N-Terminal Pro–B-Type Natriuretic Peptide Testing Improves the Management of Patients With Suspected Acute Heart Failure

Primary Results of the Canadian Prospective Randomized Multicenter IMPROVE-CHF Study

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Background—The diagnostic utility of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in heart failure has been documented. However, most of the data were derived from countries with high healthcare resource use, and randomized evidence for utility of NT-proBNP was lacking.

Methods and Results—We tested the hypothesis that NT-proBNP testing improves the management of patients presenting with dyspnea to emergency departments in Canada by prospectively comparing the clinical and economic impact of a randomized management strategy either guided by NT-proBNP results or without knowledge of NT-proBNP concentrations. Five hundred patients presenting with dyspnea to 7 emergency departments were studied. The median NT-proBNP level among the 230 subjects with a final diagnosis of heart failure was 3697 compared with 212 pg/mL in those without heart failure ($P<0.00001$). Knowledge of NT-proBNP results reduced the duration of ED visit by 21% (6.3 to 5.6 hours; $P=0.031$), the number of patients rehospitalized over 60 days by 35% (51 to 33; $P=0.046$), and direct medical costs of all ED visits, hospitalizations, and subsequent outpatient services (US $6129 to US $5180 per patient; $P=0.023$) over 60 days from enrollment. Adding NT-proBNP to clinical judgment enhanced the accuracy of a diagnosis; the area under the receiver-operating characteristic curve increased from 0.83 to 0.90 ($P<0.00001$).

Conclusions—In a universal health coverage system mandating judicious use of healthcare resources, inclusion of NT-proBNP testing improves the management of patients presenting to emergency departments with dyspnea through improved diagnosis, cost savings, and improvement in selected outcomes. **(*Circulation*. 2007;115:3103-3110.)**

Key Words: costs and cost analysis ■ healthcare economics and organizations ■ heart failure ■ natriuretic peptides

Acute heart failure (HF) has emerged as a public health problem worldwide. In the United States, hospitalizations for HF increased from 377 000 in 1979 to 1 093 000 in 2003.[1,2] In Canada, a country with universal health insurance,[3] patients admitted with acute HF experience high in-hospital and 1-year mortality[4–7] and have frequent hospital readmissions.[4,7] The total annual cost of managing HF is estimated to be between $1.4 and $2.3 billion,[8,9] underscoring potential gaps in care and a need to develop novel strategies to improve patient management.

A potential strategy to improve the management of patients with acute HF involves the use of biomarkers with demonstrated incremental value in diagnosis that would result in improved therapeutic decisions and cost savings. Among the cardiac biomarkers, the natriuretic peptides, namely B-type natriuretic peptide (BNP) and the amino-terminal fragment of the precursor protein (NT-proBNP), have been shown to be useful in establishing the diagnosis of acute HF and providing short-term prognostic information in patients presenting to urgent care settings with dyspnea.[10–18] However, previous trials, particularly those of NT-proBNP, involved a relatively small number of patients,[10,14] were conducted in single centers,[10,12,14] or were not randomized in design.[15] Further-

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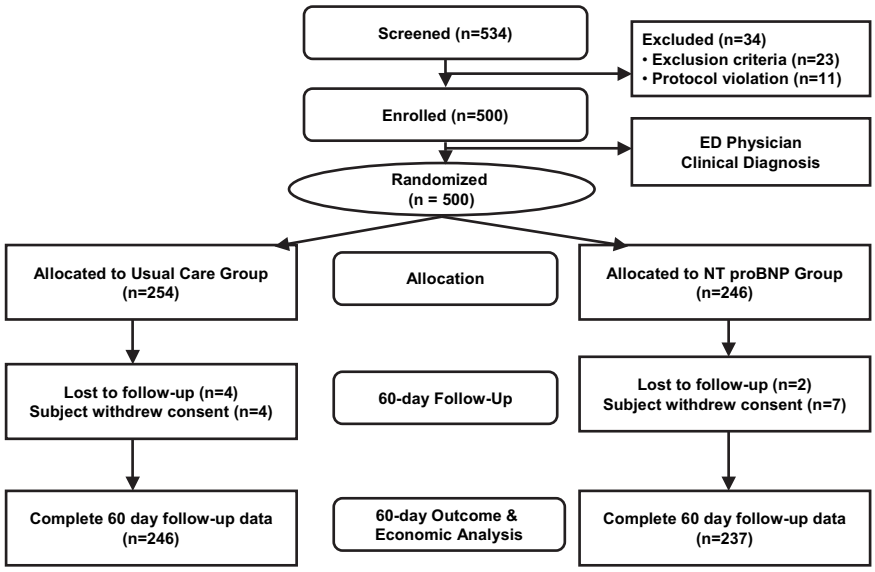


