A Canadian context for the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) trial

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Congestive heart failure comprises a major public health problem destined to grow enormously over the next decade. Paradoxically, and in contrast to acute coronary disease, acute heart failure has been relatively understudied. Current standards of care involve the use of intravenous diuretics and vasodilators; inotropic agents have been restricted to in-hospital use because of concern about their potential harmful effects. The emergence of recombinant human B-type natriuretic peptide (BNP) provides an interesting therapeutic alternative because of its capacity to promote vasodilation as well as increase salt and water excretion, and improve pulmonary congestion by reducing left ventricular filling pressure. This agent will be explored in the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF), the largest ever trial conducted in acute decompensated heart failure. Patients will be studied through day 30 with end points of all-cause mortality in rehospitalization as the primary composite outcome. A variety of mechanistic substudies are planned as well as an assessment of the health care economic implications of acute heart failure and the pathophysiological elements hypothesized to modulate the expected treatment effect examined. The trial is embedded in an academic research organization motif and promises to provide a significant contribution to the body of knowledge in acute heart failure and the care of patients so afflicted.

Key Words: *Clinical trial; Heart failure; Nesiritide*

Congestive cardiac failure comprises a major public health problem that appears destined to grow substantially over the next decade. This entity is the unhappy, but logical final path for a diverse group of cardiovascular conditions dominated by ischemic heart disease and hypertension, but also populated by valvular and cardiomyopathic disorders. It constitutes a major cause of morbidity and mortality, which in its acute form is associated with an annualized mortality of at least 21% and a high rehospitalization rate (1,2). Accordingly, heart failure accounts for not only a large burden to the health care system, but also one that has major economic repercussions; it is now the single largest expense for Medicare in the United States (3). The projected increase in heart failure morbidity, hospitalization and mortality represents a near exponential curve based on the success of contemporary medical therapy and the increased age of the population.

Somewhat paradoxically, and in contrast to acute coronary disease, acute heart failure has been relatively understudied. The current standard therapies of intravenous diuretics and vasodilators have been in use for many years. Whereas inotropic agents were commonly used intravenously as a logical therapeutic additive, their potential to

L'essai *Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure* : contexte canadien

L'insuffisance cardiaque congestive constitue un problème important de santé publique et elle devrait gagner énormément de terrain au cours de la prochaine décennie. Paradoxalement, et contrairement à la maladie coronarienne aiguë, l'insuffisance cardiaque aiguë a fait l'objet de relativement peu d'études. Les normes actuelles de soins prévoient l'administration intraveineuse de diurétiques et de vasodilatateurs; cependant, l'emploi d'inotropes est limité au milieu hospitalier en raison de possibles effets dangereux. L'arrivée du peptide B natriurétique humain, recombiné offre un nouveau traitement intéressant en raison de sa capacité à favoriser la vasodilatation ainsi que l'excrétion d'eau et de sel, en plus de soulager la congestion pulmonaire en diminuant la pression de remplissage du ventricule gauche. Le médicament fera l'objet d'analyse dans l'essai *Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure* (ASCEND-HF), essai le plus important jamais réalisé dans le domaine de l'insuffisance cardiaque aiguë décompensée. Des données sur les patients seront accumulées jusqu'au 30^e jour, et différents paramètres liés à la mortalité toutes causes confondues en cours de réhospitalisation constitueront le principal critère d'évaluation composé. Plusieurs sous-études mécanistes sont prévues ainsi qu'une évaluation des répercussions économiques de l'insuffisance cardiaque aiguë sur les soins de santé, et des éléments physiopathologiques hypothétiques visant à moduler l'effet thérapeutique prévu, soumis à l'examen. L'essai est intégré dans un réseau d'organismes de recherche universitaire et il devrait enrichir de façon substantielle le bagage actuel de connaissances sur l'insuffisance cardiaque aiguë et les soins aux patients touchés.

induce ventricular arrhythmias and augment mortality has largely restricted their use to in-hospital and dire circumstances.

Hence, the emergence of recombinant human BNP – which, in its wild-type motif is secreted by the heart in response to increased wall tension – represents a novel and potentially important advance in the care of patients with acute heart failure (4). Because BNP promotes vasodilation, increases salt and water excretion, and improves left ventricular diastolic filling properties, it has the capacity to reduce pulmonary congestion with resultant symptomatic relief.

As is often the case with the emergence of new and potentially exciting pharmaceuticals that fill unmet needs, when synthetic recombinant human BNP (nesiritide) became available for use in patients with acute heart failure in the United States, its application was quickly taken up and extended beyond the labelled indication, ie, for inpatient acute heart failure.

Subsequent review of both published and Food and Drug Administration-sponsored documentation raised questions about harmful side effects of nesiritide, including renal dysfunction and increased mortality in patients with acute decompensated heart failure (5,6). In

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response to these concerns, the manufacturer of nesiritide (Natrecor, Scios Pharmaceuticals, USA) commissioned an independent external review committee chaired by Dr Eugene Braunwald to evaluate the merits of these concerns. The panel provided clear guidelines regarding how the drug should be used in clinical practice to conform with the approved Food and Drug Administration label, and perceived that current data were inconclusive as they related to a mortality effect. Furthermore, they recommended additional studies to clarify the mechanism and reversibility of the renal effects of the drug (7).

