Aims
To determine the clinical management of cardiovascular complications, and the extent of cardiac left ventricular (LV) involvement, in a large cohort of homogenously treated patients with thalassaemia major.

Methods and results
Participants were ≥16 years of age and diagnosed with thalassaemia major requiring regular blood transfusions since the age of 2. Patient characteristics, clinical and echocardiography data for 524 patients were extracted from Webthal™, an Internet-shared database. Patients were considered to have evidence of cardiovascular disease if at least one cardiovascular drug was recorded in their file. The majority of patients (422 of 524; 80.5%) had not taken any cardiovascular drug. Among those who had angiotensin-converting enzyme-inhibitors were the most commonly used (81 patients) and these were used by significantly more males than females (P < 0.01). Patients in whom cardiovascular drugs were prescribed showed evidence of cardiac structural and/or functional abnormalities, inasmuch as fractional shortening and ejection fraction were significantly lower (31.3 vs. 35% and 54.4 vs. 60.6; both P < 0.001) and LV end-diastolic diameter index was significantly higher (32.9 vs. 31.8; P = 0.004). Interestingly, when compared with patients in whom cardiovascular drug therapy was not deemed necessary, transfusion period was longer in treated patients (26.2 vs. 24.5 years; P = 0.002).

Conclusion
Approximately 19% of regularly transfused and chelated thalassaemia major patients need cardiovascular drug therapy. This subgroup is characterized by a dilated and mildly hypokinetic left ventricle when compared with the majority of thalassaemia major patients, who do not need any cardioactive drug. These data underscore the importance of careful evaluation of cardiac functional status in patients with thalassaemia major. Moreover, this database may serve as a clinically useful reference grid for echocardiograph values in this patient population.

Keywords
Thalassaemia major • Cardiac dysfunction • LV ejection fraction

Introduction
Advances in the current treatment of β-thalassaemia major have contributed to improve prognosis, and nowadays, an increasing number of patients do survive up to the third or fourth decade. Indeed, a long-term Italian study recently reported that 68% of patients with thalassaemia major were alive at the age of 35.1–3 A wide spectrum of complications, including
Cardiovascular involvement in patients with thalassaemia major

those related to iron overload (endocrinopathies, liver disease, and heart diseases), blood-borne infections, and toxicity from iron chelation, may arise from the obligatory blood transfusions. The incidence of these complications in an Italian series of patients born after 1970 included heart failure (7%), hypogonadism (55%), hypothyroidism (11%), and diabetes (6%). Cardiac complications secondary to iron overload are the leading cause of death in thalassaemia major, occurring in ~70% of patients. Lower ferritin levels are associated with a lower probability of experiencing heart failure and increased survival. Although cardiac function remains normal for many years, once heart failure symptoms become evident, death usually occurs within 1 year. Although heart failure is mainly characterized by left ventricular (LV) dysfunction, right ventricular involvement has also been documented in a small number of patients. Available data on cardiac disease in thalassaemia major are largely derived from earlier studies, with patients who were poorly transfused, not chelated, and had reduced survival. More recently, studies have included patients undergoing intensive transfusion and chelation therapy, albeit with variable compliance. In addition, some studies were focused only on ventricular function, without investigating other significant aspects of thalassaemia-related heart disease, such as pulmonary hypertension. Furthermore, evaluation of LV structure and function in this clinical setting is subject to many influences: thalassaemia major patients have growth retardation with a small body surface area compared with unaffected subjects; the degree of chronic anaemia may affect cardiac output and secondarily ventricular size. Therefore, both definition and interpretation of LV size and function in thalassaemia major are variable and somewhat conflicting in the available literature. As a consequence, although LV size and function are known to differ between thalassaemic patients and normal subjects, standard normal range of echocardiographic data in thalassaemia major patients with adequate transfusion and chelation is currently unknown.

To assess the clinical impact of cardiac complications and of LV involvement in a large cohort of homogenously treated patients with thalassaemia major, we took advantage of Webthal®, a large co-operative project among thalassaemia centres throughout Italy. Based on Internet-shared software, Webthal® gathers information on age, gender, clinical and biochemical data, co-morbidities, transfusion treatment, iron chelation, pharmacological therapies, and echocardiographic data. It is aimed at characterizing demographic and clinical features, effects, and complications of different treatment strategies in a large cohort of patients with thalassaemia major, thalassaemia intermedia, and haemoglobin E-thalassaemia. Webthal® allows for rapid extraction of information concerning the status of patients, thus enabling investigators to select patients from different centres who have been treated homogeneously according to international guidelines, so that they may be compared with patients anywhere in the world who are treated according to such standards.

Aim of the present survey was to assess cardiac involvement in a large cohort of homogenously treated thalassaemia major patients.

Methods

Patient population

Five Italian centres (Genoa, Milan, Turin, Cagliari, and Brindisi) were involved in the current survey. All participating institutions were referral centres with specializing in haemoglobinopathies and all have similar treatment protocols for thalassaemia.

To be included in the survey, patients had to be ≥16 years old, diagnosed with thalassaemia major defined as homozygous or compound heterozygous thalassaemia requiring regular blood transfusion therapy from the age of 2 years. The observation period was from 1997 to 2007.

