortality from stroke and CAD increases almost linearly with increasing systolic blood pressure (SBP).[3] In a meta-analysis of 9 treatment trials of hypertension involving over 60,000 patients, it was found that even a 2-3 mm Hg change in SBP exerts a very large impact on cardiovascular (CV) mortality.[4] Despite the documented benefit of lowering elevated blood pressure – based on the National Health and Nutrition Examination Survey III (NHANES III, phase 2, 1991-94) – the blood pressure of close to 75% of the 50 million patients with hypertension in the United States remains uncontrolled.[5] According to NHANES III, inadequate control of SBP rather than diastolic blood pressure (DBP) is the major cause of ineffective blood pressure control in these patients.[6] The barriers to adequate hypertension control may be due to underutilization of aggressive treatment regimens,[7] but are equally likely due to the difficulty of controlling SBP with existing drugs, including combination regimens. In the Antihypertensive and Lipid Lowering Treatment to Prevent

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The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. *Cardiology Scientific Update* is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which receives educational grants from the pharmaceutical industry for the distribution of this publication.

Heart Attack Trial (ALLHAT), only 58% achieved a SBP control of <140 mm Hg at one-year follow-up.[8] Accordingly, newer therapies of hypertension that are effective and preferably organ-protective are required.

Vasopeptidase inhibition in hypertension

Vasopeptidase inhibitors (VPIs) are a novel class of cardiovascular drugs that simultaneously inhibit both neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE).[9] NEP and ACE are both membrane bound, widely distributed, zinc-containing metalloproteinases, and therefore share substrates and inhibitors. By blocking NEP, in addition to ACE, the actions of endogenous vasodilator peptides (eg, natriuretic peptides, kinins, and adrenomedullin) are enhanced, while the formation of the vasoconstrictor peptide, angiotensin II, is diminished. The simultaneous blockade contributes to vasodilatory and possibly organ-protective effects. Among the various VPIs, omapatrilat is at the most advanced stage of clinical development. In various animal models of hypertension, a single dose of omapatrilat produced a sustained decline in arterial pressure, greater than that produced by ACE inhibition.[9,10]

Extensive clinical experience with omapatrilat in patients with hypertension has accumulated. In a pilot, placebo-controlled, dose-finding study, omapatrilat produced significant dose-dependent reductions in the average 24-hour ambulatory SBP and DBP. Omapatrilat at 80 mg once daily reduced SBP by 26 mm Hg and 20 mm Hg, at peak and trough, respectively.[9] The high trough/peak ratio supported a once-daily regimen.[11] In comparative trials using ambulatory blood pressure monitoring in patients with mild to moderate hypertension, the whole-day SBP and DBP was reduced to a greater extent with omapatrilat than with the ACE inhibitor, lisinopril and the calcium channel blocker, amlodipine.[12] In another study that combined omapatrilat with the diuretic hydrochlorothiazide (HCTZ),[13] patients not responding adequately to HCTZ were randomized to HCTZ plus placebo or HCTZ plus omapatrilat, at doses of 10 mg daily titrated to 20 mg, or 20 mg titrated to 40 mg. Both omapatrilat regimens were superior to HCTZ alone in reducing blood pressure.[14]

When the OCTAVE study was initiated, about 6000 subjects, including more than 1000 black patients, were exposed to omapatrilat. Compared to placebo and lisinopril, omapatrilat produced more facial redness compared to placebo and lisinopril. The overall incidence of angioedema, regardless of severity, was 0.5% in non-black patients and 2.1 % in black patients. Four cases of airway compromise were reported, all of whom recovered. It should be noted, however, that the evaluation of angioedema was based on investigators' descriptions, with no standard definition. Head and neck swelling were not identified as angioedema and were evaluated separately. Although angioedema is a well-recognized adverse effect of ACE inhibitors, there is wide variation in the reported incidence. An analysis from the Study of Left Ventricular Dysfunction (SOLVD) trial demonstrated that the incidence of angioedema is high when specifically assessed.[15] Accordingly, the incidence of angioedema in omapatrilat- or even in ACE inhibitor-treated patients has not been well-quantified.

The OCTAVE study

The Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) study was designed to evaluate the efficacy and safety of omapatrilat relative to the ACE inhibitor, enalapril, in a broad range of patients with hypertension. The study was designed to simulate clinical practice; investigators were directed to increase study drug dose and/or use adjunctive therapies to achieve the common target blood pressure goal (<140/< 90 mm Hg). The study involved 3298 sites in 12 countries, recruiting 25,267 patients over 5 months.