Figure 1. Flow diagram for the enrollment, intervention allocation, follow-up, and data analysis.

more, the larger-scale studies of BNP and NT-proBNP were conducted in centers in the United States,[12,15] where per capita healthcare spending is about twice that of Canada.[3] These published data, although important, are not necessarily applicable to Canada or other countries with publicly funded universal healthcare coverage systems that mandate judicious allocation of health resources.[3] Although natriuretic peptide testing is proposed to be cost-effective for the evaluation and management of patients with dyspnea,[18–20] no data exist that are based on practice patterns endorsed by universal coverage systems. Accordingly, the overall objective of our prospective, randomized, controlled multicenter trial was to test the hypothesis that a strategy that included knowledge of NT-proBNP results would improve the management of patients with suspected acute HF in Canada. The specific objectives were to evaluate whether NT-proBNP added incremental value to clinical judgment in diagnosing acute HF and whether a management strategy that incorporated knowledge of NT-proBNP results would lead to cost-savings without compromising clinical outcomes compared with conventional care.

Methods

Setting

The Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) study was a randomized, controlled, double-blind, prospective multicenter study conducted in Canada. Institutional review boards of all participating sites approved the study, which was conducted according to the principles of the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines. All patients provided written informed consent before study entry.

Study Sample

A total of 534 subjects >18 years of age presenting to the emergency departments (EDs) from 7 participating sites with dyspnea of suspected cardiac origin were screened from December 2004 to December 2005. Thirty-four subjects were excluded from the study on the basis of either protocol violation or not fulfilling protocol inclusion/exclusion criteria. Exclusion criteria were advanced renal failure (serum creatinine >250 μmol/L), acute myocardial infarction, malignant disorders, and dyspnea from clinically overt origins, including pneumothorax and chest wall trauma.

Study Protocol and Data Collection

The overall study design and protocol are displayed in Figure 1. Patients were screened consecutively from the participating sites. After enrollment, baseline demographics, medical history, and clinical signs were documented, along with standard diagnostic tests such as ECG, chest x-ray, and standard blood tests. A separate blood sample was collected for NT-proBNP measurement. Open-label BNP or NT-proBNP measurements were not used at any time during the study. At the end of the clinical evaluation and with knowledge of the results of standard diagnostic tests except for NT-proBNP, the ED physician was asked to commit to a diagnosis of whether a patient had HF or not and separately to estimate on a scale of 0% to 100% the likelihood that acute HF was the cause of dyspnea. Afterward, patients were randomly assigned to 2 groups based on management strategies that involved only conventional measures (the usual care group) or conventional measures plus knowledge of NT-proBNP results (the NT-proBNP group). A randomization schedule was generated in each center in blocks of 4 patients by sealed envelope accessible only by the research coordinator. The schedule linked sequential numbers to treatment codes allocated at random and was prepared on a 1:1 basis. Details of the treatment codes were unknown to anyone except the staff who assigned the patient to one of the diagnostic arms in a consecutive manner. The results of NT-proBNP were made available only to the ED and other physicians who managed the patients in the NT-proBNP group and were provided immediately after randomization. These physicians were provided with information to interpret the NT-proBNP results based initially on data supplied by the manufacturer of the assay and later on information derived from the N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study when the primary results from the present study were published.[12] In hospitalized patients, NT-proBNP measurements also were obtained 72 hours after admission to provide predischarge NT-proBNP values to further guide subsequent management.

Confirmation of Diagnosis

For adjudication, 2 cardiologists were provided with hospital records, including the discharge summary, results of laboratory and radiographic testing, echocardiograms if performed, clinical notes from the time of ED presentation to the 60-day follow-up, and outcome of the telephone interview. Using all available data, the cardiologists assigned a diagnosis without knowledge of the NT-proBNP results. Patients were classified by diagnosis at presentation

into 1 of 3 categories: acute HF, not HF in a patient who had previous HF and/or left ventricular dysfunction, or no incident or prevalent HF.

