

# Cardiovascular Diseases (CVDs) Fact Sheet



---

European Diagnostic Manufacturers Association

*In Vitro* Diagnostics  
*Making a real difference in Health & Life Quality*

May 2007

# I. The different types of CVDs

---

## 1. *Cardiovascular Risk Factors*

- type 2 diabetes mellitus
- hypertension
- smoking
- abdominal obesity
- hypercholesterinaemia
- elevated triglycerides
- inflammatory diseases (e.g rheumatoid arthritis)
- low high- density lipoprotein-cholesterol

## 2. *Coronary Artery Disease (CAD)* *syn. Coronary Heart Disease (CHD)*

- stable CAD (CHD)
- unstable CAD (CHD)

## 3. *Acute Coronary Syndrome (ACS)*

Unstable Angina Pectoris (uAP)  
Acute Myocardial Infarction (AMI)

- STEMI (ST-Elevation Myocardial Infarction)
- NSTEMI (Non ST-Elevation Myocardial Infarction)

## 4. *Heart Failure (Chronic Heart Failure, Acute Heart Failure)*

- Dilatative cardiomyopathy
- Ischemic cardiomyopathy
- Non-ischemic cardiomyopathy
- Right heart failure (in connection with pulmonary diseases e.g. lung embolism, Chronic Obstructive Pulmonary Disease (COPD), primary pulmonary hypertension)
- Myocarditis (infection disease of the heart with heart failure like symptoms)

## 5. *Rheumatic Heart Diseases, Congenital Heart Diseases*

- Valvular disorders

## 6. *Cerebrovascular Disease*

- Stroke (ischemic, haemorrhagic)

## 7. *Peripheral Artery Disease*

# II. Epidemiology

## ***Cardiovascular Diseases: a major health problem worldwide***

- Coronary Artery Disease (CAD) and cardiovascular adverse events (Acute Coronary Syndrome (ACS)) are the leading cause of mortality in men over 45 years old and in women over 65 years throughout Europe [1](#)
- In Europe CAD and ACS are the leading causes of death accounting for over 4 million deaths each year [4](#). An estimate 17 million people die from cardiovascular diseases each year. In the world cardiovascular diseases are cause for about one-third of all deaths globally [2](#)
- By 2010 CVD is estimated to be the leading cause of death also in developing countries [2](#)
- By 2020 incidence of CVD will increase to more than 20 million a year and to more than 24 million a year by 2030 [3](#)
- Heart diseases have no geographic, gender or socio-economic boundaries
- Every 33 seconds an American dies from a cardiovascular disease [3](#)

## ***Cardiovascular Diseases: a real economic burden***

- Medical treatment and care is highly cost intensive and prolonged
- 2005 : USA – total costs for treatment of cardiovascular diseases are estimated to be \$ 393.5 billions [3](#)

## ***Europe:***

- 2005 : total costs for treatment of cardiovascular diseases are estimated to be € 200 billions [5](#)
- These amount represents 12% of total health care expenditure (12% in France, 15% in Germany, 17% in UK) € 230 per head [5](#)
- Cardiovascular diseases severely hampered the daily activities of 4.4 million people – one in every 100 EU citizens [5](#)
- Medical treatment of CVD represent 126 million hospital-bed days and 268.5 million lost working days [5](#)
- CVD affects individuals in their peak mid life years in their most productive years
- 2 Million cardiac deaths from CDV in 2003 represented a lost of 2.18 million working years [5](#)

