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Welcome

The field of Cardiology is one which has rapidly evolved over recent decades; advances in procedures, diagnosis, and treatments have progressively led to better outcomes in previously difficult-to-treat populations. The articles presented in this edition of the *European Medical Journal Cardiology* focus on the latest advances in the diagnosis and treatment of cardiovascular disease (CVD), ensuring that you are always kept up-to-date with the latest news and developments.

Leading experts within the fields of both Cardiology and Interventional Cardiology have contributed to this edition to offer insights into recent discoveries, future challenges, and ways to enhance patient experiences and outcomes. It is our aim to deliver both practical and relevant knowledge, presented in easy take-home messages.

Since 2002, transcatheter aortic valve implantation (TAVI) has been, arguably, one of the biggest breakthroughs in valvular heart disease in the past few years; TAVI has been shown to improve a patient's quality of life and may also increase their life expectancy. Salinas et al., in their paper '*State of the art aortic valve implantation: indications, outcomes, and controversies*', explore how TAVI is a suitable alternative to surgical aortic valve replacement and how it has a clear mortality benefit. However, as it is a relatively new procedure, the long-term benefits have not been fully explored; the authors have therefore suggested that more randomised trials, along with future investigations, will be able to establish a future for this procedure, and data from long-term follow-ups will help to assess patient experiences.

Although a lot of progress has been made in the area of mitral regurgitation (MR) the condition can still, at times, be challenging and controversial for clinicians in term of its management, for example, the optimal approach, timing, and effectiveness of interventions. Pepe et al. have, in their paper '*Functional mitral regurgitation: if the myocardium is guilty do we also need to 'rehabilitate' the valve?*', attempted to review both the salient aspects of functional MR pathophysiology as well as current diagnostic methods. The authors have suggested that a case-by-case evaluation of patients must take place so that the treatment is tailored according to the anatomical features and patient comorbidities.

By working together and sharing thoughts, ideas, and experiences, new discoveries, new techniques, and new technologies can be utilised and perfected, and the burden of CVD will decrease. It is with those final remarks that I hope this inspiring issue will be able to benefit both you and your patients.

Spencer Gore

Team Principal, European Medical Journal

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Foreword

Dr Fernando Alfonso

Hospital Universitario de La Princesa, Madrid, Spain

Dear Colleagues,

I have the pleasure of welcoming you to this new issue of the *European Medical Journal Cardiology* 2015. This eJournal features a plethora of articles written by leading cardiologists which detail some of the most important recent discoveries in the field, as well as looking ahead to the many challenges that lie before us. Amongst many great pieces, Andreas Schaefer takes a look at transcatheter options for the treatment of mitral regurgitation, whilst in another study, Jeetesh Patel, in his paper *'Circulating haemoglobin levels and the risk of atherosclerosis in Asian Indian populations'*, investigates the impact of migration and nutritional intake on haematological parameters amongst South Asians.

> "The main focus will be to highlight and review the most relevant developments in the diagnosis, management, and treatment of CVDs."

Additionally, a special treat for readers is provided in the form of our 'How I Treat' feature, which has on this occasion been written by Dr Piergiusto Vitulli et al. Cardiovascular diseases (CVDs) currently represent the first cause of death in industrialised countries, and here, the authors superbly outline the effect of statin therapy in reducing their impact.

The next issue of *EMJ Cardiology* will provide valuable coverage of the European Society of Cardiology (ESC) Congress that will be held in London, United Kingdom from 29th August to 2nd September 2015. The ESC Congress is expected to be the world's largest scientific meeting on CVDs in 2015, and is a must-see event for cardiologists across the world.

As is the case every year, the scientific programme of the ESC Annual Meeting will be outstanding. The main focus will be to highlight and review the most relevant developments in the diagnosis, management, and treatment of CVDs. Topics will cover the full spectrum of cardiovascular medicine, from bench to bedside, ranging from basic to clinical and population research.

This is currently a very busy and exciting period in the field of cardiology, and special thanks on behalf of EMJ must be given to all of our authors and my fellow editorial board members who have taken the time to contribute to this edition. Our main aim, as always, is to provide vital information to healthcare workers worldwide in order to improve standards of treatment.

Yours sincerely,

Fernando Alfonso

Head of Cardiology, Hospital Universitario de La Princesa; Associate Professor of Medicine, Universidad Autónoma de Madrid, Madrid, Spain.

EDITOR'S PICK

I would like to highlight the paper by Salinas et al. because it provides a comprehensive and exhaustive review on the state of the art of transcatheter aortic valve implantation (TAVI). During the last decade TAVI has revolutionised the cardiovascular field and currently represents a well-established treatment strategy for selected 'high-risk' patients with severe aortic stenosis. Now the burning question is "Where to go from here?" as, based on the excellent results currently obtained in clinical practice, the indications of this exciting procedure may be rapidly expanding.

Dr Fernando Alfonso

STATE OF THE ART OF AORTIC VALVE IMPLANTATION: INDICATIONS, OUTCOMES, AND CONTROVERSIES

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ABSTRACT

During the last decade, transcatheter aortic valve implantation (TAVI) has become a revolution in the treatment of high-risk severe aortic stenosis (AS). Current guidelines provide a Class I indication for TAVI in inoperable AS and Class IIa indication for TAVI as an alternative to surgical repair in high-risk patients. A large amount of retrospective, prospective, and randomised data has been published covering almost every angle of the procedure. Improved patient evaluation and selection, new devices, and technical refinements will reduce procedural complications and improve long-term outcomes. With a growing elderly population segment in the Western countries, the procedure has a bright perspective. The purpose of this review is to summarise the state of the art of TAVI procedures, including current indications, and describe procedural characteristics, as well as short and long-term outcomes. Controversial issues such as paravalvular regurgitation and stroke are discussed, as well as off-label indications. A shift towards intermediate risk AS patients, approval of some of the off-label indications, and device versus device competition are some of the future directions of the technique.

Keywords: Transcatheter aortic valve implantation, transcatheter aortic valve replacement, transcatheter valve, aortic valve stenosis, aortic stenosis, review.

INTRODUCTION

Senile or calcified aortic stenosis (AS) is the end-stage of a degenerative-inflammatory process with risk factors and physiopathology that, while not completely understood, is somewhat similar to atherosclerosis.[1] After a long asymptomatic period, when AS becomes haemodynamically severe and symptoms appear, the mortality suddenly rises if a valve replacement is not performed.[2,3] Several surgical techniques competed in the 60th and 70th decades (valvotomy, valve replacement with homograft) but eventually, surgical aortic valve replacement (SAVR) with a mechanical or biological prosthesis became the standard of treatment.[4,5] Although no randomised

or systematic trials were performed, SAVR showed a clear improved survival compared to non-operated controls.[6,7] SAVR procedures increased along with the ageing of the population to become the most frequent valvular heart surgery in adults today.[8] However, almost one-in-three SAVR candidates were not eventually operated on due to surgical contraindications, advanced age, and/or comorbidities.[9,10] Initially designed to overcome this treatment gap in symptomatic severe AS, from the first-in-man implantation in 2002, transcatheter aortic valve implantation (TAVI) has become a revolution in the approach to valvular heart disease.[11] A huge amount of retrospective, prospective, and randomised data has been published in the last decade, covering almost any angle of the procedure, and finally finding a place in the American and European Guidelines 10 years later.[12,13] At this moment, >125,000 TAVI implants have been performed worldwide, and the number of procedures approximately duplicates each year.[14] The purpose of this review is to provide an up-to-date overview of TAVI indications, outcomes, controversies, and future perspectives.

INDICATIONS AND OUTCOMES

Two transcatheter valves (Edwards SAPIEN from Edwards Lifesciences Corp. and CoreValve from Medtronic, Inc.) built the core of the evidence in the past 12 years. For this reason, most of the data discussed in this paper is applicable to these valves, although for educational purposes we will generalise the speaking of 'TAVI procedure', and stating specific differences if necessary. The balloon expandable Edwards SAPIEN (ES) valve was commercially approved in 2007 for the European Union (EU) and in 2012 for the United States (US), and its last evolution has recently been released (Sapien 3). The self-expandable Medtronic CoreValve (CoVa) was commercially approved in 2007 (EU) and in 2014 (US), and has also recently presented its last version (Evolut R). Many other TAVI devices have been or will soon be commercially approved in the EU:[15] Acurate (Symetis SA), Centera (Edwards Lifesciences Corp), Direct Flow (Direct Flow Medical Inc.), Engager (Medtronic Inc), Jenavalve (Jenavalve Technology), Lotus (Boston Scientific), Portico (St. Jude Medical Inc, commercialisation temporarily suspended). However, experience with these devices is still limited (Figure 1).

Indications

Beyond a large amount of observational data and multicentre registries, current indications come from three randomised trials. The PARTNER trial showed non-inferiority of TAVI with ES valve compared to SAVR in high surgical risk AS patients (PARTNER cohort A),[16] and better survival compared to medical treatment including balloon aortic valvuloplasty in inoperable patients (PARTNER cohort B).[17] In the CoVa pivotal trial, TAVI with CoVa was superior to SAVR in terms of all-cause death at 1 year in high-risk patients.[18]

The 2012 European Society of Cardiology Guidelines gave a I-B recommendation for TAVI in patients with life expectancy of >1 year if unsuitable for SAVR; a IIa-B recommendation for considering TAVI over SAVR in high-risk patients; and propose that a multidisciplinary 'Heart Team' including cardiologist, cardiac surgeons, and other specialists should guide the decisions (I-C).[12] The 2014 American Heart Association/American College of Cardiology Guidelines gives a I-B recommendation for TAVI if there is a prohibitive surgical risk and expected post-TAVI survival >12 month; a IIa-B recommendation for TAVI as an alternative to SAVR in high surgical risk patients; and also advocates case-by-case discussion in a Heart Team (I-C).[13] High risk is usually considered as logistic EuroSCORE ≥20% or Society of Thoracic Surgeons (STS) score ≥10, but taking into account other factors such as frailty, porcelain aorta, patent coronary bypass grafts, or history of chest radiation.[19] Extreme or prohibitive risk patients are those with an estimated >50% risk of morbidity or mortality, considered inoperable by at least two cardiovascular surgeons from a tertiary centre of excellence.[20]

In the recent years, patient selection has shifted from absence of TAVI contraindications in SAVR-rejected patients in the early days of TAVI to a careful and collaborative candidate evaluation to choose between SAVR, TAVI, or medical treatment. Issues such as cognitive function, poor functional outcome, frailty, quality of life (QoL), and futility are variables that are currently discussed in this setting.[21] In the high-risk subset, the global trend in TAVI is towards a high 'but not so high risk', and some ongoing trials are exploring TAVI versus SAVR in intermediate risk patients (PARTNER II;[22] and SURTAVI[23]). In the inoperable scenario the concept of futility has emerged and has been embraced by the guidelines, proposing that, after

a careful evaluation of patients, medical treatment should be offered if no benefit from correction of AS is expected (no-benefit recommendation, III-B, for TAVI).[13,24] Characteristics related to poor outcome after TAVI (defined as death, low or worsening from baseline score in a QoL scale) were low body weight, low mean aortic gradient, oxygen-dependent lung disease, and poor baseline functional and cognitive status.[24]

Procedural Characteristics

Retrograde transfemoral is the current standard transfemoral approach (although the first TAVI procedures were performed anterogradely through the atrial septum).[11,25] Vascular closure is usually obtained with percutaneous closure devices, but some groups use surgical dissection and direct arterial closure. The transapical (ES) and subclavian (CoVa) accesses followed shortly for patients with inadequate lower limb arterial tree.[26,27] Lately, a direct transaortic approach through a mini-sternotomy has become popular among surgeons performing TAVI.[28] Although alternative approaches are regularly used in patients that have a more unfavourable risk profile, the transfemoral approach is generally associated with better outcomes, even after multivariate analysis.[29] There is no consensus on the best TAVI approach, so a case-by-case decision is made taking into account local experience and patient's anatomy.

Pre-procedural assessment includes clinical evaluation, transthoracic and transoesophageal echocardiography, computed tomography, and cardiac catheterisation. Annulus measurement is crucial to optimising valve sizing, which is critical in preventing complications (annular rupture) and achieving good immediate and long-term results (paravalvular regurgitation).[30,31] Multimodality 3D cardiac imaging is encouraged as it showed improved accuracy compared to 2D assessments.[32,33] The procedure may be performed in a hybrid operating room or in the catheterisation laboratory, and is usually (although not mandatory) monitored by transoesophageal echocardiography. General anaesthesia was preferred in the early experience, but now many centres are using local anaesthesia and conscious sedation. A few studies have compared these approaches and preliminary data show similar outcomes and reduced resource consumption without general anesthesia.[34,35]

Concomitant coronary artery disease is present or detected during pre-procedural coronary catheterisation in approximately 60% of TAVI candidates.[36] EU guidelines for myocardial revascularisation provide a IIa-C recommendation for percutaneous coronary intervention (PCI) of stenosis >70% in proximal coronary segments in patients undergoing TAVI.[37] The timing, completeness, and impact of PCI is discussed separately (see controversies). Standard post-procedural medical treatment is aspirin plus clopidogrel for 3-6 months and aspirin alone thereafter. The hypothesis of aspirin alone after TAVI is supported by a small randomised study[38] and is currently tested in the larger ARTE trial.[39] Patients on warfarin are empirically treated with warfarin alone or warfarin plus aspirin or clopidogrel depending on thrombotic and bleeding risks.

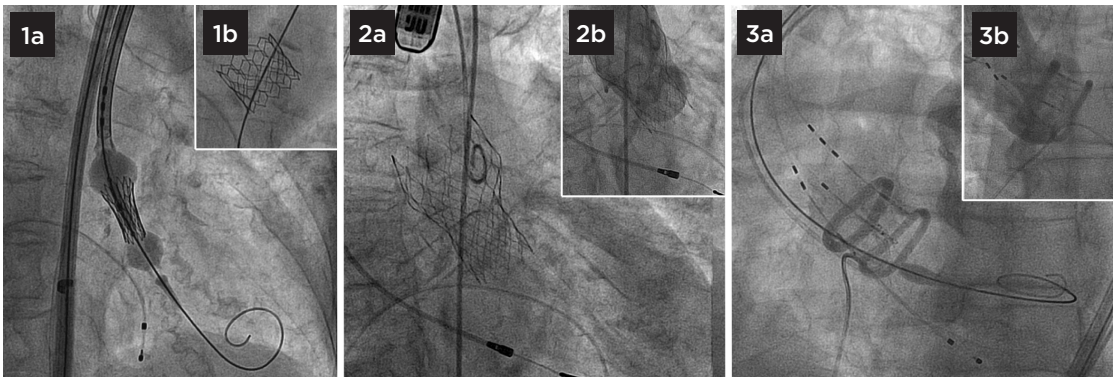

Figure 1: New generation TAVI devices. 1: Sapien 3 (Edwards Lifesciencies) during the implantation (a) and after the valve deployment (b). 2: Corevalve Evolut R (Medtronic) in the final position (a) and during simultaneous angiography (b), showing the smaller portion of the valve inside the left ventricular outflow tract of this version. 3: DirectFlow device (DirectFlow Medical) during implantation with the three positioning wires (a) and testing the final position with angiography before deployment (b).

Table 1: Short and mid-term results of main multicentre registries and randomised or controlled trials. Complication rates are given at 30 days.

	n	Device	Years	Access	Implantation success	Stroke	Permanent Pacemaker	Major vasc. complication	MI	Surgical conversion	PVR >2+	30-day mortality	1-year mortality
SOURCE registry[96,97]	1,038	ES	2007 - 08	463 TF/575 TA	93.8%	2.5%	7%	7%	0.6%	2.7%	1.9%	8.5%	23.9%
UK registry[64]	870	217 ES/452 CoVa	2007 - 09	599 TF/271 non TF	97.2%	4.1%	16.3%	6.3%	1.3%	0.7%	13.6%	7.1%	21.4%
Tamburino et al.[98]	663	CoVa	2007 - 09	599 TF/64 TS	98%	1.2%	16.6%	2%	0%	0.8%	21%	5.4%	15%
GARY registry[99 a]	697	109 ES/588 CoVa	2009	666 TF/33 non TF	98.4%	1.8%	20.8%	12.3%	0.2%	1.6%	0.4%	12.4%	–
FRANCE 2 registry[29]	3,195	2,107 ES/ 1,043 CoVa	2010 - 11	2,361 TF/834 non TF	96.9%	3.4%	15.6%	4.7%	1.2%	0.4%	0.8%	9.7%	24%
Spanish registry[100]	1,416	806 ES/610 CoVa	2010 - 11	1,114 TF/302 TA	94%	3%	10%	3%	1%	1%	6%	9%	16 - 9%[b]
TCVT EU registry[55]	4,571	2,604 ES/ 1,967 CoVa	2011 - 12	3,392 TF/1,179 non TF	96.5%	1.8%	13.2%	3.1%	0.9%	4.2%	1.3%	–	–
TVT US registry[101,102]	7,710	ES	2011 - 13	4,972 TF/2,738 non TF	92%	2%	6.6%	6.4%	0.8%	1%	8.5%	7.6%[c]	26.2%[c]
PARTNER A (TAVI arm)[16]	348	ES	2007 - 09	244 TF/104 TA	–	4.7%	3.8%	11%	0%[d]	2.6%	12.2%	3.4%[e]	24.2%[f]
PARTNER B (TAVI arm)[17]	179	ES	2007 - 09	TF	–	6.7%	3.4%	16.2%	0%[d]	0%	11.8%	6.4%[e]	30.7%[f]
CoVa Pivotal (TAVI arm)[18 d]	390	CoVa	2011 - 12	323 TF/67 non TF	99.7%	4.9%	19.8%	5.9%	0.8%	0.5%	7.8%	3.3%	14.2%
CoVa Extreme risk[103 d]	506	CoVa	2011 - 12	TF	–	4%	21.6%	8.2%	1.2%	–	11.4%	8.4%	24.3%

a) Data of complications was provided separately for TF and TA patients in the original population, for this table average percentages are provided from the complete TAVI population. b) One-year mortality was 16% for CV and 19% for ES. c) Follow-up data from 3,528 patients (30-day mortality), and 5,980 (1-year mortality). d) The PARTNER Trial excluded patients with substantial coronary artery disease requiring revascularisation. e) A-treated analysis. f) Intention-to-treat analysis.

MI: myocardial infarction; PVR: paravalvular regurgitation; ES: Edwards-SAPIEN; CoVa: CoreValve; TF: transfemoral; TA: transapical; TS: transubclavian; TAVI: transcatheter aortic valve implantation; vasc.: vascular.

Table 2: Long-term mortality after TAVI. The original procedures of these studies were performed in 2007–2012 with earlier versions of current devices.

	n	Valve	Follow-up Max. / Mean	Median survival	1-year Mort.	2-year Mort.	3-year Mort.	4-year Mort.	5-year Mort.	Valve Re-op.
Ussia et al.[60]	181	CoVa	–/3.4 years	–	23.6%	30.3%	34.8%	–	–	0%
D'Onofrio et al.[104]	774	ES	3.6/1 years	–	18.3%	23.9%	32.4%	–	–	0%
UK registry[63,64]	870	217 ES/ 452 CoVa	7.1/– years	–	21.4%	26.3%	38.8%	–	54.5%	0.8%
Rodés-Cabau et al.[59]	339	ES	4/3.5 years	–	24%	33%	49%	57%	–	0.6%
Toggweiler et al.[68 a]	88	ES	–/5 years	3.4 years	17%	26%	47%	58%	65%	1.1%
Doss et al.[105]	100	ES	5/3.8 years	–	8%	–	10%	–	13.0%	1%
El-Mawardy et al.[69]	61	CoVa	–/5 years	–	11.5%	21.3%	26.2%	39.3%	52.5%	–
PARTNER A (TAVI arm)[106,107 b]	348	ES	–/3 years	–	24.2%	33.7%	44.2%	–	–	0%[c]
PARTNER B (TAVI arm)[61,108 b]	179	ES	–/5 years	2.5 years	30.7%	43%	53.9%	64.1%	71.8%	1.1%[c]

a) Selected population, excluding implantation failure or dead before 30 days. Complete follow-up in 84 out of 88 patients.
b) Intention-to treat analysis. Crossover patients were censored at the moment of crossover.
c) Re-operation data were reported at 2 years of follow-up.
Max: maximum; Mort: mortality; Re-op: re-operation of the transcatheter valve; ES: Edwards-SAPIEN; CoVa: CoreValve; TAVI: transcatheter aortic valve implantation.

Triple antithrombotic therapy is rarely prescribed except for concomitant PCI. Factors such as new antithrombotic drugs, atrial fibrillation (AF), or concomitant PCI suggest the need for individualised therapy and further investigation on the optimal post-TAVI antithrombotic regime.[40]

Procedural Outcomes

Rigorous clinical research has been a feature of TAVI development, but until 2011 outcome data was somewhat heterogeneous. Eventually, definition of endpoints related to TAVI procedures were standardised in a position paper from the Valve Academic Research Consortium (VARC),[41] and revised posteriorly in the current, second version.[19] Successful TAVI implantation is reported in 90–95% of procedures. Device success is a VARC composite endpoint defined as implantation of one valve in the correct anatomical position without death or valve dysfunction; and is currently obtained in >80% of TAVI cases.[42] The VARC combined 30-day safety endpoint (including all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury (AKI), peri-procedural myocardial infarction, major vascular complication, or repeated procedure) was met in average in 32.7% of procedures in a recent metanalysis.[42] Short-term outcomes from most relevant multicentre studies are summarised in Table 1. Both symptoms and QoL improvements in short and mid-term have been reported after TAVI.[16,17,43,44]

Most frequent TAVI complications are: a) vascular complications, with a great range of severity (from small haematomas or femoral pseudoaneurysm, to

arterial dissection/rupture and need for covered stents or emergent surgery), are reported in 1–19% of TAVI procedures.[45] Reductions in vascular complications and related bleedings have been uniformly reported with the downsizing of delivery catheters and increased experience;[46,47] b) severe bleeding, usually related to access site complications is frequent (15–32%),[48,49] but lower than SAVR procedures[50] – blood transfusion after TAVI is associated with a worse prognosis;[51] c) cardiac tamponade (due to temporary pacemaker catheter or high-support guidewire) is contemporarily reduced to <5% of cases but it was identified as the most frequent cause of procedural mortality;[52] d) permanent pacemaker implantation (<10% with ES and 10–35% with CoVa); e) AKI, with a reported incidence of 12–28%, and related in several studies to increased mortality.[53,54]

Paravalvular regurgitation (PVR) and stroke are discussed separately (see controversies). In the largest multinational European registry, conversion to open heart surgery was needed in 4.26% of patients.[55] Rare complications (0.5–2%) are aortic annulus (AA) rupture, damage to mitral valve (MV), valve embolisation, or coronary obstruction.[56] The rate of procedural complications has declined over the years, due to improvements in device designs, better candidate selection, more accurate anatomical screening, and local experience.[57] The learning curve has been reported as an independent predictor of survival.[58]

Long-Term Outcomes

Long-term data are still scarce (mainly due to the relative youthfulness of the technique), but a few studies have available data up to 4–5 years of follow-up (Table 2). The long-term mortality in these studies is high, reaching generally 50% at 4-5 years. Nevertheless it must be reminded that these studies were performed in an elderly, comorbid population, with older versions of the valve devices and in the early stages of each centre's experience. The studies that have addressed causes of death in the follow-up show that more than half of the mortality is non-cardiovascular, suggesting the importance of candidate selection and multidisciplinary medical follow-up.[59-61] Main predictors of long-term mortality are: PVR, AKI and chronic kidney disease, stroke, chronic obstructive pulmonary disease, AF, major bleeding, left ventricular dysfunction, low stroke volume, frailty, and risk scores (STS, EuroSCORE).[59-64]

Immediate haemodynamic recovery of aortic valve parameters are obtained,[17] as well as other echocardiographic parameters that improve in the mid-term: left ventricular ejection fraction improvement,[65] pulmonary pressure decrease,[66] and even a reduction in the concomitant degree of mitral regurgitation may be obtained.[67] Valve durability is one of the questioned issues of this technique. The rate of need for replacement after a TAVI procedure is very low across studies (<1.5%, see Table 2). Haemodynamic benefits are sustained during follow-up, with available data for up to 4–5 years of follow-up.[59-61,68,69]

OFF-LABEL USE

The use of transcatheter aortic valves outside the boundaries of manufacturer recommendations and/or current indications is difficult to quantify because of its ambiguous definition, but represents at least 10% of current TAVI procedures. The most common (and probably next-to-be an accepted indication) is the 'valve-in-valve' procedure for the treatment of dysfunctional aortic bioprostheses. In a large multinational registry, a 7.6% 1-month and 16.8% 1-year mortality was reported.[70] Bicuspid AVD with severe AS has been successfully treated with TAVI without differences in major outcomes compared to tricuspid anatomy, but higher risk of PVR.[71] On pure aortic regurgitation (AR), TAVI procedure has been used with reasonable survival results (30 day survival 90.7% and 1-year survival 78.6%) but a higher rate of PVR that raised the need for a second valve to 18.6% in a multicentric experience.[72] In a different multicentre registry TAVI for AR found less device success and reduced survival (69% at 12 months) compared to TAVI for AS.[73] Other occasional off-label use is the deployment of a transcatheter valve in degenerated rings, conduits, or bioprosthesis in tricuspid, pulmonary, or mitral positions.[74-77]

CONTROVERSIES

Coronary Artery Disease Management

Contrary to coronary artery bypass grafting on top of SAVR, PCI among patients undergoing TAVI seems feasible and safe in the short term.[78-80] Despite of the lack of randomised data (ongoing ACTIVATION trial is randomising TAVI patients with stable coronary artery disease to PCI or medical treatment; ISRCTN 75836930), routine

practice in most centres is PCI at least on severe proximal lesions, whereas some centres aim for complete revascularisation.[78,81] The timing of the PCI is controversial, but both concomitant PCI and TAVI procedures, and staged procedures are valid strategies.[78,82,83] The long-term impact of concomitant coronary artery disease and PCI is still controversial. A meta-analysis of observational studies showed no differences in mortality after a median follow-up of 452 days; but a large single centre registry found that patients in the highest tertiles of SYNTAX score received less complete revascularisation and had a higher risk of death and cardiovascular events.[79,80]

Device Versus Device Comparison

There are no obvious differences in short or long-term mortality between the most studied ES and CoVa devices, however, most data come from indirect comparisons on large registries.[29,55,64,84] The main acknowledged difference is a 4-5-fold increased rate of pacemaker implantation with CoVa.[55,64] Methods like no or moderate predilatation, and less deep implantation of the device could help to reduce conduction disturbances in CoVa implantation.[85,86] Annular rupture, a rare but life-threatening complication is usually reported with oversized ES implantations.[30,87] The only randomised trial (CHOICE[88]) to date showed greater VARC device success with ES compared to CoVa, mainly driven by a higher rate of AR assessed immediately by angiography. Besides some study flaws, major clinical endpoints at 1 year are eagerly expected, and whether this increase in short-term AR is clinically relevant remains to be demonstrated.