The primary *efficacy* endpoints were:

- the change in SBP from baseline to week 8
- the need for new adjunctive therapy during a 24-week treatment period.

The primary *safety* endpoints were:

- the incidence of adverse events
- the incidence and severity of angioedema.

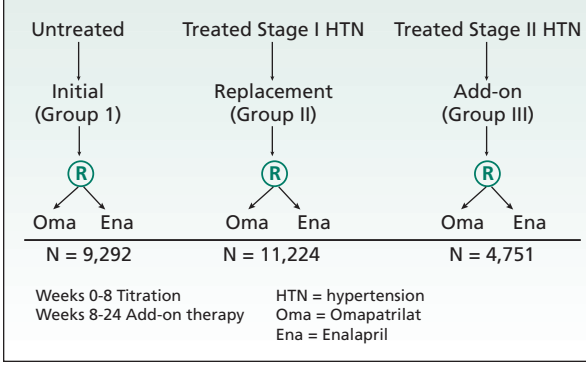
Evaluation of angioedema was based on prospectively collected data on all potential cases, including head/neck swelling. Importantly, an expert committee that was blinded to the randomizations, adjudicated potential cases.

Study design

The principal inclusion criteria were age >18 years, SBP ≥140 mm Hg or DBP ≥90 mm Hg. The principal exclusion criteria were Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VI) Stage III hypertension despite therapy and contraindication to ACE inhibitor therapy. To capture a wide range of patients and to simulate clinical practice, there were three study groups (summarized in Figure 1).

Group I – Previously untreated hypertensive patients were initiated on either omapatrilat or enalapril in a randomized fashion.

Figure 1: Study groups in the OCTAVE study



Group II – Previously treated patients with Stage I hypertension had their medications replaced with the study medications.
Group III – Treated patients with Stage II hypertension received randomized therapy as add-on therapy.

The treatment-to-target design is summarized in Figure 2. After randomization, the study drugs were up-titrated to achieve target blood pressure at week 8, adjunctive therapy was added from week 8 to 24, if required, in order to reach a common blood pressure (<140/<90 mm Hg) target.

Baseline demographics

The two treatment groups (omapatrilat n = 12,668, enalapril n = 12,634) were comparable in baseline demographics. The mean age was 57 years, 52% were males, 89% were white, and 10% (over 2500 patients) were black. Subjects enrolled in the study had concomitant disease, including:

- diabetes mellitus (n = 3377)
- hypercholesterolemia (n = 7980)
- severe hypertension (> Stage III or Stage II on treatment) (n = 7454)
- isolated systolic hypertension (N = 1364)
- atherosclerotic disease (MI, angina, cerebrovascular accident) (n = 2283)
- renal disease (n = 209)

The number of patients and degree of hypertension in Group I (untreated patients):

- 4300 (46.3%) had Stage I (140-159/90-99 mm Hg)
- 3960 (42.6%) had Stage II (160-179/100-109 mm Hg)
- 1015 (10.9%) subjects had Stage III (>180/>110 mm Hg)

Baseline blood pressures were:

- 156/96 mm Hg in Group I
- 150/91 mm Hg in Group II
- 166/97 mm Hg in Group III.

For Group II and III patients:

- 64% and 50%, respectively, were on 1 drug
- 28% and 35%, respectively, were on 2 drugs
- 8% and 15%, respectively were on ≥ 3 drugs.

Figure 2: Design of treatment-to-target with titration and use of adjunctive therapy

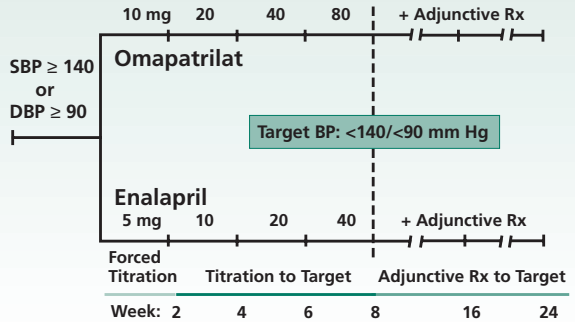
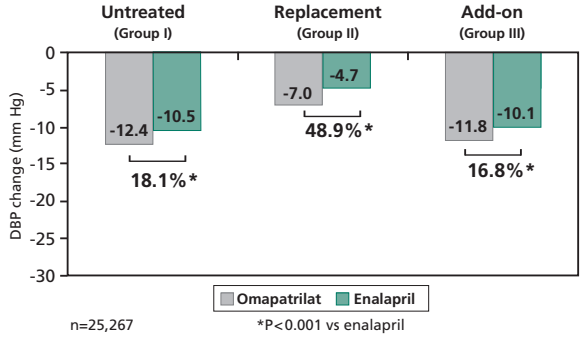