# III. Commonly used Routine Laboratory Tests

## 1. Laboratory detection of cardiovascular risk factors

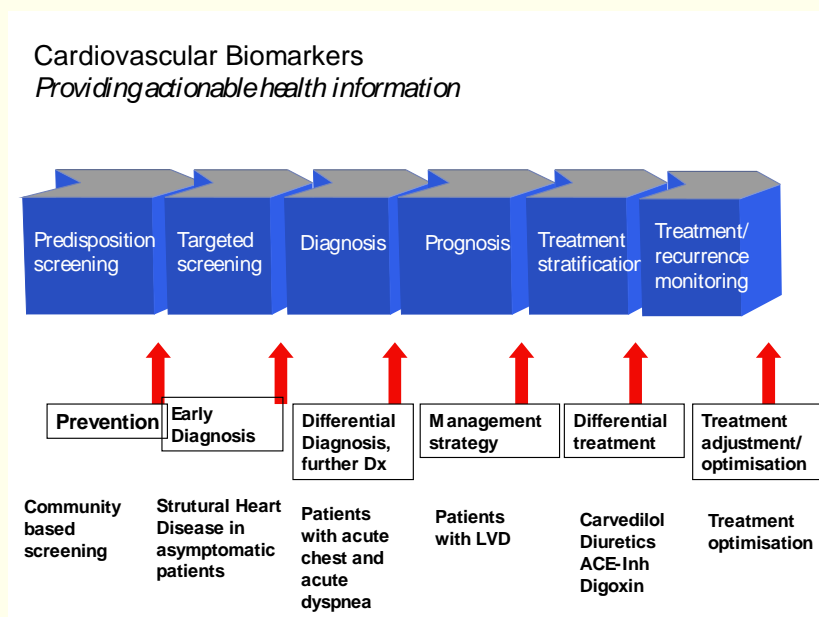
- Triglycerides
- Total Cholesterol
- LDL- and HDL Cholesterol
- Homocysteine
- Microalbuminuria
- Fibrinogen
- CRP/hsCRP

## 2. Laboratory diagnosis of coronary artery disease (CAD)

- Acute coronary syndrome (ACS) and myocardial infarction (MI):
- Troponin T and I
- Creatinkinase CK
- Creatinkinase isoenzyme CK-MB
- Myoglobin
- In symptomatic patients with chest pain presenting in the emergency department laboratory testing troponin T or I is beside ECG the gold standard for diagnosing non ST elevation myocardial infarction (NSTEMI)

## 3. Laboratory diagnosis of structural heart disease, heart failure, rheumatic and congenital heart diseases

- Natriuretic peptides: NT-proBNP and BNP

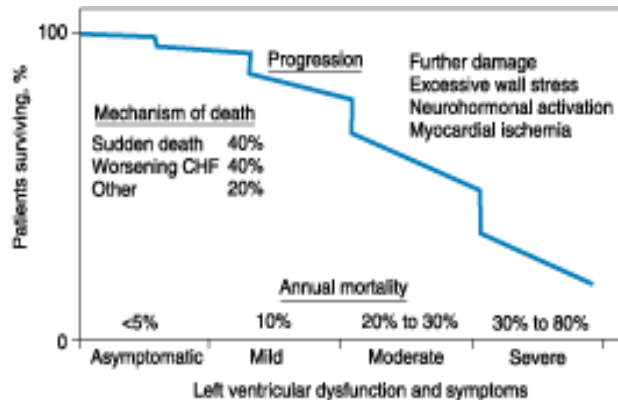


# IV. Heart Failure: Epidemiology & Healthcare Cost

## Heart failure is a fatal disease:

- Between 25 and 50% of patients presenting with decompensated heart failure are initially misdiagnosed [6](#)
- Heart Failure (HF) is a major health care problem and affects 14 million Europeans (prevalence ~ 2%-2.5 %) [7](#)
- Lifetime risk of developing HF is 20%. In individuals aged 55, almost 1 in 3 will develop heart failure during their remaining lifespan [8](#)

Prognosis of Chronic Heart Failure



- Prevalence of heart failure increases rapidly with age. As the proportion of elderly population increases, the number of individuals with HF also increases [9](#)
- Heart failure is an insidiously progressive disease and is characterized by an increasing frequency of hospitalizations [10](#)
- Survival rate after incident heart failure is 63% after one year and only 35% at 5 years of follow-up [11](#)
- Heart failure is currently the most costly cardiovascular disorder in Western countries [6](#)
- Large number and long duration of hospitalization associated with acute heart failure and decompensated congestive heart failure create a substantial economic burden on the healthcare system, consuming 2-2.5% of the total healthcare budget [9, 12](#)
- Safe and effective decompensated heart failure diagnosis and management has the potential to decrease hospitalizations and intensive care unit admissions, prevent readmissions, and improve the quality of life in the heart failure patient, as well as relieve some of the economic burden of HF management from the healthcare system [13](#)
- Consuming 2-2.5% of the total healthcare budget – the cost increase with disease progression towards more severe stages

# III. Commonly used Routine Laboratory Tests

**In asymptomatic patients with structural heart disease laboratory testing provide early diagnosis before clinical symptoms occur:**

- Allow a powerful prognosis in asymptomatic at-risk populations
- Limit or delay the manifestation of disease by detecting risk factors (Cholesterol, thrombogenesis factors, homocysteine, infectious markers, cardiac markers, genetic factors...)
- Rise diagnosis and with appropriate treatment limit or delay the progression of heart disease
- Reduce the time to the initiation of the most appropriate therapy and improve prognosis
- Prevent recurrence, complications, disability and mortality from cardiovascular diseases
- Prolong survival and improve quality of life Increase (disease-free) life expectancy
- Lead significant cost savings for healthcare systems

