Heart valve disease: a journey of discovery

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ABSTRACT

In the centenary year of the British Cardiovascular Society (BCS), this review article outlines the influence of UK cardiologists and surgeons on the field of heart valve disease, many of whom can rightly claim 'world firsts' in the field. From the description of endocarditis as we know it today at the turn of the 20th century, to the first mitral valvotomy, heart valve replacement and invention of the Ross procedure. These advances have transformed the outlook of patients with symptomatic valve disease from palliation and certain death to curative treatment and near normal life expectancy. Transcatheter aortic valve implantation (TAVI) was adopted early in the UK, and thanks to the comprehensive national database, the UK TAVI registry is one of the world's largest, contributing real-world patient data to inform clinical practice. The more recent concepts of 'Heart Valve Centres of Excellence' and specialist valve clinics have been developed by the BCS-affiliated British Heart Valve Society which continues to drive improved standards for patients with heart valve disease. The next 100 years will no doubt be equally thrilling in terms of innovation for heart valve disease, with artificial intelligence, transcatheter therapies and cutting-edge technology continuing to improve patient care and clinical outcomes.

The British Cardiovascular Society (BCS) is the world's oldest cardiovascular professional society. From its genesis as the Cardiac Club in 1922 to the large internationally renowned institution that it has become in 2022, heart valve disease has always played a prominent role—herein, we outline the impact that British cardiologists and surgeons have made in advancing diagnosis and treatment.

THE PIONEERS

From the early days, British cardiologists and surgeons took centre stage in the history of heart valve disease (figure 1). Dr James Hope (1801–1841), a Mancunian cardiologist, was an early adopter of cardiac auscultation after the invention of the stethoscope in 1816 and described the murmurs of aortic and mitral valve disease for the first time (with aortic regurgitation initially described as 'Hope's murmur'). His main research findings were derived from experiments on the exposed heart of a stunned donkey. Auscultation was a skill feared by many physicians of the time, and he dedicated his career to demonstrating the new technology to colleagues and students.[1] Shortly after, the Irish physician, Corrigan, described the arterial pulsations of aortic regurgitation, and Sir Thomas Watson (1792–1882), an English Physician, likened the palpable radial 'water-hammer' pulse to a Victorian toy of the same name in 1842.[2]

Cardiology was a specialty in its infancy at the turn of the 20th century, and plans by Sir James Mackenzie for a meet up of 'like-minded physicians interested in heart disease' were delayed by the onset of the Great War. Many among the huge swathes of troops returning to Britain from 1914 onwards had illness requiring evaluation by cardiologists. Louse-borne *Bartonella* infection (known then as 'Trench Fever') was very common and led to endocarditis in some, alongside the medically unexplained syndrome of 'Soldiers' Heart'. A government-led physician gathering to discuss evaluation of these troops resolved that those with an interest in cardiology should continue to meet.

The 'Cardiac Club' was founded by 15 members in 1922, including Carey Coombs—pioneer of rheumatic heart disease, author in 1924 of the first comprehensive English monograph on the topic,[3] and first to describe the rumbling mid diastolic murmur of acute rheumatic valvulitis that now bears his name. The murmur characteristically diminished and then disappeared as acute carditis and valve inflammation resolved, affirming the importance of meticulous and frequent examination of all patients with acute rheumatic fever.

