

N-Terminal Pro-Brain Natriuretic Peptide After Myocardial Infarction A Marker Of Cardio-Renal Function

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Abstract—N-terminal pro-brain natriuretic peptide (NT-proBNP) is increased early after acute myocardial infarction. We assessed the relationship of NT-proBNP with left ventricular function and mass as well as with renal function, hemodynamic, and anthropometric variables in 625 outpatients in the chronic phase after myocardial infarction and 465 siblings without infarction (control). NT-proBNP was measured by nonextracted, enzyme-linked, sandwich immunoassay. NT-proBNP was correlated with left ventricular ejection fraction, mass index, and renal function, in addition to infarction history, gender, and age, in univariate and multivariate analysis (all $P < 0.01$). Increases in NT-proBNP observed in subjects with infarction (96.6 ± 13.7 versus 31.2 ± 1.8 pmol/L in control subjects, $P < 0.001$) were particularly pronounced in the presence of significant left ventricular dysfunction (182.8 ± 41.9 pmol/L), left ventricular hypertrophy (214.5 ± 61.7 pmol/L), and renal dysfunction (210.3 ± 51.4 pmol/L, all $P < 0.01$). Patients with an ejection fraction $< 35\%$ were detected by NT-proBNP with a sensitivity, specificity, and negative predictive value of 75%, 62%, and 99%, respectively, at an optimal cutoff of 44 pmol/L. Patients with an ejection fraction $< 35\%$ and concomitant left ventricular hypertrophy were detected with a sensitivity, specificity, and negative predictive value of 90%, 80%, and 99.9%, respectively, at a cutoff of 76 pmol/L. Similar results were obtained for patients with an ejection fraction $< 35\%$ and concomitant renal dysfunction at a cutoff of 162 pmol/L. NT-proBNP is a biochemical marker of integrated cardio-renal function in the chronic phase after myocardial infarction and a potential diagnostic tool for the detection and exclusion of significant left ventricular dysfunction. Cutoff concentrations have to be chosen according to renal function to optimize the predictive value of NT-proBNP. (*Hypertension*. 2002;39:99-104.)

Key Words: natriuretic peptides ■ myocardial infarction ■ heart failure ■ renal disease

N-terminal pro-brain natriuretic peptide (NT-proBNP [1–76]) represents the N-terminal fragment of proBNP (1–108), the high-molecular-weight precursor of functionally active BNP. The major source of NT-proBNP and BNP is the cardiac myocyte. In these cells, NT-proBNP is cleaved from the precursor and secreted in equimolar amounts, together with BNP. NT-proBNP circulates at considerable concentrations in human plasma, can easily be detected and quantified by immunometric assay,^{1,2} and is stable in whole blood.^{2,3} ProBNP synthesis is activated during mechanic and neurohumoral stimulation of the heart,^{4–7} and the high secretion rate of BNP from hypertrophied and failing ventricles^{8,9} results in a close correlation between BNP and left ventricular (LV) systolic dysfunction^{10–13} and hypertrophy.¹⁴ Recent studies have demonstrated elevated NT-proBNP concentrations in experimental LV dysfunction¹⁵ and after acute myocardial infarction (MI).^{16,17} No

information is currently available regarding the usefulness of NT-proBNP as a biochemical marker of LV dysfunction in outpatients. Furthermore, no other parameters that might affect the association between LV dysfunction and NT-proBNP have been investigated in larger samples. It was therefore our objective to evaluate NT-proBNP as a marker of LV dysfunction in unselected outpatients in the chronic phase after MI under consideration of LV mass and renal function as potential confounding factors. We hypothesized that NT-proBNP might predict or exclude LV dysfunction in these patients and, further, might be importantly modulated by concomitant changes in LV mass as well as altered renal function.

