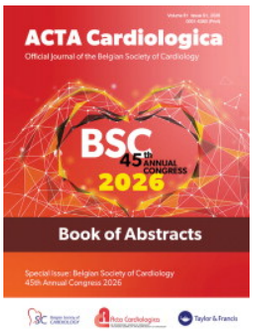

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ORIGINAL SCIENTIFIC PAPER

Rare cardiovascular diseases: diagnostic progress and organizational gaps: the Belgian perspective

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ABSTRACT

Rare cardiovascular diseases represent a heterogeneous group of conditions that are individually uncommon but collectively significant. They include inherited cardiomyopathies, infiltrative and metabolic disorders, channelopathies, aortopathies, as well as rare vascular syndromes and some congenital heart diseases. Over the last decade, major advances in multimodality imaging, genetic testing, and targeted therapies have substantially improved diagnostic accuracy and clinical outcomes. Patient-tailored management and disease-modifying treatments, particularly for cardiomyopathies and selected metabolic disorders, illustrate the transition towards precision medicine in the field. Despite these scientific advances, important organisational challenges remain. In Belgium, eight centres are recognised as reference hospitals for rare diseases since 2014, but high-level expertise and advanced technologies are available in more tertiary centres and care pathways for rare cardiovascular diseases remain fragmented. The recent Plan rare disease 2026–2030 with a development of a Central Rare Disease Registry and the extension of structured rare disease event registration to all medical services represent important steps towards improved epidemiological monitoring and coordination. However, formally organising a national network dedicated to rare cardiovascular diseases is a challenge to offer uniform access to specialised care. The framework for collaboration of the reference centres with the different partners over the lines of care, the establishment and support of multidisciplinary clinics, the development of generic and personalised care pathways and national registries are key steps towards more coordinated, equitable, and efficient management of patients with rare cardiovascular diseases in Belgium.

KEYWORDS

Rare cardiovascular diseases; cardiac amyloidosis; precision medicine; health-care organisation

Rare cardiovascular diseases represent a heterogeneous group of conditions that are individually uncommon but collectively significant. In Europe, a disease is defined as rare when it affects fewer than 1 in 2000 individuals. Many rare diseases involve the cardiovascular system, including inherited cardiomyopathies, infiltrative and metabolic disorders, channelopathies, aortopathies, as well as rare vascular syndromes and some congenital heart diseases. Although each condition is uncommon, their cumulative burden is substantial and frequently leads to heart failure, disability, arrhythmias, stroke or premature mortality [1,2]. Over the past decade, major diagnostic and therapeutic advances have transformed the management of these patients. However, important organisational challenges remain, particularly in countries where care pathways are not fully structured.

Rare cardiovascular diseases encompass a broad spectrum of clinical entities, often with genetic or systemic origins (Table 1). Inherited cardiomyopathies, including some forms of hypertrophic cardiomyopathy, as well as arrhythmogenic, restrictive, and specific forms of dilated and non-dilated cardiomyopathies, remain among the most frequent conditions in this group [3]. Channelopathies, including long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, are less common but carry a high risk of sudden cardiac death, often in young individuals with structurally normal hearts [4]. Infiltrative, inflammatory and metabolic disorders, such

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Table 1. Rare cardiovascular diseases (orphanet-based classification).

Main group	Rare disease	Short description
Rare cardiomyopathies	Familial dilated cardiomyopathy	Genetic ventricular dilation and systolic dysfunction
	Hypertrophic cardiomyopathy[a]	Genetic myocardial hypertrophy
	Restrictive cardiomyopathy	Impaired ventricular filling
	Arrhythmogenic cardiomyopathy	Fibro-fatty replacement with ventricular arrhythmias
	Left ventricular non-compaction	Congenital spongy myocardium
	Left ventricular non-dilated cardiomyopathy	Left ventricular systolic dysfunction without dilation
Rare electrical diseases	Congenital long QT syndrome	Prolonged QT with risk of torsades de pointes
	Short QT syndrome	Shortened QT with risk of sudden death
	Brugada syndrome	Channelopathy with ST elevation and sudden death risk
	Catecholaminergic polymorphic ventricular tachycardia	Stress-induced ventricular arrhythmias
Rare aortic/connective tissue diseases	Marfan syndrome	Connective tissue disorder with aortic aneurysm
	Loeys-Dietz syndrome	Aggressive arterial aneurysm syndrome
	Vascular Ehlers-Danlos syndrome	Arterial fragility and rupture
Pulmonary vascular diseases	Idiopathic pulmonary arterial hypertension	Pulmonary hypertension of unknown cause
	Heritable pulmonary arterial hypertension	Genetic PAH (e.g. BMPR2)
Infiltrative/metabolic diseases	Cardiac amyloidosis	Myocardial amyloid deposition
	Cardiac sarcoidosis	Granulomatous inflammatory infiltration causing conduction disease, arrhythmias and cardiomyopathy
	Fabry disease	Lysosomal storage disease with LV hypertrophy
	Pompe disease	Glycogen storage disease with cardiomyopathy
Rare congenital heart diseases	Truncus arteriosus	Single arterial trunk from the heart
	Tricuspid atresia	Absence of tricuspid valve
	Eisenmenger syndrome	Pulmonary hypertension due to congenital shunt
Rare cardiac tumours	Familial cardiac myxoma	Benign intracardiac tumour
	Primary cardiac sarcoma	Malignant cardiac tumour