Figure 3: DBP changes at week 8



Study results

The results presented at these two meetings are not yet published and may therefore be subject to modification. Results of the first primary efficacy endpoint, changes in blood pressure from monotherapy at week 8, are shown in Figures 3 and 4. As shown in Figure 3, for all 3 study groups, the reductions in DBP at week 8 were significantly greater in omapatrilat-treated subjects compared to enalapril-treated subjects. Changes in SBP in Group I, II, and III are depicted on the left side of Figure 4. As in DBP, the magnitude of decline in SBP was also significantly greater in the omapatrilat-treated subjects in all 3 study groups. As shown on the right side of Figure 4, the percentage of patients that required the top dose of study drug was smaller in the omapatrilat-treated patients. Furthermore, for all study groups, the percentage of patients that achieved target blood pressure control was greater in the omapatrilat-treated than in enalapril-treated patients.

Changes in SBP at week 8 in Group II according to the types of antihypertensive therapy at baseline prior to replacement with study medications are shown in Figure 5. The magnitude of decline in SBP was significantly greater (p < 0.001) in omapatrilat-

Figure 4: SBP changes at week 8 and % patients requiring top dose

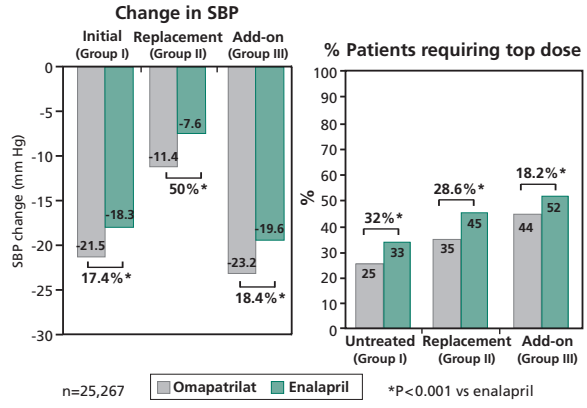
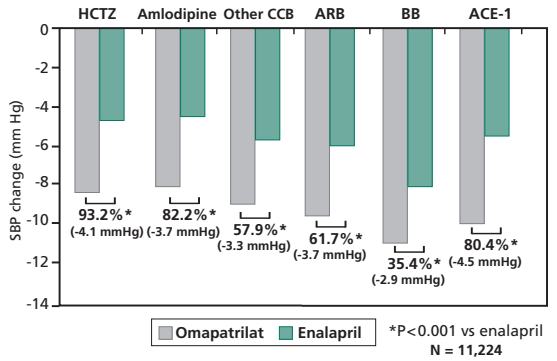


Figure 5: Change in SBP at week 8 (Replacement – Group II)



treated patients regardless of the types of therapy the study drug replaced.

Results of the second primary efficacy endpoint, the comparison of patients requiring adjunctive therapy for the 3 study groups are shown in Figure 6. OCTAVE was designed with the view that both the enalapril and omapatrilat groups would achieve equivalent BP goals. However, the percentage of patients requiring adjunctive therapy was significantly less in omapatrilat-treated patients. Furthermore, even though there was increased use of adjunctive therapy, as well as higher dosing in the enalapril group, SBP was reduced to a greater extent in omapatrilat-treated patients at week 24.

At both week 8 and week 24, the decline in SBP was greater in the omapatrilat-treated than in the enalapril-treated patients regardless whether the patients were white or black. The differences (enalapril versus omapatrilat) in the mean decline in SBP at week 8 were -5.2 mm Hg versus -3.5 mm Hg for blacks and whites respectively, and at week 24 were -3.9 mm Hg versus -3.2 mm Hg for blacks and