PVR

The rate of PVR has been heterogeneously reported because of different imaging modalities and different time to assessment (PVR is at its maximum immediately after the procedure and tends to decrease thereafter). Generally, moderate-to-severe PVR at discharge is reported in a range from 0-24%.[89] The grade of PVR is linearly related to increased short and long-term mortality, especially in cases with moderate-to-severe PVR.[89] PVR was one of the first identified flaws of TAVI procedures and has, in the last 5 years, been challenged with several improvements in valve designs (new or extended 'skirts' to seal the AA), deployment technique, and anatomical considerations (multimodality imaging of AA, optimised valve sizing).[90] As a result, a reduction in PVR rate has been reported in the preliminary results of new-generation devices.[91]

Stroke

In a meta-analysis of 10,037 TAVI patients, a relatively small rate of peri-procedural (<24 hour) stroke was found (1.5%), but increased to a 30-day 3.3% all stroke rate. Moreover, it was associated with 30-day mortality.[92] The stroke risk is persistent during follow-up with a cumulative 5-year combined (haemorrhagic and ischaemic) stroke rate of 17%.[68] TAVI and stroke have a complex relationship, with multiple identified factors that usually coexist in the same patient: aortic calcification, diabetes, operator experience, pre-existent and new-onset AF and/or intra-procedural thrombus, or debris embolisation.[93-95] Several cerebral protective devices have been developed and are currently under clinical research. Another important matter of research is the post-TAVI antithrombotic treatment, which is largely empirical at this moment.[40] Comparison with SAVR is controversial with higher stroke rates in the TAVI arm of PARTNER trial, but no differences in a meta-analysis, and a trend towards fewer strokes in the randomised US CoVa pivotal trial.[16,18,50] Stroke has been incorporated as a co-primary endpoint in the intermediate risk TAVI trials.

FUTURE PERSPECTIVES

Long-term valve durability data, up to 10 years, will become available, as some of the early experience patients will survive to be assessed. Results of randomised TAVI versus SAVR trials in intermediate risk patients are eagerly expected (PARTNER II[22] and SURTAVI,[23] with STS between 4-8%). Additional indications that currently are considered off-label will probably be embraced by the guidelines; especially valve-in-valve procedures for degenerated bioprosthesis and selected cases of combined aortic valve disease (AVD) with predominance of AR. New devices will be incorporated in daily practice and will help the refinement of the technique. Many accessories designed for the procedures such as delivery catheters, femoral and transapical closure devices, cerebral protection devices, and combined imaging modalities will help to improve procedural outcomes. The most audacious are looking into low-risk patients with bioprosthesis indication, selected severe asymptomatic AS patients, and TAVI superiority over SAVR in some candidates. Although not related to AVD, the experience with

TAVI will also promote advancements in other percutaneous valve therapies, such as tricuspid and MV diseases.

In summary, TAVI is now a suitable alternative to SAVR in high-risk patients and has a clear mortality benefit when compared to medical treatment in inoperable patients. A shift towards lower risk candidates and a withdrawal of any invasive treatment in extreme risk patients with no expected benefit from TAVI is happening. Better patient selection, device evolutions, and worldwide experience will probably further improve short and long-term TAVI results. Open issues like PVR, and stroke are a cause for concern but also are areas of intense investigation. With the currently acknowledged underutilisation of the technique, and a progressively ageing population in developed countries, the number of TAVI procedures is deemed to keep increasing. Existing registries, ongoing randomised trials and future investigation will ensure a solid future for the technique.

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COST-EFFECTIVENESS OF A NOVEL SELF-APPOSING STENT IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI) IN FRANCE

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ABSTRACT

The objective was to calculate the cost-effectiveness profile of STENTYS compared to conventional bare and drug-eluting stents (DES). Stents are widely used in the treatment of patients with ST-segment elevation myocardial infarction (STEMI). However, several reports point to the prevailing risk of coronary events such as recurrent myocardial infarction, some of which are related to in-stent thrombosis, possibly explained by poorly apposed stents. 1-year results of the self-apposing stent, STENTYS, are promising regarding the incidence of fatal and non-fatal cardiovascular (CV) events. A model was developed to simulate costs and quality-adjusted life years (QALYs) over 1-5 years. In the first 12 months, a decision tree framework was used to define different CV outcomes for STEMI patients receiving a stent. After 12 months, outcomes were categorised in a Markov stage of the model as myocardial infarction (MI), other CV events, revascularisation, and death. Cost of comparative treatments and follow-up in relation to CV events were calculated from the French health insurance perspective. The results indicated, in the base case, over a time horizon of 5 years, that STENTYS bare metal stent (BMS) is dominant (less costly and more QALYs) against conventional DES. The STENTYS DES is dominant compared with conventional DES and very cost-effective versus BMS. The results were robust for different variations in the input variables. This first analysis of the cost-effectiveness of STENTYS showed that it is dominant or very cost-effective as compared to conventional stents. Further comparative research and longer follow-up data are needed to expand on these results.

Keywords: Cost-effectiveness, self-apposing stent, France, quality-adjusted life year (QALY), STENTYS.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) has been established as the treatment of choice for patients with acute ST-segment elevation myocardial infarction (STEMI).[1] In the 1990s it was shown that, compared to balloon angioplasty, stentsoffered better outcomes for patients at a reasonable extra cost.[2] Although the use of stents has led to an important reduction in major adverse cardiac events (MACE) and cardiac death, the risk of restenosis remains high with the use of bare metal stents (BMS). The use of drug-eluting stents (DES) was intended to reduce the risk of restenosis. Based on a systematic review, Greenhalgh et al.[3] concluded that there were significant reductions in composite outcomes such as MACE but no statistically significant differences in individual parameters such as death, acute myocardial infarction (MI), or thrombosis between DES and BMS. Reductions in target lesion revascularisation (TLR) and target vessel revascularisation (TVR) were evident with all types of DES, and were demonstrated in long-term follow-up. Concerns had been raised about the cost-effectiveness of DES compared with BMS if only an effect on TVR

would be substantial,[4] but recent real-life data[5] and systematic reviews of the literature[1] suggest a benefit of DES compared with BMS, at least in the first year after the index event at minimum. However, concerns still remain about the risk of stent thrombosis and re-infarction after using DES that might be more pronounced among STEMI patients.[6] Heestermans et al.[7] investigated 5,842 STEMI patients treated with primary PCI, of which 201 (3.5%) presented with an early (<30 days) definite stent thrombosis. The strongest predictors of early stent thrombosis and re-infarction were post-procedural dissection, undersizing, and small stent diameter.

Recently a self-apposing stent, STENTYS, has been developed with the aim to provide a better fit to the vessel and therefore reduce the occurrence of re-infarctions. The first randomised study with STENTYS showed that it perfectly appose to the vessel, whereas 28% of conventional stents were malapposed (APPOSITION II).[8] The APPOSITION III study[9] evaluated the long-term clinical benefit of the STENTYS stent in STEMI patients in a real-life setting. This was a prospective, non-randomised, single-arm, multicentre study evaluating the safety and performance of the STENTYS stent in routine clinical practice in 965 STEMI patients. Both drug-eluting and bare-metal versions of the STENTYS stent were available and were used at the operator's discretion.[9] The primary endpoint at 12 months, presented at EuroPCR 2013,[10] was MACE, defined as cardiac death, target-vessel recurrent MI (re-MI), or clinically-driven TLR. Secondary endpoints were definite/probable stent thrombosis, all-cause mortality, any MI, and any TVR. 1-year cardiac death or target vessel re-MI was observed in only 3.2% of patients, and only 2.4% if post-dilation was applied. The trial results showed a lower all-death rate as compared to a meta-analysis of conventional stents. In the current healthcare environment, the need to allocate public money wisely has increased the interest in comparative effectiveness and cost-effectiveness research.[11] Hence, it is important in the development of new technologies not only to investigate their clinical effectiveness, but also to estimate potential cost savings of such technologies. The objective of this study was to calculate the cost-effectiveness of STENTYS (BMS and DES) in treating STEMI patients, and to identify the drivers of this cost-effectiveness.

METHODS

Decision Model

We developed a health economic model in MS Excel 2010, inspired by previous health economic models of DES compared with BMS.[12-14] The model has a dual structure, with a decision tree reflecting the outcomes in the first 12 months (Figure 1, Part A). After 12 months, a Markov 'state transition' model presents and predicts the further evolution of patients over a period of 5 years (Figure 1, Part B). Indeed, in coronary heart disease patients, events that occur in the first year can lead to consecutive events in the following years. Therefore, reducing the events in the first year will also have an impact on the subsequent years. A similar approach was followed by Janzon et al.,[15] whereby even a lifetime extrapolation was applied. Nevertheless, in contrast to Janzon et al.,[15] we decided to not model further than 5 years because extrapolations beyond such a period would become too speculative.

In the model, the following strategies are compared:
- Conventional BMS
- Conventional DES
- STENTYS BMS
- STENTYS DES

As noted above, a decision tree is used to assess the first 12 months of patients in a given therapy. In those first 12 months, a patient can have a fatal or non-fatal re-infarction (the latter treated or not with revascularisation), another cardiovascular (CV) event (fatal or non-fatal), a revascularisation not related to MI, or die from another cause. Patients who survive the first 12 months continue in the Markov part of the model, which runs in years 2-5, and can have one of the following outcomes: death from any cause, MI, and revascularisation (not MI-related). Hence, from years 2-5, at the end of each year, patients can stay in the same state as they were before, or have an MI (fatal or non-fatal), need a revascularisation (not MI-related), or die from a CV event or other cause.

Clinical Data Input

Clinical data related to conventional stents are shown in Table 1.[12,16,17] Montalescot et al.[10] (ACTION study group, La Pitié-Salpêtrière Hospital, Paris, France) report the results of an analysis at 30 days and 1 year of the incidence of MACE and mortality in recent studies with conventional stents after STEMI. The authors did not report detailed data on separate outcomes such as MI, revascularisation

not related to MI, and CV death. Therefore, we also used data from Garg et al.,[12] reporting on the incidence of other CV events, and from a meta-analysis from Piscione et al.[16] reporting that 32% of all revascularisations after the use of BMS were associated with an MI. The probabilities of MI, revascularisation, and death beyond 1 year were also obtained from Garg et al.[12] Finally, since these data include a mix of approximately 50% BMS/50% DES, we adjusted the estimated number of events associated with BMS by accounting for the effect of DES, based on a meta-analysis from Suh et al.[1] Table 1 provides the key input data for the model applicable to conventional BMS. The relative risks (RR) of events associated with DES versus BMS were obtained from the most recent meta-analysis from Suh et al.[1] The RR for 1 year MI was 0.77 (95% CI 0.61-0.97) and the RR for 1 year TVR was 0.48 (95% CI 0.41-0.56). Comparing the results from APPOSITION III[9] with those of the above analysis, it was assumed in the base case that the RRs associated with BMS STENTYS versus conventional BMS were 0.50 for 30 day MI, 0.80 for 1 year MI, and 1 for 1 year TVR; for DES STENTYS versus conventional BMS, 0.70 for 1 year MI and 0.48 for 1 year TVR. The RR for re-infarction beyond 1 year was not known and therefore assumed to be 0.90 for STENTYS BMS and 0.80 for STENTYS DES(P). These assumptions were tested in sensitivity analyses (see results).

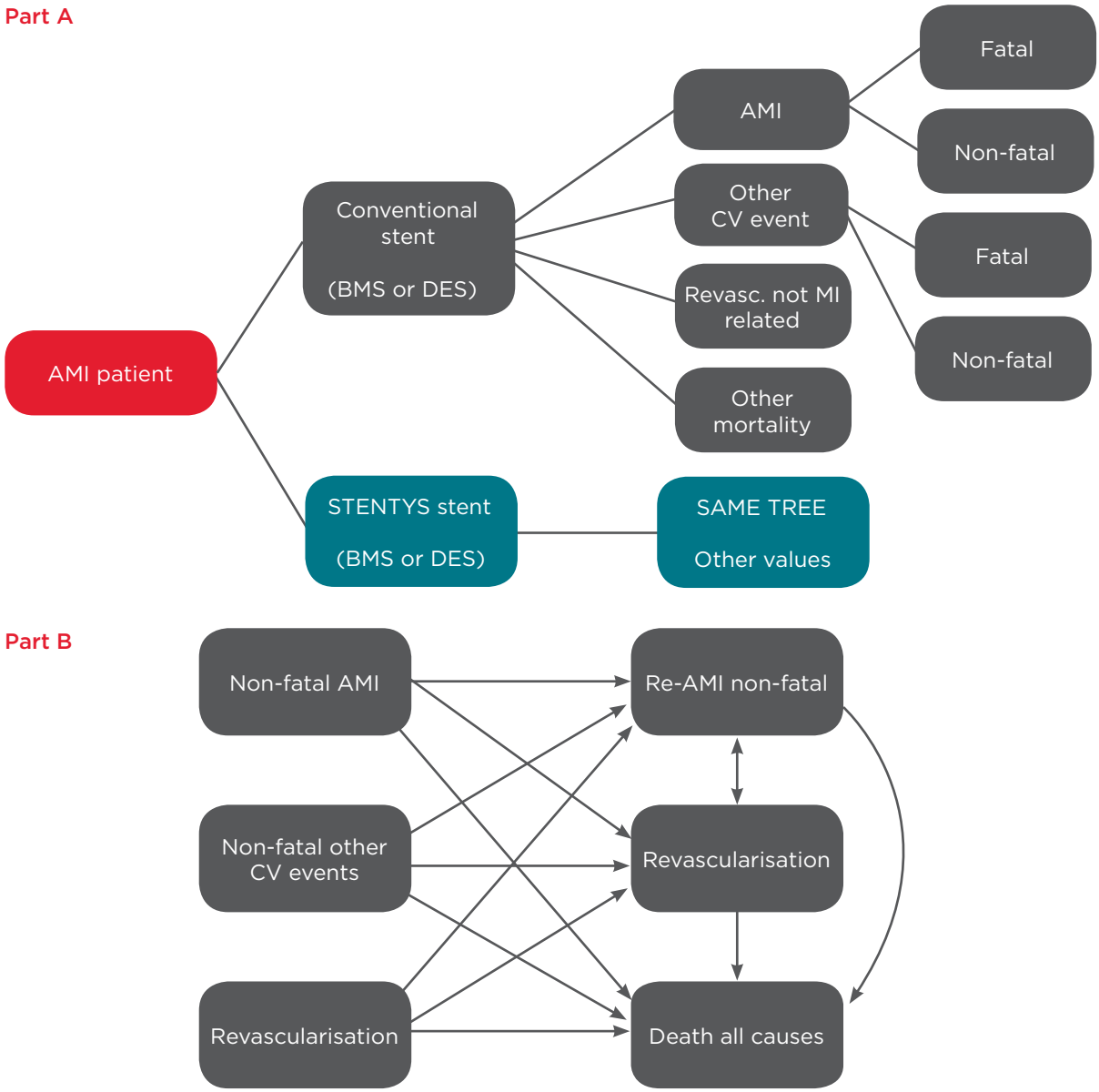

Figure 1: Graphical presentation of the health economic model.
Part A: first 12 months (decision tree); Part B: subsequent cycles of 12 months (Markov model)
AMI: acute myocardial infarction; BMS: bare metal stent; DES: drug-eluting stent; CV: cardiovascular.

Table 1: Clinical input data for first 30 days and first 12 months after STEMI, applicable to conventional BMS.

Cardiovascular events post-STEMI treatment with a conventional BMS stent	Incidence (%) 30 days	Incidence (%) 1 year	Source
Non-fatal reinfarction	2.25%	3.72%	Montalescot 2013 (adjusted)[10]
Fatal reinfarction	3.10%	3.18%	Montalescot 2013 (adjusted)[10]
Non-fatal other cardiac event	0.34%	0.95%	Garg 2008[11]
Fatal other cardiac event	0.33%	0.71%	Garg 2008[11]
Mortality, other (non-cardiac)	0.08%	0.81%	French Lifetables[16]
Revascularisation excl. reinfarction	0.00%	2.53%	Garg 2008,[11] Piscioni 2010[15]
Total (excluding non-cardiac mortality)	6.02%	11.09%	

STEMI: ST-segment elevation myocardial infarction; BMS: bare metal stent.

Table 2: Cost data applied in the model.

Item	Cost (€)	Source
In-hospital reinfarction	1,449	Canoui-Poitrine 2009[4]
Non-fatal MI post-hospitalisation	4,815	Colin, 2007, adjusted for health index[17]
Fatal MI	4,610	Colin, 2007, adjusted for health index[17]
TVR	5,531	Haute Authorité de Santé (HAS)/SED/SEESP/2009, adjusted for health index[20]
Other CV event	3,984	Haute Authorité de Santé (HAS)/SED/SEESP/2009, adjusted for health index[20]
BMS	550	LegiFrance[21]; Canoui-Poitrine 2009[4]
DES	1,100	LegiFrance[21]
STENTYS BMS	840	Oral communication from STENTYS S.A.
STENTYS DES	1,200	Oral communication from STENTYS S.A.

MI: myocardial infarction; TVR: target vessel revascularisation; CV: cardiovascular; BMS: bare metal stent; DES: drug-eluting stent.

Cost Data Input

A French social insurance perspective was used, therefore productivity lost through illness or costs incurred directly by patients were not included. Discount rates of 3% are applied to both future costs and health benefits, consistent with prevailing guidelines. Cost data for all events are reported in Table 2.[18-20] The cost of re-infarction during the index hospitalisation was obtained from a study by Canoui-Poitrine et al.[4] and costs of re-infarctions after discharge (hence during the rest of the analytical period) were obtained from an earlier paper by Colin et al.[18] The cost of a fatal MI came from the latter source. Acute costs of revascularisation and other CV events were obtained from the French Health Authority. All costs were actualised to the year 2012. The costs of the STENTYS BMS and DES(P) were obtained from the company. In the model, an average of 1.2 stents per patient was assumed. The costs for current BMS and DES were obtained via the LegiFrance website. In the base case the cost data from 2012 were applied. In a sensitivity analysis, the most recently published costs for conventional DES were applied (€875 per stent).

Table 3: Utility data applied in the model.

Event/condition	Utility level		Source
First year after MI	0.80		Chevalier et al.[21]
Re-MI	0.70		Chevalier et al.[21]
TVR	0.70		Chevalier et al.[21]
Follow-up without events	0.85		Chevalier et al.[21]

MI: myocardial infarction; TVR: target lesion revasuclarisation.

Table 4a: Base case results at 1 year.

	COST (€)	QALY	INCR COST versus BMS (€)	INCR QALY versus BMS	ICER (€/QALY)	INCR COST versus DES (€)	INCR QALY versus DES	ICER (€/QALY)
Conventional BMS	1268.3	0.7681						
Conventional DES	1741.2	0.7717	472.9	0.0036	**131,067**			
STENTYS BMS	1550.3	0.7764	282.0	0.0083	**33,839**	-190.9	0.005	**dominant**
STENTYS DES	1838.2	0.7777	569.9	0.0096	**59,606**	97.0	0.006	**16,291**

INCR: incremental; QALY: quality-adjusted life year; ICER: Incremental Cost-Effectiveness Ratio; BMS: bare metal stent; DES: drug-eluting stent.

Table 4b: Base case results at 5 years.

	COST (€)	QALY	INCR COST versus BMS (€)	INCR QALY versus BMS	ICER (€/QALY)	INCR COST versus DES (€)	INCR QALY versus DES	ICER (€/QALY)
BMS	3471.9	3.5207						
DES	3822.2	3.5723	350.4	0.0516	**6,793**			
STENTYS BMS	3613.3	3.6123	141.4	0.0916	**1,543**	-208.9	0.040	**dominant**
STENTYS DES	3813.7	3.6346	341.8	0.1139	**3,001**	-8.5	0.062	**dominant**

INCR: incremental; QALY: quality-adjusted life year; ICER: Incremental Cost-Effectiveness Ratio; BMS: bare metal stent; DES: drug-eluting stent.

UTILITY DATA

In order to calculate quality-adjusted life years (QALYs), utility data are required. The QALY is a common measure of health improvement used in cost-effectiveness analyses. It combines mortality and quality of life gains by adjusting the number of years a person lives at the appropriate quality level (called utility) during those years. The maximum utility value is 1 and a value of 0 is assigned to death.[21] We applied utility values reported by Chevalier et al.[22] (Table 3).

RESULTS

Base Case

Table 4a and 4b show the base case results of our analysis for a time horizon of 1 year (hence not accounting for any additional benefits for STENTYS stents beyond 1 year) and 5 years, respectively. After 1 year, the STENTYS BMS is borderline cost-effective in comparison with conventional BMS and dominant (costing less and adding QALYs) against DES. The STENTYS DES is cost-effective compared

to conventional DES (€16,291/QALY) but not cost-effective versus conventional BMS. DES (all) are not cost-effective compared to BMS (all). After 5 years, assuming a continued benefit on re-MI as described in the methods, the STENTYS BMS is very cost-effective against conventional BMS and dominant against conventional DES. The STENTYS DES is very cost-effective against conventional BMS and moreover dominant versus conventional DES.

Sensitivity Analysis

Sensitivity analyses showed that, as expected, the relative benefit of STENTYS stents in the short and long-term are the key drivers of the results. The recently reduced costs of conventional BMS and DES strongly influence the Year 1 results but have a modest effect on the Year 5 results. In Table 5, the impact of different variables on the ICER (Incremental Cost-Effectiveness Ratio) is shown for the 5 year analysis.

DISCUSSION

Although huge progress has been made in the management of STEMI patients, not least with the introduction of BMS and DES, there is still a clear need for further improvement in the treatment of STEMI, with currently >10% MACE in the first year. The Self-Apposing STENTYS stent showed favourable 1 year clinical outcomes in a real-life STEMI population, supporting the hypothesis that correct stent sizing and elimination of malapposition after primary PCI may lead to improved long-term results. This model shows that under the current assumptions, the STENTYS DES(P) is already cost-effective at 1 year compared with conventional DES. However, applying the most recent price reductions of conventional stents, this conclusion no longer holds. Both the STENTYS BMS and DES(P) are very cost-effective if outcomes to 5 years are simulated, even with reduced prices of conventional stents. Yet, given this preliminary evidence, our model could still be called an 'early economic evaluation'. This practice of economic models in the early development phase of technologies has existed for more than a decade,[23,24] but has been largely applied only over the last few years.[25] The idea is clear: based on anticipated or preliminary results from a new technology and its costs to the healthcare system, the potential cost-effectiveness can be estimated, hence advising all stakeholders – manufacturers, policy makers, physicians, and patient advocacy groups – about what to expect from market access of the technology.