Accordingly, an academic Executive and Steering Committee was recruited under the Chairmanship of Dr Robert Califf from Duke University (Durham, North Carolina, USA) and the trial management was delegated to the operational academic research organization arms emanating from the study leadership by the sponsor (see Appendix). Primary outcome measures of the ASCEND-HF trial include rehospitalization due to heart failure and all-cause mortality from randomization through day 30 and dyspnea symptoms measured by a self-assessed Likert scale at 6 h and 24 h after initiation of study drug (8). Secondary outcome measures include overall well-being that is self-assessed and number of days alive in and outside of hospital from randomization through day 30.

Eligible patients must be admitted to hospital with dyspnea at rest or with minimal activity and exhibit either tachypnea (greater than 20 breaths/min) or pulmonary congestion evident over at least one-third of the lung bases. Additional objective evidence will be required by one or more of the following: chest x-ray exhibiting pulmonary congestion; BNP or anti-pro-BNP elevation of 400 pg/mL or greater or 1000 pg/mL or greater, respectively; pulmonary capillary wedge pressure greater than 20 mmHg; or left ventricular ejection fraction of less than 40%. Nesiritide or placebo added to best standard care will be evaluated. Nesiritide will be administered at a dose of 0.01 µg/kg/min with or without a 2 µg/kg initial bolus and the infusion administered for at least 24 h and up to seven days. ASCEND-HF aims to enroll approximately 7000 patients in approximately 29 countries including 600 centres (of which 40 are expected to be Canadian). The study will be monitored externally by an independent Data and Safety Monitoring Board to ensure appropriate progress and the safety of enrolled subjects and an independent clinical events committee will adjudicate key end point events including death and rehospitalization. As the largest trial ever conducted in acute decompensated heart failure, ASCEND-HF is likely to provide a new standard of care and an understanding of this important clinical entity. Additional studies to be conducted in the ASCEND-HF protocol include pharmacogenomics to provide insight into genes relevant to any treatment effect of nesiritide or the occurrence of acute decompensated heart failure. Mechanistic substudies of myocardial structure and function are planned using magnetic resonance imaging, and an assessment of the health care economic implications of acute heart failure and any treatment effect will be examined.

In addition to the anticipated important contribution of Canada to the overall ASCEND-HF study, members of the Executive Committee (PW Armstrong, JL Rouleau and other Canadians on the Steering Committee – J Ezekowitz, J Howlett and S Lepage – will be collaborating with a subsidiary of Scios Pharmaceuticals in Canada (Ortho Biotech) to perform some Canada-specific subsidiary research aimed at enhancing our overall understanding of the trial and its implications for this important group of patients. These include the following:

1. A registry to describe patients with heart failure, either not screened or screened but eligible for ASCEND-HF, in participating institutions so as to enhance the generalizability of the subsequent result. We anticipate an overall enrollment of approximately 400 Canadian patients in ASCEND-HF and will conduct a comprehensive registry for at least one month in each participating centre after a stable enrollment period has been achieved to assess the overall incidence of acute decompensated heart failure.

2. We will undertake measurements of peak expiratory flow at baseline and intermittently over the subsequent 24 h in 200 patients to evaluate the effects of nesiritide on peak expiratory flow and establish the relationship between patients' own symptomatic assessment of dyspnea and that of the corresponding quantitative measurement.
3. An economic evaluation of Canadian patients in ASCEND-HF will involve two major components:
 - a) A cost saving per patient analysis if nesiritide is the dominant strategy, or an incremental cost per primary composite end point avoided if nesiritide is not dominant.
 - b) We will estimate the long-term cost-effectiveness of the treatment strategy in nesiritide compared with placebo.
4. Because of previous evidence suggesting seasonal variation in presentation and outcome of acute heart failure, we will undertake a full assessment of all ASCEND-HF patients in the 29 countries participating to establish variations in outcomes of mortality and rehospitalization associated with season, time of day, temperature, wind speed, humidity, barometric pressure, altitude and environmental pollution. These data are now available through the Internet and national weather service surveillance systems and are expected to provide unique insights that may ultimately be helpful and lead to proactive preventive measures to circumvent some of the negative outcomes of acute decompensated heart failure.

In summary, the ASCEND-HF trial addresses a fundamentally important element of the cardiovascular epidemic, namely the final common pathway of heart failure and the nefarious implications of its morbidity and mortality. The trial organization is embedded in academic research organizations with appropriate transparency and ongoing evaluation to ensure patient safety. In addition to addressing a major public health issue, it will provide novel information about the epidemiology, pathophysiology, pharmacogenetics and health care costs and as such, is positioned to provide a significant contribution to the body of knowledge in heart failure and the care of the patients afflicted with it.

DISCLOSURE: Dr Paul Armstrong has received research grants from Scios Pharmaceuticals, and research grants and honoraria from Ortho Biotech. Dr Rouleau has received honoraria from Scios. He is a consultant and has given lectures for Novartis and Pfizer.

APPENDIX

ASCEND-HF Executive Committee

- Study Chair – Rob Califf
- Co-Principal Investigators – Chris O'Connor, Randy Starling
- Executive committee – Paul Armstrong, Henry Dargie, Kenneth Dickstein, Michel Komajda, Barry Massie, Markku Nieminen, Brian Gibler, John McMurray, Jean Rouleau, Karl Swedberg

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