Methods

Study Population

All subjects suffering from premature MI (first MI before the age of 60 years) in the urban and surrounding rural areas of Augsburg,

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Germany, from 1984–1996 were identified through the Augsburg MONICA MI register. The diagnosis of MI was established according to the MONICA diagnostic criteria. MI patients (elapsed time since MI, 1 to 10 years, mean 5.6 years) and their siblings were invited to participate in this study. Subjects were examined in a study center and provided information regarding medication and medical history, including history of heart failure. Blood pressure was measured, and subjects were classified as hypertensive when anti-hypertensive pharmacotherapy was taken, systolic blood pressure was >140 mm Hg, or diastolic blood pressure was >90 mm Hg. Heart failure status was determined as self-assessed heart failure (present, absent, or unknown). Body weight and height were determined and body mass index was calculated as weight divided by the square of height. An echocardiogram was obtained for assessment of LV function and mass, and blood was drawn for biochemical measurements. NT-proBNP measurements were available for 625 subjects with MI and 465 siblings without MI. A complete data set, including measurement of NT-proBNP, echocardiographic assessment of LV function and mass, and assessment of renal function, was available for 594 MI patients and 449 siblings without MI.

Echocardiography

A 2D guided M-mode echocardiogram was performed on each subject by an expert sonographer (Sonos 1500, Hewlett Packard). LV diameters (end diastolic diameter, end systolic diameter) and septal and posterior wall thickness were measured according to the guidelines of the American Society of Echocardiography.¹⁸ LV mass in grams was calculated from M-mode echocardiograms according to the formula described by Devereux et al.¹⁹ LV mass was indexed to body surface area as LV mass index (LVMI) in g/m^2 body surface area. LV hypertrophy by M-mode criteria was considered when LVMI was >2 SD above the mean of the respective control gender group (women >138 g/m^2 , men >145 g/m^2). An additional 2D echocardiogram from the apical view was used for the determination of systolic ejection fraction (EF) by planimetry of the LV (modified Simpson method).

Biochemical Measurements

Blood was drawn with the subject in a supine resting position. From serum creatinine concentration, age, and body weight, glomerular filtration rate (GFR) was estimated as a parameter of renal function according to the method of Cockcroft.²⁰ EDTA plasma was chilled, immediately centrifuged at 4°C , and stored at -80°C until measurement of NT-proBNP. NT-proBNP was measured from 10 μL of plasma by nonextracted, enzyme-linked, sandwich immunoassay,² and all measurements were performed in duplicate. Intra- and interassay precisions are 1.3% and 4.8%, respectively. The lower limit of detection of this assay is 3.0 pmol/L.

Statistics

Differences in mean NT-proBNP concentrations between subgroups were tested for statistical significance by Mann-Whitney U test because NT-proBNP was not normally distributed. NT-proBNP concentrations in Figures 1 to 3 are depicted as “box and whiskers” plots, where the center horizontal line is drawn at the sample median, the bottom and the top edges of the box are drawn at the sample 25th and 75th percentiles (interquartile range), and the vertical lines extend from the box as far as the data extend, to a distance of, at most, 1.5 interquartile ranges. Differences between studied groups with respect to hemodynamic and anthropometric data were compared by Student's t test, and differences with respect to categorized data by χ^2 test. Receiver operator characteristic (ROC) analysis was performed to determine sensitivity, specificity, positive predictive value, and negative predictive value of NT-proBNP in detecting LV dysfunction and combinations of LV dysfunction, hypertrophy, and impaired renal function. P values <0.05 were defined as statistically significant, and P values <0.01 as highly significant.

An expanded Methods section can be found in an online data supplement available at <http://www.hypertensionaha.org>.

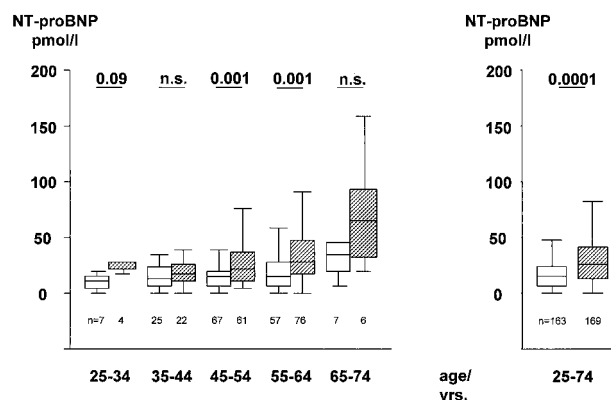


Figure 1. Subgroup analyses according to gender (white box, male; shaded box, female) and age-class in normal subjects without prior MI, LV dysfunction, LV hypertrophy, or renal dysfunction. See Statistics section for description of the “box and whiskers” plot.