Largely missing from the history books is the remarkable story of Sir Henry Sessions Souttar—a British surgeon based at the London Hospital and the first to describe mitral commissurotomy, performed on a 15-year-old girl, Lillian H from Bethnal Green, in 1925.[4] His bravery to perform such a daring procedure was remarkable and some physician colleagues suggested that he may be prosecuted for manslaughter if the patient did not survive, while others commented that an adverse outcome should at least prompt resignation. In his 1925 BMJ publication, he outlined insertion of a finger via the left atrial appendage to dilate the stenosed rheumatic heart valve—the first description of blind open heart surgery.[5] Lillian survived a further 7 years after the operation, finally succumbing to cerebral embolism. When asked why he did not repeat the procedure given its relative success, he volunteered that he was never referred another patient, physicians declaring it 'all non-sense'[6] and failing to believe that the symptoms of mitral stenosis could be ascribed to a simple obstruction between the left atrium and ventricle. Indeed, Carey Coombs was among these sceptics, declaring that 'the operation can never become a general method of treatment for a disease of which the mitral lesion is only one feature—to say nothing of the technical difficulties attending surgical approach to this structure'.[7] Sir Thomas Lewis was also dismissive, writing 20 years later that 'although many symptoms may be complained of by the patients suffering of mitral stenosis, there are none that can be ascribed properly and usefully to this deformity of the valve'.[7] Souttar became a BCS member and eventually spoke about the operation at the 1957 Autumn Meeting. Meanwhile, valve surgery was not further

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Figure 1 A history of heart valve disease in the UK. Image credits: British Cardiovascular Society Archive, BMJ journals[5] and Kings College London archive.

attempted until 1947, when Thomas Sellors reported direct relief of pulmonary stenosis in a 20-year-old man with Tetralogy of Fallot at the Middlesex Hospital, London,[8] followed by closed mitral commissurotomy performed by Lord Russell Brock at Guy's Hospital, London in 1948.[6] The same year, Brock joined with Cardiac Club Secretary, Dr Maurice Campbell, to form the 'Peacock Club' at Guy's Hospital following a visit to the unit by Blalock (of Blalock-Taussig shunt fame) to educate on all matters concerning congenital heart disease.[9] Over 30 years later in 1984, the first transcatheter mitral balloon valvuloplasty was performed by Inoue using his innovative balloon catheter,[7] and 6 years later, Wilkins published his mitral echocardiographic score in the *British Heart Journal*, paving the way for current selection algorithms.[10]

Scarcely reported in the literature is the worlds' first mitral valve replacement at the City General Hospital in Sheffield by cardiothoracic surgeon, Mr Judson Chesterman. The Perspex valve was designed on principles used in automotive design and implanted during beating heart surgery with de-airing achieved via a syringe and needle.[11] The design was flawed and valve embolism proved fatal, but future modifications of the valve more closely resembled those of Albert Starr who implanted the Starr-Edwards valve 7 years later in the USA. Alfred Gunning (an Oxford University scientist) donated freeze-dried aortic valves to Donald Ross who successfully implanted them in a patient with aortic stenosis at Guy's Hospital in 1962. This homograft procedure was the first subcoronary bioprosthetic aortic valve replacement in the world and took place prior to availability of the Starr-Edwards valve in the UK.[12] Ross had not had the opportunity to attempt the technique in an animal model, but used the experimental subcoronary homograft as a salvage procedure following extensive destruction of the native aortic valve following attempted leaflet decalcification—the patient subsequently survived 3 years.[13] The freeze-drying method of homograft preparation was subsequently modified to address the problem of premature degeneration, while Ross built on this early experience to conceive the Ross procedure that is still performed across the world. Similarly, Hugh Bentall and Antony De Bono described treatment of aortic root aneurysm with a composite valve-graft and side-to-side coronary anastomosis in 1968, an operation still considered the gold standard over 50 years later.[14]

The curious case of Benjamin Britten, the great English composer, highlights the perilous state of those with valve disease in this era. Although initial rumours suggested he suffered with syphilitic aortic disease, his operation report suggests a degenerative aetiology. The burden of disease was so great that it was said by Sir Peter Pears, the English tenor, that the effort of composing the opera 'Death in Venice' was killing him. Indeed, the tempo of the clarinet in the opening scenes may reflect his underlying atrial fibrillation or ventricular ectopy at the time. Ross performed his eponymous procedure on Britten in 1973 but surgery was complicated by a stroke and Britten never fully recovered, passing away 3 years later of congestive cardiac failure.[15]