Data on age, gender, age at first transfusion, duration of transfusion treatment, mean yearly values of pre-transfusional haemoglobin, and ferritin levels over the last ten years, splenectomy, age at splenectomy, the use of cardiovascular drugs, complications, and data from echocardiographic examinations performed within the last 6 months were extracted from Webthal®. These characteristics were compared with cardiac status. Data on chelation therapy (age at start, dose, compliance, and type of chelator) were not collected, due to the difficulty in organizing and correlating this kind of information over such a long period.

Patients were considered to have evidence of cardiovascular disease at least one cardiovascular drug [diuretics, digoxin, angiotensin-converting enzyme (ACE)-inhibitors, or antiarrhythmic drugs] was recorded in their file. Echocardiographic variables in this group were compared with patients who did not need any cardiovascular drug.

Echocardiography

LV dimensions, obtained from parasternal long- and short-axis views using two-dimensional-targeted M-mode echocardiography, were normalized by body surface area calculated from patient height and weight. LV ejection fraction (LVEF%) was calculated using the area-length method. Systolic pulmonary artery pressure (PAP) was estimated using continuous wave Doppler recordings of tricuspid regurgitation. All echocardiographic measurements were obtained as previously described. Data were evaluated by two independent cardiologists blinded to the patient status, as defined by the presence or absence of cardiovascular therapy.

Statistical analysis

Percentages were calculated on the total data available. Frequency tables were reported for qualitative variables and, if a comparison was required, a χ² test was performed; in cases where subgroups were small (<5 patients), Fisher’s exact test was applied. Quantitative variables were tested by one way ANOVA and mean, standard deviation, and 95% confidence interval were reported. For all tests, a P-value <5% was considered statistically significant and <1% considered highly significant.

Results

Patients characteristics

A total of 544 patients with thalassaemia major were identified at the five participating institutions by searching the Webthal® database, and the 524 of these (mean age 26.17, range 16–46) who met the inclusion criteria for this survey were included in the final cohort. An equal number of male and female patients were
The use of cardiovascular drugs ranged from 12.1 to 25.5% among participating centres. In total, 102 out of 524 patients (19.5%) received one or more cardiovascular drugs; the majority were males (66%; n = 67), with a mean age of 28 years. Monotherapy was prescribed to one-third of patients taking cardiovascular drugs, whereas co-medication with at least one additional cardiactive drug was recorded in 66 patients (65%). ACE-inhibitors were the most commonly used drugs (81), followed by diuretics (39), β-blockers (24), antiarrhythmics (16), and digitalis (8; Table 2).

There were statistically significant gender differences in the use of ACE-inhibitors and antiarrhythmics, which were more often prescribed in male than in female patients (56 vs. 25, respectively). No significant differences were found for other cardiovascular drugs. When compared with control patients, the presence of cardiovascular drug prescription was associated with higher prevalence of splenectomy (P = 0.006) and of complications resulting from iron overload: acquired hypoparathyroidism (P = 0.018), insulin-dependent diabetes (P = 0.004), hypogonadism (P = 0.001), and impaired glucose tolerance (P = 0.008).

Control patients, i.e. those in whom no cardiovascular drug was ever prescribed (n = 422 out of 524; 80.5%), did not experience symptoms of heart failure or clinically relevant arrhythmias.

**Echocardiography**

In the whole cohort, mean values of fractional shortening (FS%), EF%, and LV end-diastolic diameter index were 34.2, 59.3%, and 32 mm/m², respectively. Global LV systolic function was significantly lower in males compared with females: EF% [58.1 (range 57.0–59.2) vs. 60.6 (range 59.6–61.5); P < 0.001] and FS% [33.7 (range 33.0–34.5) vs. 34.8 (range 34.1–35.5); P = 0.05], respectively.

Systolic PAP was elevated (>25 mmHg) in 46 patients (8.8%) and was >30 and >35 mmHg in 29 (5.5%) and 16 (3.1%) patients, respectively.

When compared with patients not taking any cardiovascular drug (n = 422, 80.5%), subjects with cardiac therapy had a significantly lower FS% (P < 0.001) and EF% (P < 0.001), a higher LV end-diastolic diameter index (P = 0.004) and had been on transfusion therapy for a longer period (P = 0.002; Table 3).

**Discussion**

The current survey was aimed at assessing cardiac involvement in patients with thalassaemia major who had been adequately treated according to international standards. To date, no clear definition of cardiac involvement in thalassaemia syndromes, with particular attention to thalassaemia major, has been established. The most recent edition of Braunwald’s Heart Disease describes cardiac involvement in haemochromatosis as ‘a mixed dilated cardiomyopathy—restrictive cardiomyopathy pattern with both systolic and diastolic dysfunction often with associated arrhythmias’. However, this definition is based on data from small cohorts of patients affected by haemochromatosis with a variety of aetiologies and is not specifically related to patients with thalassaemia major with transfusional iron overload.