Results

Study Population

Anthropometric, metabolic, hemodynamic, and echocardiographic characteristics, as well as the medical history of the study subjects, are depicted in Table 1 according to MI status and LV function. Patients with MI were predominantly male and had a more frequent history of diabetes, arterial hypertension, and heart failure than individuals without MI. Pharmacotherapy was more frequently used in MI patients, and approximately half of the MI patients with an EF $<35\%$ used ACE inhibitors, β -adrenergic receptor antagonists, and diuretics. MI patients with preserved EF were characterized by lower heart rates and lower systolic blood pressures compared with controls, most likely because of the frequent use of

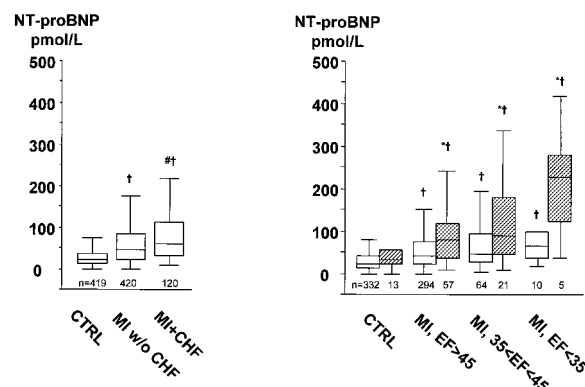


Figure 2. Left, Subgroup analysis according to history of MI and congestive heart failure (CHF). CTRL indicates subjects without prior MI and with preserved LV function; MI w/o CHF, subjects with prior MI but without history of CHF; and MI+CHF, subjects with prior MI who affirm a history of CHF. Right, Subgroup analysis according to LV mass index (white box, normal LVMI; shaded box, increased LVMI) in subjects with normal GFR. CTRL indicates subjects without prior MI and preserved LV function; MI, EF >45 , subjects with prior MI and preserved LV function; MI, 35 $<$ EF $<$ 45, subjects with prior MI and marginal LV dysfunction; and MI, EF $<$ 35, subjects with prior MI and significant LV dysfunction. † $P<0.05$ vs CTRL; # $P<0.05$ vs MI w/o CHF; * $P<0.05$ vs normal LVMI. See Statistics section for description of the “box and whiskers” plot.

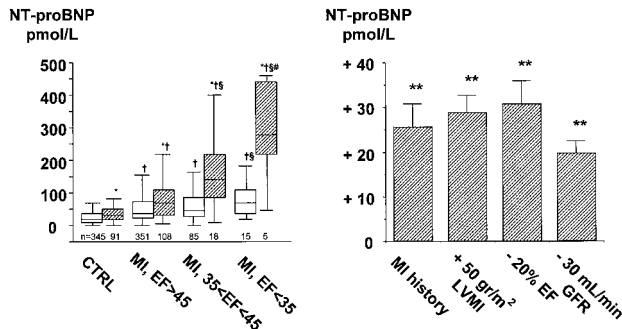


Figure 3. Left, Subgroup analysis according to renal function (white box, normal GFR; shaded box, impaired GFR). * $P<0.05$ vs normal GFR; † $P<0.05$ vs CTRL; § $P<0.05$ vs MI, EF>45; # $P<0.05$ versus MI, 35<EF<45. Right, Contribution of different parameters on NT-proBNP concentrations. Bars and error bars reflect adjusted β -coefficients and SEs. ** $P<0.01$ by multivariate regression analysis.

pharmacotherapy, particularly β -adrenergic receptor antagonists. MI patients with an EF <35% were characterized by slightly lower systolic blood pressures compared with subjects with preserved EF. In patients with MI, atrial and LV diameters and LV mass increased progressively with worsening LV function. There was no difference in renal function between controls and MI subjects with preserved EF. Renal function was, however, significantly reduced in MI patients with EF <35%.

Normal Values and Frequency Distribution of NT-proBNP

In control subjects without LV or renal dysfunction, the mean and median NT-proBNP concentrations were 26.6 pmol/L and 19.3 pmol/L, respectively. In the whole study population, the frequency distribution of NT-proBNP was markedly skewed (mean 70.1 pmol/L, median 33.7 pmol/L) but was normally distributed after logarithmic transformation (ln [NT-pro BNP], mean 3.55, median 3.54).

