

Guidelines for Heart transplantation

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Introduction

Although the first human heart transplantation was performed in 1967, the annual number of transplants only began to grow substantially from the eighties, declining again after 1996, due to the shortage of donor hearts. Meanwhile, more than 73.000 heart transplants have been performed worldwide, of which more than 800 have been performed in the Netherlands.¹ Heart transplantation in the Netherlands began in 1984, after a long period of decision making by the government. The use of strict and congruent protocols and yearly evaluation and reporting to the Ministry of Health were prerequisites. In 1998 the Dutch guidelines for heart transplantation were published after approval by the Dutch Society of Cardiology (NVVC).²

In 1998 specific legislation on organ donation (WOD, Wet op de Orgaan Donatie) was instituted to regulate the fair allocation of organs and the correct handling of organ donors. It was hoped that this law, in combination with an intensive public awareness program would raise the number of donor organs. All initiatives so far, however, have not resulted in more donor hearts. On the contrary, the number of heart transplantations has decreased in recent years, as it has in all countries over the world (Fig 1)

The main explanation for the low number of donor hearts in the Netherlands is the low and even still decreasing mortality of traffic accidents in comparison to other European countries. The mortality of traffic accidents per million inhabitants in the Netherlands is 2-2 ½ times lower than in Belgium, Spain and Austria, countries with high numbers of transplantations.³ In these countries traffic accidents account for 70% of the organ donors, while in the Netherlands this is only $\pm 30\%$. More than 65% of our donor hearts are obtained from patients who died because of stroke. In general, these patients are older than traffic victims, thus potentially have more cardiovascular problems, limiting their use as cardiac donors, where lung donation may still be possible. Worldwide the mean age of donors used for heart donation at present is 33 years, in contrast to a mean age of 41 years in the Netherlands.¹ Furthermore, in the Netherlands, the percentage of donors older than 56 years used for heart transplantations is much higher than in other Eurotransplant countries (Netherlands 12%; Belgium 8%; Austria 5%; Eurotransplant data 2002).

A development that may have negative effects on the number of heart transplantations is the shift from heart-beating donation to non heart-beating procedures. Non-heart beating donation can be performed in patients who are not (yet) brain-dead, but have an unfavorable prognosis and in whom therapy will be withheld. Ventilation is switched off and shortly after the ensuing circulatory arrest the patient is transferred to the operating room for the donation procedure. In this way kidneys, liver and lungs can be used for transplantation, but not the heart due to the extended period of (warm) ischemia. Non-heart beating donation was introduced in the Netherlands to expand the pool of donor organs, beyond patients meeting the well defined criteria for brain-death. The procedure is logistically easier for the intensive care, and shorter than a multi-organ (including the heart) procedure, however, and is therefore sometimes preferred by the relatives of the donor and also by the donor hospital. Whether this shift to non heart-beating procedures really substitutes heart beating donation is not quite clear and will be investigated.

Due to the above mentioned developments, it is not expected that the numbers of donor hearts will increase in the near future.⁴

In contrast, the number of patients with heart failure is growing, due to aging of the population and improved survival after myocardial infarction, as well as improved survival of heart failure patients.⁵

On the one hand, this increase in heart failure patients may result in more potential heart transplant candidates; on the other hand, the improved survival of patients with heart

failure raises the question which patients actually will need a transplant.⁶ The widespread use of beta-receptor blockers, ACE-inhibitors, AT-II blockers, aldosterone blockers, exercise training, cardiac resynchronization therapy and implantable defibrillators has had a favorable impact on the prognosis of heart failure patients and warrants continuous re-evaluation of existing transplant indications.⁷ Today, the prognosis of many stable heart failure patients is comparable to the one-year post-transplant survival of 85%-90%, questioning the benefit of heart transplantation in these patients. Therefore fewer ambulatory patients are being transplanted. In stead, heart transplantation in patients on the waiting list, hospitalized because of acutely decompensated heart failure (ADHF), is increasing. Especially the use of ventricular assist devices (LVAD) has enabled these acutely deteriorated patients to survive until heart transplantation. Due to the low number of donor hearts, waiting time can be too long, even when the acute patient would get priority on the waiting list. The results of bridging to transplantation with LVAD's in selected patients are very favorable and the patients can lead a reasonable normal life awaiting their heart transplantation.^{8,9}