Table 5: Sensitivity analysis.

Simulation 1 year	**STENTYS DES versus conventional BMS**	**STENTYS DES versus conventional DES**
Basecase	€59,606/QALY	€16,291/QALY
Patient risk level -50%	€137,606/QALY	€35,677/QALY
Cost of events -50%	€70,593/QALY	€18,225/QALY
Cost of conventional BMS and DES resp. €500 and €875	€65,882/QALY	€61,647/QALY
RRR MI STENTYS -50%	€129,924/QALY	€126,362/QALY
Simulation 5 years	**STENTYS DES versus conventional BMS**	**STENTYS DES versus conventional DES**
Basecase	€3,001/QALY	dominant
Patient risk level -50%	€9,085/QALY	€1,628/QALY
Cost of events -50%	€4,925/QALY	€894/QALY
Cost of conventional BMS and DES resp. €500 and €875	€3,528/QALY	€4,196/QALY
RRR MI STENTYS -50%	€7,981/QALY	€16,171/QALY

QALY: quality-adjusted life year; BMS: bare metal stent; DES: drug-eluting stent; RRR: relative risk reduction; MI: myocardial infarction.

Early economic models have some limitations, as is also the case for the current one. Firstly, the key model input is based on non-comparative data. Confirmation of the results of APPOSITION III in a comparative setting is required to verify our results. The APPOSITION V, FDA-approved randomised study will bring a more definite answer to the comparative evidence, and will allow the assessment of the predictive validity of the current analysis. Even then, longer follow-up data are required to confirm the predicted over a period beyond 1 year. This should ideally be the case for all innovative technologies for which only rather short-term data exist. The model was based on a recently presented systematic literature search which was performed to find the most relevant effectiveness and complication data related to conventional stents. The search suffered from the lack of transparent reporting of the individual events in most of the studies in the review. Often events such as in-stent thrombosis, MI, and revascularisation are reported without clearly showing how many of the MIs were related to in-stent thrombosis, and how many revascularisations were related to MIs. We needed to rely on other data to obtain more granular estimates of the different individual events. Moreover, some studies in the systematic review were rather old, and others reported only 30 day data and no 1 year data, while other studies showed the reverse. We performed a secondary analysis thereby looking only at recent trials and imputing missing 1 year data based on the principle of proportionality. In that analysis, the total number of events at 30 days and 1 year became 5.39% and 10.70% and the number of CV deaths became slightly higher than in our base case analysis. However, the final results were not affected.

The model comparison did not adjust for baseline characteristics. In the systematic review, the average patient age was 61.4 years which is comparable with the mean age of 60 years in the APPOSITION III study.[9] However, other population baseline and procedural characteristics such as thrombolysis in myocardial infarction flow at baseline, culprit lesion location, thromboaspiration use, and novel P2Y12 use, although sometimes similar, do vary between trials in the review and also in comparison with the APPOSITION III trial. Finally, since the perspective of this analysis was the social health insurance in France, we did not account for possible savings due to reduced productivity. Patients with MI are often still at a productive age and therefore societal losses occur due to their absence from work. Annemans et al.[26] reported that the productivity related costs of CV events are at least as high as the direct medical costs. Taking these into account would lead to even more possible savings due to a new stent with improved features.

CONCLUSION

In conclusion, the current analyses in the French setting suggest favourable cost effectiveness of the STENTYS BMS and DES in comparison to conventional stents in patients with STEMI, when a time horizon beyond 1 year is applied. These conclusions are based on a 1 year prospective trial with STENTYS and a systematic review of current stents. Long-term and comparative clinical data are required to confirm these results.

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LEFT VENTRICULAR CARDIOMYOPATHY IN MITRAL VALVE PROLAPSE: FACT OR FICTION?

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ABSTRACT

In most patients with mitral valve prolapse (MVP) without severe mitral regurgitation (MR), left ventricular (LV) function is preserved. There are, however, patients with MVP who have unexplained LV dilatation and/or decreased LV function. An association between MVP and sudden cardiac death has also been reported. LV size and function may be affected by the type of MVP, severity of regurgitation, and cause of MVP (myxomatous degeneration versus fibroelastic deficiency). There is increasing evidence suggesting an intrinsic cardiomyopathy associated with MVP. The cardiomyopathy associated with MVP can also affect the right ventricle (RV). Although the impact on ventricular dimensions and function are usually subtle, these abnormalities can affect clinical and echocardiographic estimation of the severity of MR and may thus have an impact on therapeutic decisions. Particularly in patients with the most extreme forms of MVP (Barlow disease), and in patients with Marfan syndrome or other connective tissue disorders, a cardiomyopathy affecting the LV and RV may thus occur occasionally. A better understanding of LV impairment associated with MVP is important for risk assessment and clinical decision-making.

Keywords: Mitral valve prolapse, cardiomyopathy, heart failure, ventricular function, asymmetric hypertrophy.

INTRODUCTION

Mitral valve prolapse (MVP) is defined as displacement of one or both mitral leaflets during systole of >2 mm above the mitral annular plane into the left atrium with or without mitral regurgitation (MR).[1,2] The prevalence of MVP in the general population is 0.6-2.4%. It is the most common cause of referral for mitral valve (MV) surgery in developed countries.[2-6] Typically, MVP is caused by a myxomatous degeneration of the MV leaflets, which in its extreme form is called 'Barlow disease' (BD). This is characterised by myxomatous infiltration of the entire MV with excess thickening of the leaflets, detectable at a young age.[7] Myxomatous MV disease can occur as an isolated finding, in Marfan syndrome (MFS) or other connective tissue disorders. Less often, MVP is caused by fibroelastic deficiency with thinning and elongation of the leaflet tissue and chordal tissue often associated with chordal rupture;[2,7] this usually affects older patients. The natural history of MVP is very heterogeneous, ranging from an incidental finding in an asymptomatic patient to a severe disease with considerable morbidity and mortality.[8-11] MVP can lead to MR, endocarditis, cerebral embolism, arrhythmias, sudden cardiac death (SCD), and heart failure (HF).[9] The most common complication is, however, progressive MR, which can be associated with left ventricular

(LV) dysfunction and clinical features of HF. An association between MVP and SCD has been reported, even in the absence of severe MR.[12-20]

GLOBAL AND REGIONAL VENTRICULAR FUNCTION IN MVP

In a small proportion of patients with MVP unexplained LV dilatation and/or decreased LV function is observed that cannot be explained by the degree of valvular dysfunction. This suggests an intrinsic cardiomyopathy may be associated with MVP. Abnormal LV structure has been reported in patients with MVP.[21] This abnormal structure could potentially explain the increased incidence of life-threatening arrhythmias reported in patients with MVP.[22-25] Several groups have reported myocardial abnormalities in patients with MFS, suggesting that the underlying connective tissue disorder causing aortic dilatation and valvular abnormalities may also lead to a specific cardiomyopathy affecting both ventricles.[26-29] In patients with MVP, LV wall motion abnormalities can be observed[14,24,25] in the absence of significant coronary artery disease or MR. Typical wall motion abnormalities include the early diastolic posterior dip which can be best shown by M-Mode echocardiography and other abnormal contraction patterns such as the 'ballerina foot' pattern (Figure 1).[14] These asynchronies do not usually cause a decrease in LV function. However, an otherwise unexplained decrease in left and/or right ventricular ejection fraction[30,31] can still occur. An example of LV changes of a 17-year-old male adolescent with bileaflet MVP, mild MR, and a mild decrease of LV function of an enlarged LV is shown in Figure 2. Enlargement of the LV in MVP in the absence of significant regurgitation was also described in the literature in a small study.[32] HF symptoms in patients with MVP are usually related to severe MR, but intrinsic myocardial dysfunction (MD) may be another cause.

The natural history of asymptomatic MVP in the community shows that apart from progressive MR, an ejection fraction of <50% is one of the most important independent predictors for cardiovascular mortality.[9] In multiple studies it has been shown that reduced LV ejection fraction in MR worsens the prognosis considerably.[33] Since LV ejection fraction is an imperfect measure of LV systolic performance, and grossly dependent on loading conditions, additional parameters of LV function in patients with MVP may be required.[34]

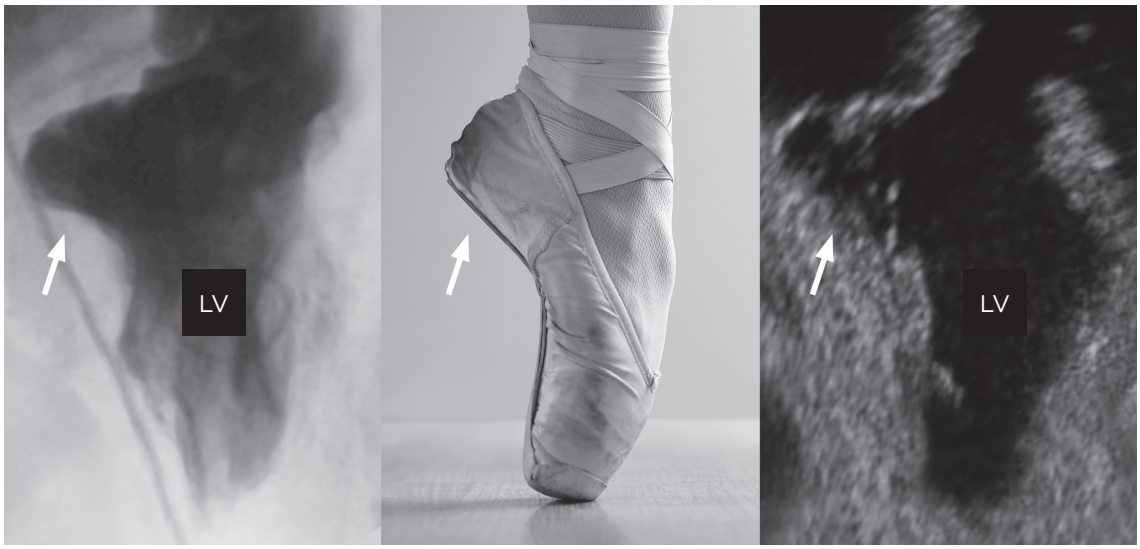

Figure 1: 'Ballerina foot' pattern in mitral valve prolapse (MVP).
The 'ballerina foot' pattern (middle) as an example of typical wall motion abnormality in pronounced MVP is observed during left ventriculography in the right anterior oblique projection (left) and in a transthoracic echocardiogram (right). A vigorous early contraction of the midventricular portion of the left ventricle at end-systole, coupled with anterior wall bulge causes this pattern and is the most frequent wall motion abnormality observed in patients with MVP. Arrow points to the dyskinetic region which mimics the ballerina foot heel.
LV: left ventricle.

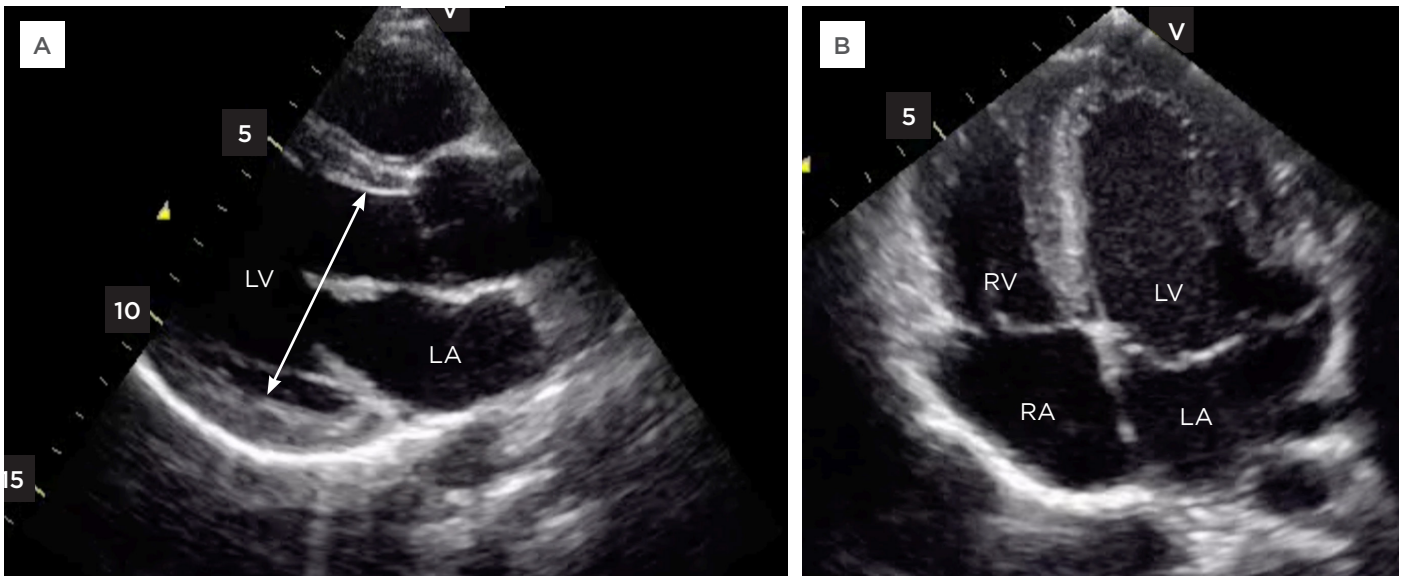

Figure 2: Left ventricular enlargement in the absence of significant mitral regurgitation (MR).
A: Parasternal long axis view of a 17-year-old male with mild MR due to bileaflet prolapse; his left ventricle (LV) is enlarged (arrow: 5.8 cm; 3.2 cm/m^2 body surface area) despite a normal sized left atrium (LA).
B: Apical four-chamber view of this 17-year-old with bileaflet mitral valve prolapse shows the enlarged LV at end-systole; his biplane left ventricular ejection fraction is 42%.
L/RA: left/right atrium; L/RV: left/right ventricle.

A recent study examined myocardial strain in 78 asymptomatic young patients with MVP (none to maximally mild MR) and 80 control patients:[35] they included 29 patients with 'classic' MVP (defined as MVP with leaflet thickness of >5 mm) and 49 patients with 'non-classic' MVP. Patients with MFS and Ehlers-Danlos syndrome (EDS) were excluded. In classic MVP, there was a significant reduction in global strain (-15.5±2.9%) compared with non-classic MVP (-18.7±3.8; p=0.0002) and control patients (-19.6±3.4%; p<0.0001). Transforming growth factor-β_1 (TGF-β_1) and β_2 serum levels were elevated in the classic MVP group compared with the control group and the non-classic MVP group. In non-classic MVP, only regional septal myocardial deformation indexes were decreased so this might be due to mechanical stress to the myocardium owing to the prolapsing leaflets. However, in patients with classic MVP, this reduction in global strain could be due to an underlying cardiomyopathy, due to increased TGF-β signalling.[35] In this study, in patients with classic MVP, LV end-systolic and end-diastolic diameters were significantly larger than in non-classic MVP despite similar left atrial size and LV ejection fraction.

OTHER LV ABNORMALITIES IN MVP

In our experience, as well as multiple descriptions in the literature, LV abnormalities are relatively common in patients with MVP. These abnormalities include LV diverticula[36,37] (Figure 3), posterobasal LV free wall hypertrophy,[38] asymmetric septal hypertrophy,[39] and LV non-compaction.[40] Thus, LV abnormalities should be carefully sought by echocardiography in all patients with MVP. The combination of LV diverticulum and MVP has been described in occasional cases.[36,41] LV diverticula can be associated with ventricular arrhythmias.[36] Additionally, MVP by itself has been suspected not to be an innocent bystander, but to have a direct impact on ventricular structure by the prolapsing valve.[42,43] The traction of the prolapsing MV on the LV walls may not only cause LV wall motion abnormalities and fibrosis of papillary muscles,[43] but possibly also causes asymmetric muscular hypertrophy of the basal walls. These changes may exacerbate the MVP and lead to a vicious cycle.[43]

Myxomatous MV disease is common in dogs. A recent interesting study was performed in 50 euthanised dogs with myxomatous MV disease. Autopsies and plasma collection were performed 70 days after the last examination.[44] In this study,

circulating troponin I concentration correlated well with the degree of cardiac fibrosis and arteriosclerosis. *In vivo* troponin I concentrations in these dogs with myxomatous mitral valves reflected myocardial fibrosis, fibrosis in the papillary muscles, and the degree of arteriosclerosis ($p<0.001$). Papillary muscle fibrosis has also been observed in a small study with cardiac magnetic imaging in humans (46%).[45] Thus it may be interesting to test, if troponin I levels in patients with MVP could identify a subset of patients prone to myocardial fibrosis and whether this translates into adverse outcomes. So far, this has never been examined in humans. In patients with MVP, asymmetric hypertrophy of the basal septum and posterior LV wall motion abnormalities can occur independent of MR. These findings are, however, more common in patients with at least moderate MR. Hypertrophy of the basal posterior wall has recently been described as a distinct form of hypertrophic cardiomyopathy.[38] An interesting combination of MVP and LV non-compaction together with MVP has been recently described and associated with sinus node dysfunction and *HCN4* mutation in two papers.[46,47] This intriguing occurrence of MVP in patients with *HCN4* mutation might be another explanation for an increased incidence of arrhythmias in MVP.[40]

CARDIOMYOPATHY IN MFS AND OTHER CONNECTIVE TISSUE DISORDERS

In the setting of connective tissue disorders,[48] such as MFS,[49-52] MVP is found in approximately 35% of patients and primary cardiomyopathy with reduced LV ejection fraction can be detected in at least 25% of cases (Table 1).[49] The intrinsic MD can affect both ventricles.[53]

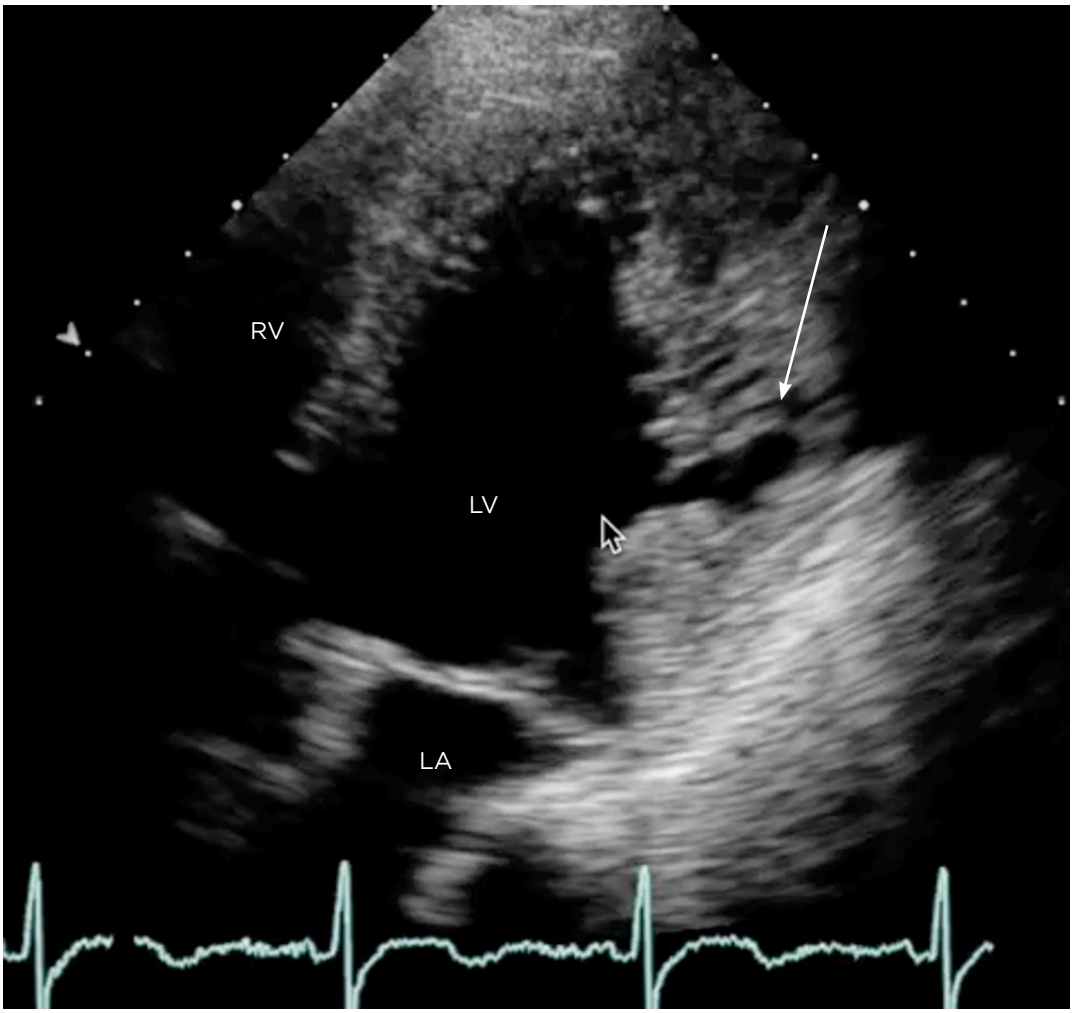

Figure 3: Diverticulum of the posterior wall of the left ventricle (LV).
Apical two-chamber view of the LV with the posterior wall on the right side in a patient with mitral valve prolapse showing a diverticulum of the inferior wall. Arrow points to the diverticulum.
RV: right ventricle; LA: left atrium.

Table 1: Summary of left and right ventricular abnormalities described in mitral valve prolapse (MVP) with or without Marfan syndrome (MFS).

Author/ imaging method	Number pt	Mean age, y	%MFS	Significant MR	Reduced LV EF	Increased LVEDD	Reduced RV EF	Comment
Alpendurada et al.[50] CMR	68	34±12	100% of pt	0%	25%	25%	10%	-
Malev et al.[35]/ echo/speckle tracking	79	18±2	0%	0%	NA (no difference to normal)	NA	NA	TGF-β_1 and β_2 elevated in classic MVP; speckle tracking of LV decreased
Kiotsekoglou et al.[66]/ echo/strain imaging	44	30±12	100% of pt	45% MVP	Significantly lower than normal	20%	NA	Uniform reduction in biventricular deformation in MFS
Roman et al.[67]	59 MFS, 59 MVP, 59 controls	29±13	50% of pt	?	No	No	No	-
Savolainen et al.[27]/echo	22 MFS, 22 controls	3-17	100% of pt	?	No	No	No	Diastolic dysfunction in MFS
Yetman et al.[68]/echo	70 MFS	17 Median (birth-52)	100% of pt	2/70	11%	49%	NA	4% Death of arrhythmias
Chatrath et al.[28]/echo	36 MFS	26	100%	0% (Exclusion criteria 50% MVP)	0%	19%	NA	No change LV size first to last echo
Meijboom et al.[29]/ echo	234	29 First, 6y FU	100%	0% (?MVP)	0%	7%	NA	-
De Backer et al.[69]/echo/ strain/CMR	26 MFS, 26 controls	32±11	100%	0% (?MVP, at least 2 pt)	Yes	Yes	NA	Diastolic dysfunction in MFS
Das et al.[70]/ echo	40 MFS, 40 controls	17±12	100%	0% (Exclusion criterion)	0% (Exclusion criteria)	Yes	Unknown	Diastolic dysfunction in MFS
Rybczynski et al.[71]/ echo/strain	66 MFS, 61 controls	31±13	100%	?	?	17%?	Unknown	Abnormal systolic and diastolic function
Kiotsekoglou et al.[72]/echo	72 MFS, 73 controls	32±12	100%	0% (Exclusion criterion) 47% MVP	0%	?	?	Significant biventricular diastolic and biatrial systolic and diastolic dysfunction

Pt: patient; y: years; MR: mitral regurgitation; LVEDD: left ventricular end-diastolic diameter; R/LV: right/ left ventricle; EF: ejection fraction; NA: not available; CMR: cardiac magnetic resonance imaging; echo: echocardiography; TGF-β: transforming growth factor β; FU: follow-up.
Modified from Kiotsekoglou et al.[55]

Myocardial impairment including abnormal LV relaxation is increasingly noticed in MFS.[54] In a mouse model of MFS, it was shown that fibrillin 1 plays an important role in cardiac muscle function: partial fibrillin 1 gene inactivation precipitated dilated cardiomyopathy due to abnormal mechanosignalling.[55] Normal cardiac size and function could be restored in these mice with an angiotensin II Type 1 receptor antagonist but not by angiotensin-converting enzyme inhibition. Fibrillin 1 assemblies are distributed in the myocardium coupling individual myocytes to the pericellular matrix. So analogous to the media of the aortic wall, the interconnected meshwork of fibrillin 1 assembled in the myocardium may represent a key component of the structure believed to support proper muscle function and fibrillin 1 also modulates TGF bioavailability.[55-57] These data suggest that patients with MVP, due to a connective tissue disorder, have an increased incidence of impaired LV function independent of the degree of MR. Additionally, right ventricular dysfunction can occur in MVP. This has been described to occur in 10% of 68 patients with MVP without significant valvular regurgitation.[50] In EDS, characterised by joint hypermobility, skin hyperextensibility, tissue fragility, and occasional MVP in a few patients with diastolic dysfunction and low normal systolic function, have been described.[58] HF in EDS has not been described so far.