NT-proBNP Assays

NT-proBNP analysis was performed with the commercially available immunoassay using the Elecsys 1010, 2010, or E170 proBNP assay (Roche Diagnostics GmbH, Manheim, Germany). Details of the assays, including cross-reactivity and coefficients of variation, have previously been reported.[12,21]

Cost Analysis

The total direct medical costs, including the costs of the NT-proBNP test at the initial ED visits, initial and subsequent ED visits, hospitalizations, physician fees, and outpatient services, were calculated. The frequencies of ED visits and hospitalizations were collected from hospital chart records, and those of outpatient services were estimated from the 60-day patient telephone interviews and chart records. The total costs were calculated by multiplying the frequencies by the unit costs. All costs were translated into 2005 Canadian dollars using the Consumer Price Index healthcare component for Canada and converted into 2005 US dollars using the Bank of Canada annual exchange rate for 2005 (1.21163).[22] Economic analysis was conducted from the perspective of third-party payers with an analytic horizon of 60 days.[23,24] Time to discharge from the ED between the patient's arrival and clinical decision by an ED physician regarding patient disposition was calculated. The costs of the ED visits were based on the ED hospital budget records of 496 reporting hospitals using the Canadian Institute of Health Information Database, the national data source for financial and statistical information. Standard Canadian Institute of Health Information costing methodology was used to calculate hospital costs.[25] Briefly, the medical records of 2.4 million patient records of all discharges from hospitals were categorized annually by the Canadian Institute of Health Information into case-mix groups. Each case-mix group was assigned a relative intensity weight, further divided into 4 complexity levels and 3 age groups,[25] and then translated into costs. Physician fees and costs of outpatient diagnostic and laboratory services were estimated using the average reimbursement fees

TABLE 1. Baseline Demographic and Clinical Characteristics of the NT-proBNP and Usual Care Groups

Characteristics	NT-proBNP (n=246)	Usual Care (n=254)
Age, mean±SD (range), y	70±15 (20 to 96)	71±14 (20 to 99)
Body mass index, mean±SD (range), kg/m^2	29±8 (17 to 67)	28±7 (10 to 61)
Male, n (%)	122 (50)	136 (54)
White, n (%)	229 (93)	235 (93)
Nonsmoker, n (%)	69 (30)	93 (39)
Medical history, n (%)		
Hypertension	138 (60)	128 (54)
HF/left ventricular dysfunction	81 (35)	90 (38)
Previous myocardial infarction	75 (33)	76 (32)
Chronic obstructive pulmonary disease	67 (29)	78 (33)
Diabetes mellitus	60 (26)	67 (28)
Previous medications, n (%)		
Angiotensin-converting enzyme inhibitors	108 (44)	105 (42)
Oral loop diuretics	100 (41)	97 (38)
Symptoms and signs, n (%)		
Dyspnea at rest	142 (58)	135 (53)
Rales	116 (47)	122 (48)
Orthopnea	114 (47)	114 (45)
Lower-extremity edema	111 (45)	113 (45)
Paroxysmal nocturnal dyspnea	83 (34)	79 (31)
Wheezing	82 (34)	77 (30)
Elevated jugular venous pressure	71 (29)	59 (23)
Vital signs, mean±SD (range)		
Systolic blood pressure, mm Hg	134±25 (60 to 215)	137±27 (83 to 220)
Diastolic blood pressure, mm Hg	78±17 (30 to 170)	78±18 (41 to 192)
Respiratory rate, breaths/min	23±6 (12 to 52)	23±7 (11 to 70)
Heart rate, bpm	86±22 (20 to 157)	87±22 (38 to 170)
Basic diagnostic tests, mean±SD (range)		
Blood urea nitrogen, mmol/L	8±6 (2 to 63)	9±9 (1 to 86)
Hemoglobin, g/L	130±19 (63 to 183)	129±18 (65 to 183)
Serum sodium, mmol/L	139±4 (123 to 154)	138±4 (123 to 153)
Serum creatinine, μmol/L	93±35 (30 to 248)	91±35 (35 to 221)
Estimated glomerular filtration rate, mL · min^{-1} · 1.73 m^{-2}	75±31 (23 to 205)	77±30 (25 to 211)