Marian Ionescu was a surgeon based at Leeds General Infirmary with a lifetime obsession concerning the development of prosthetic heart valves. In 1967, he implanted a porcine aortic valve with a Teflon cloth collar that evolved over time to a Dacron-covered titanium frame. Durability was poor owing to the formaldehyde preservation technique and attempts to address this using fascia lata harvested from the patients' own thigh suffered similar issues in the high-pressure left heart system. Glutaraldehyde-treated bovine pericardium was associated with greater success and this valve was marketed commercially as the 'Ionescu-Shiley' pericardial xenograft. Although widespread uptake was again hampered by poor longevity resulting from torn leaflets, this extensive work made a major contribution to advances in bioprosthetic valve technology.[16]

NEW AND OLD CHALLENGES

The modern history of heart valve disease can be considered in four discrete phases (figure 2). Acquired heart disease was the focus at the turn of the 20th century, involving the as-yet untreatable conditions of infective endocarditis, syphilitic aortic disease and acute rheumatic carditis (and ensuing rheumatic heart disease) that gave rise to a myriad of symptoms and signs, and accompanying eponymous syndromes ascribed to British cardiologists.

Antibiotics were introduced in the mid-20th century and allowed the treatment of endocarditis, syphilis, streptococcal throat infection and acute rheumatic carditis,[17] while the concurrent advent of cardiac surgery meant that curative treatment was

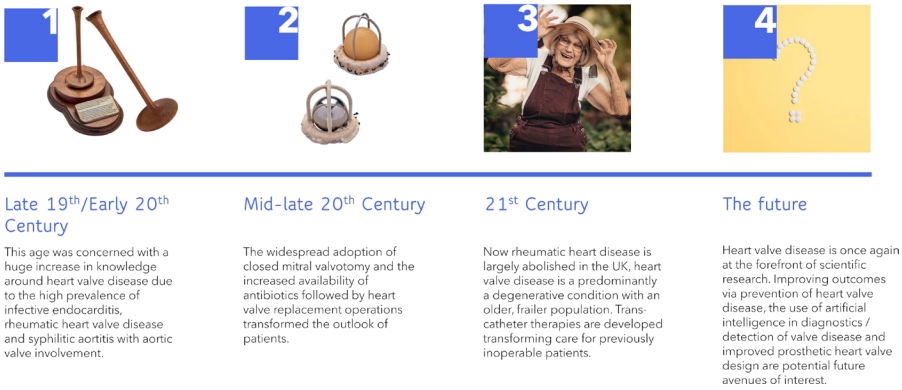

Figure 2 'The four ages of heart valve disease'. Archive photos reproduced with permission from the British Cardiovascular Society Archives.

suddenly available for those previously on a palliative trajectory. The development of transcatheter balloon therapies to treat pliable, non-calcified stenotic heart valves came later in this period, with widespread application of balloon mitral and pulmonary valvuloplasty.[18] Stuart Shaw and colleagues at the Western General Hospital in Edinburgh subsequently extended this experience to an inoperable, frail population with 'burnt out' calcific rheumatic mitral stenosis, a risky business which occasionally led to Inoue balloon rupture (figure 3).[19]

The new millennium has been dominated by degenerative valve disease affecting a frail, more elderly population that may not survive open heart surgery, paving the way for an age of further innovation. The widespread application of transcatheter therapies has ironically bought the treatment of heart valve disease 'full circle' from the days of closed mitral valvotomy and these new techniques have in turn led to renewed interest in aetiology, pathogenesis and natural history. In the UK, much of this research has been led by Professors David Newby (BCS Mackenzie Medal 2018) and Marc Dweck (BCS Young Research Workers Prize 2012, Michael Davis Early Career Award 2016) at Edinburgh University, focusing on aortic valve inflammation and the myocardial impact of aortic stenosis.[20 21]