CORRELATION OF LV FUNCTION WITH VENTRICULAR ARRHYTHMIAS IN MVP

The increased risk of ventricular arrhythmia and SCD in a small subset of patients with MVP is of great concern but not well understood.[1,59,60] In autopsy series after SCD, the incidence of MVP has been reported to be about 4-5%, which exceeds the prevalence of the disease in the general population (0.6-2.4%).[61] It is thought that SCD in the setting of MVP is mainly arrhythmic, and autopsy reports of previously asymptomatic patients who experience SCD have demonstrated MVP with or without MR.[15,62-64] A recent paper by Sriram et al.[20] investigated a small group of patients with MVP who had survived a SCD event and received an internal cardioverter defibrillator (ICD) for secondary prevention (24 patients). Ten of these patients had MVP. Only bileaflet MVP was found to be an independent predictor of subsequent appropriate ICD shocks for ventricular fibrillation. This subset of patients was characterised by female preponderance and frequent complex ventricular arrhythmias including ventricular premature contractions of the outflow tract alternating with papillary muscle/fascicular origin.

CONCLUSION

In patients with MVP, especially in conjunction with a connective tissue disorder or in the presence of BD, LV, and possibly RV myocardial abnormalities can be found, independent of the degree of MR. Additional LV abnormalities such as asymmetric hypertrophy or diverticula can be found, some of which may be explained by abnormal mechanosignalling caused by the prolapsing valve. We suggest that cardiologists should actively screen patients with MVP, for abnormal LV morphology by echocardiography or cardiac magnetic resonance imaging. In the absence of definitive data on the impact of these findings, it may be wise to closely follow such patients for progressive LV dysfunction, HF, and arrhythmias. To date, unfortunately, the identification of patients with MVP at risk for SCD death is imperfect and evaluation must be individualised, based on symptoms, findings on imaging, exercise testing, and electrocardiogram-monitoring. The detection of myocardial abnormalities may add to the individual risk assessment and risk stratification.

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FUNCTIONAL MITRAL REGURGITATION: IF THE MYOCARDIUM IS GUILTY DO WE ALSO NEED TO 'REHABILITATE' THE VALVE?

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ABSTRACT

Mitral regurgitation (MR) is the most frequent valvulopathy in the general population with an incidence that grows with age and is associated with a poor prognosis. Regardless of its primary cause, which can be both ischaemic and non-ischaemic cardiomyopathy, it finally activates a self-feeding process. Due to the complexity of mitral valve (MV) apparatus and its interaction with the myocardium, even the diagnosis could represent a challenge for physicians. Higher technological instruments such as 3D echocardiography and cardiac magnetic resonance could play an important role in the evaluation of MV. In this paper we reviewed the most salient aspects of functional MR pathophysiology as well as the current diagnostic methods. The management of functional mitral regurgitation (FMR) is even more challenging and controversial; the optimal approach, timing, and effectiveness of interventions are still debated. Treatment of FMR begins with optimal medical therapy for left ventricular dysfunction, including cardiac resynchronisation when indicated. While functional improvement after surgery is well established, the benefits in terms of survival are still questionable. Moreover, in patients with high perioperative risk there is a growing interest in emerging percutaneous techniques. Among a variety of medical, surgical, and percutaneous opportunities, authors support an accurate case-by-case evaluation to find a tailored and stepwise treatment according to anatomical features and patient comorbidities.

Keywords: Functional mitral regurgitation, cardiomyopathy, heart failure, cardiac resynchronisation therapy, new interventional therapies.

DEFINITION AND CLASSIFICATION

Mitral regurgitation (MR) is a common valvular defect with an incidence that grows with age, up to 9.3% in the population over 75 years old; a further worsening of these epidemiologic data can be expected as a consequence of an ageing population. Mitral valve (MV) performance is the result of a complex interaction of many different components: mitral leaflets (ML), mitral annulus (MA), left ventricle (LV), and subvalvular apparatus made of papillary muscles (PM) and chordae tendineae. The MA is a non-planar saddle-shaped structure that interconnects the other moving elements while being dynamic itself: the MA systolic apical bending allows a sphincter-like shrink with an area reduction of about 30%; this adjustment decreases leaflet tissue stress and maintains coaptation. The failure of this perfect interplay leads to a pathologic retrograde blood flow from the LV to the left atrium (LA) during systole. From the pathophysiological point of view, MR can be defined according to Carpentier Classification: Type 1: normal leaflet motion at the annular plane but annular dilatation or leaflet perforation; Type 2: coaptation beyond the plane secondary to leaflet

prolapse or PM rupture; Type 3: coaptation proximal to annular plane associated with valvular and subvalvular sclerosis with restrictive leaflet motion (3A: systolic and diastolic, 3B: systolic). Functional mitral regurgitation (FMR) is defined as secondary to myocardial pathology and rules out a primary disease of the valvular tissues; with respect to the Carpentier system, FMR corresponds to a I or IIIB Class.[1] Moderate-to-severe MR can be diagnosed in about 12% of patients with systolic heart failure (HF) and is associated with poor prognosis; already in 1997, the Survival and Ventricular Enlargement trial demonstrated that FMR detected within the first 16 days after myocardial infarction (MI) is an independent predictor of mortality.[2,3] Recent studies reported similar results in HF patients regardless of the ischaemic or non-ischaemic genesis of the cardiomyopathy.

PATHOPHYSIOLOGY

MR activates a self-feeding process: LA systolic regurgitant blood returns to the LV during diastole causing volume overload and progressive chamber dilatation, leading to increased LV wall stress, worsening of LV myocardial function, displacement of PM, and annular dilatation. Regardless of the underlying cardiomyopathy, FMR is driven by several mechanisms: LV chamber dilatation, subvalvular apparatus, dyssynchrony of the LV, and insufficient mitral leaflet adaptation.

LV chamber dilatation causes an enlargement of the annulus and a distortion of its typical 'D' shape with assumption of a circular geometry and a consequent malcoaptation of the leaflets; Yiu et al.[4] demonstrated that ventricle dilatation is also associated with the loss of the systolic annular contraction that worsens regurgitation degree (Figure 1). Subvalvular apparatus is composed of PM and chordae. Under physiological conditions PM stay parallel to the LV long axis and their contraction balances the systolic forces generated on MV leaflets by ventricular pressure. Despite this, it has been a longstanding thought that PM impairment was only due to the ischaemic/infarctual injury of the PM themselves. Recent evidence, in animal models first and in patients afterwards, support the hypothesis that peri-PM myocardium dysfunction (particularly of the lateral wall) is responsible, via PM displacement, for leaflet malapposition.[5]

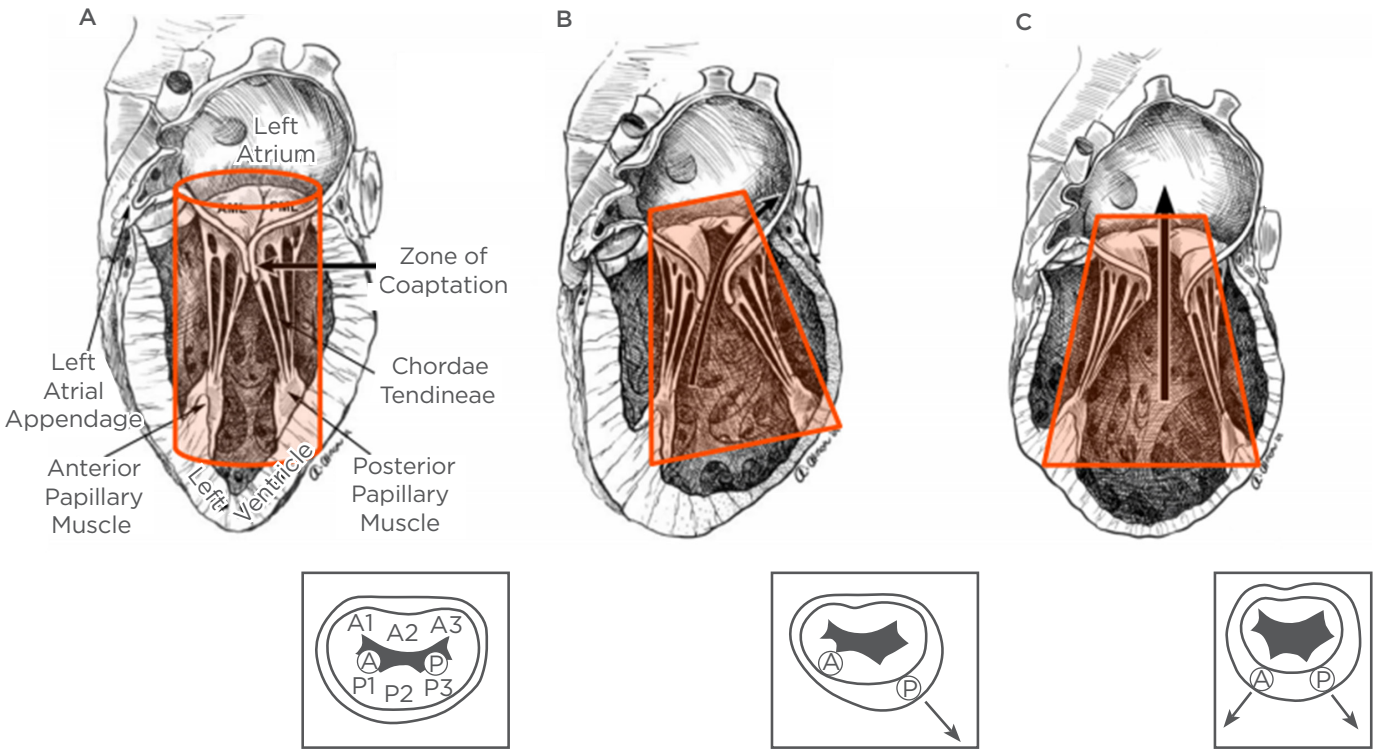

Figure 1: Normal mitral valve apparatus (A); mitral regurgitation (MR) with eccentric jet due to lateral left ventricular wall dilatation and posterolateral papillary muscle displacement (B); MR with concentric jet due to global left ventricular wall dilatation, leaflets malcoaptation, and displacement of both papillary muscles (C).

Dyssynchrony of the LV results in the dyssynchrony of adjacent PM contraction and in leaflet closure; this process has been demonstrated regardless of the dyssynchrony cause: intraventricular conduction defects (very common in dilated ventricles) as well as ischaemic regional contraction defect; in particular LV dyssynchrony in the setting of anterior MI showed to be an independent predictor of FMR.[6] Insufficient mitral leaflet adaptation: 3D echocardiography (3DE) has recently demonstrated, in the setting of LV dilatation, a further compensatory mechanism, as a response to chronic leaflet tethering, which leads to an increase in mitral leaflet tissue and a larger leaflet area; the deficiency of this compensatory system favours MR.[7] The latter described mechanism threatens the definition of FMR itself; it is nowadays accepted that in FMR chronic mechanical stretch stimulates both ML growth and enlargement as a means to prevent regurgitation in the setting of severe LV dilatation.[8] Anatomopathological studies confirmed the reactivation of embryonic processes, partly mediated by transforming growth factor beta expression, with consequent abnormal matrix composition, increased collagen concentration, and activation of valvular interstitial cells.[9] This also represents a challenge during the diagnostic process: to distinguish secondary compensatory modifications from a primary damage of ML that would rule out FMR diagnosis.

DIAGNOSIS

History and physical examination are insensitive for FMR diagnosis; symptoms include effort dyspnoea, asthenia, and reduced exercise capacity but appear to be nonspecific. Physical examination can be misleading as well because the typical systolic murmur related to MR can become low-pitched and soft in the presence of decreased LV pressures. Echocardiography is thus the mainstay for FMR diagnosis and quantification (Figure 2). Assessment of MR severity by echocardiography is complex and requires high accuracy. The 'eyeball' evaluation of the size of the colour Doppler MR jet in the LA is strongly discouraged; current European Association of Echocardiography guidelines support an integrative approach with both quantitative and qualitative parameters.[10] Qualitative parameters include LA size, mitral filling pattern, density of the MR signal on Continuous-Wave Doppler, pulmonary veins (PVs) flow pattern, and pulmonary artery pressure. Despite being qualitative, some of these parameters are either highly specific or sensitive and help mitigate quantitative method errors: for instance, inverted systolic flow in PVs supports MR severity while conversely, an 'A-wave dominant' mitral inflow pattern excludes severe MR. The most accepted quantitative method is the effective regurgitant orifice area (EROA) calculation that is usually derived by the proximal isovelocity surface area (PISA) method. The assumption of a circular regurgitant orifice is the main limitation of the PISA use in FMR, typically characterised by an elliptical shaped orifice, and leads to an underestimation of the MR grade. Current guidelines indicate the need to consider severe primary MR if the EROA is ≥40 mm^2, while the threshold for severity is 20 mm^2 in FMR.[10]

To date, higher technological instruments such as 3DE and cardiac magnetic resonance (CMR) can help physicians in the complex study of MV structures. 3DE allows the calculation of vena contracta sectional area and thus a direct assessment of EROA without any geometric and flow assumptions and the carried bias. 3DE is rapidly developing and correlates with CMR results. Nevertheless, CMR remains the gold standard diagnostic tool for accuracy, reproducibility, and precision in evaluating LV function and LV volumes, and offers an excellent alternative for directly quantifying EROA and LV regurgitant volume; this technique presents some limitations as well (arrhythmias, non-compatible pacemakers or cardioverter defibrillators, claustrophobia) and should be reserved to cases in which echocardiography is technically difficult or equivocal.[11] Further evidences are needed to better define the role of these new methods and to integrate them into a linear and reliable diagnostic process: nowadays, what does one do with a FMR patient with an EROA ≥20 mm^2 accurately measured by CMR or transesophageal 3DE?

THERAPY

We described the complexity of FMR pathophysiology and of the diagnostic process (Figure 3). Treatment of FMR is also challenging and controversial: indications, types of intervention ranging from drugs administration to surgery, timing, and interplay among different approaches are still debated. The first enigma physicians need to decipher is about the main target of therapy: the myocardium, or the valve itself?

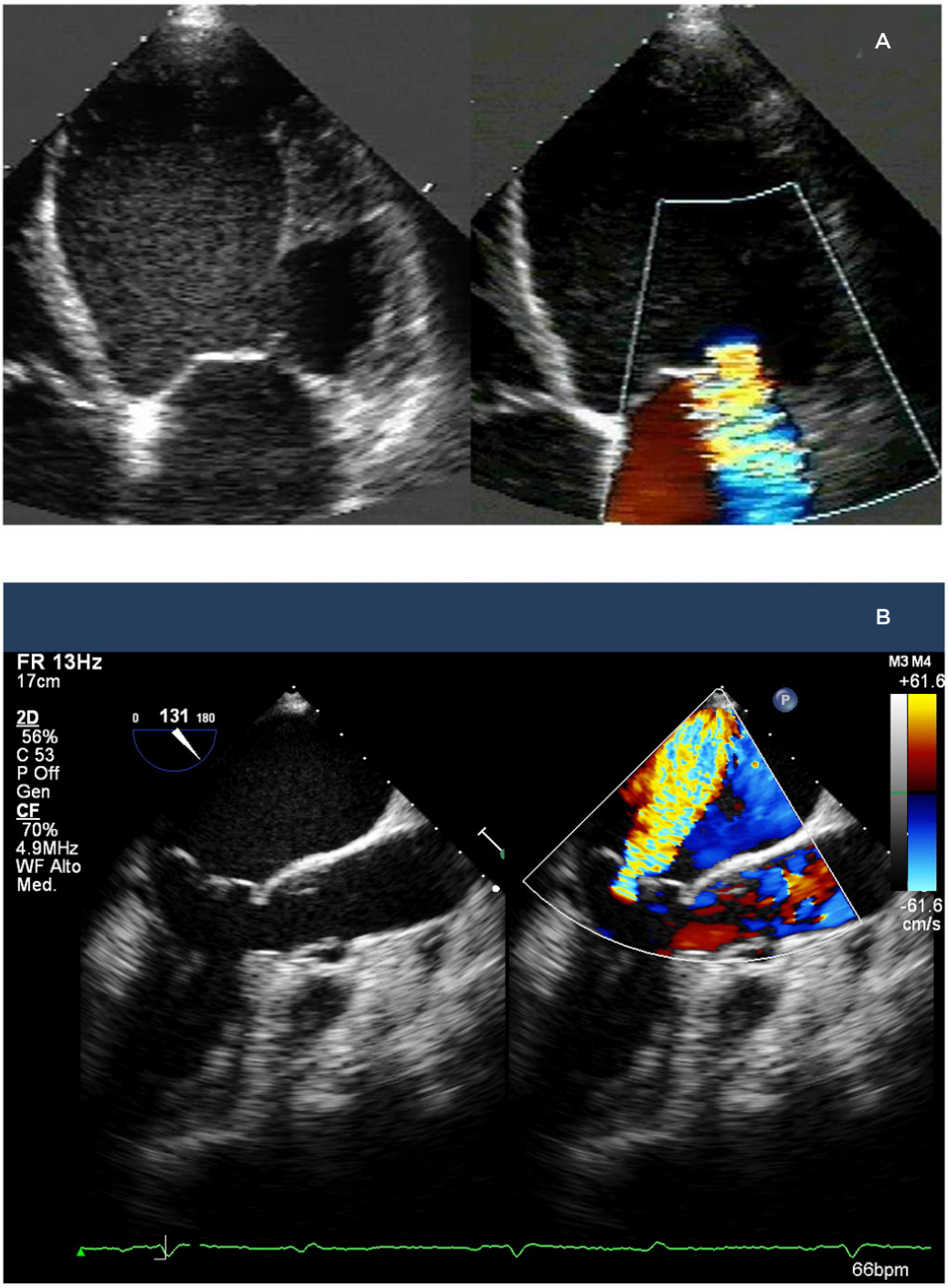

Figure 2: Severe functional mitral regurgitation (MR) in transthoracic echocardiography apical four-chamber view (A); severe functional MR in transoesophageal echocardiography long axis view (B).

Optimal Medical Therapy (OMT)

OMT is the mainstay of therapy. The therapy goal is to improve survival, increase cardiac performance, and reduce symptoms. Beta blockers, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonists are drugs that are able to address myocardial dysfunction by counteracting apoptosis and fibrosis; the resulting effect is the reduction of LV remodelling.[12,13] Vasodilators and loop diuretics act in concert to reduce LV pre and post-load, reduce the entity of MR, and finally improve HF symptoms.

Cardiac Resynchronisation Therapy (CRT)

The rationale for CRT is that approximately 30% of patients with LV dysfunction and chronic HF present not only depressed contractility but also impairment of conduction pathways.

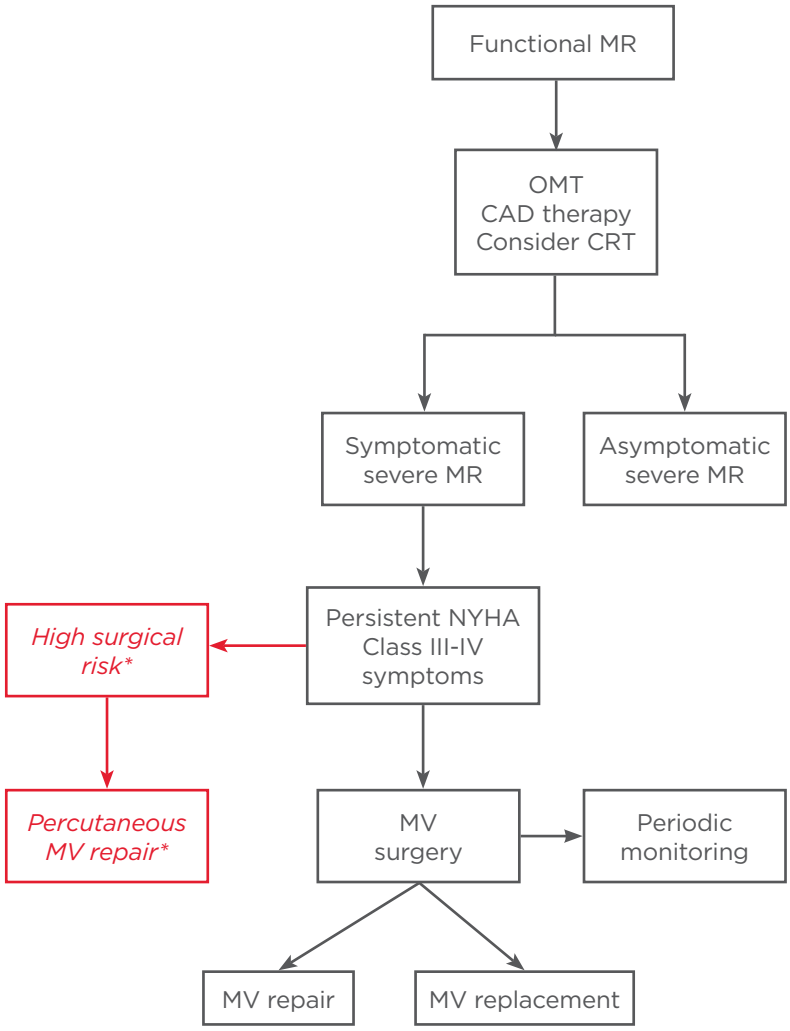

Figure 3: Algorithm for the management of functional mitral regurgitation.
MR: mitral regurgitation; OMT: optimal medical therapy; CAD: coronary artery disease; CRT: cardiac resynchronisation therapy; NYHA: New York Heart Association; MV: mitral valve.

It is well known that inter and intra-ventricular conduction delays lead to asynchronous contraction of LV wall segments, impaired LV efficiency, and uncoordinated PM motion. CRT is a mini-invasive technique able to improve ventricular synchrony, which is thus transmitted to valvular and subvalvular apparatuses, by stimulating both ventricles at the same time; in particular, LV is reached by a pacing lead positioned distally into the coronary sinus (CS). FMR reduction is consequently gained by improvement of myocardial contractility, reversal of LV remodelling, PM resynchronisation, and by increasing MA contraction forces. Van Bommel et al.[14] demonstrated a significant reduction of MR in 98 high-surgical risk patients with moderate-to-severe FMR undergoing CRT: 1 Grade or more MR improvement was observed in 49% of patients and was an independent predictor of survival.

The CARE-HF trial[15] enrolled 813 HF patients in III/IV New York Heart Association (NYHA) Class and showed that the incidence of the composite endpoint of death and all-cause rehospitalisation was 39% in the CRT group versus 55% in medical-therapy group. Moreover CRT reduced the mitral regurgitant jet area and increased LV performance, leading to symptom relief and better quality of life.[15] The MADIT-CRT trial[16] confirmed, in patients with severe LV dysfunction, a MR significant reduction: 1 grade or more improvement occurred in 15.3% of the CRT group patients versus 8.3% of the control group. In the same study, the extent of improvement of echocardiographic measures was directly related to 1 year incidence of death or HF hospitalisations.[16] Nevertheless, response to CRT is not always predictable; despite numerous and heterogeneous criteria having been proposed in the literature to define a

positive response to CRT, it appears unquestionable that a quote of about 30% of patients have little or no benefits from CRT. This failure can be attributed to procedural issues (inappropriate LV lead positioning), and to the extent and location of the scar tissue in ischaemic patients, as well as to the natural history of the underlying progressive disease.[17] Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines[18] on valvular disease recommend CRT in symptomatic patients with chronic severe FMR who meet the other criteria for device therapy (Class 1A).