Based on the changes in the field of heart transplantation and the treatment and prognosis of patients with heart failure it was deemed necessary to actualize the existing guidelines of 1998. This was supported by a request of the BOTX (Begeleidingscommissie Orgaan Transplantatie) of the CvZ (College voor Zorgverzekeringen) to provide more transparency in the acceptance or denial for heart transplantation as well as the acceptance of donor hearts. For this reason an ad hoc committee was formed under supervision of the NVVC (Nederlandse Vereniging Voor Cardiologie) and the NVT (Nederlandse Vereniging voor Thoraxchirurgie) and chaired by a representative of the BOTX. The participants of this committee are mentioned in the appendix. A meeting of this committee was organized on May 18, 2006. These updated guidelines are the result of this meeting.

Criteria for acceptance on the transplant waiting list (Table 1)

“End-stage heart disease not remediable by more conservative measures”¹⁰

In the light of the foregoing, selection of those patients who may expect to have the greatest benefit in terms of both life expectancy and quality of life from a scarce societal resource is inevitable.

Patients who should be considered for heart transplantation are those with severe symptoms of heart failure, intractable angina or rhythm disturbances, without any alternative form of treatment available and with a poor prognosis. As mentioned in the introduction, new treatment options have modified the prognostic significance of the variables traditionally used to identify heart transplant candidates e.g. maximal oxygen consumption on exertion (VO₂ max).¹¹ Therefore, “end-stage” heart disease has become a “moving target”; many patients referred for heart transplantation end up improving their clinical status with judicious use of newer therapies.¹⁰

The presence of a low left ventricular ejection fraction or a history of functional class III or IV symptoms of heart failure, as such, and a peak VO₂ greater than 15 ml/kg/min (or >55% of predicted uptake) are insufficient indications for heart transplantation.¹²

The patient must be willing and capable to undergo intensive medical treatment, and be emotionally stable so as to withstand the many uncertainties likely to occur both before and after transplantation.¹¹

Given a 1-year mortality after heart transplantation of 10-15%, the expected 1-year mortality in a potential transplant candidate should be at least as high as that. Recent trials of patients with advanced heart failure, like the COPERNICUS trial, demonstrated a yearly mortality of 11%, in patients using ACE-inhibitors and beta-blockers.¹³ In this trial, patients with truly end-stage heart failure were not included, but it underlines the difficulty of identifying real transplant candidates.

Considering the difficulties in defining end-stage heart disease, estimating prognosis in the individual patient and the continuing evolution of available therapies, the present criteria are broadly defined. The decision to accept a patient for transplantation will be made after careful evaluation by the transplant team with broad experience in this increasingly complex field and which will try to make the most optimal management plan for the individual patient. This includes optimal pharmacological and non-pharmacological management, like ICD, CRT, revascularization and alternative surgical options. Only on optimal therapy, patients should be considered for transplantation.⁶ The general experience is that the majority of patients referred for transplantation are never listed and that those who are listed, rarely are listed immediately after referral.¹⁴ Deferring transplantation in eligible patients, not believed to need immediate listing, appears safe and may potentially increase their overall survival, as the post-transplant course is associated with a limited life expectancy.^{1,14}

Estimation of prognosis in patients with heart failure

Estimation of the prognosis in individual patients is extremely difficult, because of the large variability in the clinical course of heart failure. Stable periods alternate with acute deteriorations, which may or may not stabilize again.