[a]The most frequently encountered rare cardiovascular diseases in clinical practice include some forms of hypertrophic cardiomyopathy, dilated cardiomyopathy of genetic origin, arrhythmogenic right ventricular cardiomyopathy, congenital long QT syndrome, Brugada syndrome, Marfan syndrome, pulmonary arterial hypertension, cardiac amyloidosis, and Fabry disease.

as cardiac sarcoidosis, cardiac amyloidosis, Fabry disease, Pompe disease, or mitochondrial disorders, often mimic more common cardiac conditions, leading to diagnostic delays [5,6]. Connective tissue disorders, including Marfan syndrome, Loeys–Dietz syndrome, and vascular Ehlers–Danlos syndrome, represent another important subgroup, characterised by progressive aortic or vascular complications [7].

The last decade has witnessed remarkable progress in the diagnosis of these conditions. Multimodality imaging has become central to the evaluation of rare cardiac diseases. Echocardiography remains the first-line tool, but cardiac magnetic resonance provides essential information on tissue characterisation, fibrosis, and infiltration [8]. Nuclear imaging techniques, particularly bone-avid tracer scintigraphy, have revolutionised the non-invasive diagnosis of transthyretin cardiac amyloidosis [9,10]. At the same time, genetic testing, supported by major advances in sequencing technologies, variant interpretation, and the understanding of genetic disease architecture, has become a cornerstone of the diagnostic pathway for inherited cardiac conditions. It enables the identification of causative variants, supports personalised patient management, and facilitates risk stratification of relatives through cascade screening and, when appropriate, prenatal counselling [3,4].

Therapeutic options have also evolved substantially. Several rare cardiovascular diseases now benefit from disease-modifying treatments, or even targeted therapies. The introduction of transthyretin stabilisers such as tafamidis and acoramidis has significantly improved outcomes in patients with transthyretin amyloid cardiomyopathy, reducing mortality and cardiovascular hospitalisations in randomised trials [11,12]. More recently, gene-silencing therapies targeting transthyretin production have emerged. Small interfering RNA and antisense oligonucleotide therapies, such as patisiran, vutrisiran, and inotersen, have demonstrated clinical benefits in hereditary transthyretin amyloidosis and are increasingly evaluated in patients with cardiac involvement [13,14]. Gene editing approach, as well as antibody-based approaches are currently under development [15].

Beyond amyloidosis, enzyme replacement therapies have also modified the natural history of several metabolic cardiomyopathies, particularly Fabry and Pompe diseases [5,6]. In these conditions, treatment directly targets the underlying enzymatic defect, reducing substrate accumulation and slowing the progression of myocardial involvement. In Fabry disease, treatment relies mainly on enzyme replacement therapy or on migalastat, for selected amenable mutations, aiming to restore the deficient enzyme (alpha-galactosidase A) and slow the progression of renal and cardiac involvement [5]. Clinical studies have shown that early initiation of therapy is associated with better preservation of left ventricular function and improved functional

status, whereas delayed treatment is often less effective once advanced fibrosis has developed.

Beyond enzyme replacement strategies, gene-based therapies are rapidly emerging in cardiomyopathies. By targeting the underlying genetic defect, these approaches may provide novel therapeutic perspectives not only for inherited cardiac diseases but also for related neuromuscular and mitochondrial disorders [16].

The Belgian organisational challenge

Despite these scientific advances, the organisation of care for rare cardiovascular diseases remains a major challenge. The complexity of these conditions requires multidisciplinary expertise, advanced diagnostic tools, and long-term follow-up in specialised settings. Many countries have therefore developed structured national networks of expert centres to ensure coordinated and equitable care. At the same time, therapies for rare diseases are frequently associated with significant medical and socio-economic challenges. Many of these treatments are complex to administer and entail substantial costs, placing an increasing burden on national healthcare systems.

Belgium benefits from several important strengths. Eight university hospitals have been recognised as reference hospitals for rare disease since 2014. Besides these university hospitals large non-university tertiary centres have developed specialised centres with dedicated multidisciplinary teams with significant expertise in cardiomyopathies, inherited arrhythmias, aortopathies, and infiltrative diseases. Advanced imaging modalities, including cardiac magnetic resonance and nuclear techniques, are widely available in these Belgian institutions, allowing a rapid access to diagnosis when combined with awareness and educational campaigns. Belgian centres are actively involved in international registries and European research initiatives, and patients generally have access to innovative therapies, including disease-modifying treatments for conditions such as transthyretin amyloidosis or cardiomyopathy, including Fabry disease. At the European level, collaboration between expert centres is further supported by European Reference Networks (ERNs), including ERN GUARD-Heart, VASCERN, euro-NMD and ERN-lung, which facilitate access to expertise and coordinated care for rare and complex cardiac diseases.