Surgical Treatment

When symptoms persist despite OMT, patients are often referred to surgery, which may represent the final therapeutic option. As mentioned before, the prognosis of dilated and ischaemic cardiomyopathy worsens when FMR complicates the disease.[19,20] Surgical intervention has been associated with improvement of HF symptoms and LV reverse remodelling; even so, the best surgical technique and the prognostic impact of surgery are still debated. Mihaljevic et al.[21] indeed, in their propensity matched analysis of 390 patients with moderate-to-severe FMR referred to coronary artery bypass graft (CABG), demonstrated that additional MV annuloplasty reduced FMR and improved symptoms but was not associated with longer survival. The same topic has been addressed in a recent randomised trial: RIME investigators[22] evaluated whether MV repair during CABG in patients with moderate FMR may improve functional capacity and LV reverse remodelling. Compared to CABG alone, additional mitral annuloplasty increased peak oxygen consumption, NYHA class, and reduced LV volumes and MR severity; moreover recurrent moderate or greater FMR was observed at 1 year in 4% of treated patients, and in 50% of CABG alone patients. Despite improvement of these clinical and echocardiographic parameters, driven by the higher surgical risk, death incidence at 1 year was higher (9% versus 5%, p=0.66) in the annuloplasty group.[22]

In a very recent study Smith et al.[23] demonstrated that the addition of MV repair to CABG resulted in a reduction of MR but found no significant differences in terms of LV reverse remodelling and 1 year survival. These disappointing results on survival after MV surgery during CABG can be explained by both the predictable increased morbidity in the perioperative time and by the main feature of FMR itself: a myocardial rather than a valvular disease. The benefits of a combined procedure need thus to be carefully balanced against the higher surgical risk. It appears unquestionable that FMR worsens patients outcome but, conversely, there is no clear evidence that FMR correction contributes to better it. Nevertheless, the reported data must be interpreted with caution since most studies are retrospective, observational, single-centre, or underpowered for hard endpoints, and thus suffer from potential referral, selection, and reporting biases. Moreover, the majority of the enrolled patients underwent surgery according to old and nowadays suboptimal approaches: flexible rings, incomplete bands, inadequate size of the annuloplasty rings. Since surgical techniques evolve so rapidly, further studies are certainly needed.

To date, the state of the art of MV repair is restrictive annuloplasty: an undersized, rigid, D-shaped ring implantation able to accomplish leaflet coaptation and valve competency. The major concern of MV repair is the recurrence of significant MR, that ranges from 10-30% at 1 year; echocardiographic predictors of mid-term failure have been proved to be extreme leaflets tethering (posterior leaflet angle >45°, distal anterior leaflet angle >20°) and/or advanced remodelling (end-diastolic diameter >65mm, end-systolic volume >100 ml/m^2, sphericity index >0.7). Whenever the above mentioned conditions are present, undersized annuloplasty should be avoided and chordal-sparing MV replacement should probably be preferred. However, despite higher MR recurrence, MV repair in the past few years has greatly exceeded MV replacement. According to the Society of Thoracic Surgeons between the years 2008 and 2012, about 66% of MV surgeries have been performed using a conservative approach, and this choice was mainly motivated by lower perioperative mortality.[24] Because MR recurrence after repair has been proposed as responsible for surgery failure in reducing mid to long-term mortality, renewed interest in more radical techniques has recently been raised. Acker et al.[25] have very recently published the results of a randomised trial including 251 patients with severe ischaemic MR undergoing MV repair or chordal-sparing replacement. Authors demonstrated, as expected, a higher MR recurrence in the repair group (32.6%

versus 2.3%) but a similar perioperative mortality. Despite the fact that the trial showed no significant difference with respect to the primary endpoint (reduction of the left ventricular end-systolic volume at 12 months) and to major adverse cardiovascular events the study was not powered to show a survival difference at 1 year.[25] Moreover, the above mentioned echocardiographic predictors of repair failure were not considered as exclusion criteria and the high recurrence of MR might have compromised the repair approach potential benefit; therefore it remains debatable as to which one, between repairing and replacing, is the best approach.

Despite the fact that these results are expected to improve on longer term follow-up, doubt about the real target of therapy remains the real challenge for physicians. As a consequence, recent surgical techniques have gone beyond the MV and targeted the subvalvular structures (chordal resection, relocation of PM) and the LV. The latter seems to be the most promising approach: infarct plication, infarct excision and patching, septal reshaping, and external restraint are some of the proposed techniques. Two extracardiac devices have been introduced in the last decade. The CorCap is a LV passive restraint device that was shown in the Acorn trial to provide significant additional benefit in terms of LV reverse remodelling, when added to MV surgery alone in patients with idiopathic dilated cardiomyopathy (IDC).[26,27] Coapsys is the second device and consists of two epicardial pads (anterior and posterior) connected and drawn together by a transventricular chord: the few data available suggest a potential reduction of MR severity and improvement of clinical parameters. Most of the published data pertain predominantly to ischaemic MR, which is the most diffuse form of FMR; fewer data are available about the long-term outcome of surgical MV repair in non-ischaemic LV dysfunction. De Bonis et al.[28] demonstrated that MV repair for FMR in IDC can be performed with a low in-hospital mortality with long-term benefits in terms of NYHA functional class and LV dimensions and function. On the basis of all these evidences, current European Society of Cardiology guidelines[29] recommend surgical treatment for severe FMR in patients with an ejection fraction >30% undergoing CABG (Class I, level of evidence C), while according to the ACC/AHA guidelines[18] in the same subset, MV surgery is reasonable (Class IIa, level of evidence B). Conversely few evidences support MV surgery in patients not requiring myocardial revascularisation; according to both American and European guidelines, MV surgery "may be considered" (Class IIb) only for severely symptomatic patients despite OMT.

Percutaneous Options

In recent years percutaneous valve therapy greatly advanced: the complexity of the mitral apparatus makes the conception and the evaluation of mitral devices as compared to aortic ones more challenging. Nevertheless, the need for percutaneous techniques is motivated by the population ageing phenomenon which carries higher comorbidities in older patients: about 70% of these patients are either not referred or denied MV surgery.[30] Several transcatheter MV therapies have been adapted from surgical techniques and are being applied in patients at high operative risk. Even though the percutaneous approach has not received approval according to AHA/ACC guidelines, MitraClip technology proved to be safe and effective and rapidly reached a widespread diffusion with over 10,000 patients treated[31] (Figure 4).

Based on the edge-to-edge surgical technique, it is a percutaneous device able to deliver on anterior and posterior leaflets one or more clips via transseptal access and to restore coaptation. The EVEREST II randomised trial[32,33] compared MitraClip to MV surgery in a cohort of 279 patients with severe MR, including a quote of FMR of almost 30%. Although surgery was more effective at reducing MR, both groups showed a similar degree of LV reverse remodelling and NYHA class improvement. Moreover, the rates of primary efficacy endpoint at 12 months (a composite of freedom from death, from surgery for valve dysfunction, from Grade 3+ or 4+ MR) was lower in percutaneous-repair group as compared to surgery group (55% versus 73%); the same advantage was kept at 4 years follow-up.[32,33] These findings were confirmed by the ACCESS-EU[34] - the largest real-world database on MitraClip therapy, which included a larger quote of FMR patients (70%). Despite these promising results, a challenge lies ahead: mortality represents the hardest endpoint and it will require years or even decades to be unquestionably defined.

Devices and techniques are continuously evolving: a recently proposed alternative technique is the

indirect annuloplasty. Based on the anatomical proximity of the CS to the posterior mitral annulus, the devices inserted into the CS are meant to create tension that is transmitted to the annulus and reduces annular circumference. The CARILLON is the only device currently approved for use in Europe but its penetration in clinical practice is limited by several issues: increased distance between CS and mitral apparatus in dilated hearts, left circumflex artery proximity and the correlated risk of compression, and preclusion of future CRT.[31] New devices for transvascular direct annuloplasty, such as Mitralign, Accucinch, and Valtech systems are already showing up in the FMR skyline; all these promising techniques will drive physicians to less invasive approaches and will widen the therapeutic opportunities for very high risk patients.

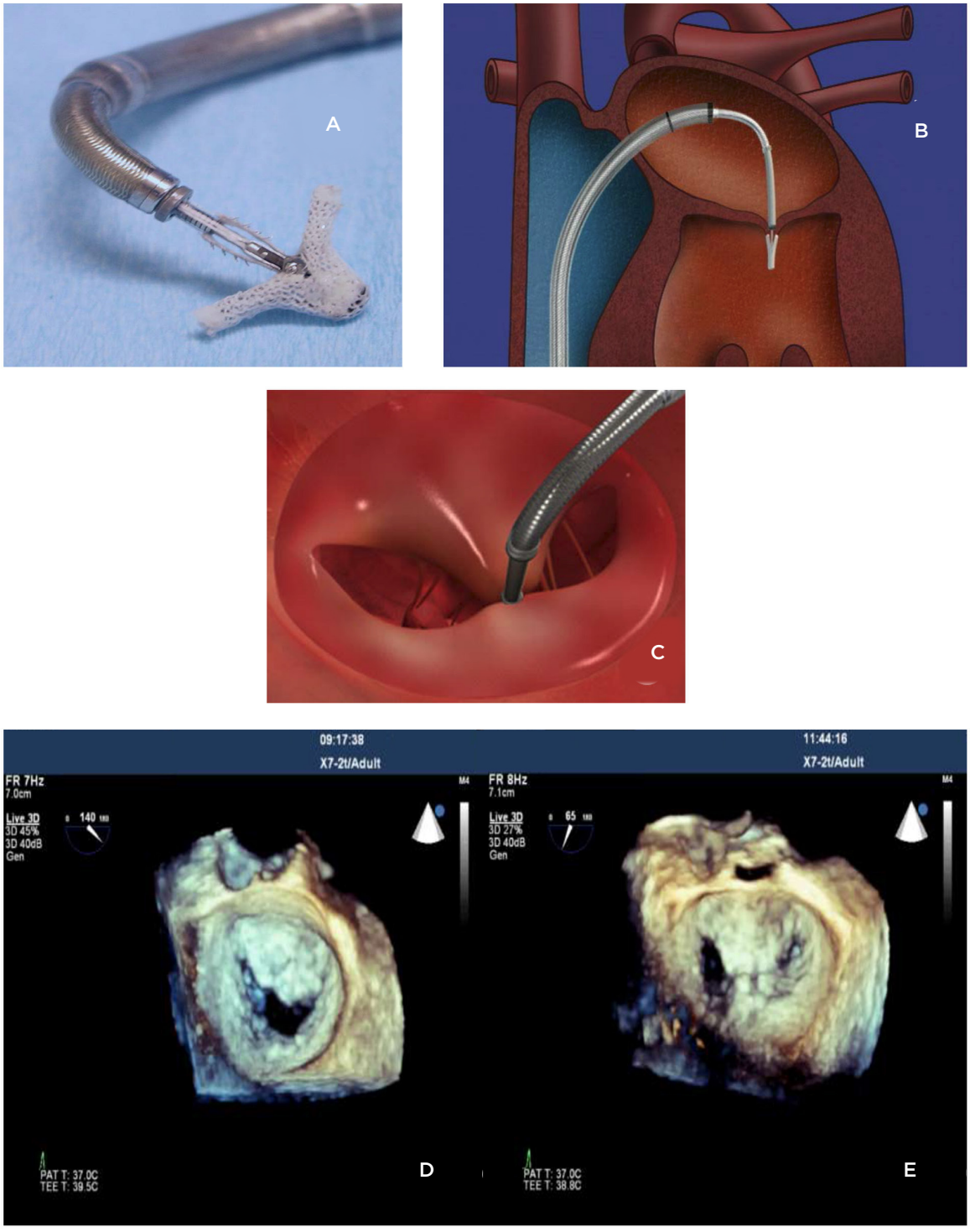

Figure 4: MitraClip device (A); MitraClip deployment (B and C); 3D echocardiographic view before (D) and after MitraClip deployment (E).

CONCLUSION

FMR is a complex disease presenting both diagnostic and therapeutic challenges. It is the author's opinion that FMR has to be considered as a LV pathology and that the LV needs to be the first target of therapy. Medical therapy, and revascularisation therapy for ischaemic FMR as well as CRT indeed showed the best results in terms of hard clinical endpoints. The valve itself, meant in the complexity of its anatomical interactive structures, has to be addressed as a second-line approach; the variety of both surgical and percutaneous techniques available suggests the need for an accurate case by case evaluation and a tailored strategy driven by valve and ventricle anatomy as well as patients' characteristics and comorbidities.

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TRANSCATHETER OPTIONS FOR TREATMENT OF MITRAL REGURGITATION

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ABSTRACT

Transcatheter therapy for valvular heart disease (VHD) as an alternative for surgery, as the standard of care, has emerged rapidly over the last 10 years. Since the first transcatheter heart valve (THV) implantation in pulmonary position, in 2000, and in aortic position, in 2002, an enormous number of high-risk patients have undergone percutaneous aortic valve implantation and a wide variety of commercially available THVs have emerged within the medical sector. Interventional mitral valve repair (MVR) and implantation started with a variety of devices developed by industry, but few are available at the moment. In this article percutaneous systems for the treatment of mitral regurgitation (MR) in high-risk patients are introduced and discussed. Technologies currently under development can be classified by their anatomical approach. To date, only the percutaneous edge-to-edge approach is applied on a larger scale in clinical routine with the MitraClip device. Several other technologies for percutaneous MVR have achieved first-in-man results. For comparable results of transcatheter MVR to surgical MVR a combination of these technologies may be required. The field of transcatheter mitral valve implantation is evolving quickly as well. With half a dozen devices under development right now and a few entering the clinical test stage it may be just a matter of time until a THV for the mitral position will become commercially available. Considering that MR is among the most frequent entities in VHD and, furthermore, that life expectancy will continue to increase, it can be anticipated that in the near future there will be percutaneous strategies needed for the treatment of MR in high-risk patients. At present, all devices have to be restricted to inoperable patients or to compassionate use settings. However, once clinical proof of safety and efficacy have been demonstrated, extension to a broader patient spectrum seems likely. To ensure cautious and safe clinical introduction of these novel therapeutic options, guidance by interdisciplinary dedicated heart teams is of paramount importance.

Keywords: Mitral regurgitation, mitral valve repair, minimally-invasive, transcatheter mitral valve repair, MitraClip, heart team.

INTRODUCTION

Transcatheter therapy for valvular heart disease (VHD) as an alternative for surgery, as the standard of care, has emerged rapidly over the last 10 years.[1] Since the first transcatheter heart valve (THV) implantation in pulmonary position in 2000, and in aortic position in 2002, an enormous number of high-risk patients have undergone percutaneous aortic valve implantation and a wide variety of commercially available THV have penetrated the medical sector.[2,3] Transcatheter mitral valve repair (TMVR) and mitral valve implantation (TMVI) started with a variety of devices developed by the industry, but only a few are available at the moment. Currently there is only one catheter-based leaflet repair system with published randomised trial data available: the MitraClip (Abbott Laboratories, Abbott Park, IL, USA), which mimics the surgical edge-to-edge MVR initially described by Alfieri and co-workers.[4,5] Despite that, a great number of alternative technologies are under development right now. These systems can be classified by the point

of application, following established surgical approaches for MVR and MVI.[6] Considering that mitral regurgitation (MR) is among the most frequent entities in VHD, with a prevalence of 1.7% in Western societies, and furthermore life expectancy will continue to increase, it can be anticipated that, in the near future, there will be percutaneous strategies needed for the treatment of MR in high-risk patients.[7-9] In low-risk patients it has to be emphasised that all novel percutaneous and endovascular strategies for MVR and MVI have to compete with mitral valve (MV) surgery, which is the gold standard of MR treatment, and shows low perioperative risk and excellent long-term outcome.[10] In high-risk patients effectivity can not be compared to surgical outcomes due to a large proportion of patients who are denied surgery.

TRANSCATHETER OPTIONS FOR MVR AND MVI

Even though surgical intervention is recommended in patients with symptomatic severe MR or asysmptomatic severe MR with left ventricular (LV) dysfunction or enlargement, only 50% of these patients receive surgical treatment.[11,12] This is mainly due to advanced age, relevant comorbidities, and/or impaired LV function of the other 50% and thus, denial of surgery. In the following, percutaneous systems for treatment of MR in high-risk patients are introduced.

The Leaflet Approach

Leaflet plication

The aim of the leaflet plication technique is to create a 'double orifice' by bringing the anterior mitral leaflet (AML) and posterior mitral leaflet (PML) together, as first described by Alfieri et al.[5] as surgical procedure. The surgeon places a suture between the A2 and P2 segment of the mitral leaflets. Thereby leaflet coaptation is re-established and MR is minimised. Advantages of the edge-to-edge technique are the simplicity and the possibility of customisation on the basis of the location of the regurgitant jet with both central and paracommissural leaflet approximation. The edge-to-edge technique always involves the risk of creating a mitral valve stenosis. Transcatheter techniques follow this approach with different access routes.

The MitraClip system (Figure 1A and 1B) consists of a polyester-covered cobalt-chromium clip. It is introduced by a 24 Fr delivery catheter via the femoral vein into the right atrium (RA) and, after transseptal puncture, advanced into the left atrium (LA). Under 2D and 3D echocardiographic and fluoroscopic guidance, the clip is positioned above the MV, opened, and advanced into the LV. Subsequently, it is retracted so that the free edges of AML and PML are loaded onto the clip at the origin of the regurgitant jet; closure of the clip results in a 'double-orifice' MV. The MitraClip system was initially evaluated in the EVEREST I (Endovascular Valve Edge-to-Edge Repair Study) and EVEREST II trials.[13,14] Out of 107 patients, acute success with residual MR ≤Grade 2+ was noted in 74%. In 66% of successfully implanted patients, MR was ≤Grade 2+ at 12 months. Severe adverse events were documented in 9% at 30 days. Randomisation for the EVEREST II trial[15] allocated 279 patients in a 2:1 ratio to MitraClip or surgery. Degenerative MR was present in 73% of patients. Primary efficacy endpoint was defined as survival, freedom from reoperation, and freedom from MR ≥Grade 2+ at 12 months, and it was reached in 55% of interventional and 73% of surgical patients in an intent-to-treat analysis (p=0.007). The combined safety endpoint (incidence of severe adverse events to 30 days) was reached in 15% of interventional and 48% of surgical patients (p<0.001), even though transfusion of ≥2 units represented the majority of adverse events. Excluding transfusion, no significant difference in safety was seen (p=0.23). In both interventional and surgical cohorts, ventricular remodelling, improved New York Heart Association (NYHA) functional class, and improved quality of life were noted. It has to be emphasised that 20% of MitraClip patients underwent secondary MV surgery. In 46% of interventional patients MR was ≥Grade 2+ at 12 months. Further follow-up resulted in MitraClip FDA approval in October 2013. Efficacy of the MitraClip device is currently evaluated in randomised controlled trials against best medical therapy in the COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy)[16] and RESHAPE-HF (MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation)[17] trials.

Extensive real-world experience with the MitraClip system exists in Europe. The first implantation performed in Europe was at the University Heart Center in Hamburg, Germany, in January 2008. In an interim analysis of 51 patients,[18] marked reduction of MR and an excellent safety profile of

the procedure was documented. Until January 2014, >500 patients have been treated. This represents the world´s largest single-centre experience. Meanwhile 2-year data of 202 successfully treated patients (74±9 years, 65% male, The logistic European System for Cardiac Operative Risk Evaluation I 25 [16-43]%) from our centre have been reported.[19] 140 patients were treated for secondary MR, while primary MR was present in 62 patients. Freedom from MR ≥Grade 2+ was 89% at 2 years. Presently, a second device for leaflet plication is undergoing preclinical testing: the Mitraflex system (TransCardiac Therapeutics, Atlanta, GA, USA) combines the possibility of deploying a clip for leaflet plication and implanting an artificial chord during the same procedure via the transapical route.

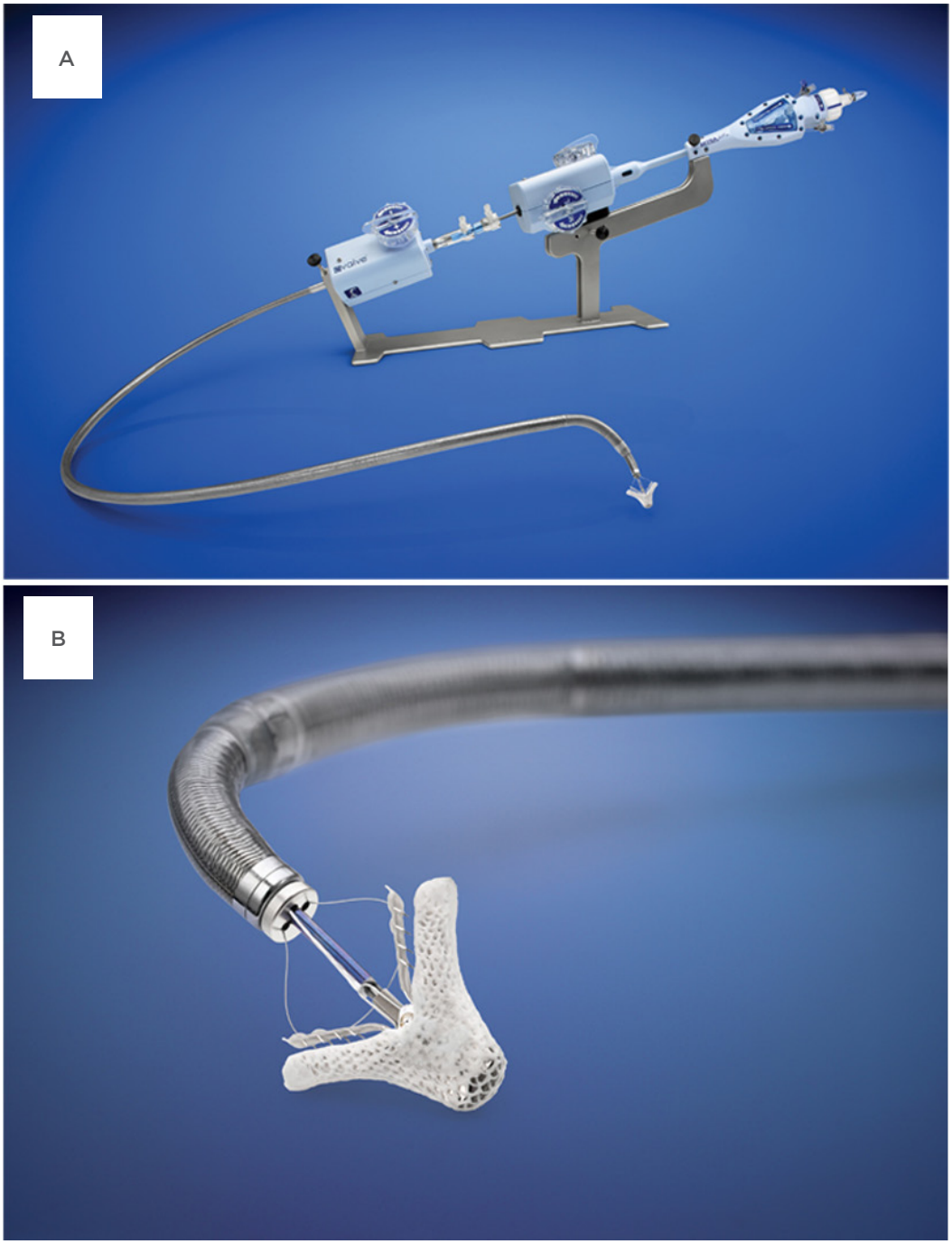

Figure 1: The MitraClip system consists of a polyester-covered cobalt-chromium clip. It represents the interventional extension of the surgical 'edge-to-edge' technique. Displayed here are the delivery system (A) and the clip (B).