TABLE 2. Clinical Outcomes in the NT-proBNP and Usual Care Groups

	NT-proBNP (n=246)	Usual Care (n=254)	P*
Duration of ED visit, median (Q1 to Q3), h	5.6 (4.0 to 8.0)	6.3 (4.3 to 8.6)	0.0309†
Duration of ICU stay, median (Q1 to Q3), d	6 (1 to 11)	5.5 (3 to 11)	0.7229†
Initial hospitalization from ED, n (%)	139 (57)	146 (58)	0.8255
Hospital LOS, median (Q1 to Q3), d	6 (4 to 11)	7 (4 to 13)	0.3019†
In-hospital mortality, n (%)	11 (4.5)	6 (2.4)	0.1932
Deaths by 60 d, n (%)‡	13 (5.5)	11 (4.4)	0.5794
Patients rehospitalized by 60 d, n (%)	33 (13)	51 (20)	0.0463

ICU indicates intensive care unit; LOS, length of stay.
*Test of proportions unless otherwise specified.
†Nonparametric analysis (Wilcoxon 2-sample test).
‡Excluding hospital mortality.

from the provinces of Ontario and Quebec,[26,27] representing >60% of healthcare expenditures. The cost of the NT-proBNP test provided in the ED, including operating and capital costs, was estimated to be $37.

Data and Statistical Analyses

Receiver-operating characteristic (ROC) curve analyses were performed for NT-proBNP with the adjudicated diagnosis as the reference standard. ROC curves for NT-proBNP and ED physician–estimated likelihood of HF were plotted. A logistic regression model that contained a combination of NT-proBNP and physician-estimated likelihood was analyzed in predicting the final adjudicated diagnosis. A likelihood-ratio χ^2 test obtained from the logistic regression models was used to assess whether NT-proBNP added incremental value to clinical judgment in predicting HF.

The primary analysis was a comparison of the 2 study groups, with the duration of the initial ED visit and the total direct medical costs of treatment as primary end points. Secondary end points included initial hospital length of stay, in-hospital and 60-day mortality, and rehospitalization. In the sample size calculation, the trial was designed to enroll at least 239 patients in each group, providing a power of 80% to detect a reduction in ED time from 9 to 7.2 hours (20% reduction) with the use of NT-proBNP–guided strategy. Assumptions included the use of a 2-tailed test, a 5% level of significance, and an SD of 7 hours in both groups. All data were analyzed according to the intention-to-treat principle. Comparisons were made with the Student unpaired 2-sided *t* test and the Wilcoxon 2-sample test when the values were not distributed normally. Between-group comparisons of baseline clinical characteristics were performed with χ^2 or Fisher exact test for categorical data and *t* tests or Wilcoxon rank sum tests for continuous data when appropriate. Blood NT-proBNP levels and other data that are not normally distributed are expressed as medians and interquartile range (Q1 to Q3). Comparisons of NT-proBNP values between the diagnostic categories were performed with the Kruskal-Wallis test. All analyses were performed with SAS software version 9.1.3 for Windows (SAS Institute Inc, Cary, NC). A value of $P<0.05$ was considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 534 subjects were screened from December 2004 to December 2005 (Figure 1). Thirty-four subjects were excluded on the basis of either protocol violation or not fulfilling protocol inclusion/exclusion criteria. Therefore, 500 patients were randomized to NT-proBNP–guided management (n=246) or usual care (n=254). All 500 randomized patients had complete data obtained from the ED and the first hospitalization if they were admitted. After the first hospital discharge, 11 patients withdrew consent and did not wish to be followed up long term, and 6 were lost to follow-up. Thus, 483 patients (97%) had 60-day outcome and economic data beyond the ED and/or the first hospitalization.

Baseline Patient Characteristics

Baseline demographic and clinical characteristics of the NT-proBNP and usual care group are shown in Table 1. Both groups had similar characteristics. Patients recruited were mostly elderly with an even gender distribution. More than a third had prior history of HF or left ventricular dysfunction by self-report or medical records. By definition, all patients presented with dyspnea; however, fewer than half of the patients had symptoms and signs that were conventionally associated with HF.