No single test or measurement has enough predictive power to stratify patients.¹⁵

In patients with stable heart failure, measurement of peak oxygen consumption with exercise (VO₂ max) can be used to select those with the worst prognosis. In general a peak VO₂ = 14 ml/kg/min, or less than 50% of predicted for age and gender, during anaerobic exercise (respiratory quotient, RQ =1.05) is thought to delineate a group of patients who potentially benefit from heart transplantation.¹⁶ In patients on beta-blockers a survival advantage of heart transplantation at 1 and 3 years has been demonstrated only in those with a peak VO₂ <12 ml/kg/min.¹⁷

In addition to peak VO₂ one can use the ventilatory response to exercise (VE/VCO₂, EqCO₂) as a prognostic marker, because this can be measured throughout the entire exercise duration and is independent of patient motivation. The VE/VCO₂ slope during exercise is steeper in patients with more severe heart failure and can be regarded as a continuous risk factor for mortality. A VE/VCO₂ slope > 35 identifies an increased risk for early mortality and this risk is even higher when this slope is > 40-45.¹⁸⁻²⁰

The combination of several other non-invasive measures can contribute to the estimation of prognosis in patients with heart failure. Of the many risk factors available, 7 have been used and validated in patients undergoing transplant evaluation: the Heart Failure Survival Score (HFSS), (Table 2).²¹ Although this risk score was made in the days before widespread use of beta-blockers, also in patients on beta-blocker this scoring system provides effective risk stratification.²²

Nowadays, the levels of BNP or NT-pro-BNP and their reactions on therapy can also be taken into consideration as predictors of a bad prognosis, although large studies are lacking.^{23,24}

The timing of evaluation is an important aspect of the risk assessment in heart failure patients. It will be clear that the risk score is considerably worse in severely congested patients and can be improved by increasing the medication. Therefore, evaluation should only be done in optimally treated patients. Worsening of condition over time, for instance a gradual decrease in peak VO₂ in consecutive exercise tests, or repeated admissions in hospital for the treatment of decompensation, may also delineate transplant candidates.²⁵

The estimation of prognosis in hospitalized patients with acute heart failure is even more difficult than in stable, ambulatory patients. Some patients deteriorate so rapidly that only an urgent heart transplantation or mechanical support can save them. Others, however, stabilise and may show gradual improvement in the course of months or years. This is especially the case in patients with a first manifestation of a cardiomyopathy.²⁶

The HFSS is not validated for patients hospitalized with acute heart failure.

The Acute Decompensated Heart Failure National Registry (ADHERE) identified 3 variables at hospital admission which correlated with increased mortality: serum urea >15 mmol/L, systolic blood pressure <115 mm Hg. and serum creatinine > 240 µmol/L (Fig 2).²⁷

The Heart Failure Mortality Predicting Score predicts 30-day and 1-year mortality using several admission data, including age, systolic blood pressure, respiratory rate, serum urea, hyponatremia and some co-morbid conditions.²⁸ An electronic version of this risk score is available at: <http://www.ccort.ca/CHFriskmodel.asp>.

Both risk scores, however, apply more to the general heart failure population with older age, than to patients thought of as realistic transplant candidates. Regular consultation of a heart transplant center to discuss therapeutic options in these difficult patients is therefore advisable.²⁵

Given the dynamic nature of the clinical course of heart failure, patients on the waiting list for heart transplantation, as well as patients deemed too good for transplantation at first evaluation, should be regularly re-evaluated. (see “decision making”)

The implications of co-morbidities (Table 1)

- *Irreversible pulmonary hypertension / elevated pulmonary vascular resistance (PVR)*
- *Active systemic infection*
- *Active malignancy or history of malignancy with probability of recurrence*
- *Inability to comply with complex medical regimen*
- *Severe peripheral or cerebrovascular disease*
- *Irreversible dysfunction of another organ*

Irreversible pulmonary hypertension / elevated pulmonary vascular resistance

Irreversible elevated PVR is generally poorly tolerated by the right ventricle of the donor heart. This may result in acute right sided failure, sometimes resulting in peri-operative

death of the recipient.^{29,30} An absolute cutoff value, however, does not exist. Elevated pulmonary vascular resistance has to be seen as an incremental risk factor from low to high values.