Figure 6: SBP changes at week 24 and % of patients requiring adjunctive therapy

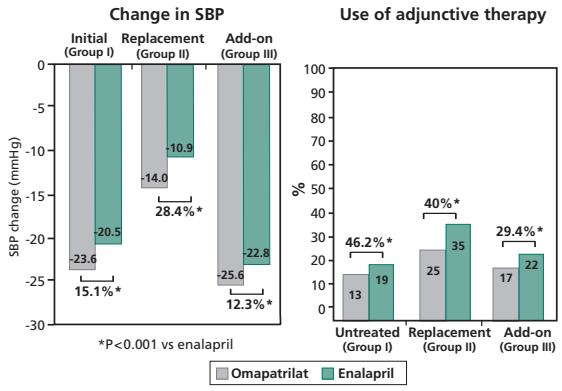
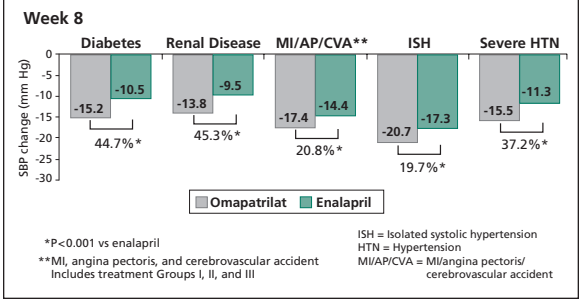


Figure 7: OCTAVE: Change in SBP by clinical subgroups



whites respectively. Likewise, the superior effects of omapatrilat over enalapril at 8 weeks were seen in all pre-specified subgroups (Figure 7), namely, patients with diabetes (difference in the mean decline in SBP, enalapril versus omapatrilat, -4.7 mm Hg), renal diseases (-4.3 mm Hg), history of MI, angina and cerebrovascular accidents (-3.0 mm Hg), isolated systolic hypertension (-3.4 mm Hg), and severe hypertension (-4.2 mm Hg). Similar differences in the same subgroups were seen at week 24.

Results of two safety outcomes, the proportion of subjects with adverse events and the incidence of the most common adverse events are shown in Tables 1 and 2, respectively. Omapatrilat- and enalapril-treated subjects experienced a similar incidence of adverse effects and commonly reported adverse effects, with the exception of flushing, which was more common in omapatrilat-treated subjects, and headaches, which were more common in enalapril-treated patients. As mentioned earlier, angioedema was looked for rigorously. This potentially serious side-effect was classified by severity, depending on whether treatment was required and whether there was airway compromise. As shown in Table 3, the incidence of angioedema of all severities was low for both omapatrilat- and enalapril-treated patients, with a slight excess in omapatrilat-treated subjects. Of the two cases with airway compromise, one was a white patient who presented with swelling of eyelids, lips, and neck, but not the oropharynx and with rapid onset of dyspnea. The patient rapidly responded to epinephrine and was discharged from the hospital the same day. The second case was a black patient who presented with swelling of face, tongue, and oropharynx that progressed to airway obstruction after 3 hours. This patient required epinephrine, steroids, and airway support; the patient recovered and was extubated in 5 days. The overall incidence of angioedema was 2.17% in the omapatrilat-treated group and 0.68% in the enalapril-treated group. The incidence of angioedema according to pre-specified subgroups (ie, non-blacks versus blacks and non-smokers versus current smokers) are shown in Table 4. In both the enalapril- and omapatrilat-treated

Table 1: Proportion of subjects with adverse events (excluding angioedema)

	Omapatrilat (n=12,609)	Enalapril (n=12,557)
Adverse events	51.0%	50.4%
Serious adverse events	3.5%	3.7%
Death	0.15%	0.18%
Discontinuation due to adverse event	8.0%	7.6%

Table 2: Most common adverse events (>3%)

Event	Omapatrilat (% subjects)	Enalapril (% subjects)
Cough	8.7	8.8
Headache	7.4	8.9
Dizziness	6.8	6.9
Upper respiratory tract infection	6.8	6.9
Musculoskeletal pain	5.2	5.5
Sinus abnormality	3.2	3.3
Nausea/vomiting	3.1	3.0
Fatigue	3.0	3.0
Flushing	2.3	1.3

patients, the risk for angioedema was significantly higher in black subjects and current smokers. The incidence of angioedema over time is shown in Table 5. In the omapatrilat group, the incidence was highest on the first day of exposure, but could be present at any time.

Although OCTAVE was not designed to examine clinical outcomes, data for CV events were available for the 24-week follow-up. The cumulative incidence of CV events (CV deaths, MI, and stroke) is shown in Figure 8. As expected, the event rate over the short follow-up period was low for the entire study group. At the end of follow-up, the event rate was lower in the omapatrilat-treated than enalapril-treated patients (absolute difference of 1.5%).