TABLE 3. Direct Medical Costs to 60 Days of Follow-Up in the NT-proBNP and Usual Care Groups

Cost Category	NT-proBNP (n=246)	Usual Care (n=254)	P*
All ED visits, hospitalizations, and outpatient services	5180 (3005 to 8416)	6129 (3384 to 9991)	0.0232
Initial ED visit	1813 (1337 to 2507)	1982 (1385 to 2652)	0.1023
Initial and subsequent ED visits	2342 (1478 to 3460)	2550 (1574 to 4251)	0.0840
Initial hospitalization	3423 (2237 to 5842)	3883 (2237 to 7435)	0.3170
Initial and subsequent hospitalizations	4062 (2285 to 6904)	4889 (2661 to 8389)	0.0731
Initial ED visits and initial hospitalization	3634 (2132 to 6123)	4008 (2393 to 7667)	0.1052
All ED visits and all hospitalizations	4958 (2679 to 8287)	5853 (2967 to 9809)	0.0159

Data expressed as median (Q1 to Q3) in 2005 US dollars.
*Nonparametric analysis (Wilcoxon 2-sample test).

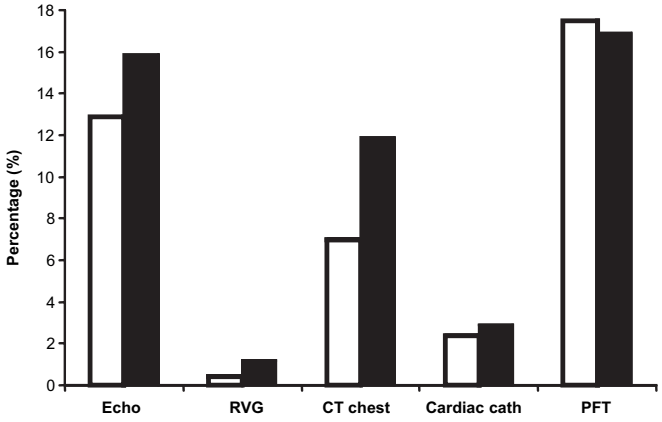


Figure 2. Resource use after the initial patient discharge of diagnostic tests in the 2 study groups, including echocardiography (echo), radionuclide ventriculography (RVG), diagnostic cardiac catheterization (Cardiac cath), and pulmonary function tests (PFT).

Clinical Diagnoses and Decisions

The final diagnoses adjudicated by 2 cardiologists blinded to the results of NT-proBNP were acute HF in 230 subjects (46%), not acute HF in patients with a history of HF and/or left ventricular dysfunction in 45 subjects (9%), and not acute HF in patients without prior HF in 225 subjects (45%). For all patients, the mean duration of stay in the ED was 7.2±5.4 hours (mean±SD). Two hundred eighty-five patients (57%) were subsequently admitted to hospital from the ED.

Comparison of Strategies of Usual Care and NT-proBNP–Guided Care

The clinical outcome data for the 2 randomized groups in all 500 patients are shown in Table 2. The median duration of the initial ED visit was 5.6 hours in the NT-proBNP group and 6.3 hours in the usual care group ($P=0.0309$). The differences in initial hospitalizations, the hospital length of stay, the initial intensive care unit admissions and length of stay, and initial and 60-day mortality were not statistically significant. However, a significant reduction in the number of patients rehospitalized by 60 days (13% versus 20%; $P=0.0463$) was observed. Direct medical costs over 60 days of follow-up are shown in Table 3. The use of NT-proBNP tests reduced total direct medical costs to the healthcare system by 15% from $6129 to $5180 ($P=0.0232$). To understand the contribution of outpatient use of diagnostic tests to the overall cost reduction, the proportion of patients who had undergone various advanced diagnostic tests related to the assessment of dyspnea are shown in Figure 2. Overall, the frequency of outpatient use of these diagnostic tests was relatively low, but there was a tendency for less use of echocardiography, radionuclide ventriculography, and computed tomography scan of the chest in the NT-proBNP group. Finally, to understand whether the benefit of knowing NT-proBNP results was derived from patients with an intermediate likelihood of a diagnosis of HF as judged by the ED physicians, the data of clinical outcomes and direct medical costs of the 2 treatment groups were analyzed for the 219 patients with a 20% to 80% likelihood of HF. As shown in Tables 4 and 5, knowledge of NT-proBNP results appears to have a greater impact on the duration of ED visits and the costs of initial and subsequent ED visits in these patients compared with the entire study group.

NT-proBNP Combined With Clinical Judgment in the Diagnosis of HF

Median NT-proBNP level (3697 pg/mL) was significantly greater in patients with a confirmed diagnosis of acute HF than in patients whose dyspnea was not due to HF (212 pg/mL) (Figure 3). ROC curves comparing the sensitivity and specificity of clinical judgment alone, NT-proBNP testing, and the 2 combined are shown in Figure 4. Clinical judgment alone using different levels of certainty generated an area under the curve (AUC) of 0.83 (95% CI, 0.80 to 0.84; $P<0.001$). When clinician assessment of acute HF was expressed as a binary outcome, the sensitivity and specificity were 78% and 81%, respectively.