Regimens for transfusion and chelation therapy for patients with thalassaemia major vary by country depending on healthcare system regulations and drug availabilities. Consequently, data from different countries are heterogeneous and not easily comparable in clinical studies, which has hindered a clear definition of the pathophysiological features of the disease. To achieve this goal, a
co-operative project among thalassaemia centres based on an Internet-shared database for thalassaemia (Webthal®) was established. This database contains information from a large population of patients with haemoglobinopathies and allows the rapid extraction of information.

In the present survey, Webthal® was used to select homogeneously treated patients over a long follow-up period, according to the current international guidelines, throughout different centres. The majority of patients (80.5%) did not take any cardiovascular drug, nor did they experience symptoms of heart failure or clinically relevant arrhythmias. In these patients, clinical and echocardiographic variables may be viewed as ‘reference values’ for a regularly transfused and chelated thalassaemia major population. Indeed, echocardiographic parameters were similar to those previously reported in thalassaemia major patients with no obvious cardiac disease.2,15 Interestingly, estimated systolic PAP was elevated (>25 mmHg) in 8.8% of patients, thus confirming our previous data showing a low prevalence of pulmonary hypertension in a thalassaemia major population.16

In the current survey, evidence of cardiac involvement was defined by the use of cardiovascular drugs,12 as recorded in the Webthal® database. The most commonly used cardiovascular drug were ACE-inhibitors, with a significantly higher prescription rate in male than in female patients (P < 0.001). Notably, none of the patients was affected by arterial hypertension, one of the main indications for ACE-inhibitors use. Since these drugs are used not only in treatment of heart failure but also in its prevention, it is possible that they were used in asymptomatic patients with signs of early LV dysfunction, such as LV enlargement. Indeed, the ACE-inhibitor enalapril has been shown to improve LV dysfunction in asymptomatic or minimally symptomatic patients with thalassaemia major, although it is not known whether this leads to improved long-term prognosis.17

Patients taking cardiovascular drugs were older and had had regular transfusions for significantly longer than control patients. Moreover, patients treated with cardiovascular drugs had a significantly lower FS% and EF% and significantly higher LV end-diastolic diameter index. Reduction in LVEF is associated with increased mortality in thalassaemia major.18

Taken together, these data indicate that cardiac involvement is mainly characterized by a dilated and mildly hypokinetic LV and that this occurs in ~19% of the regularly transfused and chelated adult thalassaemia major population.

LV dysfunction is likely to be related to long exposure to iron overload in the heart. A significant relationship between increasing myocardial iron loading and decreasing LV function has been demonstrated19,20 arguing that patients with decreased LV systolic function should be considered a priori as having cardiac iron overloading and that chelation treatment should be increased. Numerous studies have shown that lower ferritin levels reduce the occurrence of complications, resulting in a better prognosis.1,8,9 Depending on when patients were born and subsequently entered into Webthal® in relation to the study period, not all patients underwent cardiac magnetic resonance imaging (MRI) evaluation for myocardial iron, and therefore, these data are not reported in this survey.

Webthal® offers easy access to a large dataset of patients, which is important for pathologies such as thalassaemia major because patients are scattered among different specialized centres. This survey has allowed us to define a profile of patients with thalassaemia major not requiring cardiovascular drugs that may be useful in everyday clinical practice for distinguishing between patients with and without cardiac involvement. For example, the echocardiographic mean EF% reported herein differs significantly from MRI calculated EP% in thalassaemia major patients with normal myocardial iron recently reported by Westwood et al.15 This discrepancy is not explained by technical differences between MRI and ultrasound (US), since discrepancies in the estimation of volumes affect both diastolic and systolic measurements.21

In conclusion, our survey has shown that cardiac involvement, as assessed by prescription of cardiovascular drugs, is characterized by a dilated and mildly hypokinetic left ventricle and occurs in ~19% of a regularly transfused and chelated thalassaemia major population. These data underscore the importance of careful evaluation of cardiac functional status in patients with thalassaemia major. Moreover, this database may serve as a clinically useful reference grid for echocardiograph values in this patient population.

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**Table 3** Mean clinical and echocardiographic data for patients with and without left ventricular dysfunction

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Normal patients [mean (95% CI)]</th>
<th>Patients with LVD [mean (95% CI)]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-transfusional Hb (g/dL)</td>
<td>9.4 (9.3–9.5)</td>
<td>9.5 (9.4–9.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Ferritin (mcg/dL), mean of last 10 years</td>
<td>2027.7 (1864–2191)</td>
<td>2389.6 (2022–2756)</td>
<td>ns</td>
</tr>
<tr>
<td>LVEDD index (mm/m²)</td>
<td>31.8 (31.5–32.2)</td>
<td>32.9 (32.2–33.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>LVFS%</td>
<td>35.0 (34.4–35.5)</td>
<td>31.3 (30–32.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF%</td>
<td>60.6 (59.8–61.3)</td>
<td>54.4 (52.7–56.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of transfusion period (years)</td>
<td>24.5 (24–25)</td>
<td>26.2 (25.1–27.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; EF, ejection fraction; FS, fractional shortening; LV, left ventricular; EDD, end-diastolic diameter; LVD, left ventricular dysfunction.
Conflict of interest: none declared.

References
10. G. Derchi et al. 246