Table 3: Incidence of angioedema based on severity

	Omapatrilat (n=12,609)	Enalapril (n=12,557)	Absolute difference
No treatment, or treated with antihistamines only	162 (1.28%)	65 (0.52%)	0.76%
Treated with epinephrine or steroids; no airway compromise	110 (0.87%)	21 (0.17%)	0.71%
Airway compromise			
• Treatment with epinephrine	1	0	–
• Mechanical airway protection	1	0	–
TOTAL	274	86	–

Table 4: Incidence of angioedema by subgroups

	Incidence	Relative risk 95% CI
Non-black		
Omapatrilat (n=11309)	1.79%	
Enalapril (n=11320)	0.58%	
Black		
Omapatrilat (n=1300)	5.54%	2.96 (2.22,3.93)
Enalapril (n=1237)	1.62%	2.71 (1.61,4.57)
Non-smokers		
Omapatrilat (n=10308)	1.79%	
Enalapril (n=10277)	0.66%	
Smokers		
Omapatrilat (n=2264)	3.93%	2.58 (1.92,3.46)
Enalapril (n=2233)	0.81%	1.48 (0.83,2.64)

Discussion

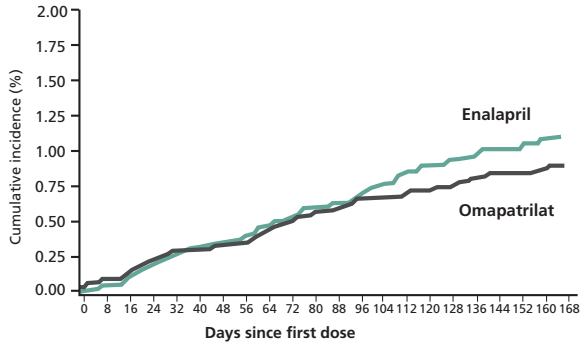
The OCTAVE study provides novel and comprehensive information regarding the effectiveness and safety of the VPI, omapatrilat, relative to an ACE inhibitor, enalapril, in a broad spectrum of patients with hypertension. OCTAVE was designed so that both the enalapril group and the omapatrilat group would achieve equivalent BP goals. In the end, omapatrilat produced significantly greater SBP and DBP reductions, as well as significantly higher BP control rates. This was achieved despite significantly increased use of adjunctive therapies and significantly higher dosing in the enalapril group. Whether omapatrilat was used as monotherapy or in combination with other anti-hypertensive agents, its superior effect on SBP and DBP is consistently observed across all patient subgroups, as an initial therapy, replacement therapy, or add-on therapy.

It is unclear at this point whether the superior blood pressure reduction produced by omapatrilat will translate into improved clinical outcome. A recent meta-analysis of 9 randomized trials using meta regression to compare treatments of "old" and "new" agents in 62,605 hypertensive

Table 5: Incidence of angioedema over time

	Omapatrilat (n=12,609)	Enalapril (n=12,557)
Overall*	2.17%	0.68%
Day 1	0.70%	0.02%
Day 2-Week 4	0.66%	0.34%
Weeks 5-8	0.38%	0.19%
Weeks 9-12	0.23%	0.03%
Weeks 13-16	0.13%	0.06%
Weeks 17-20	0.09%	0.04%
Weeks 21-24	0.10%	0.04%

Figure 8: Cumulative incidence of cardiovascular endpoints



patients, has demonstrated that even a 2-3 mm Hg decline in SBP may have an important favourable impact on CV mortality.[4] In this regard, it is useful to note that the difference in SBP reduction between omapatrilat- and enalapril-treated patients in the OCTAVE study has consistently exceeded the 2-3 mm Hg range. This suggests that patients treated with VPI may derive additional CV protection over patients treated with ACE inhibitors, just based on better lowering of SBP alone and not considering other ancillary properties of VPI.

In OCTAVE, the CV event rate of omapatrilat-treated patients was slightly lower than that of enalapril-treated patients, even though the follow-up was short and the Kaplan-Meier curves should be interpreted with caution.

With regard to safety, omapatrilat has the same safety profile as the ACEI, enalapril, with the exception that the incidence of angioedema broadly, but rigorously defined is slightly higher in the omapatrilat-treated patients. However, the incidence of angioedema that requires treatment is still very low and airway compromise is very rare. The risk of angioedema with omapatrilat is highest on the first day, and decreases thereafter, although it may occur at any time. Risk factors for the development of angioedema are black race (for both omapatrilat and enalapril) and current smoking (for omapatrilat).

In summary, the VPIs constitute a promising class of agents for the treatment of hypertension. Results of the OCTAVE study demonstrate that omapatrilat has a very favourable efficacy/safety ratio in a broad spectrum of patients with hypertension.

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SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Bristol-Myers Squibb Inc. to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.