TABLE 4. Comparison of Clinical Outcomes in the NT-proBNP and Usual Care Groups in Patients With Intermediate Likelihood (20% to 80%) of a Diagnosis of HF Based on ED Physician Assessment

	NT-proBNP (n=105)	Usual Care (n=114)	P*
Duration of ED visit, median (Q1 to Q3), h	5.4 (3.8 to 7.7)	7.5 (4.8 to 9.3)	0.0028†
Duration of ICU stay, median (Q1 to Q3), d	8 (3 to 12)	5.5 (3 to 10)	0.6737†
Initial hospitalization from ED, n (%)	62 (59)	70 (61)	0.7219
Hospital LOS, median (Q1 to Q3), d	6 (4 to 11)	7 (4 to 14)	0.5174†
In-hospital mortality, n (%)	4 (3.8)	3 (2.6)	0.6205
Deaths by 60 d, n (%)‡	5 (5.0)	6 (5.4)	0.8814
Patients rehospitalized by 60 d, n (%)	7 (11.3)	6 (8.6)	0.6008

ICU indicates intensive care unit; LOS, length of stay.
*Test of proportions unless otherwise specified.
†Nonparametric analysis (Wilcoxon 2-sample test).
‡Excluding hospital mortality.

TABLE 5. Comparison of Direct Medical Costs in the NT-proBNP and Usual Care Groups in Patients With Intermediate Likelihood (20% to 80%) of a Diagnosis of HF Based on ED Physician Assessment

Cost Category	NT-proBNP (n=105)	Usual Care (n=114)	P*
All ED visits, hospitalizations, and outpatient services	5243 (3077 to 9176)	6739 (3751 to 10676)	0.1264
Initial ED visit	1759 (1288 to 2420)	2324 (1550 to 2856)	0.0074
Initial and subsequent ED visits	2376 (1388 to 3406)	2730 (1841 to 4357)	0.0183
Initial hospitalization	3930 (2237 to 6742)	4071 (2655 to 8339)	0.6345
Initial and subsequent hospitalizations	4593 (2237 to 8140)	5084 (2826 to 10 238)	0.2156
Initial ED visits and initial hospitalization	3728 (2240 to 6782)	4448 (2595 to 8272)	0.0780
All ED visits and all hospitalizations	5126 (2679 to 8888)	6541 (3484 to 10 556)	0.0836

Data expressed as median (Q1 to Q3) in 2005 US dollars.
*Nonparametric analysis (Wilcoxon 2-sample test).

Adding NT-proBNP results to those of clinical judgment alone significantly improved performance, increasing the AUC to 0.90 (95% CI, 0.90 to 0.93; $P<0.0001$; $P=0.00001$ versus clinical judgment alone). Although not a prespecified analysis, compared with clinical judgment alone, NT-proBNP results had an AUC of 0.86 (95% CI, 0.84 to 0.89; $P<0.001$), which was numerically superior to clinical judgment, but the difference was not statistically significant.

Discussion

Prior studies have suggested the utility of natriuretic peptide testing for the evaluation of patients with dyspnea,[10,12–15,18] with potential cost savings associated with testing of NT-proBNP or BNP for such patients.[19,20] General applicability of these studies to clinical practice, however, is limited by the fact that they were nonrandomized, argued for cost-effectiveness using decision-analytic framework analyses rather than randomized comparisons, or demonstrated cost savings in the context of clinical care delivered in a manner distinct from that of a nationalized healthcare system. Accordingly, ours is the first prospective randomized analysis to definitively address the question of the additive value of natriuretic peptide testing from both a diagnostic and a cost perspective in a universal healthcare system.