Therefore, in patients evaluated for transplantation, a right heart catheterization is mandatory. As mentioned before, this should only be done in an optimally treated patient. A vasodilator challenge should be administered when the pulmonary artery systolic pressure is ≤ 50 mm Hg and either the transpulmonary gradient (TPG = PA mean-PCWP) is ≤ 15 mmHg or the PVR is > 3 Wood Units (> 240 dynes.sec.cm⁻⁵). Drugs mostly used for this acute challenge are prostacyclin, nitroglycerin and nitroprusside. Other drugs, like nitric oxide, dobutamine and milrinone can also be used.

A severely increased risk of right heart failure and mortality after heart transplantation is thought to be present.³¹

- when the PVR is > 5 Wood Units (> 400 dynes.sec.cm⁻⁵), or the PVRI is > 6 Wood Units.m² (in children), or the TPG exceeds 16-20 mm Hg.
- if the systolic pulmonary artery pressure exceeds 60 mm Hg in conjunction with any 1 of the preceding 3 variables.
- If the PVR can be reduced to < 2.5 with a vasodilator only at the cost of a fall of arterial systolic blood pressure < 85 mm Hg.

Active systemic infection

An active systemic infection at the time of heart transplantation, when recipients are treated with high doses of immunosuppressive drugs, is still seen as an important contraindication, at least temporary. Persistent infections, like HIV pose a problem, as the chronic use of immunosuppressive drugs in this already immunodeficient population is generally thought to give rise to serious complications. There are scarce, but growing data of organ transplantation in these patients, although data about long-term outcome are lacking. Given the increasing shortage of donor hearts one has to wonder if these patients really are the optimal candidates for this form of therapy.

Active malignancy or history of malignancy with probability of recurrence

Active neoplasm from origins other than skin is an absolute contraindication to heart transplantation due to the limited survival rates.³¹ Patients with a history of malignancy can be considered for heart transplantation when the risk of tumor recurrence is low, preferable after a reasonable time of complete remission, depending on tumor type, response to therapy and negative metastatic work-up.

Inability to comply with complex medical regimen

Compliance, the capacity to adhere to a complex lifelong regime of drug therapy, lifestyle changes and regular follow-up, is a crucial element in attaining long-term success after transplantation.³¹ This includes the adequate use of all medication, because suboptimal use of immunosuppressive medication plays a roll in most acute rejections occurring more than 6 months after transplantation and that it is also related to subsequent cardiac allograft vasculopathy (chronic rejection).³²

Also substance abuse (alcohol, drugs) and tobacco use have to be taken into consideration as it is thought that especially substance abuse is an important predictor of non-compliance.³³ Tobacco use continues to be the foremost avoidable cause of death in the

western world with an enormous impact on cardiovascular diseases and malignancies. Small studies have demonstrated increased incidence of coronary allograft vasculopathy and malignancy, along with decreased survival in those patients who return to smoking after transplantation.³⁴ Active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation and therefore considered a relative contraindication.³¹

To evaluate the patient's ability to comply with instruction including drug therapy, a psychosocial assessment should be performed before listing for transplantation.

Severe peripheral or cerebrovascular disease

Systemic vascular disease may contribute to both poor prognosis for survival as well as poor quality of life on a noncardiac basis and therefore should be considered as a major co-morbidity that can preclude eligibility for heart transplantation.¹⁰

The severity of symptoms and the potential options for revascularization may affect this decision.

It has been suggested that the progression of vascular disease may be accelerated after heart transplantation, especially in patients transplanted for ischemic heart disease.³⁵

Irreversible dysfunction of another organ

Co-morbidities can have an important impact on the decision about acceptance for transplantation and should be searched for in every patient. All co-morbidities which adversely influence prognosis after transplantation should be weighed individually.

In this respect, renal function is a very important risk factor for mortality post transplantation.^{1,36} Irreversible renal dysfunction with a GFR < 40 ml/min, as estimated by the creatinine clearance or sMDRD equation, can be considered as a relative contraindication for heart transplantation.³¹ In general, renal function will further deteriorate after heart transplantation, partly as a result of the nephrotoxic immunosuppressive drugs. The incidence of chronic renal failure (GFR < 29 ml/min), 5 years after heart transplantation is estimated to be 7-21% and severely compromises prognosis.³⁷ Many patients after heart transplantation end up on dialysis or even secondary kidney transplantation.