Reproduced from Abbott Vascular®, Menlo Park, CA, USA

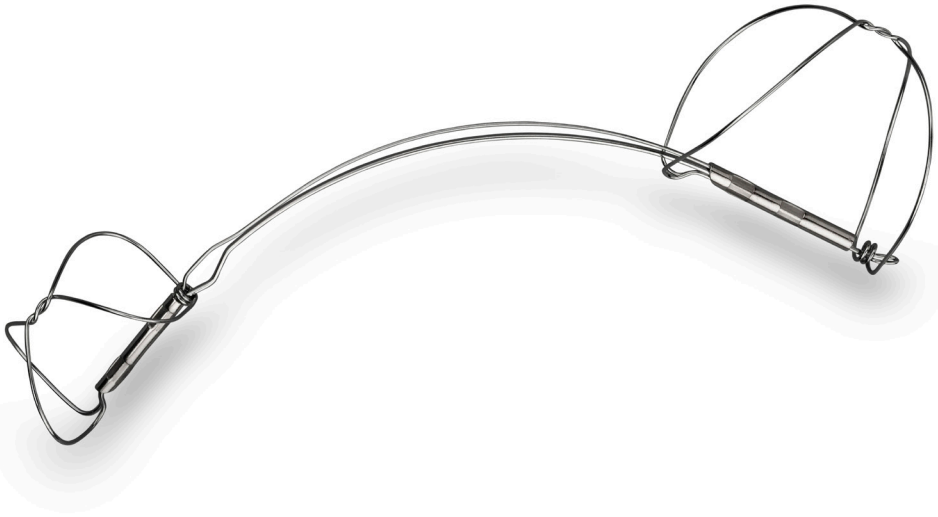

Figure 2: The Carillon Mitral Contour System consists of a central nitinol element connecting distal anchors and a proximal anchor.
Reproduced from Cardiac Dimensions®, Inc., Kirkland, WA, USA

Leaflet ablation

For treatment of degenerative MR the leaflet ablation technique can be used. The Thermocool irrigation ablation electrode (Biosense Webster, Inc., Diamond Bar, CA, USA) applies radiofrequency energy to the leaflets, thus reducing motion by inducing fibrosis. Feasibility was proven in the animal model.[20]

Leaflet coaptation

The principle of space occupying in the regurgitant orifice is implemented by the Mitra Spacer™ device (Cardiosolutions, Stoughton, MA, USA), which is currently undergoing Phase I trial. A balloon-shaped spacer, percutaneously transseptal delivered and made of a polyurethane-silicone polymer, is advanced into the mitral orifice and anchored to the LV apex. The device acts like a buoy and provides a surface the leaflets can coapt against, thus reducing MR.[21]

The Annuloplasty Approach

Indirect annuloplasty

The anatomical proximity of the coronary sinus (CS) to the posterior aspect of the mitral annulus (MA) and the uncomplicated transvenous access have led to the development of different systems for indirect annuloplasty. The Carillon Mitral Contour System (Cardiac Dimensions®, Inc., Kirkland, WA, USA) (Figure 2) consists of a central nitinol element connecting distal anchors and a proximal anchor. After transjugular access the anchoring portions are placed in the vena cordis magna and proximal CS. By stepwise foreshortening of the central element, the device allows for remodelling of the posterior periannular tissue. Results of the prospective, multicentre AMADEUS trial (Carillon Mitral Annuloplasty Device European Union Study)[22] have been published. Implantation of the device was successful in 30 of 48 patients (63%). The device carries a Conformité Européenne (CE) mark. The Monarc System (Edwards Lifesciences, Irvine, CA, USA) has self-expanding distal and proximal anchoring segments connected by a central spring. This spring is held under tension by resorbable spacers. During the first weeks following implantation, the central portion foreshortens successively and reduces septal-lateral circumference of the MA. 1-year data of the multicentre EVOLUTION-I trial[23] (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for The

Treatment of Mitral Regurgitation) have been published. In 82% of 72 patients, successful implantation was documented. In 30%, compression of coronary arteries was noted. The primary safety endpoint was reached by 91% and 82% at 30 days and 12 months, respectively. In 50%, reduction of MR by ≥1 Grade was noted at 12 months. In light of these results, the device is no longer available.

Currently, devices are under development which add a second traction force on the LA or RA. A device by St. Jude Medical (Minneapolis, MN, USA) implants helical screws into the myocardium at the posteromedial mitral annulus. Feasibility was proven in pigs.[24] The National Institutes of Health cerclage technology also proved feasibility in the animal model of a suture and tension-fixation device.[25] It has to be emphasised that with increasing diameter of the atrium, the distance of the CS to the mitral plane is also increasing, mainly in the posterolateral location. Thus, it can be anticipated that the indirect annuloplasty approach should be considered suitable for small atriums in short-term MR.[26-28]

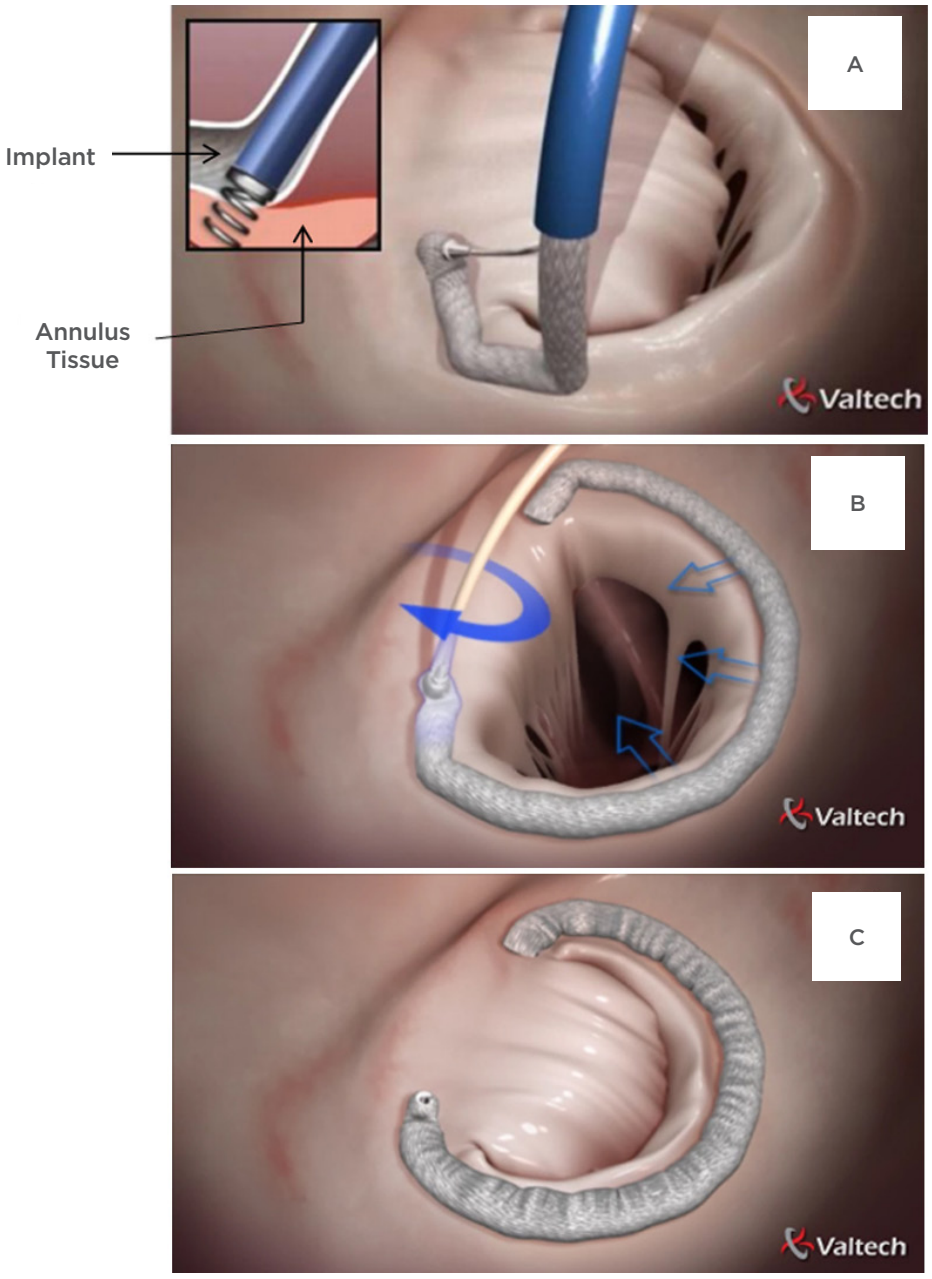

Figure 3: The Valtech Cardio B uses nitinol screws inserted into the atrial aspect of the mitral annulus (A). Subsequently the annulus is cinched (B) until mitral regurgitation decreases (C).
Reproduced from Valtech Cardio®, Or Yehuda, Israel

Direct annuloplasty

Several devices for direct annuloplasty exist mimicking surgical annuloplasty. The risk of circumflex artery compression inherent with CS approaches is reduced by these techniques. One of the devices with early clinical experience is the Valtech Cardio B (Valtech Cardio, Or Yehuda, Israel) (Figure 3A-C), which is delivered via a transvenous, transseptal route, and uses nitinol screws inserted into the atrial aspect of the MA in a commissure-to-commissure fashion. In a second step, a wire is tightened to allow for cinching of the annulus. Experimental and early clinical data have been presented.[29] The Mitralign system (Mitralign Inc., Tewksbury, MA, USA) delivers pledgets via a transventricular route and after puncture of the MA to the atrial aspect. Pledgets are cinched by a suture. A CE mark study is currently being persued.[30] The Quantum Cor device (QuantumCor, Lake Forest, CA, USA) has been tested in animal models and works with heat energy applied to the MA, causing constriction.[31] Hybrid solutions, with surgical implantation of an annuloplasty ring and postoperative adjustment of that ring via transseptal access, are currently under pre-clinical development: the Dynamic annuloplasty Ring System (MiCardia, Inc., Irving, CA, USA) and the Adjustable Annuloplasty Ring (MitralSolutions, Fort Lauderdale, FL, USA).

The Chordal Approach

A novel device for transapical implantation of neochordae has been evaluated clinically, and recently received a CE mark (NeoChord DS1000, NeoChord Inc., Minneapolis, MN, USA). Via standard transapical access, the delivery catheter is inserted into the LV. Under 2D and 3D echocardiographic guidance, the free edge of the prolapsing segment of PML or AML are grasped. Colour-sensitive fibre optics ensure grasping of sufficient leaflet tissue. Neochordae are subsequently externalised through the LV apex and fixed at adequate length under echo guidance. Clinical feasibility and safety have recently been demonstrated in the Transapical Artificial Chordae Tendineae trial and further evaluation is being pursued in a post-market registry at present.[32]

The LV Remodelling Approach

In patients with ischaemic or cardiomyopathy-induced functional MR, a reduction of LV dimensions can lead to a reduction of MR. The idea is to decrease the septal-lateral annular distance and bring the LV papillary muscles to the leaflets by reducing the anterior-posterior dimension of the LV. Currently there is one device following this principle: the Mardil-BACE (Mardil, Inc., Morrisville, NC, USA) has shown feasibility in the animal model and proof-of-concept demonstration in 15 patients. The device is implanted into a beating heart through a mini-thoracotomy with placement of a silicone band around the atrioventricular groove. Inflatable chambers are built in the silicone band and can be inflated at the height of the MA. After implantation adjustment is possible for better leaflet coaptation.

Transcatheter mitral valve implantation (TMVI)

Recently, very early clinical experience has been gathered with devices for transapical and transatrial TMVI. These new devices have the conceptual advantages of potentially abolishing MR altogether without risk of recurrence. Contrary to the aortic valve the anatomy of the MV leads to a challenging development process regarding paravalvular leakage and left ventricular outflow tract (LVOT) obstruction. The eccentric geometry of the mitral orifice does not allow simple solutions for device delivery and anchoring. Nitinol-based devices, which are currently under development, are the Endovalve (Micro Interventional Devices, Inc., Newtown, PA, USA) device, the former Lutter-Lozonschi, now Tendyne valve (Tendyne Holdings, Roseville, MI, USA), the CardiAQ (CardiAQ valve Technologies Inc, Irvine, CA, USA) device, the Edwards Fortis (Edwards Lifesciences, Irvine, CA, USA), the MitrAssist (MitrAssist Ltd., Misgav, Israel) device, and the NeoVasc Tiara (NeoVasc Inc., Richmond, Canada).

The Endovalve is implanted via a right mini-thoracotomy and delivery of the catheter-based valve through the LA. The prosthesis consists of a ring and leaflets with a foldable tripod frame. A gripper feature is integrated for attachment in the beating heart. While a true percutaneous version is under development, the thoracotomy approach was successfully tested in the animal model. The Lutter-Lozonschi, now Tendyne valve, is also radially self-expandable and is delivered via a transapical approach. It consists of an atrial fixation system, a tubular piece with a mounted tricuspid pericardial valve, and a ventricular fixation system. First-in-men procedures were undertaken in Paraguay with promising results.

It has to be emphasised that both patients received a conventional MVR 2 hours after TMVI.[33] First-in-men experiences were made with the Edwards Fortis valve in London, UK and Bern, Switzerland.[34] The valve consists of a central valve body, paddles, and an atrial flange and is only available in 29 mm. The valve is nitinol-based, self-expanding, and has three bovine pericardial leaflets. The paddles are supposed to capture the native leaflets and secure them between the Fortis valve body and the paddles. This THV is delivered transapically with a 42 Fr system. First implants in eight patients showed an MR Grade 0 in three subjects, trace MR in one patient, and MR Grade 1+ in three patients. One patient had to be converted to conventional surgery. Four patients died in the 90 days follow-up.

The MitrAssist valve works with fixation of the transapically delivered valve at the papillary muscles. Chronic animal models showed no trauma to the leaflets, no leaflet adhesion, and no thrombus formation 35 days after implantation. First-in-human procedures are awaited. The Neovasc Tiara consists of a nitinol-based, self-expanding frame, bovine pericardium leaflets, and ventricular anchors to fix the valve onto the fibrous trigone and the posterior annulus. The valve is anatomically D-shaped. It is introduced by a 32 F sheathless system with a self-dilating tip via a transapical approach. First-in-human implants were successful in three patients in Canada: two of them suffered from an ischaemic cardiomyopathy and one from a dilated cardiomyopathy. There were no complications during the implants with MR Grade 0 in two patients and trivial MR in one patient postoperatively. All patients showed a lowering of the pulmonary pressure immediately post implant. A feasibility study with 30 patients is planned for the end of 2014.[35]

The CardiAQ TMVI system is made for both transfemoral and transapical access. It is placed intra- and suprannular to preserve the LV contractility and maximise the LVOT area. The anchoring frame is designed for annular attachment without the use of radial force and preservation of chordate and leaflets. It consists of a bi-level self-expanding nitinol frame.[36] Four successful first-in-human implants were undertaken in Copenhagen, Denmark, two of these patients died on days 3 and 9 due to Systemic Inflammatory Response System and pneumonia, and two patients are still alive with a good haemodynamic outcome and competent THV. A CE mark trial with 100 patients is scheduled for 2015.

COMMENTARY

Refinement of reconstructive techniques has made surgical MVR the reference treatment for patients with relevant MR. Surgery can be performed with low perioperative complication rates and excellent long term outcomes. Therefore, surgery may also be justified in asymptomatic patients. In Germany, rates of MVR as compared to prosthetic valve replacement have constantly increased. Minimally invasive techniques have further improved surgical results and have become the standard of care at specialised centres. Even though surgical MVR is an established therapeutic concept for patients with relevant MR, a large proportion of patients are denied surgery. Due to this fact, percutaneous strategies for MVR and MVI are brought forward after several years. Technologies currently under development can be classified by their anatomical approach. To date, only the percutaneous edge-to-edge approach is applied on a larger scale in clinical daily routine with the MitraClip device. Recently, MitraClip therapy has been incorporated into international guidelines for treatment of primary or secondary MR in inoperable or high-risk patients. Patient selection, performance of the procedure, and post-procedural care should be performed by an interdisciplinary team of cardiologists and cardiac surgeons. Several other technologies regarding percutaneous MVR have achieved first-in-man results. For comparable results of transcatheter MVR to surgical MVR a combination of these technologies will be required.

In the years following the introduction of an interventional MV programme at our centre, surgical MV activity has increased.[37,38] This increase in surgical caseload amounted to 32.2% from 2007-2012, and it was well above the national background, which showed an increase in caseload during the same timeframe of 10.2%.[39] The overall caseload of interventional and surgical MV patients increased by 71.3% from 2007-2012. In summary, it seems likely that, in addition to some crossover of patients initially considered for surgery but then deemed to be high-risk, MitraClip patients stem mainly from an 'on-top recruitment' process. Thus, addition of a MitraClip

programme likely relieved undertreatment of patients with relevant MR.

The field of TMVI is also evolving quickly. With half a dozen devices under development at present and a few entering the clinical test stage, it may be just a matter of time until a THV for the mitral position will become commercially available. However, the anatomical challenges are prominent and results of a greater series of patients have to be awaited. In summary, the field of transcatheter MV therapies is quickly evolving with multiple new repair and replacement strategies in early clinical use. At present, all devices have to be restricted to inoperable patients or to compassionate use settings. However, once clinical proof of safety and efficacy have been demonstrated, extension to a broader patient spectrum seems likely. For a successful clinical programme, an interdisciplinary heart team of multiple specialities, but mandatorily including cardiologists and cardiac surgeons, is needed to ensure optimal patient care and careful evaluation of new techniques against the current surgical gold standard.

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CIRCULATING HAEMOGLOBIN LEVELS AND THE RISK OF ATHEROSCLEROSIS IN ASIAN INDIAN POPULATIONS

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ABSTRACT

Background: The global burden of coronary heart disease (CHD) is estimated to be the highest on the Indian subcontinent. The pathophysiology of this increased risk is complex, multifactorial, and its magnitude increases with migration from India to Britain. Haemoglobin disorders, which also frequent this ethnic group, have been linked to cardiovascular disease. We investigated the impact of migration and nutritional intake on haematological parameters amongst South Asians, with a focus on their relation to molecular indices of oxidative atherogenesis.

Methods: Haematology, diet, oxidised low-density lipoprotein (LDL), and serum paraoxonase activity were measured in 230 migrant Indian Gujaratis (Britain), and 305 matched contemporaries living in rural villages (India).

Results: Median levels of haemoglobin were higher amongst migrant men (14.5 μmol/l) compared to rural men (15.0 μmol/l, P=0.004) and higher in migrant women (12.7 μmol/l) compared to rural women (11.8 μmol/l, P<0.001). Irrespective of site, haemoglobin levels in South Asians were positively associated with high blood pressure, high serum cholesterol, low high density lipoprotein (HDL) cholesterol levels, and increased CHD risk scores (P<0.001). Haemoglobin concentrations were higher amongst migrants compared to rural contemporaries (P<0.001). In rural women, red cell volume was lower, and co-ordinated with lower levels of oxidised LDL compared with migrant women (P<0.001). On multivariate analysis, haemoglobin was independently associated with oxidised LDL (P=0.001) and paraoxonase activity (P=0.025).

Conclusion: Levels of haemoglobin were independently associated with indices of atherogenesis in our populations of rural and migrant Indians. Iron availability may underline the pathogenesis for the oxidative modification of LDL in this group.

Keywords: Haemoglobin, paraoxonase, oxidised LDL, South Asian, dietary iron, coronary heart disease.

INTRODUCTION

Rates of coronary heart disease (CHD) mortality are disconcerting amongst South Asians. The burden of CHD amongst people originating from the Indian subcontinent is estimated to be the highest worldwide,[1] and there is a markedly earlier presentation of disease in this population.[2] Attention to this threat of CHD stems from the excessive disease rates reported in migrant South Asian populations,[3,4] including those in Western countries[5] where CHD is indigenously high.

Changes in diet and lifestyle promoted by the host environment (acculturation) following migration is likely to play an important role in the increased risk.[6] However, despite this higher risk, cardiovascular events in South Asians occur at clinically insignificant levels of classic CHD risk factors, as inferred from Western Societies.[7,8] For example, absolute levels of low-density lipoprotein (LDL) cholesterol are observed to be the lowest in South Asian populations compared with groups from other countries, and at a given level of LDL, the risk of CHD is higher in this group.[9] The pathophysiology of this increased CHD risk amongst South Asians is unclear and it persists in the wake of conventional antihypertensive and lipid-lowering therapy.[10]

We have reported that CHD risk amongst South Asians resident in rural India, and their contemporaries who have migrated to Britain, is underpinned by glucose intolerance, nutritional deficiency, and protein toxicity; specifically, low levels of serum folate and vitamin B_{12} and raised plasma homocysteine,[6] which are also common to other South Asian populations elsewhere.[11,12] Such a phenotype is intuitive of aberrant and increased erythropoiesis,[13-15] which may reflect the antecedents that many South Asians share for diabetes[16] and haemoglobinopathies.[17] Haemoglobin concentrations amongst South Asians may play an important role in the pathogenesis of CHD in this group, supporting established and emerging mechanisms for disease.[18] Proof of concept is supported by observations that (i) the oxidative susceptibility of LDL is increased and the protective activity of high-density lipoprotein (HDL) is reduced in thalassaemia,[19] (ii) aberrant haemoglobin metabolism can oxidise LDL,[20] and (iii) haemoglobin abnormalities in South Asians are associated with atherosclerotic disease.[21]

With an aim to understand the pathophysiology of heightened CHD risk amongst South Asians, we investigated indices of erythropoietic activity and haemoglobin levels and their relation with CHD risk. We hypothesised that an increasing gradient of haemoglobin and altered erythropoiesis facilitates an atherogenic lipid profile, increasing the oxidation of LDL and sequestration of the biological antioxidant action of HDL (paraoxonase activity).[22] In addition, we looked at the impact of the dietary transition between rural Indians and migrant contemporaries on this proposed mechanism of increased CHD risk.

METHODS

We compared a Gujarati community who had migrated to Sandwell (West Midlands, UK) from rural villages around Navsari (Gujarat, North-West India) with age, gender, and caste-matched contemporaries still living in those villages in India, as previously described in detail.[6] The ethnicity of both migrant and rural cohorts was exclusively Gujarati Indian, specifically those originating from the Kantha, near Navsari in Gujarat. Randomly sampled participants from electoral rolls were invited to clinic sessions (between 1997 and 2002) that started with venepuncture (fasting), the completion of a lifestyle questionnaire, and an analysis of dietary intake. All participants in the study gave informed consent. Ethical approval for the study was obtained both in Sandwell and Gujarat from the respective local research ethics committees.

Laboratory Methods

Details relating to the separation, storage, and transport of blood, and the analysis of lipids, lipoproteins, insulin, C-reactive protein, and homocysteine are detailed elsewhere.[6] Between 1997 and 2002 venous blood was collected in ethylenediaminetetraacetic acid (EDTA) from all participants and was analysed for a full blood count using haematology analysers at either the Clinical Haematology Department, Sandwell Hospital, West Bromwich, UK (STAK S, Beckman Coulter Corp., Hialeah, Florida, USA) or the Mankodi Laboratory, India (Bayer Advia, Bayer Diagnostics, Baroda, India). Oxidised LDL was determined using a sandwich enzyme-linked immunosorbent technique involving a two-site immunoassay (Mercodia, Uppsala, Sweden)[23] on EDTA plasma. Commercial and in-house quality controls were used and the intra-assay coefficient of variation (CV) was <8%, while the inter-assay CV was <7%. The limit of detection was 1 mU/l. Paraoxonase activity determined by the rate of generation of p-nitrophenol was determined at 405 nm, 25 °C, with the use of a continuously recording spectrophotometer (described in detail elsewhere).[24]

Key outcome measures were atherogenic indices of lipid metabolism (oxidised LDL, paraoxonase activity) and haemoglobin levels. Other cardiovascular outcome measures included C-reactive protein, serum lipids, and lipoproteins (total cholesterol, triglycerides, HDL cholesterol,

apolipoproteins A1 and B), anthropometry (body mass index [BMI], waist girth), glucose tolerance, blood pressure, and serum insulin. Comprehensive data were available in 228 participants from Sandwell and 285 from Navsari.

Cardiovascular Risk Estimation

The absolute risk (%) of developing non-fatal CHD or coronary death over the next 10 years was estimated using the algorithm derived from the Framingham Heart Study (based on the risk factors age, gender, smoking status, systolic blood pressure, total cholesterol levels, HDL cholesterol, left ventricular hypertrophy, and diabetes status).[25]

Power Calculation and Statistical Analysis

The power calculation for this study was not *a priori* and was done retrospectively. We hypothesised a relationship between haemoglobin with atherogenic indices of lipid metabolism. For a statistically significant (P<0.05, 2-sided) correlation coefficient 'r' (at least 0.20), with a power of 80%, 193 subjects were needed. Data were analysed in SPSS modeler and data mining v14 (SPSS Inc., Chicago, Illinois, USA) using standard and non-parametric tests and Kolmogorov-Smirnov normality plots. Central tendencies and variation for parametric data are presented as mean (standard deviation) or median (interquartile range [IQR]) for non-parametric data. Comparisons were made by T-test or Mann-Whitney U test, as appropriate. Univariate analysis of the association of haemoglobin and blood counts with cardiovascular risk factors was reported with Spearman rank correlation coefficients (r). Partial correlation analysis (two-tailed) was used to adjust the effects of gender and site for bivariate analysis among all subjects. Those factors that were significantly associated with haemoglobin on univariate analysis were selected for multivariate analysis. Linear regression models were calculated to test the strength of association - beta (95% confidence interval [CI]) from independent predictors of oxidative modification of lipoprotein indices. The beta coefficients presented allowed direct comparison (along a scale of 0-1) of the strength of each association within the model.

Table 1A: Concentrations of haemoglobin amongst migrant Indians living in the UK.