ENDOCARDITIS: MODERN APPROACHES TO AN ANCIENT DISEASE

Although endocarditis was probably first described in 1646 in France, Matthew Baillie (1761–1823), a London-based physician and pathologist, made the first diagnosis of 'rheumatic carditis' in 1797, followed by reports of the embolism of infected vegetations in 1852 by William Senhouse Kirkes, a physiologist at St Batholomew's Hospital, London.[22] Sir Samuel Wilks, the 'grand old man' of British medicine and physician to Queen Victoria, was celebrated for many medical achievements, including the first association of fatal arterial pyaemia with cardiac vegetations in 1882 (commonly mistaken for typhoid at the time),[23] while Sir William Osler's Goulstonian lectures on 'malignant endocarditis' at the Royal College of Physicians in 1885 describing the clinical and postmortem features of the disease remain famous to this day.[24] Thomas Horder and HJ Starling were founding members of the Cardiac Club and leading experts in infective endocarditis (figure 4), and Horder delivered a topical lecture on the subject at the inaugural club meeting in 1922. The more recent recognition that high-quality care for these complex patients requires input from many different specialty-led UK endocarditis specialists to propose the concept of the 'endocarditis team'.[25] The effectiveness of this approach was confirmed in a study from Kings' College Hospital, London, demonstrating a 24% reduction in mortality after the introduction of this model of care.[26]

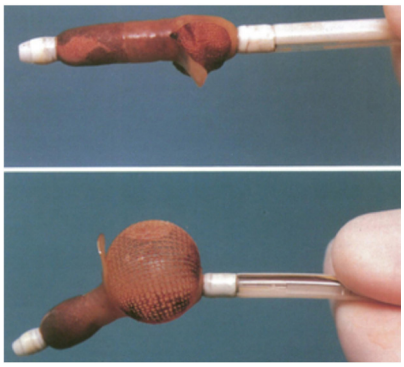

Figure 3 Inoue balloon demonstrating a torn outer rubber layer due to attempted balloon dilatation of a calcified mitral valve. Images reproduced with permission from BMJ journals.[19]

In no other country in the world has the topic of antibiotic prophylaxis for endocarditis been more hotly debated. The 2008 NICE guidelines recommending cessation of the practice in all patients (regardless of underlying risk) provoked a backlash from the cardiology community, and inevitable dissent from patients with longstanding heart valve disease who felt uneasy with such a dramatic change in practice.[27] Adding fuel to the fire (and perhaps creating more questions than answers), a subsequent UK epidemiological study published in the *Lancet* demonstrated a significant rise in the incidence of endocarditis coincident with the guideline publication.[28] Although lack of microbiological data prevented a causal association, the wording of the NICE guidelines was changed 2 years later to afford more flexibility with clinical decision-making. This compromise was reinforced by a 2018 NICE guideline implementation report from the Scottish Dental Clinical Effectiveness Programme (SDECP) and endorsed by the BCS and the British Heart Valve Society (BHVS).[29]

THE RISE AND RISE OF TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

The significant impact of transcatheter intervention on the treatment of pulmonary and mitral stenosis did not translate to the aortic valve as a result of rapid restenosis, rendering balloon aortic valvuloplasty a predominantly palliative procedure in those unfit for conventional valve surgery.[30] However, this did

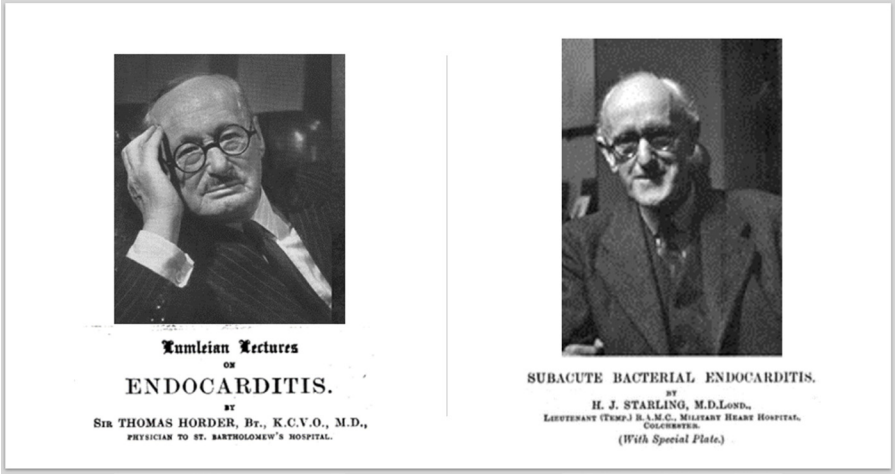

Figure 4 Founding members of the cardiac club and leading authorities in valve disease. Left hand panel: Sir Thomas Horder (1871–1955). Right hand panel: Dr Henry J Starling (1873–1950). Archive photos reproduced with permission from the British Cardiovascular Society Archives.