Although combined transplantation of a heart and a kidney from the same donor is now technically feasible it should only be considered in the most appropriate individuals to maximize the supply of limited organs.³¹

Other co-morbidities which should be emphasized are diabetes mellitus and obesity. In the early years of heart transplantation, diabetes mellitus was considered an absolute contraindication by all centers. With growing experience it was recognized that selected patients with uncomplicated diabetes demonstrated the same prognosis after heart transplantation as patients without diabetes. This was recently confirmed in a large study on 20,000 heart transplant recipients of which 3600 had diabetes before transplantation. Patients with diabetes-related complications, including renal failure (Serum Creatinine > 220 µmol/L), peripheral vascular disease, cerebrovascular accident and severe obesity had a significant worse survival than nondiabetics however. Therefore, diabetes with complications should be considered as a relative contraindication.³⁸

Regarding obesity, there are many data of its adverse influence on prognosis.¹ One study demonstrated a 5-year mortality post-transplantation almost twice as high in obese patients (BMI > 30 kg/m²) in comparison to normal-weight patients (53% vs 27%,

respectively).³⁹ Given the poor outcome of obesity after transplantation, weight loss should be mandatory to achieve a BMI < 30 kg/m² before listing for transplantation.³¹

All other diseases that may limit prognosis after heart transplantation should be discussed on an individual basis.

Donor selection and management

This subject is extensively covered in the new protocol of the Dutch Transplant Society (NTS, Nederlandse Transplantatie Stichting),⁴⁰ which has been published recently. Here, it suffices to say that in principle every brain-dead patient is regarded as a potential multi-organ donor and that heart-beating donation is preferred over non-heart beating procedures. For heart donation, the upper age limit is \pm 65 years. The only absolute specific cardiac contra-indication for heart donation is the presence of important heart disease, like angina pectoris, myocardial infarction, prior coronary bypass surgery, moderate to severe valvular disease, cardiomyopathy and important arrhythmias. General contra-indications for all donations are for example, untreated sepsis, malignancies and active infections.

In the work-up of a potential heart donor, the medical history, an electrocardiogram and a Trans-Thoracic Echocardiogram (TTE) are essential, besides hemodynamic data and markers for cardiac damage, including troponin. In case the left ventricular function cannot be reliably evaluated by TTE, because of insufficient acoustic window in a ventilated patient, Trans Esophageal Echocardiography (TEE) is mandatory. In hemodynamically unstable patients, a Swan-Ganz catheter should be used to optimize the filling status of the patient. Given the generally older donor age in the Netherlands, coronary angiography can be helpful to rule out significant coronary artery disease in elderly donors or other patients with risk factors for coronary artery disease.

Patient-oriented allocation of donor organs is done by Eurotransplant (ET), according to blood group, body size, medical urgency and waiting time. The final acceptance of a donor heart is the responsibility of the transplantation team, which will weigh all the donor data in combination with the actual situation of the potential recipient. Although donor age especially has increased in our country, it still plays an important role in this decision because the results of heart transplantations with older donor hearts (= 50 years) are worse than with younger donor hearts. This relates to early post-operative mortality, but correlates also with the early presence of transplant related coronary artery disease.⁴¹⁻⁴³ Donor age therefore has to be seen as an important continuous risk factor for mortality post heart transplantation, especially combined with long ischemic times of the donor heart.¹ The higher risk of using hearts from older donors will always be weighed against not transplanting at all due to lack of a younger donor.

Decision making

As stated before, the indications and contraindications for heart transplantation as well as the guidelines for the acceptance of donor hearts are broadly defined. The final acceptance is done by the transplant team which has extensive knowledge of the treatment of patients with advanced heart failure on the one hand and thorough experience with heart

transplantation and mechanical circulatory support on the other hand. Heart transplantation is a very laborious treatment modality for only a few patients. It requires a dedicated team of specialists, consisting of at least a cardiologist trained in infectiology and immunology, a cardio-thoracic surgeon, an anesthesiologist, and specialized nurses. One has to realize that, in contrast to other medical therapies, heart transplantation is a form of therapy with very limited “resources” and therefore requires extensive judgment to make the most optimal use of this modality.