The findings of the present study confirm our primary hypothesis that the use of NT-proBNP–guided strategy is superior to a sole conventional clinically guided strategy in the management of patients with suspected acute HF. Our patients were representative of patients assessed at the participating sites. As expected, NT-proBNP levels were higher in patients with an adjudicated diagnosis of HF compared with those without, consistent with previous nonrandomized studies of BNP and NT-proBNP,[12,13,15] and the addition of NT-proBNP testing to clinical judgment provided incremental value to help establish a diagnosis of HF. Interestingly, NT-proBNP testing was not statistically superior to clinical judgment alone, which differed from findings of previous trials.[12,16] The reasons for the smaller AUC of the ROC curve of NT-proBNP testing alone in the present study are unclear but may relate in part to the fact that the present study was a multicenter trial and in part to demographic differences in our patient population. Furthermore, we did not perform age-stratified analyses in this primary report, which, in the PRIDE and International Collaborative of NT-proBNP studies, yielded higher sensitivity and specificity for the "rule-in" cutoffs.[12,13] Our findings therefore strongly support the position adopted by recently published HF consensus guidelines that advocate the use of NT-proBNP as a complement rather than an alternative to clinical assessment.[28]

Although the additive diagnostic value of NT-proBNP is important to define in our healthcare system, the primary study objective was to prospectively evaluate potential cost savings

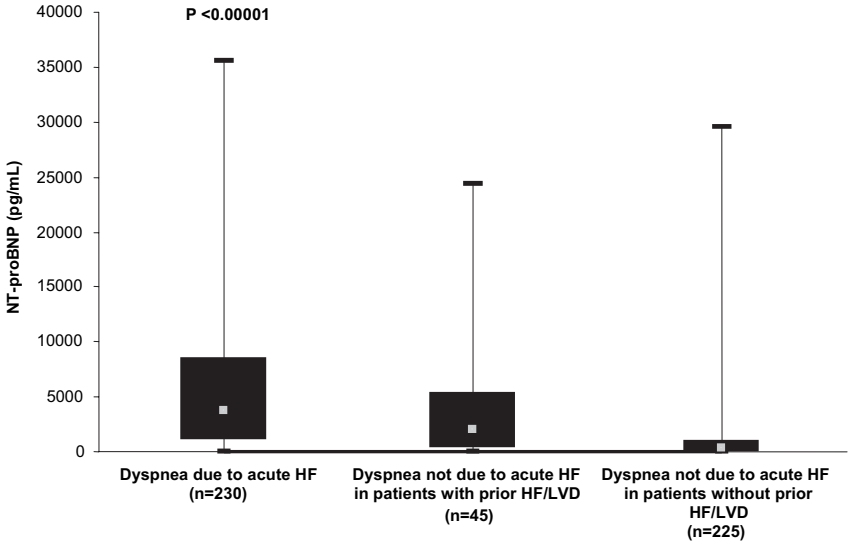
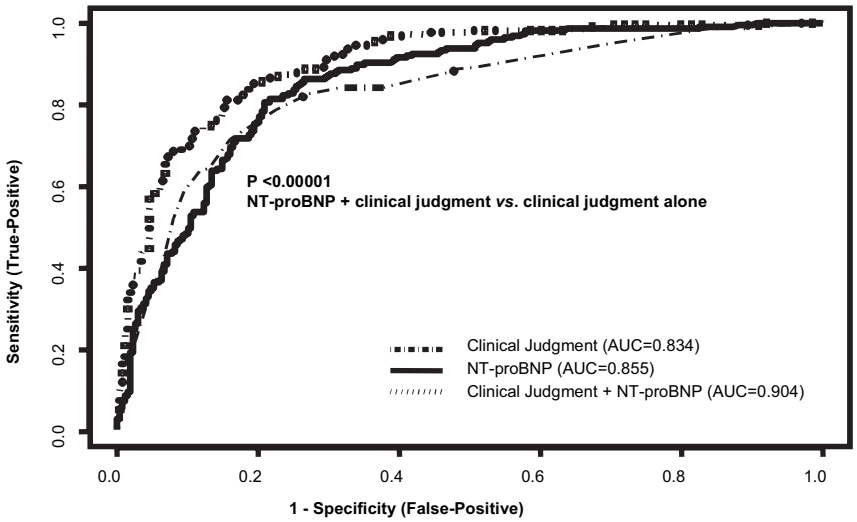


Figure 3. Median NT-proBNP levels among the adjudicated diagnostic categories: dyspnea caused by HF, dyspnea not caused by acutely destabilized HF in patients with prior HF and/or left ventricular dysfunction (LVD), and dyspnea not resulting from incident or prevalent HF. The probability value was derived from the Kruskal-Wallis test. Boxes represent interquartile ranges (Q1 to Q3); whiskers represent maximum and minimum values.