not deter Henning Andersen and Alain Cribier, the pioneers of transcatheter aortic valve implantation based in Denmark and France, respectively. Early prototypes developed in animal models during the 1990s were plagued with problems, including coronary occlusion and valve embolism. Early publications were rejected by leading journals with comments that the concept was 'too low a priority for publication'[31] and the medical device industry reacted with cynicism. However, the new millennium saw Cribier's team perform the first successful animal procedure followed shortly by the first-in-man implant in 2002.[32] A decade later, Cribier delivered the BCS 2013 Paul Wood Lecture in recognition of his contribution to the field.

The UK adopted the procedure early and the TAVI acronym was coined by Simon Redwood, Martyn Thomas and Jan Kovac (all high-volume operators) in time for publication of the PARTNER 1B trial,[33] although mysteriously (and inexactly) translated to 'TAVR' in the ensuing PARTNER 1A trial.[34] The first UK procedure was performed at Glenfield Hospital, Leicester, in 2007, and the first valve-in-valve procedure at Kings College Hospital, London in 2009. Indeed, almost 400 procedures had already been performed by the end of 2008, demonstrating the enormous potential of the new procedure.[35] Building on the UK's heritage of registry data and the advantages offered by unique NHS identifiers, the UK TAVI registry was rapidly established by the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS), and swiftly became one of the world's largest TAVI registries, providing valuable insights into real-world patient outcomes.[36] Building on this collaboration, the UK TAVI trial has recently provided important evidence supporting the use of TAVI in younger, low-risk patients and endorsed the Heart Team approach to case selection.[37]

INNOVATION IN AN ECONOMICALLY CONSTRAINED ENVIRONMENT

The OxVALVE study was the first to highlight the emerging epidemic of valve disease in the ageing UK population and demonstrated that mitral regurgitation is the most common valve lesion, affecting >20% of adults aged >65 years.[38] Mitral valve anatomy and pathophysiology are far more complex than the aortic valve and the development of transcatheter technologies has proved to be a significant interventional and engineering challenge. Adopting a strictly evidence-based approach, the UK has been a slow adopter of transcatheter mitral therapies while awaiting the outcome of a prolonged NHS 'Commissioning Through Evaluation' process. Recommendations were finally provided in 2019[39] and proved consistent with the conclusions of the landmark EVEREST trial published 10 years previously.[40] Despite these challenges, the team at St Thomas' Hospital, London performed one of the world's first transcatheter mitral valve replacements in 2012 and continue to drive the innovation agenda in conjunction with other groups in Brighton, Leeds, Oxford and London.[41]

SUB-SPECIALISM AND MODELS OF CARE

Management of heart valve disease was the domain of the 'general cardiologist' for decades but more recent advances in imaging and expansion of treatment options have made the field increasingly complex, requiring subspecialists with experience in investigation, evaluation and treatment. Dedicated heart valve clinics were pioneered by John Chambers at Guy's Hospital, London, facilitating standardised care and improved outcomes. Elaboration of this model to incorporate 'Hub and Spoke' arrangements across geographical networks supporting specialist 'Heart Valve Centres' is now strongly recommended within European and US practice guidelines.[42 43] These guidelines further emphasise a patient-centred multidisciplinary 'Heart Team' approach, as endorsed by the BCS collaborative document outlining standards for multidisciplinary meetings[44] and NHS England 'Getting it Right First Time' Cardiology report prepared by BCS past-Presidents, Sarah Clarke and Simon Ray.[45]