That is why it is also important that outpatients on the waiting list for heart transplantation should be regularly re-evaluated (every 6 months) preferably with cardio-pulmonary exercise testing. If they have improved significantly, they may be candidates for delisting.³¹

In case a patient or his/her referring physician does not agree with the decision of the transplant team, a second opinion in one of the other centers is possible.

The heart transplantation centers will organize a meeting, twice a year, in the presence of outside observers eg referring cardiologists, to discuss referred patients and the reasons for listing or not-listing. Furthermore, potential donor offers can be discussed. In this way the whole process of decision making will hopefully be more transparent for those interested.

Referral

Referral of a patient to a transplant center should be preceded by sending extensive written information including a summary of the complete medical history and actual data (Table 3).

Table 1: The indication and contraindications for heart transplantation

Indication for heart transplantation:
End-stage heart disease not remediable by more conservative measures
Contraindications:
<ul style="list-style-type: none"> • Irreversible pulmonary hypertension /elevated pulmonary vascular resistance • Active systemic infection • Active malignancy or history of malignancy with probability of recurrence • Inability to comply with complex medical regimen • Severe peripheral or cerebrovascular disease • Irreversible dysfunction of another organ, including diseases that may limit prognosis after heart transplantation

Table 2: The Heart Failure Survival score

Clinical characteristic	Value (a)	Coefficient (β)	Product
Ischemic cardiomyopathy	Yes = 1 No = 0	+0.6931	a x β
Resting heart rate /min	+1.9440	a x β
LV-EF %	-0.0464	a x β
Mean BP mm Hg	-0.0255	a x β
IVCD	>120 msec = 1 < 120 msec = 0	+0.6083	a x β
Peak VO ₂ ml/kg/min	-0.0546	a x β
Serum sodium mmol/L	-0.0470	a x β

The Heart Failure Survival Score (HFSS) is calculated by taking the absolute value of the sums of the products of each component's variable value and its model coefficient.

Low-risk strata: = 8.10; Medium-risk strata: 7.20 to 8.09; High-risk strata: < 7.20

(IVCD = intra ventricular conduction delay)

Table 3: Requested information for referral of a potential heart transplant candidate

• Summary of the complete medical history (cardiac as well as non-cardiac)
• Actual medication and history of intolerance to medication
• Surgery report in case of prior cardiac surgery
• Heart catheterization data (left- and right sided pressures, cardiac output, PVR, SVR and coronary angiography)
• Evaluation of the present status of the patient:
a) Functional class and predominant symptoms/problems
b) Physical examination including peripheral/carotid vessels, and oral cavity (dental status)
c) ECG
d) Chest X-ray
e) Blood type and Rhesus factor, electrolytes, renal and liver function, glucose, ESR or CRP, Hb, white blood count and differentiation, platelets. Serology for HBV and HCV and HIV. Urine analysis for protein, glucose and sediment. Stool tests for blood loss.
f) Echocardiogram (dimensions, systolic and diastolic ventricular function, estimation of right sided pressures, valvular abnormalities)
g) Exercise test, preferably with determination of peak VO ₂ .
h) Pulmonary function testing