Subgroup Analysis

Effect of Gender

Female control subjects (without prior MI, LV dysfunction, and hypertrophy) were characterized by significantly higher NT-proBNP than male control subjects over a wide range of age classes. Furthermore, NT-proBNP showed a tendency to increase progressively with age in both genders (Figure 1).

Effects of MI, Heart Failure, LV Dysfunction, and Mass

Patients with MI were characterized by significantly higher NT-proBNP than patients without prior MI. Patients with MI who affirmed a history of heart failure were characterized by significantly higher NT-proBNP than those who denied a history of heart failure (Figure 2 left). In patients with MI, concomitant LV dysfunction and concomitant LV hypertrophy were associated with increased NT-proBNP concentrations (Figure 2, right).

TABLE 1. Study Population

Parameter	No MI	MI		
	Normal EF (n=436)	Normal EF (n=465)	35%<EF<45% (n=106)	EF<35% (n=23)
Male, %	45	84*	93*†	100*†
Age, y	54±9	56±7*	57±8*	55±9
BMI, kg/m ²	27.6±4.2	28.6±3.9*	28.2±3.8	27.1±3.0
Diabetes, %	6	13*	17*	39*†‡
Hypertensive, %	59	87*	93*	83*
Heart failure, %	3	19*	17*	30*
ACE-I, %	8	25*	28*	57*†‡
Beta-blocker, %	9	64*	69*	52*
Diuretic, %	8	18*	27*†	52*†‡
HR, bpm	71±12	66±12*	65±12*	70±13
SBP, mm Hg	138±18	133±17*	134±16*	123±16*†‡
DBP, mm Hg	86±11	84±10*	85±10	82±11
LA, mm	36±5	40±5*	42±8*†	44±8*†
LVEDD, mm	49±5	54±7*	58±7*†	62±8*†‡
EF, %	59±6	55±7*	41±3*†	29±4*†‡
LVMI, g/m ²	96±22	119±31*	129±30*†	149±41*†‡
GFR, mL/min	105±27	105±28	105±28	91±26*†‡

Values are mean±SD.

Hypertensive: blood pressure above 140/90 mm Hg or therapy; ACE-I, medication with angiotensin-converting enzyme (ACE) inhibitor; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LA, left atrial diameter; LVEDD, LV end diastolic diameter.

* $P<0.05$ vs no MI; † $P<0.05$ vs MI+normal EF; ‡ $P<0.05$ vs MI with 35%<EF<45%.

TABLE 2. Univariate and Multivariate Predictors of NT-proBNP

Parameter	Univariate		Multivariate	
	r Value	P Value	β Coefficient	P Value
Age, y	0.25	0.01	0.04	0.01*
BMI, kg/m ²	-0.03	NS	NI	
Gender, f vs m	NA		19.6	0.001
MI history	NA		25.7	0.001
HR, min ⁻¹	0.002	NS	NI	
SBP, mm Hg	0.01	NS	NI	
DBP, mm Hg	-0.12	0.01	-0.62	0.003
EF, %	-0.26	0.01	-1.55	0.001
LVMI, g/kg	0.34	0.01	0.58	0.001
GFR, mL/min	-0.32	0.01	-0.66	0.001

Analyses performed in subjects with GFR > 15 mL/min. The multivariate model included gender, age, history of MI, diastolic blood pressure, EF, LV mass index, and GFR as independent variables.

NA indicates not applicable; NS, not significant; NI, not included into model for lack of significance in univariate analysis.

* $P < 0.01$ for ln(NT-proBNP), NS for NT-proBNP.

Effect of Renal Dysfunction

NT-proBNP was further increased significantly in the presence of renal dysfunction, both in control patients and patients with prior MI, and increased further stepwise and significantly inversely to EF (Figure 3, left). Excessively increased NT-proBNP was present in the few MI subjects with markedly impaired renal function (GFR < 50 mL/min) in the absence of LV dysfunction (376 ± 127 pmol/L, $n=6$) and in the presence of marginal (438 ± 180 pmol/L, $n=3$, $P=NS$) and significant LV dysfunction (529 ± 187 pmol/L, $n=3$, $P=NS$ versus both). Four subjects with terminal renal failure were also characterized by excessive NT-proBNP concentrations (1447 to 6463 pmol/L).