In parallel, Belgium has initiated national efforts to better identify and monitor patients with rare diseases. A Central Rare Disease Registry has been established to collect data at the national level [2]. Until recently, this registry mainly relied on information derived from genetic consultations. However, in September 2024, Sciensano extended the scope of data collection to all medical services, in collaboration with the national rare disease functions. This evolution represents an important step towards a more comprehensive overview of rare diseases, including cardiovascular conditions. Within this framework, hospitals are progressively implementing structured rare disease event registration systems. These systems allow the creation of a dedicated rare disease record for each patient, the registration of one or multiple rare conditions, and the integration of alerts within the medical file when appropriate. They also provide a global view of follow-up, treatment, and disease evolution. At an institutional level, such structured encoding enables identification of rare disease cases across services, the generation of epidemiological listings, and the estimation of diagnostic delay. Semi-automated data transfer to the national registry is expected to progressively improve the completeness and quality of national data.

Nevertheless, despite these positive developments, the Belgian system remained only partially structured from a cardiology and health economic perspective. Care for patients with rare cardiovascular diseases often depends on local initiatives and individual expertise rather than on clearly defined referral pathways. As a result, the diagnostic journey may vary considerably between regions or institutions. Some patients are rapidly referred to specialised centres, while others experience prolonged delays before reaching an expert multidisciplinary team. In addition, the relatively high number of hospitals per capita in Belgium, including a large proportion of tertiary centres, contributes to a fragmentation of clinical activity. As a result, many centres are exposed to relatively low patient volumes for certain rare conditions, which may limit the consolidation of expertise and raise questions regarding the optimal organisation of care and access to costly therapies.

One of the key limitations was the absence of a formal organisation of the national network of reference centres for rare cardiovascular diseases. Despite the recognition of the expert centres in 2014, Belgium has not yet implemented a clearly defined structure with standardised referral criteria, and coordination between reference and other tertiary centres based on generic and personalised care pathways in this field. This lack of formal organisation leads to variability in diagnostic strategies, therapeutic decisions, and follow-up protocols. Coordination between specialties also remained inconsistent. Many rare cardiovascular diseases involve multiple organ systems and require close collaboration between cardiologists,

geneticists, neurologists, internists, paediatricians and metabolic specialists. In this context, the Belgian Council for Cardiovascular Genomics (Belcargen) has recently been established at the interface between the Belgian Society of Cardiology and the Belgian Society of Human Genetics to promote collaboration, awareness, and education in cardiovascular genomics. Although such multidisciplinary approaches exist in some institutions, they are not uniformly implemented across the country. Access to genetic counselling and structured family screening programs also varies, which may limit early detection in relatives of affected patients. Recently, a plan rare disease 2026–2030 was announced [17]. In a first stage expertise in existing reference centres, but also in other hospitals will be catalogued. Afterwards generic care pathways for every disease will be developed to tackle the described challenges. The care pathways will ensure integrated care with efficient coordination between involved healthcare providers and should be future proof incorporating clinical input and scientific innovations.

Administrative and reimbursement processes represent another practical challenge. Access to advanced diagnostics or high-cost therapies may involve complex and time-consuming procedures, potentially delaying treatment initiation. Furthermore, although the national registry represents a major step forward, comprehensive registries specifically dedicated to rare cardiovascular diseases are still lacking, limiting disease-specific epidemiological knowledge and outcome assessment. Addressing these organisational gaps requires a more coordinated national strategy as outlined in the recent strategy.

The development of this structured network of accredited centres, with clearly defined referral pathways, will improve access to expertise and ensure more homogeneous care. Multidisciplinary clinics integrating cardiology, genetics, and systemic disease specialists should become the standard of care for these complex conditions. The systematic use of national registry data will provide essential insights into disease prevalence, natural history, and treatment outcomes, thereby supporting evidence-based health-care planning.

Rare cardiovascular diseases illustrate the transition of modern cardiology towards precision medicine. Advances in imaging, genetics, and targeted therapies have dramatically improved diagnostic accuracy and treatment options. These scientific achievements must be accompanied by appropriate organisational structures to ensure that all patients benefit from them. Belgium possesses the necessary expertise and technological capabilities, and the coordinated national framework as outlined in the recent plan for rare diseases 2026–2030 should translate this in clinical reality. Bridging this gap will represent a decisive step towards more equitable, efficient, and patient-centered care for individuals affected by rare cardiovascular diseases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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