***The utility of laboratory diagnostics spans the continuum of care from early detection to health outcomes:***

|  | <b><i>At least one available Test</i></b> |
|--|---|
| Specific diagnostic used to rule in specific disease or condition  | yes                                       |
| Specific diagnostic used to rule out specific disease or condition   | yes                                       |
| Diagnostic recommended for establishing diagnosis by evidence-based clinical practice guidelines             | yes                                       |
| Diagnostic recommended for patient care or disease management by evidence based clinical practice guidelines | yes                                       |

And then... A recent study conducted by Rand Corporation reported that diagnostics are underused on average 51% of the time...

# V. Coronary Artery Disease & Acute Coronary Syndrome

---

In symptomatic patients with chest pain presenting in the emergency department laboratory testing troponin T or I is beside ECG the gold standard for diagnosing non ST elevation myocardial infarction (NSTEMI)

- Treatments are available
- Angina a common sign of heart attack accounts for approximately 5.6 million emergency departments visits annually
- The cost of unnecessary hospital admissions for chest pain is estimated to exceed \$ 12 billion annually
- Some 2-10% of individual experiencing acute myocardial infection mistakenly are send home due to incorrect diagnose increasing risk for sudden death or heart damage due to treatment delay (→ legal consequences..) [15](#)

# VI. Cardiac Markers in the Management of Heart Failure

---

## **NT-proBNP and BNP:**

- diagnosis of heart failure in patient presenting with dyspnoea in the doctor's office or with acute breathlessness in the emergency department
- monitoring and therapy guidance

## **Laboratory benefit**

- easy -rapid measurement (less than 20 min) and reliable, available on standard lab equipment

## **Clinical benefit**

- Improve the diagnosis accuracy Decrease the clinical uncertainty for 74%
- Help to grade the severity of heart failure
- High prognostic value: predicts an increased risk of recurrent events or death

## **Economic benefit**

- Reduce the need to hospitalization in intensive care
- Reduce the total cost of treatment by 26%
- Reduce intensive care costs per patient: in the BNP group: 5 410 \$ in the control group: 7 264 \$

## **Patient satisfaction**

- Reduce time to the initiation of the most appropriate therapy and reduce time to discharge
- Reduce the duration of hospitalization
- Less subsequent readmissions
- Improve quality of life
- Improve life expectancy

# VII. Cardiac Markers in the Management of Artery Disease and Acute Coronary Syndrome

---

## *Cardiac Troponin T or I*

### **Clinical benefit**

- High diagnostic accuracy and safety
- gold standard in diagnosis of ACS
- Troponin patients without acute coronary syndromes had fewer hospital admissions
- Troponin patients with acute coronary syndromes had shorter telemetry and coronary care lengths of stay

### **Economic benefit**

- Low cost method
- Total hospital charges were reduced in troponin patients with and without coronary syndromes compared to controls (\$ 900 lower)

### **Patient satisfaction**

- Improve disease management
- Improve quality of life (less days inpatient)
- Facilitating a well-planned discharge

[Cf. 25-26](#)

# VIII. Cardiac Markers in Risk Stratification of Kidney Disease

---

Cardiovascular disease is the leading cause of death in patients with chronic renal failure accounting for 45% of all deaths.

In dialysis patients 20% of cardiac deaths are attributed to acute myocardial infarction (AMI). AMI is a fatal clinical event in end-stage renal disease patients with a 2-year mortality of 73%.

An elevated troponin is a poor prognostic factor and is associated with an increased risk of morbidity and mortality in patients with renal failure.

Troponin is a helpful marker to identify a high-risk group of patients with stable chronic kidney disease for more intensive therapeutic management.