P-value was obtained by comparing two logistic models.

Figure 4. Receiver-operating characteristic curves for ED physi l judgment, NT-proBNP, and combin 13.6ped clinical judgment and NT-proBNP results. The area under the curve for the logistic model combining NT-proBNP and clinical judgment was superior to either component in isolation.

associated with a management strategy that involves knowing NT-proBNP testing. Knowledge of NT-proBNP results reduced the time spent in the ED, the number of patients hospitalized, and the total direct medical costs over the 60-day follow-up. The observation that less expensive tests associated with the investigation of dyspnea were performed in patients from the NT-proBNP group raises the possibility of a contribution of a more careful outpatient use of resources to the overall cost savings demonstrated. Finally, the demonstration that the knowledge of NT-proBNP results appeared to have greater impact on patients with an intermediate probability of a diagnosis of HF suggests that the NT-proBNP–guided strategy should be valuable in this patient subgroup.

The cost savings observed in the present study are consistent with those reported in another randomized trial, the Acute Shortness of Breath Evaluation (BASEL) study,[18] which used the point-of-care BNP assay. In this single-center study, a cost reduction of 25% over 180 days was reported.[19] Cost savings also have been reported recently in a decision model analysis of the PRIDE study.[20] Our health economic findings, the first derived from a randomized multicenter study sample, fit well with those from other healthcare systems and therefore provide a strong rationale for the inclusion of natriuretic peptides testing in the ED.

Several limitations of the present study are worthy of mention. Other than reducing the number of subjects readmitted to the hospital during the first 60 days from evaluation, knowledge of NT-proBNP results did not result in any major improvement in clinical outcomes to 60 days, including lack of statistically significant differences in the initial rate of hospitalization, hospital length of stay, or mortality rates, among those in the NT-proBNP–guided arm. This lack of improvement also was observed in the BASEL study.[18] These findings, however, are not unexpected given that both studies were not powered to assess hard clinical outcomes and follow-up was relatively short. In addition, we point out that, while nonsignificant, the cost and outcome results are all directionally consistent, favoring NT-proBNP–guided evaluation over usual care. The mechanism for the reduced number of patients rehospitalized remains unclear. It is possible that a more confident diagnosis of HF led to use of therapies that favorably affected outcome; alternatively, for those with low NT-proBNP levels, physicians might have diverted more to outpatient instead of inpatient management. Finally, in light of the multiple testing without corresponding adjustment of per-test significance levels, even though our results provide evidence of benefit from NT-proBNP–based evaluation of the dyspneic patient on the primary end point of the present study, interpretation of our results for other end points should be approached with caution. Further studies should evaluate potential reductions in morbidity or mortality and the cost-effectiveness related to natriuretic peptide–guided management of dyspnea.

In summary, the present study shows that, in a universal-access publicly funded healthcare system that mandates judicious resource allocation, a strategy that uses NT-proBNP testing in conjunction with clinical assessment improves the overall management of patients presenting to the ED with suspected acute HF through the facilitation of diagnosis and provides health cost savings that are accompanied by an improvement in selected clinical outcomes.

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CLINICAL PERSPECTIVE

In the Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) study, a prospective, multicenter, randomized trial, we tested the hypothesis that amino-terminal pro–B-type natriuretic peptide (NT-proBNP) testing would improve the management of 500 patients presenting with dyspnea to emergency departments in Canada by prospectively comparing the clinical and economic impact of a management strategy guided by NT-proBNP results. As expected, median NT-proBNP level among the 230 subjects with heart failure was 3697 compared with 212 pg/mL in those without heart failure ($P<0.00001$). Adding NT-proBNP to clinical judgment enhanced the accuracy of the diagnosis; the area under the receiver-operating characteristic curve increased from 0.82 to 0.90 ($P<0.00001$). Knowledge of NT-proBNP results reduced the duration of the emergency department visit (6.3 to 5.6 hours; $P=0.031$), the number of patients rehospitalized (51 to 33; $P=0.046$), and direct medical costs of all emergency department visits, hospitalizations, and subsequent outpatient services (US $6129 to US $5180 per patient; $P=0.023$) within 60 days. Therefore, in Canada, with a universal health coverage system mandating judicious use of healthcare resources, inclusion of NT-proBNP testing improved the management of patients presenting to the emergency department with dyspnea through improved diagnosis, cost savings, and an improvement in selected outcomes.