Univariate and Multivariate Analyses

As depicted in Table 2, NT-proBNP was significantly correlated with age, diastolic blood pressure, EF, LVMI, and GFR by univariate correlation analysis. No significant univariate correlation was present with body mass index, heart rate, and systolic blood pressure. A significant and independent relationship could be demonstrated between NT-proBNP and

gender, as well as history of MI, diastolic blood pressure, EF, LVMI, and GFR in a multiple regression model. In addition, the relative contribution of these parameters with statistically significant and independent effects on NT-proBNP is illustrated in Figure 3 (right). A significant and independent relationship was further present between age and ln (NT-proBNP) ($P < 0.01$) in multiple regression analysis.

NT-proBNP as Predictor of Impaired LV Function

The predictive values of NT-proBNP at given cut-points in detecting marginal or significant LV dysfunction are depicted in Table 3. Because LVH and renal dysfunction markedly affect NT-proBNP, these calculations were also performed for the detection of LV dysfunction with concomitant LVH and concomitant renal dysfunction and resulted in significantly improved ROC values and predictive values. The area under the ROC curve for the detection of significant LV dysfunction was significantly greater than marginal LV dysfunction and increased further for the detection of concomitant LV hypertrophy, renal dysfunction, or both.

Discussion

The current study is the first to demonstrate that measurement of NT-proBNP allows the exclusion of LV dysfunction in an outpatient population with a high negative predictive value and with remarkable sensitivity and specificity. Thus, NT-proBNP might provide a benefit in patients with suspected LV dysfunction, particularly when imaging of LV function is not readily available.

NT-proBNP and LV Dysfunction

The high negative predictive value indicates that NT-proBNP might be particularly useful for the exclusion of impaired LV function, and a normal test result would allow us to virtually rule out significant LV dysfunction. Furthermore, the sensitivity of NT-proBNP was sufficient to biochemically identify the majority of subjects with LV dysfunction, and this provided valuable information, even without taking into account further clinical information. Specifically, three fourths of subjects with significant LV dysfunction (EF < 35%) were identified at the given cut-points. Because biochemical markers for LV dysfunction are not yet established in current practice, subjects may still often remain

TABLE 3. Predictive Values of NT-proBNP

Condition	Cases (n)/ Prevalence (%)	ROC Area (95% CI)	Sensitivity/ Specificity (%)	PPV/NPV (%)	Cutoff (pmol/L)
EF < 45	146/13	0.66 (0.63–0.68)	68/54	18/92	34
EF < 45 + LVH	42/3.8	0.78 (0.75–0.80)	76/62	7/99	44
EF < 45 + RD	33/2.9	0.81 (0.79–0.83)	79/78	10/99	70
EF < 45 + LVH + RD	15/1.3	0.90 (0.89–0.92)	93/78	5/99.9	70
EF < 35	24/2.1	0.77 (0.75–0.80)	75/62	4/99	44
EF < 35 + LVH	10/0.9	0.91 (0.89–0.92)	90/80	4/99.9	76
EF < 35 + RD	8/0.7	0.94 (0.92–0.95)	88/94	9/99.9	162
EF < 35 + LVH + RD	5/0.4	0.98 (0.97–0.99)	100/94	7/100	162

In subjects with glomerular filtration rate > 15 mL/min.

ROC indicates receiver operator characteristic; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LVH, LV hypertrophy; RD, renal dysfunction (GFR < 85 mL/min).

misdiagnosed and thus be treated insufficiently. Indeed, in the current study, only 57% of patients with significant LV dysfunction were treated with ACE inhibitors. Thus, NT-proBNP might help to identify these subjects earlier and optimize their treatment.²¹

Compared with sensitivity, the specificity of NT-proBNP did not reach a similarly high level at the given cut-points. This finding is explained best by the circumstance that not only impaired LV function, but also MI with preserved LV function, was related to increased NT-proBNP concentrations, albeit to a lesser extent. This fact is of relevance because $\approx 80\%$ of MI patients in the current study population were characterized by preserved LV function. Thus, the present sample may well reflect a commonly encountered clinical situation in which individuals with LV dysfunction are relatively rare.