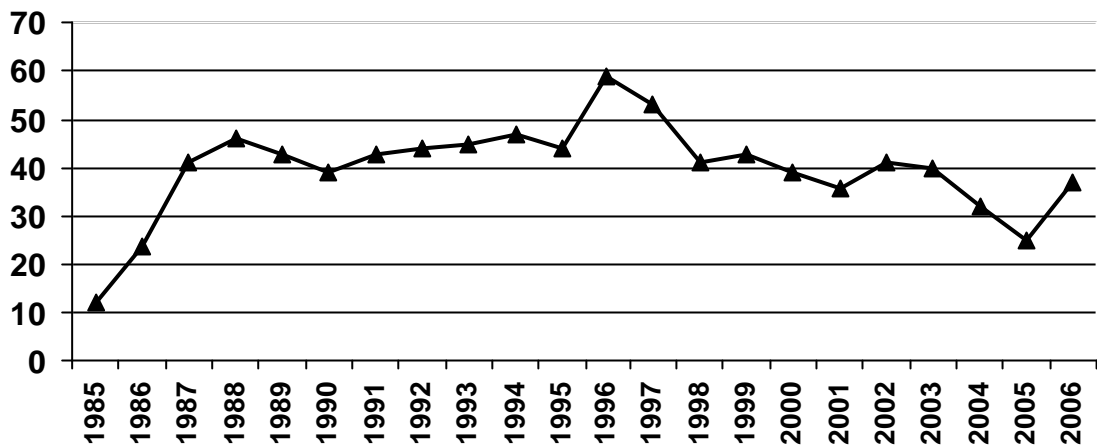


Figure 1a.

The number of heart transplantations in the Netherlands per year.

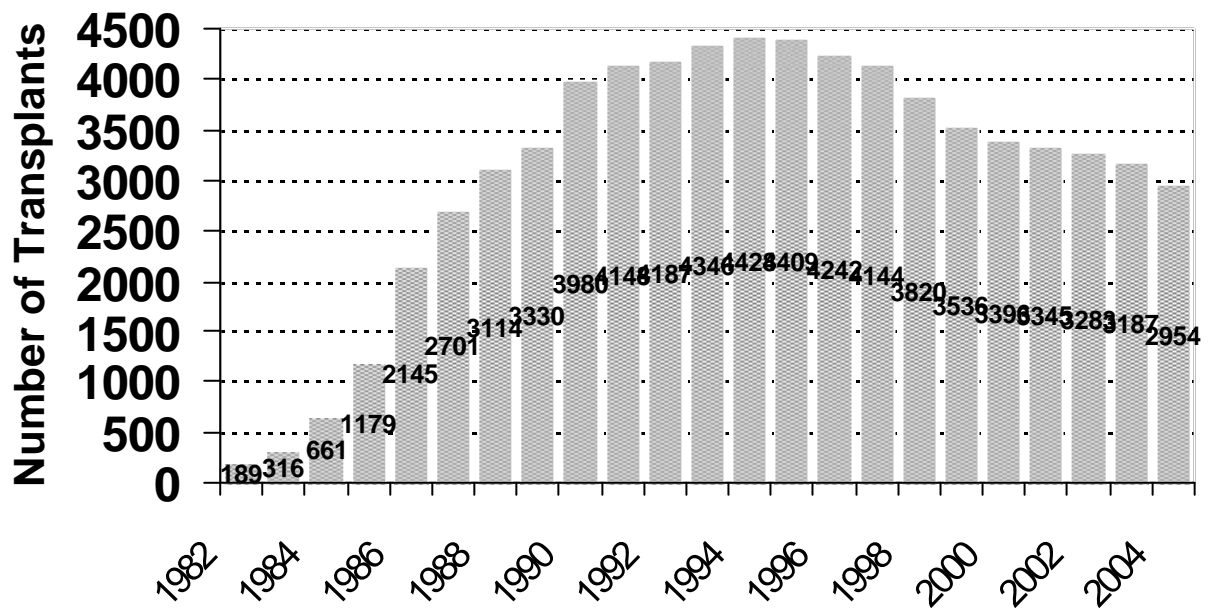


Figure 1b.