Risk factors, dietary intake, and energy expenditure		N	Haemoglobin (µmol/l)	Median (IQR)		P
Overall		230	13.7	(12.5,	15.1)	
Country of birth	India	50	13.7	(13.3,	15.3)	0.24
	Outside India	71	14.0	(12.6,	15.2)	
Body mass index (kg/m^2)	<27	141	13.7	(12.6,	15.1)	0.82
	≥27	88	13.7	(12.4,	15.1)	
Smoking habit in men	Non-smoker	85	15.0	(14.2,	15.6)	0.73
	Smoking history	28	15.1	(14.0,	15.6)	
Glucose tolerance	Normal	168	13.8	(12.6,	15.3)	0.33
	Impaired	13	13.8	(13.2,	14.8)	
	Diabetes	35	13.5	(13.0,	14.6)	
Systolic blood pressure (mmHg)	≤130	119	13.2	(12.0,	14.7)	0.03
	>130	74	14.2	(13.0,	15.3)	
Diastolic blood pressure (mmHg)	≤85	143	13.3	(12.3,	14.8)	0.015
	>85	50	14.2	(13.1,	15.3)	
Serum cholesterol (mmol/l)	≤4	15	12.5	(12.2,	15.0)	0.07
	>4 and ≤5	76	13.3	(12.0,	14.7)	
	>5	133	14.0	(12.8,	15.3)	
Serum triglycerides (mmol/l)	≤1.7	195	13.6	(12.4,	15.0)	0.14
	>1.7	32	14.2	(13.1,	15.3)	
HDL cholesterol (mmol/l)	≤0.9 for men and ≤1.0 for women	128	14.2	(12.9,	15.3)	<0.001
	>0.9 for men and >1.0 for women	99	13.1	(12.0,	14.7)	
Hyperinsulinaemia**	None	139	13.6	(12.4,	15.2)	0.72
	Present	90	14.0	(12.5,	15.0)	
C-reactive protein (g/l)*	≤71	53	13.5	(12.6,	15.2)	0.71
	>216	54	13.2	(12.2,	14.8)	

Table 1A continued.

Risk factors, dietary intake, and energy expenditure		N	Haemoglobin (µmol/l)	Median (IQR)		P
Homocysteine (µmol/l)*	≤9.4	88	13.1	(12.0,	14.6)	0.013
	>14.2	38	14.0	(12.9,	15.3)	
Daily energy intake (Kcal)*	≤1,410	26	13.1	(12.2,	13.6)	<0.001
	>1,960	80	14.3	(13.1,	15.3)	
Energy from dietary protein (%)*	≤12.0	50	13.3	(12.4,	14.5)	0.13
	>14.1	51	14.0	(12.8,	15.3)	
Energy from dietary fat (%)*	≤35.0	37	14.0	(12.8,	15.3)	0.14
	>40.0	58	13.2	(12.3,	15.1)	
Energy from dietary carbohydrate (%)*	≤48.6	65	14.6	(12.9,	15.5)	0.002
	>54.4	35	13.0	(12.1,	13.7)	
Daily energy expenditure (Kcal)*	≤1,580	119	13.2	(12.0,	14.7)	0.012
	>1,950	74	14.2	(13.0,	15.3)	
Cardiovascular risk score (%)*	≤4	87	13.1	(12.1,	14.3)	0.002
	>4 and ≤8	58	14.4	(12.8,	15.5)	
	>8	63	14.0	(12.7	15.0)	

IQR: interquartile range; HDL: high-density lipoprotein. * Cut-offs are tertiles (e.g. highest and lowest) calculated for the combined population. ** World Health Organization defined hyperinsulinaemia (subjects with normal glucose tolerance, but insulin levels in the upper quartile for the combined population of migrants and non-migrants).

RESULTS

Levels of haemoglobin for the combined population of 535 Indian Gujaratis were non-parametrically distributed with a median value of 13.3 (µmol/l) (IQR, 11.9-14.7). Haemoglobin was higher in men (median 14.7 µmol/l) compared to women (12.1 µmol/l), and was typically 5% higher in migrants compared with rural contemporaries (P<0.001).

Levels of Haemoglobin in Relation to Cardiovascular Risk Factors and Diet (Table 1A and 1B)

Across migrants and rural Indians combined, haemoglobin was consistently higher in those with raised blood pressure (at least 7% higher, P<0.001), raised serum cholesterol (2-6% higher, P<0.001), low HDL cholesterol (8% higher, P<0.001), and increased cardiovascular risk score (at least 7% higher, P<0.001). There were no differences in haemoglobin levels by obesity (various anthropometric variables including waist circumference). Haemoglobin differed by glucose tolerance status only amongst those in rural India, where levels were also higher in those with hyperinsulinaemia and high serum triglycerides. Amongst migrant Indians, haemoglobin levels were higher in those with raised homocysteine. Amongst male smokers in rural India, levels of haemoglobin were lower than in non-smokers. With respect to dietary intake and energy expenditure, levels of haemoglobin were highest in those with higher energy intake. Levels of haemoglobin were 5-10% higher amongst those with higher protein and 10% lower amongst those with higher carbohydrate intake. Amongst those with higher energy expenditure, levels of haemoglobin were 7% higher irrespective of site.

Haematology and Oxidative Indices of Atherogenesis

Amongst the men, levels of haemoglobin were lower and red blood cell volume was higher (non-significantly) amongst those in rural India. With respect to rural males, platelet count and oxidised LDL were all comparable to migrant men. In women, those in rural India also had lower haemoglobin, but red cell volume was also lower in comparison to migrant women. Amongst women, platelets and oxidised LDL were all significantly lower amongst rural women compared to migrant contemporaries (Table 2).

Interrelationships between Haematological, Lipoprotein-Related, and Dietary Indices

Levels of haemoglobin were positively associated with oxidised LDL (partial correlation coefficient

= 0.18, P<0.001) and paraoxonase activity (partial correlation coefficient = 0.28, P<0.001), controlling for the effects of gender and site. Amongst those with normal glucose tolerance, levels of oxidised LDL were highest in those individuals in the highest tertile of haemoglobin (gender specific).

Table 1B: Concentrations of haemoglobin amongst rural Indians living in villages in India.

Risk factors, dietary intake, and energy expenditure		N	Haemoglobin (µmol/l)	Median (IQR)		P
Overall		305	13.0	(11.3,	14.4)	
Body mass index (kg/m^2)	<27	272	13.0	(11.3,	14.4)	0.49
	≥27	32	13.1	(11.4,	15.2)	
Smoking habit in men	Non-smoker	77	14.6	(13.6,	15.7)	0.04
	Smoking history	62	14.2	(12.7,	15.3)	
Glucose tolerance	Normal	190	12.9	(11.3,	14.5)	0.03
	Impaired	54	13.0	(11.0,	14.6)	
	Diabetes	41	13.9	(11.9,	15.4)	
Systolic blood pressure (mmHg)	≤130	213	12.9	(11.2,	14.2)	0.02
	>130	57	13.8	(12.0,	15.7)	
Diastolic blood pressure (mmHg)	≤85	237	12.9	(11.1,	14.3)	<0.001
	>85	33	14.5	(12.8,	16.0)	
Serum cholesterol (mmol/l)	≤4	62	12.6	(10.1,	13.7)	0.003
	>4 and ≤5	107	12.8	(10.9,	14.4)	
	>5	126	13.4	(11.9,	14.7)	
Serum triglycerides (mmol/l)	≤1.7	272	13.0	(11.3,	14.4)	0.046
	>1.7	21	13.9	(12.1,	15.8)	
HDL cholesterol (mmol/l)	≤0.9 for men and ≤1.0 for women	132	13.4	(12.1,	14.8)	<0.001
	>0.9 for men and >1.0 for women	161	12.4	(11.0,	14.2)	
Hyperinsulinaemia**	None	187	12.8	(11.2,	14.1)	0.01
	Present	115	13.5	(11.5,	14.9)	
C-reactive protein (g/l)*	≤71	70	13.2	(10.9,	14.6)	<0.001
	>216	33	14.5	(13.0,	16.2)	
Homocysteine (µmol/l)*	≤9.4	54	12.3	(10.5,	14.6)	0.20
	>14.2	107	12.9	(11.1,	14.6)	
Daily energy intake (Kcal)*	≤1,410	69	13.0	(11.1,	14.1)	0.005
	>1,960	2	15.9	(15.7,	16.1)	
Energy from dietary protein (%)*	≤12.0	32	12.1	(10.5,	13.2)	0.018
	>14.1	31	13.4	(11.7,	14.6)	
Energy from dietary fat (%)*	≤35.0	49	12.9	(10.8,	14.1)	0.30
	>40.0	22	13.1	(11.1,	14.7)	
Energy from dietary carbohydrate (%)*	≤48.6	19	13.5	(11.1,	14.5)	0.07
	>54.4	49	12.4	(10.6,	13.5)	
Daily energy expenditure (Kcal)*	≤1,580	213	12.9	(11.2,	14.2)	<0.001
	>1,950	57	13.8	(12.0,	15.7)	
Cardiovascular risk score (%)*	≤4	111	12.7	(11.0,	14.1)	0.07
	>4 and ≤8	56	12.8	(11.1,	14.0)	
	>8	90	13.8	(13.8,	15.3)	

IQR: interquartile range; HDL: high-density lipoprotein. * Cut-offs are tertiles (e.g. highest and lowest) calculated for the combined population. ** World Health Organization defined hyperinsulinaemia (subjects with normal glucose tolerance, but insulin levels in the upper quartile for the combined population of migrants and non-migrants).

Table 2: Haematological parameters and oxidative indices of atherogenesis amongst migrant Indian Gujaratis and contemporaries in rural India.

	Rural Indian men (n=140)		Migrant Indian men (n=115)		P	Rural Indian women (n=165)		Migrant Indian women (n=115)		P
Haemoglobin (g/dl)	14.5	(13.2, 15.4)	15.0	(14.2, 15.6)	0.004	11.8	(10.5, 13.0)	12.7	(11.8, 13.3)	<0.001
Mean cell volume (fl)	87.1	(82.1, 90.7)	85.0	(81.0, 89.0)	0.06	81.6	(73.8, 85.5)	84.0	(78.8, 87.0)	0.014
Red blood cell count ($U \times 10^{12}/l$)	5.02	(4.62, 5.50)	5.20	(4.92, 5.47)	0.09	4.50	(4.16, 4.90)	4.53	(4.26, 4.97)	0.45
Platelet count ($U \times 10^{9}/l$)	224	(184, 279)	215	(193, 247)	0.11	232	(184, 281)	259	(212,313)	0.06
Paroxonase activity (nmol/min/ml)	140	(88, 180)	229	(186, 293)	<0.001	123	(75, 172)	216	(169, 299)	<0.001
Oxidised LDL (U/l)	39.0	(29.0, 51.0)	41.9	(29.0, 52.0)	0.54	33.0	(25.2, 43.8)	38.0	(30.0, 51.8)	0.002

Data are Median (IQR). LDL: low-density lipoprotein; IQR: interquartile range. * Cut-offs are tertiles (e.g. highest and lowest) calculated for the combined population. ** World Health Organization defined hyperinsulinaemia (subjects with normal glucose tolerance, but insulin levels in the upper quartile for the combined population of migrants and non-migrants).

Other haematological indices were unrelated to lipoprotein variables, and there were no interaction effects with haemoglobin in models of univariate analysis of variance. On bivariate analysis, levels of serum cholesterol and apolipoprotein B were associated with haemoglobin in men and women from both sites, and the magnitude of this association was greatest in rural India ($r=0.27$, $P<0.001$). In addition, amongst rural Indian women, haemoglobin was associated with apolipoprotein A1 levels ($r=0.25$, $P<0.05$). On multivariate analysis, levels of oxidised LDL (in a model that included haematological indices, site, gender, glucose tolerance status, smoking, systolic blood pressure, and serum lipids) were independently associated with triglycerides, total to HDL cholesterol ratio and haemoglobin levels (Table 3). Levels of haemoglobin were independently related to gender, diastolic blood pressure, oxidised LDL, and paraoxonase activity (Table 3). On regression analysis of cardiovascular risk scores across the whole population, levels of haemoglobin, oxidised LDL, BMI, and site were all independently associated.

Across the whole population, levels of oxidised LDL were associated with dietary intake of iron and vitamin B complex constituents (particularly riboflavin and thiamine), controlling for the effects of site and gender. Within rural Indian men, levels of oxidised LDL were associated with dietary niacin ($r=0.40$, $P=0.018$) and vitamin B_{12} ($r=0.33$, $P=0.05$), while in migrants, dietary intake of iron ($r\leq-0.27$, $P<0.03$) and thiamine ($r\leq-0.31$, $P<0.02$) were negatively associated with paraoxonase activity. On multivariate analysis, dietary factors were not independently associated with lipoprotein-related indices. However, in rural Indian men, there was a modest negative association between the variation of oxidised LDL levels and the percentage of energy derived from carbohydrate ($r=0.42$, $P<0.001$). Across sites, levels of homocysteine were negatively associated with paraoxonase activity ($r=-0.16$, $P=0.002$).

DISCUSSION

Amongst migrant Indians and rural contemporaries, levels of haemoglobin were associated with common risk factors for CHD, including blood pressure, lipids, and direct indices of atherosclerosis, irrespective of site and gender. Data here suggest that the molecular basis for this relationship involves the oxidative modification of LDL by haem. The potential pathway is likely to be borne from the culmination of nutritional deficiency (folate and B vitamins), toxins such as homocysteine, and (unmeasured)

genetic predisposition to bloodborne disorders and aberrant erythropoietic activity. Further work is warranted. The implication of these findings is that haemoglobin levels are intimately co-ordinated with quantitative and qualitative features of lipoproteins, and may provide insight into the increased CHD risk amongst people originating from the Indian subcontinent.

The idea that haemoglobin is a risk factor for CHD is not novel, and the Iron-Heart Hypothesis, which suggests that increased iron stores are a CHD risk factor, was presented by Sullivan in 1981.[26] Data presented here reflects a close relationship between haemoglobin levels and both quantitative and qualitative aspects of lipid metabolism. There is increasing evidence to support an interactive physiological role between lipoproteins such as LDL and HDL with haemoglobin and iron transport.[27,28] In the presence of a nutritional deficiency of folate and vitamin B_{12}, this process is likely to render HDL dysfunctional.[29] Of note, levels of paraoxonase activity in this population were closely reflected by HDL cholesterol concentrations.[30] Hence, in this population it would appear that levels of cholesterol transport on HDL also reflect other aspects of HDL functionality.

Previously we reported that migration-related changes included increases in total cholesterol, fasting triglycerides, apolipoprotein B, and blood pressure within this group of Gujarati Indians.

Table 3: Multivariate analysis of haemoglobin levels, oxidised LDL, and paraoxonase activity amongst migrant Indians and contemporaries who remained in rural villages.

Multivariate models	Beta	(95% CI)		P
1. Dependent variable: Haemoglobin (µmol/l)				
Female gender	-1.85	-2.39	-1.32	<0.001
Diastolic blood pressure (mmHg)	0.047	0.025	0.069	<0.001
Oxidised LDL (U/l)	0.019	0.005	0.033	0.01
Paraoxonase activity (nmol/min/ml)	0.56	0.07	1.04	0.025
2. Dependent variable: Oxidised LDL (U/l)				
Serum cholesterol (mmol/l)	8.0	5.3	10.7	<0.001
Haemoglobin (µmol/l)	1.70	0.38	3.02	0.012
HDL cholesterol (mmol/l)	-10.8	-19.9	-1.7	0.02
3. Dependent variable: paraoxonase activity (nmol/min/ml)				
Migrant status	0.563	0.405	0.721	<0.001
HDL cholesterol (mmol/l)	0.489	0.259	0.720	<0.001
4. Dependent variable: cardiovascular risk score (%)				
Haemoglobin (µmol/l)	0.68	0.297	1.054	0.001
Oxidised LDL (U/l)	0.05	0.008	0.094	0.021
Body mass index (kg/m^2)	0.34	0.153	0.535	<0.001
Migrant status	-3.11	-5.057	-1.156	0.002

Variables in multivariate model 1 included migrant status, homocysteine, serum cholesterol, serum triglycerides, HDL cholesterol, percentage of energy intake as carbohydrate, serum insulin, C-reactive protein, and physical activity. Model 2 included age, paraoxonase activity, diastolic blood pressure, migrant status, homocysteine, serum triglycerides, percentage of energy intake as carbohydrate, serum insulin, C-reactive protein, and physical activity. Model 3 included homocysteine, serum cholesterol, serum triglycerides, diastolic blood pressure, oxidised LDL, percentage of energy intake as carbohydrate, serum insulin, C-reactive protein, and physical activity. Model 4 included paraoxonase activity. The multivariate models were developed to include independent confounding factors (non-normally distributed variables were normalised by log-transformation).
LDL: low-density lipoprotein; HDL: high-density lipoprotein; CI: confidence interval.

However, HDL cholesterol and homocysteine were not adversely affected by migration.[6] This novel advance in CHD in this group may be explained by the findings in this analysis, which additionally reflect aberrant haemoglobinisation and erythropoiesis. Also, in the current analysis it is apparent that a greater intake of carbohydrate is associated with lower levels of oxidised LDL, underlining the deleterious effects of the nutritional transition between India and the UK for this group. These findings also suggest that increased dietary iron may pose a healthcare concern in this group, which is compounded, given that the normalisation of body iron status in response to anaemia is a common primary care intervention amongst South Asian populations.[31-33]

Patients with chronic anaemias and high erythropoietic activity (e.g. beta thalassaemia) are known to have low levels of serum and HDL cholesterol[34,35] (possibly through the increased cholesterol requirement associated with erythroid hyperplasia[36]). Also, in patients with a susceptibility to hyperlipidaemia, the presence of beta thalassaemia has an LDL cholesterol-lowering effect.[37] While there were no observations of overt anaemia within the present study, measures of lipoproteins and lipids were positively related to haematological indices. Of note, in rural India, where levels of haemoglobin were lowest, there were morphological differences in red blood cells between men and women. In rural Indian men, low levels of haemoglobin were manifest with large red blood cells (relative to migrant men), suggesting folate deficiency as a cause for differences in haematology. In rural Indian women, red blood cells were relatively smaller than for Sandwell counterparts, indicative of an iron-related deficiency as a cause for low levels of haemoglobin. In relation to iron-related deficiency, our results amongst rural Indian women suggest that this phenotype is cardio-protective, and support observations that paraoxonase activity is reduced in this cause of anaemia. However, while genetic disorders such as beta thalassaemia are endemic to India,[38] there is no evidence that this is a cause of increased erythropoeitic activity for the populations observed here. The erythropoietic demand that is generated by the development of diabetes could also represent an underlying haematological consequence amongst South Asians.

The independent association between haemoglobin levels and CHD risk scores in these populations is interesting, and may underpin novel approaches for the early identification of South Asians at increased CHD risk. Haemoglobin levels were independently associated with blood pressure levels, and one hypothesis is that the higher levels of haemoglobin in this population reflect a status of greater oxidative stress. For example, the vasodilator activity of nitric oxide (NO) is mitigated by the expression of the haem-containing NO receptor soluble guanylyl cyclase, which is impaired by the oxidative modification of its haem component.[39] In our own data, levels of haemoglobin remain associated with systolic and diastolic blood pressure, even after controlling differences in dietary intake.

The limitations of this work include the cross-sectional nature of our approach, which precludes our ability to determine cause and effect. Our stratified random sampling approach for the population was used as an attempt to minimise sources of confounding, and multivariate models were developed with the assumption that factors were normally distributed and were independent. However, we cannot rule out residual confounding and unmeasured factors related to haemoglobin, oxidised LDL, and paraoxonase activity. For example, genetic analysis of beta thalassaemia trait, haemochromatosis trait, and paraoxonase polymorphism remain unmeasured.

In summary, these findings support a link between haemoglobin levels with CHD risk factors and oxidative indices of atherosclerosis in these populations of South Asians. Iron availability may underline the pathogenesis for the increased CHD in this group and further work is warranted.

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THE PROGRAM ON THE SURGICAL CONTROL OF THE HYPERLIPIDEMIAS (POSCH) AND THE LIPID REGULATORY HYPOTHESIS

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ABSTRACT

Background: The Lipid Regulatory Hypothesis (LRH) states that the best way to regress atherosclerotic plaque is to simultaneously decrease the cholesterol being transported into the arterial wall by low-density lipoprotein (LDL) and increase the cholesterol being removed from the arterial wall, via reverse cholesterol transport, by high-density lipoprotein (HDL). The cholesterol retention fraction (CRF) is defined as (LDL cholesterol minus HDL cholesterol) divided by LDL cholesterol. The Program on the Surgical Control of the Hyperlipidemias (POSCH), which employed partial ileal bypass as the intervention modality, was selected for verification of the LRH and the validity of the CRF.

Methods: POSCH coronary arteriographic plaque progression or non-progression (stabilisation/regression) from baseline to 3 years was stratified on a five-by-five factorial grid with 25 cohort cells combining LDL cholesterol and HDL cholesterol changes from baseline to 1 year following intervention. Predictive capacity for arteriography changes of LDL cholesterol and CRF were compared. Statistics used were logistic regressions.

Results: There were 731 paired arteriographic assessments of individual POSCH patients: 163 progression (22%) and 568 non-progression (stabilisation/regression) (78%). A reciprocal LDL cholesterol and HDL cholesterol relationship represented as a five-by-five factorial showed non-progression above and progression below the dividing diagonal. 100% (163/163) of patients with plaque progression had a rise in their CRF; and 100% (568/568) of patients with plaque non-progression had a fall in their CRF. LDL cholesterol, HDL cholesterol, and CRF were all highly significant predictors of plaque progression and non-progression ($p<0.0001$).

Conclusion: In POSCH, the partial ileal bypass-induced changes in the LDL cholesterol, HDL cholesterol, and the CRF are highly correlated with the sequential coronary arteriography changes of plaque progression and non-progression. This study affirms that individual patient prognosis can be predicted by the magnitude of response to lipid intervention.

Keywords: Atherothrombotic disease, dyslipidaemia, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, plaque stabilisation/regression, plaque progression, the Lipid Regulatory Hypothesis.

INTRODUCTION

The holy grail of interventional lipidology (Harvey Hecht, M.D., used with permission) and preventive cardiology is the prevention of atherothrombotic disease (ATD), defined as atherosclerotic disease with emphasis on the associated thrombosis that produces the acute clinical ATD event (e.g. acute myocardial infarction [MI] and acute cerebral infarction). The basis of ATD is the atheromatous plaque. The efficacy of various therapies for preventing ATD relies on their ability to stabilise or regress that plaque.[1-3] Lipids comprise a significant portion of the ATD plaque. It is well established

that cholesterol is transported to the arterial wall by low-density lipoprotein (LDL) and is removed from the arterial wall by reverse cholesterol transport mediated by high-density lipoprotein (HDL). These two processes have been combined in The Lipid Regulatory Hypothesis (LRH), advanced by Dr. Esko Nikkila in the 1970's[4] and supported angiographically.[5] The LRH states that maximal regression of ATD plaque occurs when therapy to simultaneously lower LDL cholesterol and raise HDL cholesterol is utilised.

In 2000, a meta-analysis of eight published angiographic studies, comprising 2,089 paired serial angiograms, to assess the capability of various forms of dyslipidaemia therapy to stabilise and regress ATD plaque was published.[6] The outcomes of one of these trials, the Program on the Surgical Control of the Hyperlipidemias (POSCH),[1,7-9] will be analysed in relationship to the balance between LDL cholesterol and HDL cholesterol, specifically the cholesterol retention fraction (CRF): (LDL cholesterol minus HDL cholesterol), divided by LDL cholesterol ([LDL-HDL]/LDL). The derivation of the CRF has been reported.[10,11] The CRF has been shown to be an accurate predictor of the population at risk of ATD,[12] and when combined with systolic blood pressure, to accurately guide therapeutic measures to stabilise/regress coronary plaque angiographically.[6] Because the CRF represents the balance between the cholesterol entering the artery wall (LDL) and the cholesterol being removed from the arterial wall by reverse cholesterol transport (HDL), the CRF provides a superior means of monitoring plaque progression versus plaque non-progression (PNP), as is evident from the findings of the National Heart, Lung, and Blood Institute (NHLBI) study[5] and the 2000 meta-analysis.[6] In POSCH[1,7-9] there were marked changes in both LDL (lowering) and HDL (raising), as well as the greatest degree of PNP. Therefore, the CRF would appear to be the ideal tool with which to analyse POSCH results.

METHODS

Study Design

The POSCH trial was selected for verification of the LRH and the validity of the CRF because it had numerically and statistically significant LDL cholesterol reductions and HDL cholesterol elevations,[7] it was a combined clinical and arteriographic study with highly significant outcomes,[1,7] and it showed a reduction in overall mortality[8] that has persisted for 25 years.[9] POSCH was a secondary intervention trial, utilising the partial ileal bypass operation as the intervention modality; both the control and the intervention groups were placed on an American Heart Association diet protocol. POSCH was funded by the NHLBI, in four geographically separate centres, with a study population of 838 (421 surgeries, 417 controls). No patients in this trial dropped out. A single electrocardiogram and enzyme documented MI, and a total plasma cholesterol of at least 5.69 mmol/l or a LDL cholesterol of at least 3.62 mmol/l if the total cholesterol was between 5.17 mmol/l and 5.66 mmol/l were the inclusion criteria; obesity, diabetes, and a left main stem coronary artery (or equivalent) lesion >75% on coronary angiography were the main exclusion criteria. POSCH showed highly statistically significant reductions in mortality and recurrent MIs, angina pectoris, peripheral vascular disease, and the need for coronary artery surgery or angioplasty, as well as coronary arteriography (CA) demonstration of significant reductions in atherosclerotic plaque progression and actual plaque regression. POSCH was the first and only lipid/atherosclerosis trial to use a metabolic surgery procedure as the intervention modality.