[Cf. 27-30](#)



# IX. Cardiac Markers and Chemotherapy of Cancer

## ***CANCER is a disease which concerns us all:***

- Cancer in USA is the second leading cause of death
- One of every four deaths is due to the cancer in the USA
- In Europe 1.2 millions of death/year
- USA overall annual cost of cancer would be in 2005 \$ 209.9 billion
- In 2002 the cost of the cancer in France reached 15 billions of euros
- Almost one man on two and one woman on 3 will have a cancer in their life
- Cardiotoxicity is a common complication of chemotherapy

**The commonly applied chemotherapy is associated with cardiotoxic side effects. These cardiotoxic effects could be detected already in the initial phase of chemotherapy by using cardiac markers (troponines or natriuretic peptides)**

## ***Pronostic value of troponin T and I evaluation in cardiac risk stratification of cancer patients undergoing high dose chemotherapy***

### **Clinical benefit:**

- Easy test and non invasive
- Stratify the risk of cardiac events in cancer patients in the 3 years after therapy
- Identify low risk patient who do not require close cardiac surveillance after chemotherapy
- Anticipate the development of cardiac dysfunction
- Stratifies cardiac risk in early phase, long before impairment of heart function and development of clinical symptoms

### **Economic benefit:**

- Is a low cost method
- Avoid expensive long term monitoring program such as echocardiography, radionuclide angiography by patients who do not need it
- start preventive therapy before impairment in heart function
- avoid expensive complications

### **Patient satisfaction:**

- Improve disease management
- Improve quality of life
- Improve life expectancy

# List of References

## Epidemiology

1. Screening of family members of patients with premature coronary heart disease Results from the EUROASPIRE I family survey -European Heart Journal (2003) 24, 249-257
2. World health organization. Atlas of heart disease and stroke. 2004
3. American heart association ([www.americanheart.org](http://www.americanheart.org))
4. British heart foundation ([www.heartstats.org](http://www.heartstats.org))
5. Leal J et al. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006; DOI: 10.1093/ehi733. Available at: <http://eurheartj.oxfordjournals.org>

## Heart Failure

6. Bayes-Genis, A. et. al. The European Journal of Heart Failure 2004; 6: 301–308
7. Cowie, MR et. al: The epidemiology of heart failure. Eur Heart J 1997; 18: 208-225. Davies, MK et. al: Prevalence of left ventricular systolic dysfunction and heart failure in the Echographic Heart of England Screening Study: a population based study. Lancet 2001; 358: 439-444.
8. Lloyd-Jones, DM et. al: Lifetime risk for developing congestive heart failure. The Framingham Heart Study. Circulation 2002; 106: 3068-3072.
9. Bleumink, GS et. al: Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. Eur Heart J 2004; 25: 1614-1619.
10. Remme, WJ et. al: Public awareness of heart failure in Europe: first results from SHAPE. Eur Heart J 2005; 26: 2413-2421.
11. Peacock, WF: Rapid Optimization: Strategies for Optimal Care of Decompensated Congestive Heart Failure Patients in the Emergency Department. Reviews in Cardiovascular Medicine 2002; 3, Suppl. 2: 41-48.
12. Bleumink, GS et. al: Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. Eur Heart J 2004; 25: 1614-1619.
13. European Society of Cardiology: Guidelines for acute heart failure- update. Eur Heart J 2005; 26: 384-416.
14. Peacock, WF: Rapid Optimization: Strategies for Optimal Care of Decompensated Congestive Heart Failure Patients in the Emergency Department. Reviews in Cardiovascular Medicine 2002; 3, Suppl. 2: 41-48.

## Coronary Heart Disease and Acute Coronary Syndrome

15. The Value of Diagnostic: innovation, adoption and diffusion into health care» 2005. The Lewin Group.  
<http://www.advamed.org/publicdocs/thevalueofdiagnostics.pdf>



# List of References

## Cardiac Markers in the Management of Heart Failure

16. Graine H, Lefevre G. Contexte medico-économique de l'utilisation des facteurs natriurétiques. *Spectra Biologie* Nov2005; 148:35-38
17. Muller C et al. Use of b6type Natriuretic peptide in the evaluation and management of acute dyspnea. *N Eng J Med.* 2004; 350(7): 647-53 –
18. Mc Cullough PA et al. B type natriuretic peptide and clinical judgement in emergency diagnosis of heart failure: analysis from BNP Multinational study. *New eng J Med.* 2002, 347:161-167
19. Giuliani I et al. Assay for Measurement of Intact B-Type Natriuretic Peptide Prohormone in Blood. *Clinical Chemistry* 52, No. 6, 2006
20. Svendstrup-Nielsen L et al. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea
21. Troughton RW et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; 355: 1126-30
22. Kebel F et al. NT-proBNP in acute heart failure: Correlation with invasively measured hemodynamic parameters during recompensation. *J Card Fail* 2005; 11(5 Suppl) 38-41
23. Gavin I.W. et al. What is the most cost-effective strategy to screen for left ventricular systolic dysfunction: natriuretic peptides, the electrocardiogram, hand-held echocardiography, traditional echocardiography, or their combination? *European Heart Journal* (2006) 27, 193–200
24. Siebert U et al. Cost-effectiveness of using N-terminal pro-brain natriuretic peptide to guide the diagnostic assessment and management of dyspneic patients in the emergency department. *Am J Cardiol.* 2006 Sep 15;98(6):800-5.