Although the current predictive values support NT-proBNP as one of the best available biochemical markers of LV dysfunction, a further improvement would be desirable. A possible strategy toward further improvement might be the combined assessment of 2, or even several, neurohormones and should be explored in additional studies. Such an approach has previously also been suggested by Yamamoto et al¹⁰ who demonstrated in a clinical study that the combined assessment of BNP and N-terminal atrial natriuretic peptide (ANP) further increased sensitivity to enable biochemical detection of LV dysfunction, although the univariate association with LV function was closer for BNP than for N-terminal ANP in a head-to-head comparison.^{11,13}

NT-proBNP, LV Mass, and Renal Dysfunction

In addition to the LV EF, NT-proBNP was correlated with LVMI and GFR in univariate and multivariate analyses. Notably, the univariate correlation coefficients for LVMI and renal function slightly exceeded that for LV EF. The clear effects of these parameters on NT-proBNP were also observed in subgroup analyses, and patients with significant LV dysfunction were particularly characterized by marked and significant further increases in NT-proBNP in the presence of concomitant LV hypertrophy or renal dysfunction.

The finding of an independent effect of LV mass on NT-proBNP in the presence and absence of LV dysfunction is similar to our finding for BNP in a recent population-based study.¹³ It is also supported by studies that have demonstrated a close correlation between the extent of LV hypertrophy and BNP plasma concentrations¹⁴ in hypertensive heart disease. The effect of LV mass on NT-proBNP also suggests the ability of NT-proBNP to even better detect LV dysfunction in subjects with concomitantly increased LV mass.

The current finding of a close association of NT-proBNP with renal function confirms and extends small clinical studies.¹ Such association has not been reported previously for a biochemical marker of LV dysfunction and suggests renal excretion as a major route of elimination of NT-proBNP. Thus, NT-proBNP detects LV dysfunction particularly well in subjects with impaired renal function. However, the current observation also demonstrates that the assessment of renal function should be mandatory to allow for correct interpretation of NT-proBNP measurements; ie, cutoff con-

centrations have to be adjusted upwards if renal dysfunction is present. Our observations in the few subjects with terminal renal failure, where NT-proBNP was excessively elevated, further indicate that NT-proBNP might not be a helpful screening test in this small subgroup. Further studies should more clearly define the cut-points to suggest LV dysfunction in patients with various degrees of mild-to-moderate renal dysfunction.

Because a superior prognostic value has recently been suggested for NT-proBNP in subjects after MI¹⁷ and because concomitant renal dysfunction is an independent predictor of poor prognosis in subjects with LV dysfunction,²² it is tempting to speculate that part of the prognostic information of NT-proBNP might be related to the association with renal function. However, this hypothesis needs further testing.

NT-proBNP and Anthropometric Parameters

NT-proBNP was correlated with gender and age in the current study population, a finding that is similar to our recent findings for BNP in a population-based study.¹³ This relationship is particularly evident in control subjects (Figure 1), and it is likely that optimal cutoff values will differ accordingly. However, because of the small numbers of patients with significant LV dysfunction in age- and gender-stratified subgroups, these cutoffs could not be generated from this study.

Potential Implications of False Testing

Even if NT-proBNP is used at optimized cutoff concentrations, some falsely positive and falsely negative classified subjects have to be taken into account. Analyses of falsely positive classified subjects in the current study population demonstrated that these subjects were likely to have lower EFs, higher LV mass, and lower GFR than controls (data not shown). Therefore, these subjects might have a greater risk for subsequent development of cardiac or renal disease and might particularly profit from early identification, preventive measures, and potential therapy. In contrast, analysis of falsely negative classified subjects demonstrated that these subjects were likely to have higher EFs, lower LV mass, and higher GFR than properly identified subjects with LV dysfunction (data not shown). Furthermore, only one of these subjects was without pharmacotherapy. Because effective therapy may decrease NT-proBNP, this circumstance might explain lower concentrations in these subjects. Furthermore, identification of untreated and falsely negative classified subjects might be possible at a later stage if subsequent testing is performed.

Summary

NT-proBNP is a promising marker for the exclusion and detection of impaired LV function and the first neurohumoral marker of integrated cardio-renal function. It detects cases with LV dysfunction particularly well in the presence of concomitant LV hypertrophy or renal dysfunction. To obtain optimal results, cutoff concentrations have to be adjusted for renal function.

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