The number of heart transplantations worldwide, according to the ISHLT

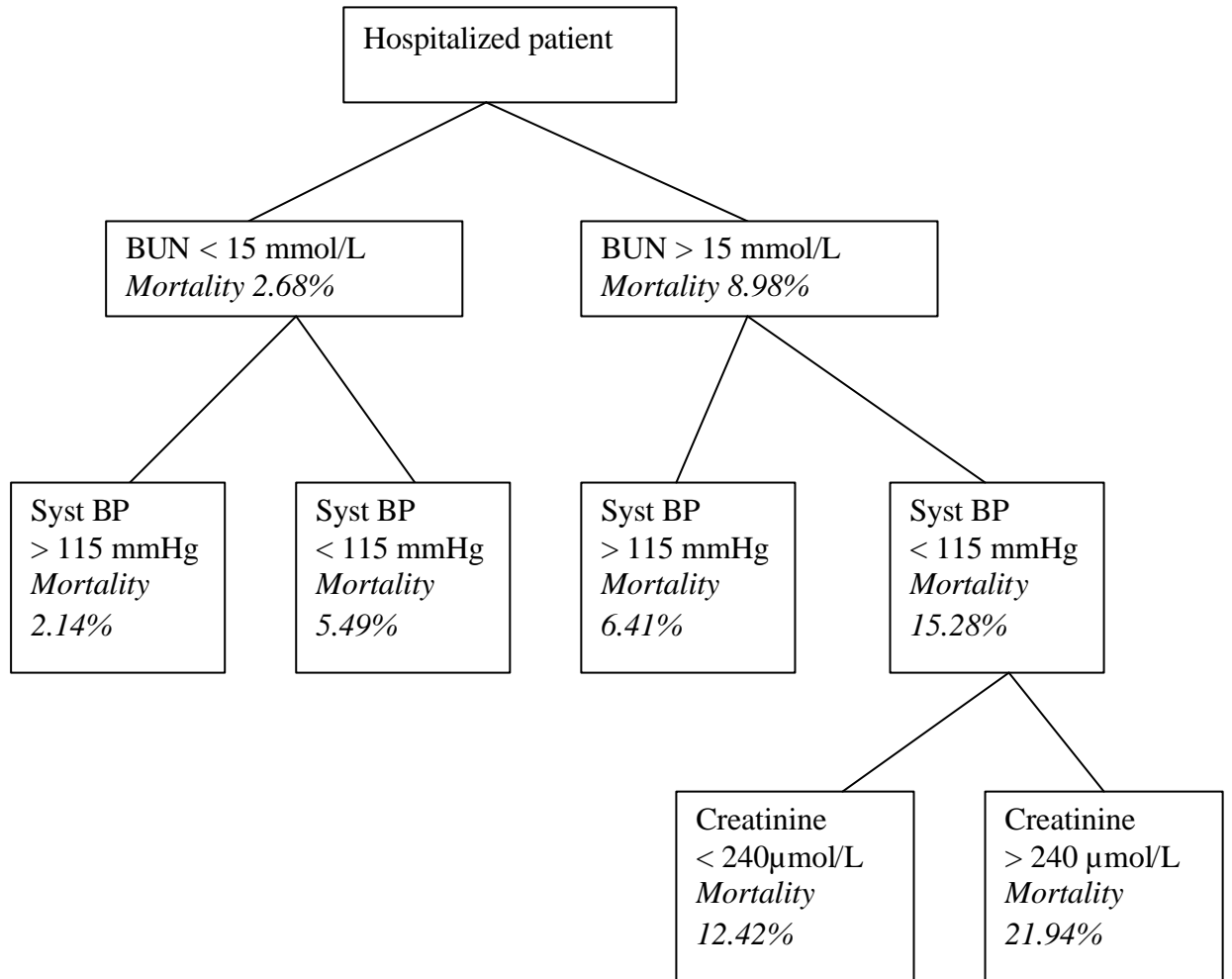


Figure 2.

Predictors of In-Hospital mortality according to the Acute Decompensated Heart Failure National Registry (ADHERE).

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Appendix

The committee consisted of the following persons:

Chairman: prof.dr. P. Sergeant
 Dr. N. de Jonge, Dr. A.H.M.M. Balk, C. Klöpping, A. Oosterom, A. Oomen, Dr. E.T. Bal, Prof.Dr. J-W. Lammers, A. Golüke, D. Nicastia, M. Koole, H.F. Verwey, Prof.Dr. P.W. Boonstra, Prof.Dr. P. Doevendans, Dr. J.H. Kirkels, Dr. J Brügeman, Dr. M.E. Erasmus, Dr. R.J.M. Klautz, M.L.M. Versteegh, C. Lucas, C.H. Peels, Prof.Dr.Mr.Ir. H.A. van Swieten, E. de Buijzer, K. Calsikan, A.P.W.M. Maat, Dr. J.R. Lahpor.