## Cardiac Markers in the Management of Artery Disease and Acute Coronary Syndrome

25. Zarich S et al. Impact of troponin T determinations on hospital resource utilization and costs in the evaluation of patients with suspected myocardial ischemia. *Am J Cardiol* 2001. Oct 1; 88(7) : 732-6
26. Lynch D et al. Using early troponin I testing to improve cardiac care. *Nurs Times* 2005. Dec; 101(50): 30-1

## Cardiac Markers in Risk Stratification of Kidney Disease

27. Wolfe RA et al.: Annual data report of the United States renal disease saytem VI. *Am J Kidn Dis Suppl* 1998; 32: S81-8
28. Janak R De Zoysa: Cardiac troponins and renal disease. *Nephrology* 2004; 9: 83-8
29. Apple FS et al.: Predictive value of cardiac troponin for subsequent death in end-satge renal disease. *Circulation* 2002; 106: 2941-5
30. Goicoechea M et al.: Clinical significance of cardiac troponin T levels in chronic kidney disease patients: Predictive value for cardiovascular risk. *Am J Kidn Dis* 2004; 43: 846-53

# List of References

## Cardiac Markers and Chemotherapy of Cancer

31. Daniela Cardinale MD et al. Pronostic value of troponin I in cardiac Risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004; 109: 2749-2754 –
32. Salomaa V et al. A new definition for myocardial infraction: what difference does irt make?"*Eur Heart J* 2005; 26:1749-1725.

## Primary care setting

33. Gustafsson F. et. al.: Diagnostic and Prognostic Performance of N-Terminal ProBNP in Primary Care Patients With Suspected Heart Failure. *J Card Fail*. 2005 Jun;11(5 Pt 2):15-20.
34. Nielsen, LS et. al.: N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. *Europ J Heart Fail* 2004; 6: 63-70.
35. Fuat A. et. al.: A comparison of the two commercially available assays for B-type natriuretic peptide when selecting patients with suspected heart failure in primary care. Which should we use? *Heart* 2003;89(Suppl 1):A38
36. Citation: *European Journal of Heart Failure Supplements* 2003; Vol. 2(1): 131.
37. Zaphiriou, A.: Can we use BNP and NTproBNP to rule out heart failure in clinical practice? Results of the UK natriuretic peptide study. *European Journal of Heart Failure Supplements* 2003; Vol. 2(1):131.
38. Tschoepe C. et. al.: The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements.
39. *Eur Heart J*. 2005 Jul 13; [Epub ahead of print].
40. Dao Q et al. Utility of B-Type Natriuretic Peptide in the Diagnosis of Congestive Heart Failure in an Urgent-Care Setting. *JACC* 2001, 37/2: 379-385

## Emergency room setting

41. Januzzi JL et. al.: The value of NT-proBNP for the evaluation of acute CHF: A Multicenter, International Meta-Analysis of 1256 subjects. *J Am Coll Cardiol* 2005; 45 Suppl A.
42. Januzzi JL et. al.: The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study. *Am J Cardiol*. 2005 Apr 15;95(8):948-54.
43. Bayés-Genís A. et al. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. *Eur Heart J* 2004;6:301-308
44. McCullough P et al., B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure. *Circulation* 2002;106:r1-r7

# List of References

## Natriuretic peptide levels correlate with the severity of the disease

45. Karabulut A. et. al. The association between NT-proBNP levels, functional capacity and stage in patients with heart failure. *Acta Cardiol.* 2005; 60(6):631-8.
46. Adams JE. Et. al: Correlation of Levels of NT-proBNP and NYHA Functional Classification in Patients with Congestive Heart Failure. *Clin Chem* 2003; Vol 49:No.6; Suppl: A66
47. Williams SG. Et. al: Complementary roles of simple variables, NYHA and N-BNP, in indicating aerobic capacity and severity of heart failure. *Int J Cardiol.* 2005 Jul 10; 102(2):279-86
48. Giuliani I et al. Assay for Measurement of Intact B-Type Natriuretic Peptide Prohormone in Blood. *Clinical Chemistry* 52, No. 6, 2006