Groups linked to the BCS have made significant contributions to the improved care of heart valve disease in the UK. The British Cardiovascular Intervention Society and British Society of Echocardiography were affiliated to the BCS in 1987, while the BHVS was established in 2010 to represent all professional groups involved in the care of patients with heart valve disease. Recently, BHVS publications include a blueprint framework for the delivery of heart valve services in the UK (figure 5)[46] and guidance for the management of patients with heart valve disease during the COVID-19 pandemic.[47]

FUTURE CHALLENGES AND DIRECTIONS

Renewed interest in heart valve disease over the past 20 years has led to an exciting era of innovation and research. Furthermore,

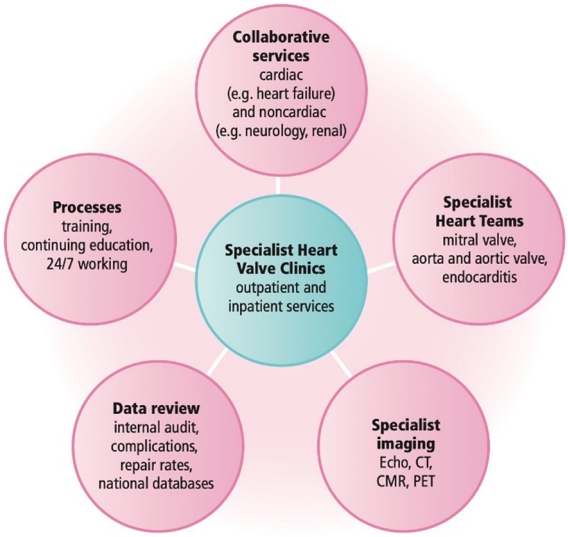

Figure 5 Key components of specialist heart valve clinics extracted with permission from British Heart Valve Society blueprint endorsed by British Cardiovascular Society.[46] CMR, cardiovascular magnetic resonance; CT, computerised tomography; PET, positron emission tomography.

the recent pandemic has accelerated advances in management, with increased focus on transcatheter technology,[48] app-based technology, virtual consultations and Heart Team meetings, electronic stethoscopes, and wearable technology outlined in the recently published BCS 'Future of Cardiology' report.[49]

Several ongoing UK-based trials promise to further our understanding of the potential benefits of earlier treatment of valve disease and seem likely to impact on international guideline recommendations within the next decade. Of note, the EASY-AS study led by Gerry McCann in Leicester aims to investigate the role of surgical or transcatheter intervention in asymptomatic severe aortic stenosis,[50] while the EVOLVED study led by Marc Dweck in Edinburgh is evaluating the use of a screening algorithm incorporating ECG, serum and MRI biomarkers to triage patients with asymptomatic severe aortic stenosis and determine those who benefit most from early intervention.[51]

The need for lifelong anticoagulation is burdensome for patients with mechanical valves while bioprosthetic valves have limited durability, particularly in younger patients. Development of a bioprosthetic valve that would last a lifetime would have huge impact, avoiding the need for repeat interventions and the clinical risks and considerable morbidity associated with lifelong anticoagulation. A design with significant promise is the Poli-Valve, a polymer-based valve with potential durability of up to 25 years under development by teams of biomaterial engineers, computational modellers and cardiologists at Bristol and Cambridge Universities funded by the British Heart Foundation.[52]

James Hope, the original exponent of cardiac auscultation, would be most impressed with the resurgence of the stethoscope. The ancient art of cardiac auscultation may be about to experience a renaissance in the form of 'Jade', a low-cost artificial intelligence-enabled digital stethoscope developed at Cambridge University.[53]

Challenges remain despite these exciting advances. The global healthcare burden of heart valve disease is increasing inexorably with widespread socioeconomic and geographical disparities, while the outlook for symptomatic patients remains dismal, with prognosis worse than many cancers.[54] The urgent attention of clinicians, healthcare economists, public-health specialists, global healthcare agencies and the cardiovascular device industry is required to ensure that future histories remain positive.

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