## Prognostic value

49. George J. et. al: Circulating erythropoietin levels and prognosis in patients with congestive heart failure: comparison with neurohormonal and inflammatory markers. *Arch Intern Med.* 2005 Jun 13;165(11):1304-9
50. Wang TJ et. al.: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med.* 2004 Feb 12;350(7):655-63.
51. De Sutter J, de Bacquer D, Cuypers S, Delanghe J, De Buyzere M, Kornitzer M, de
52. Backer G.: Plasma N-terminal pro-brain natriuretic peptide concentration predicts coronary events in men at work: a report from the BELSTRESS study. *Eur Heart J* 2005 26: 2644-2649 [Epub ahead of print 2005 Oct 4].
53. Kellett J.: The prediction of in-hospital mortality by amino terminal pro-brain natriuretic peptide (NT-proBNP) levels and other independent variables in acutely ill patients with suspected heart disease. *Eur J Intern Med.* 2005 Jun;16(3):195-199.
54. Kistorp C. et. al: N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 2005 Apr 6;293(13):1609-16.
55. Bettencourt P. et. al: N-Terminal-Pro-Brain Natriuretic Peptide Predicts Outcome After Hospital Discharge in Heart Failure Patients. *Circulation*, 2004; 110:2168-2174.
56. Kirk V. et. al: N-terminal proBNP and mortality in hospitalised patients with heart failure and preserved vs. reduced systolic function: data from the prospective Copenhagen Hospital Heart Failure Study (CHHF). *Eur J Heart Fail.* 2004;6(3):335-41.
57. De Lemos J et al. the Prognostic Value of B-Type Natriuretic Peptide in Patients with Acute Coronary Syndromes. *N Engl J Med*, Vol. 345, No. 14, October 4, 2001
58. Logeart D et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *JACC* 2004 Feb 18;43(4):635-41



# List of References

## Monitoring of treatment / Treatment guidance

59. Jourdain P. et. al: Benefit of BNP for optimising therapy in patients with heart failure due to systolic dysfunction: The Systolic heart failure treatment supported by BNP trial (STARS-BNP) multicenter randomised study. J Am Coll Cardiol 2005;45:(Supplement A):3A
60. Richards M, Troughton RW: NT-proBNP in heart failure: therapy decisions and monitoring. Eur J Heart Fail. 2004;6(3):351-4.
61. Bettencourt P. et. al: N-Terminal-Pro-Brain Natriuretic Peptide Predicts Outcome After Hospital Discharge in Heart Failure Patients. Circulation, 2004; 110:2168-2174.
62. Troughton RW et. al: Treatment of heart failure guided by amino-terminal brain natriuretic peptide concentrations. Lancet 2000; 355:1126-30

## Websites

63. Fédération française de cardiologie : [www.fedecardio.org](http://www.fedecardio.org)
64. American college of cardiology: [www.acc.org](http://www.acc.org)
65. European society of cardiology: [www.escardio.org](http://www.escardio.org)
66. British heart foundation statistics website: [www.heartstats.org](http://www.heartstats.org)
67. American Heart Association: [www.americanheart.org](http://www.americanheart.org)
68. Lab Tests Online: [www.labtestsonline.co.uk](http://www.labtestsonline.co.uk)
69. Medical Lab: [www.medical-lab.info](http://www.medical-lab.info)

This paper has been prepared by the **EDMA Value of IVDs Task Force**. **EDMA, the European Diagnostic Manufacturers Association** is the voice of the In Vitro diagnostic industry active in Europe. EDMA membership brings together National Associations and the major companies, representing in total more than **500 companies (or over 700 legal entities)** engaged in **the research, development, manufacture or distribution of IVD products**. EDMA cooperates with other European and international trade associations as well as with scientific societies and patients organisations, to **make a real difference in health and life quality**.

### **European Diagnostic Manufacturers Association 2007**

All rights reserved. The information contained in this Fact Sheet is issued by EDMA, in cooperation with its members, as background information for general distribution. Any use of information provided here should be accompanied by an acknowledgment of EDMA as the source.

Fact Sheets information may be reviewed on a regular basis, thus the Association does not warrant that the information contained in this publication is complete and correct in all circumstances and shall not be liable for any damages incurred as a result of its use. Reproduction or translation of the Fact Sheet or any use other than for educational or non-commercial purposes, require explicit, prior authorization in writing. Applications and enquiries should be addressed to the EDMA Secretariat.