Coronary Arteriography

Sequential coronary arteriograms in POSCH were obtained in all patients at baseline and in all available patients at 3, 5, 7, and 10 years postoperatively. Paired arteriograms were read by two-member panels blinded to the temporal sequence of the arteriograms, which were labeled A and B. In addition to reading the percentage of stenosis of individual coronary arterial segments, the readers gave an overall disease comparison score. The POSCH Coordinating Center, using the scores of the arteriography panels and with knowledge of the temporal sequence of a paired set of patient arteriograms, graded the paired arteriograms as demonstrating progression of atherosclerotic plaque disease or non-progression, which included plaque stabilisation and regression. For the current analysis, baseline arteriograms were compared with the first available post-randomisation study (follow-up 3 years up to 5 years). Due to patient attrition, arteriographic follow-up after 3 years diminished and these studies were not available for this assessment of the CRF.

Table 1: Change in low-density lipoprotein (LDL) versus change in high-density lipoprotein (HDL) in angiographic outcomes in POSCH.

Change in LDL cholesterol (mmol/l)	Change in HDL cholesterol (mmol/l)				
	Increase ≥0.26 mmol/l	Increase 0.13-0.23 mmol/l	Increase 0.10 to decrease 0.10 mmol/l	Decrease 0.13-0.23 mmol/l	Decrease ≥0.26 mmol/l
Decrease ≥0.78 mmol/l	70	79	193	56 2	26 9
Decrease 0.26-0.75 mmol/l	11	14	47 2	2 16	10
Decrease 0.23-Increase 0.23 mmol/l	13	19	24 27	11	12
Increase 0.26-0.75 mmol/l	3	5 3	3 35	11	4
Increase ≥0.78 mmol/l	3	2	12	2	5

POSCH: Program on the Surgical Control of the Hyperlipidemias.

Table 2: Comparison of cholesterol retention fraction (CRF) and low-density lipoprotein (LDL) sextiles in predicting percentage of angiographic progression in POSCH.

CRF		LDL (mmol/l)	
Sextile	**% Progression**	**Sextile**	**% Progression**
VI (CRF ≥0.80) n progression n total % progression	 88 137 64%	**VI (LDL ≥5.17)** n progression n total % progression	 26 41 63%
V (CRF = 0.75-0.79) n progression n total % progression	 51 130 39%	**V (LDL = 4.53-5.15)** n progression n total % progression	 44 71 62%
IV (CRF = 0.70-0.74) n progression n total % progression	 16 94 17%	**IV (LDL = 3.88-4.50)** n progression n total % progression	 51 133 38%
III (CRF = 0.65-0.69) n progression n total % progression	 4 79 5%	**III (LDL = 3.23-3.85)** n progression n total % progression	 27 109 25%
II (CRF = 0.60-0.64) n progression n total % progression	 0 66 0%	**II (LDL = 2.59-3.21)** n progression n total % progression	 12 106 11%
I (CRF ≤0.59) n progression n total % progression	 2 223 1%	**I (LDL ≤0.56)** n progression n total % progression	 2 269 1%

POSCH: Program on the Surgical Control Hyperlipidemias.

Table 3: Change in cholesterol retention fraction (CRF) in POSCH.

	Progression versus non-progression			
Change in CRF	**NP**	**P**	**Σ**	**%NP**
Decreased				
≥0.15	277	0	277	100%
0.10-0.14	77	0	77	100%
0.05-0.09	92	0	92	100%
0.01-0.04	112	0	112	100%
No Change				
0.00	10	13	23	43%
Increased				
0.01-0.04	0	93	93	0%
0.05-0.09	0	42	42	0%
0.10-0.14	0	8	8	0%
≥0.15	0	7	7	0%

POSCH: Program on the Surgical Control of the Hyperlipidemias; P: progression; NP: non-progression.

LDL cholesterol and HDL cholesterol values, comparing baseline values to the 1-year post-intervention values, were stratified as follows: LDL cholesterol (mmol/l): decrease ≥0.78, decrease 0.26-0.75, decrease 0.23 to increase 0.23, increase 0.26-0.75, and increase ≥0.78; HDL cholesterol (mmol/l): increase ≥0.26, increase 0.13-0.23, increase 0.10 to decrease 0.10, decrease 0.13-0.23, and decrease ≥0.26. This classification schema allowed for the construction of a five-by-five factorial comparison table containing 25 cohort cells. The numerical content of each of the 25 cohort cells were stratified by angiographic outcomes: progression versus non-progression (stabilisation/regression). For example, a patient whose LDL cholesterol went down by 1.29 mmol/l and whose HDL cholesterol went up by 0.31 mmol/l would be placed in the left uppermost cohort of the table; whereas a patient whose LDL cholesterol went up by 0.13 mmol/l and whose HDL cholesterol went down by 0.5 mmol/l would be placed in the centre cohort. The boxed table was constructed so that for each cohort a number in the right lower most corner represented progression and a number in the left uppermost corner represented non-progression. If a corner contains no number, then there were no patients in that category (Table 1).

The predictive capacity of the CRF ([LDL – HDL]/LDL) was tested against the POSCH arteriography data. This was done by construction of a table of sextiles for the 1-year interval CRF and LDL cholesterol levels stratified as a function of plaque progression (Table 2). Further, the change in the CRF from baseline to the 1-year interval value - from decreased, to no change, to increased - was categorised for progression, non-progression, and percent non-progression (Table 3).

Laboratory Methods

HDL cholesterol was measured by the precipitation technique, using dextran sulfate (50,000 Mw) and magnesium in the reagent. LDL cholesterol and very low density lipoprotein cholesterol are removed by centrifugation, leaving HDL cholesterol in the supernatant. The HDL cholesterol in the supernatant is then measured by a timed endpoint method. In the reaction, cholesterol esterase hydrolyses cholesterol esters into free cholesterol and fatty acids. The free cholesterol is oxidised into cholestene-3-one and hydrogen peroxide by cholesterol oxidase. Peroxidase then catalyses the reaction of hydrogen peroxide with 4-aminoantipyrine and phenol to produce a coloured quinoneimine product, which is then

measured colourimetrically. Once HDL cholesterol is known, then LDL cholesterol is calculated by the Friedewald equation.[13]

Statistics

The data were examined by independent and multiple logistic regression analyses.

RESULTS

At the first post-randomisation comparison of available arteriograms for individual POSCH patients there were 731 paired assessments: 163 cases of angiographic plaque progression (22%), and 568 cases of PNP, consisting of plaque stabilisation and plaque regression (78%). Considering changes in the LDL cholesterol independently, 47% (267/568) of those patients with PNP achieved 1-year post intervention LDL cholesterol lowering ≤2.56 mmol/l; whereas only 1% (2/162) of those patients with plaque progression had 1-year post intervention LDL cholesterol level reductions ≤2.56 mmol/l. Table 1 represents comparison of the changes in the LDL cholesterol and the HDL cholesterol stratified according to arteriographic progression (ArP) or non-progression. Of the 25 cohort cells, those in a diagonal line between the left lower most corner and the right upper most corner contained a population mixture of patients with angiographic progression (AnP) and non-progression. Essentially all cohorts above this diagonal represent patients with pure angiographic non-progression, and virtually all cohorts below this diagonal represent patients with pure AnP. This relationship is pictorially represented in Figure 1.

Certain inferences can be made from these data: plaque progression and non-progression, including actual plaque regression, are a function of a reciprocal LDL cholesterol and HDL cholesterol relationship. Most cases of PNP occur when the LDL cholesterol is lowered by at least 0.78 mmol/l; however, if the HDL cholesterol falls by as little as 0.13 mmol/l cases of plaque progression are seen, and the more the HDL cholesterol falls the more cases of progression occur. Conversely, even if LDL cholesterol levels rise, but the HDL cholesterol rises simultaneously by at least 0.26 mmol/l, PNP is the rule. The predictive capacity of the CRF was tested against POSCH arteriographic findings. This was done by constructing a table of sextiles for the 1-year interval CRF and LDL cholesterol levels, stratified as a function of plaque progression. Table 2, illustrating ArP stratified by sextiles of the 1-year interval CRF and LDL cholesterol levels, shows that the CRF sextiles proceeding from highest risk (sextile VI) to lowest risk (sextile I) sequentially predict less plaque progression than do the corresponding LDL sextiles. (Figure 2) Sextile VI for CRF contains all CRF values ≥0.80; Sextile V, CRF values 0.75-0.79; Sextile IV, CRF values 0.70-0.74; Sextile III, CRF values 0.65-0.69; Sextile II, CRF values 0.60-0.64; Sextile I, CRF values ≤59.0. For LDL, Sextile VI contains all LDL values ≥5.17 mmol/l; Sextile V, LDL values 4.53-5.15 mmol/l; Sextile IV, LDL values 3.88-4.50 mmol/l; Sextile III, LDL values 3.23-3.85 mmol/l; Sextile II, LDL values 2.59-3.21 mmol/l; Sextile I, all LDL values ≤2.56 mmol/l.

Table 3 demonstrates that 92% (150/163) of patients with plaque progression had a rise in their CRF; whereas 98% (558/568) of patients with PNP had a fall in their CRF. No-one whose CRF declined had plaque progression, and no-one whose CRF had risen had angiographic evidence of non-progression. 3% (23/731) had no change in their CRF values at 1 year. In an attempt to refine angiographic outcomes in those 23 patients whose CRF (when calculated to two decimal places) did not change, it was decided to calculate the CRF to four decimal places. When this was done, the 10 patients whose angiograms had shown regression all had declines, albeit minute, in their CRF values, and the 13 patients whose angiograms had shown progression all had rises, albeit minute, in their CRF values. Thus when the CRF is calculated to four decimal places, then all patients with a decline in their CRF values showed plaque stabilisation/regression and all patients with a rise in their CRF values sustained plaque progression. Independent regression analyses for LDL cholesterol, HDL cholesterol, and CRF are all highly significant for predicting ArP or regression/stabilisation ($p<0.0001$). The LDL cholesterol is the strongest predictor, followed by the CRF, and then HDL cholesterol.

DISCUSSION

The LRH of Nikkila[4,5] is strongly supported by the arteriography data of the POSCH trial.[1,7-9] The hypothesis, in brief, states that therapy to lower LDL cholesterol and simultaneously raise HDL cholesterol will halt the process of atherogenesis or ATD. The current analysis clearly confirms the reciprocal and complimentary relationship of the

two cholesterol transport fractions in predicting arteriographic changes over time. In a POSCH paper in preparation (not yet published) it is demonstrated that the arteriographic changes will in turn predict clinical events and overall mortality during 25 years of follow-up. Thus, life expectancy, at least in patients who have sustained a single MI (a POSCH inclusion criterion) may be predictable by coronary plaque progression or non-progression on arteriography, and these arteriography changes are predictable by therapy-engendered LDL cholesterol lowering in concert with HDL cholesterol elevation, as reflected by the CRF. Though the lipid-atherosclerosis hypothesis has long been considered a theory or even fact, the current study adds undeniable substantiation to its proof.

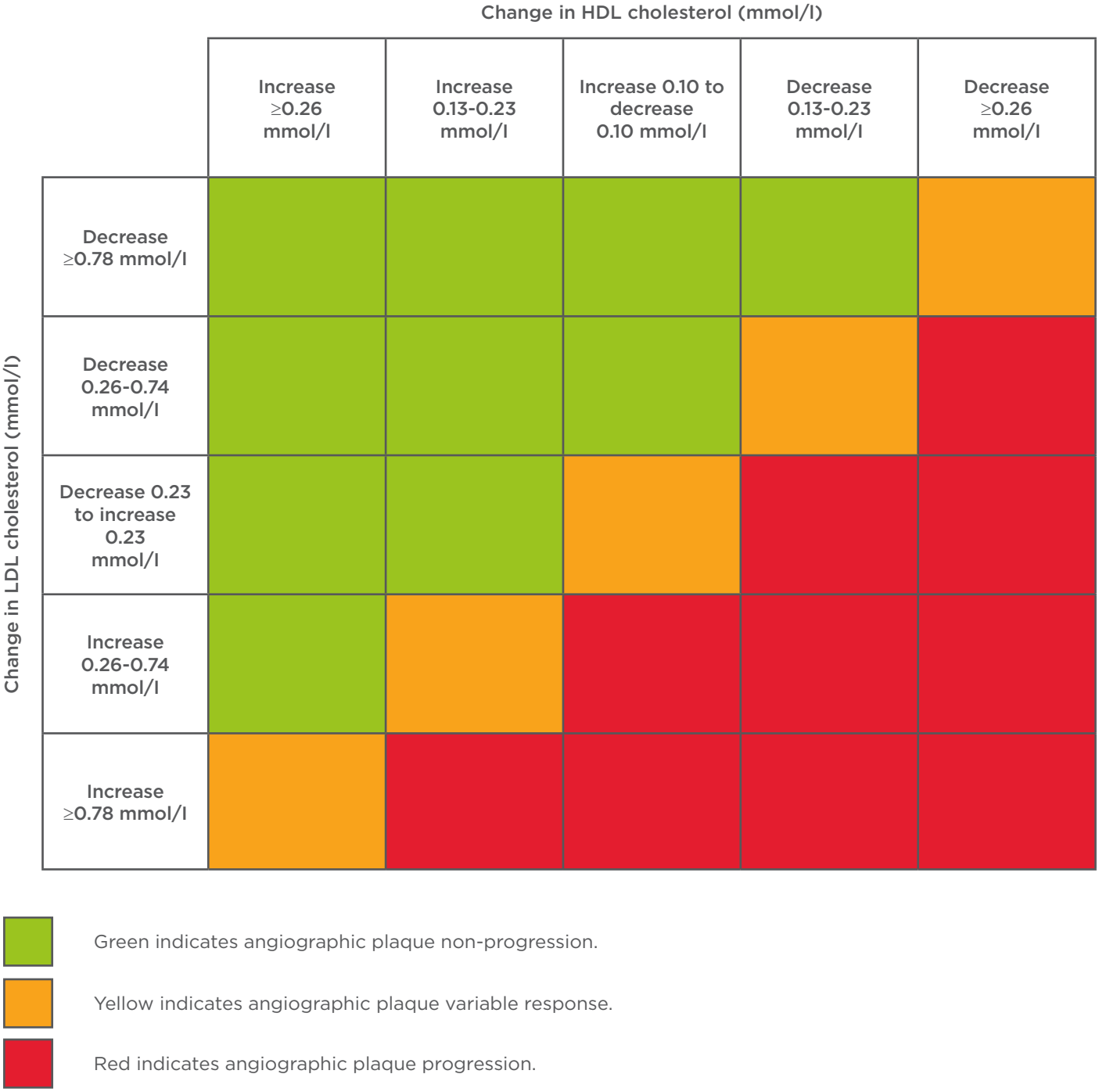

Figure 1: Change in low-density lipoprotein (LDL) versus change in high-density lipoprotein (HDL) in angiographic outcomes in POSCH.

POSCH: Program on the Surgical Control Hyperlipidemias.

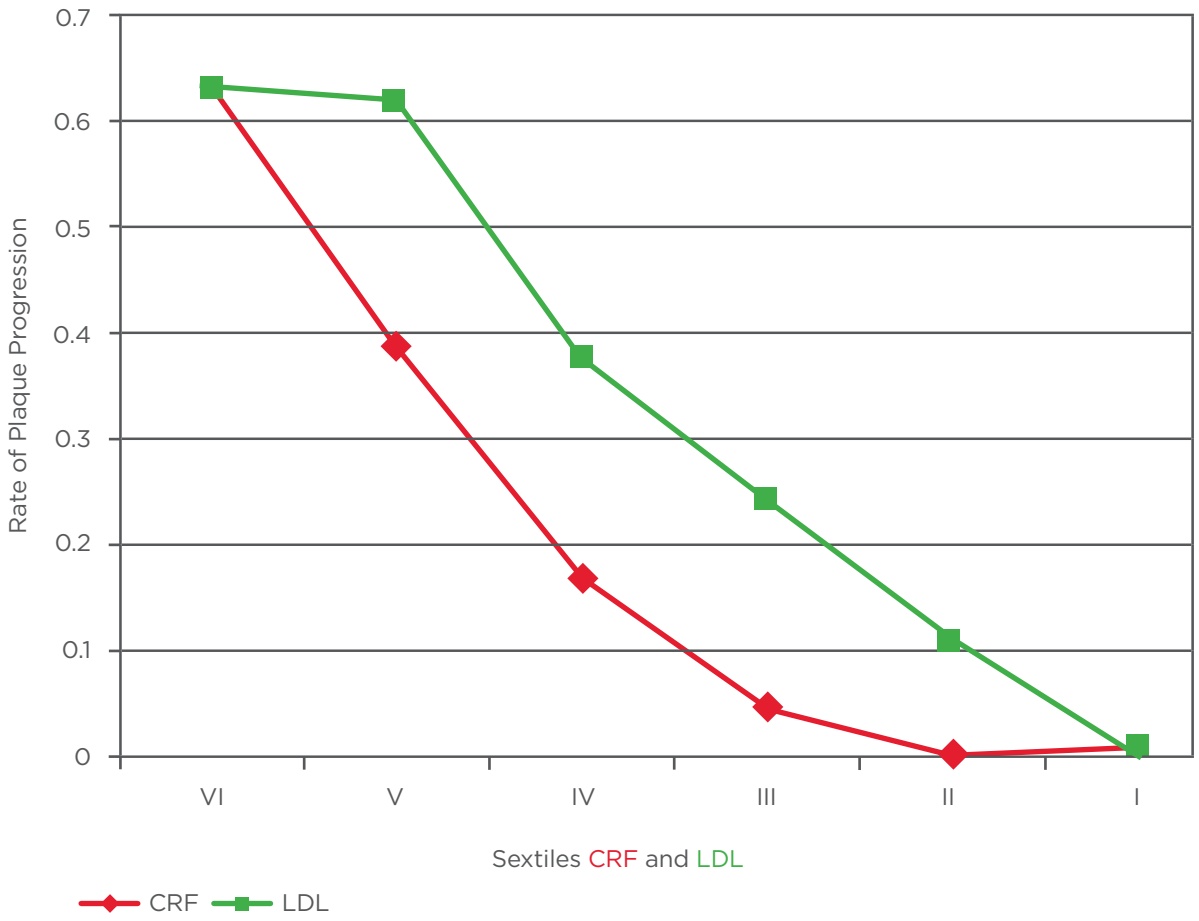

Figure 2: The incidence of plaque progression in sextiles of CRF versus sextiles of LDL cholesterol.
CRF: Cholesterol retention fraction; LDL: Low-density lipoprotein.

The efficacy of favourable lipid modulation exhibited in the POSCH trial was responsible for the selection of this study in relationship to the CRF. The overall correlation of arteriographic prognosis with the CRF is independent of whether the POSCH patients were in the intervention or control groups. Of course, the favourable changes in the cholesterol fractions were dominant in the partial ileal bypass intervention group and, therefore, the favourable changes in arteriographic progression/non-progression occurred in that group as well. The CRF incorporates the key cholesterol fractions of LDL cholesterol and HDL cholesterol, and expresses them in an equation that is predictive of the progression or non-progression of ATD. Table 1 and Figure 1 demonstrate this concept and reveal that for PNP, lowering LDL and raising HDL play complementary roles. Clearly lowering LDL is associated with PNP, though less so when HDL levels fall sufficiently. It is also clear that raising HDL is associated with PNP, though less so when LDL levels rise sufficiently. This is interpreted to mean that it is the balance between LDL and HDL that is critical to plaque progression versus non-progression, and that this balance would be best expressed by the CRF, rather than by LDL or HDL individually, since the CRF will define the extremes of lipid disorders, as well as intermediate imbalances in LDL and HDL as well. Further, in a study of drug-naïve diabetic patients, the CRF was compared to the non-HDL cholesterol component for correlation with inflammation, a key factor in ATD. The two were highly correlated (p=0.0001) as inflammatory markers, whereas the LDL cholesterol fraction was not.[14]

Figure 2 confirms the superior ability of the CRF to predict plaque stabilization/regression with respect to LDL cholesterol. While the sixth and first sextiles of both predictors show the same rates of plaque progression, plaque progression rates are lower in the intermediate CRF sextiles than in the intermediate LD cholesterol sextiles. In the intermediate sextile range, the CRF predicts less plaque progression than does LDL cholesterol, and

thus is superior to LDL cholesterol in predicting plaque non-progression.

The 2000 meta-analysis of published lipid/arteriographic studies included, in addition to POSCH, the St. Thomas Angiographic Regression Study (STARS),[15] the Heidelberg Study,[16] the NHLBI Type II Secondary Prevention Trial,[5] the Lipid Angiography Trial (LOCAT),[17] the Lipoprotein and Coronary Atherosclerosis Study (LCAS),[18] the Familial Atherosclerosis Lipid Study (FATS),[19] and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-1) study.[20] There are several other reports of the benefits of LDL cholesterol and HDL cholesterol modification as well.[21-25] However, the end-of-trial LDL cholesterol reduction demonstrated in POSCH was achieved in only a few of these studies (e.g. FATS[19] and NHLBI[5]). The end-of-trial reciprocal blend of LDL cholesterol and HDL cholesterol values was unique to the POSCH study. Interestingly, in the six trials[5,15-20] in which we were able to perform comparable plaque evolution comparisons with the LDL cholesterol, HDL cholesterol, and the CRF, we found no relationship as compelling as the POSCH findings. Further, there are a number of trials in which large lipid modifications have been achieved, but no effect on the atherosclerotic plaque has been evident. These studies include two trials using cholesterol ester transfer inhibitors,[26,27] two trials employing the addition of ezetimibe,[28,29] and two trials where niacin was added to patients pretreated with statins.[30,31]

POSCH adds support to the role of HDL raising as a protective mechanism to stabilise/regress plaque as part of dyslipidaemic therapy. This role has been challenged in the above cited studies.[25,26,29,30] However, POSCH powerfully supports the LRH as regards HDL raising. The reason for the difference between POSCH and the other studies may be that some lipid-modifying medications may interfere with HDL functionality or fail to reduce the role of gut bacteria, leading to reduced reverse cholesterol transport.[32] This in turn proposes that dyslipidaemic medications must be shown to stabilise/regress plaque or reduce adverse ATD outcomes before they can be recommended for use.

Human metabolic studies have clearly demonstrated the mechanisms of action and causative effects of the partial ileal bypass operation: marked reduced cholesterol and bile acids (an end-product of cholesterol metabolism) absorption and reabsorption by their respective enterohepatic cycles, reciprocally marked faecal increased cholesterol and bile acid excretion, increased cholesterol synthesis, increased cholesterol turnover, and reduction in the freely miscible (including plasma), and the less freely miscible (including the arterial wall) cholesterol pools.[7] This being said, the pleiotropic effects often attributed to the statins[32,33] would not be present when the intervention modality is the partial ileal bypass operation. On the other hand, is the partial ileal bypass effect purely that of lipid modification? Can the bypass of the ileum elicit some change in the gut flora that mitigates the atherosclerotic plaque? A recent paper by Tang et al.[34] found a deleterious effect of gut organisms by their metabolising of phosphatidylcholine into trimethylamine-N-oxide, which is associated with an increase in ATD events. There is also evidence to support that gut bacteria play a role in the aetiology of other diseases, notably obesity.[35,36] Can partial ileal bypass have an opposite or beneficial effect on intestinal bacteria and the substances they elaborate? This suggestion warrants further investigation.

The POSCH study is pertinent in clinical practice today, since it is the cornerstone for the lipid/atherosclerosis theory. In essence, all of the POSCH outcomes regarding prediction of risk and prognosis have been verified and therefore serve as tested metrics now and most likely in the future. Further, POSCH is the precedent randomised controlled clinical trial utilising metabolic surgery, an emerging discipline that will contribute to our knowledge of mechanisms and therapeutics. The limitations of this study include that the validity analysis of the CRF is based on the historical and therefore immutable POSCH trial. POSCH is, however, a landmark study and the most definitive of the lipid/atherosclerosis trial evaluations. The POSCH subject population was predominantly male and Caucasian and, therefore, the comparative findings may or may not be applicable to women or non-Caucasians.

Caveat: The POSCH trial and the other studies described in the 2000 meta-analysis[6] were all performed prior to a change in the laboratory determination of the HDL cholesterol level from a precipitation method to an enzymatic method.[37] These different methodologies do not give the same results for HDL cholesterol. The older precipitation method gives a value for the HDL cholesterol fraction that is of the order of

0.25 mmol/l lower than one calculated by the new enzymatic method. Consequently, since LDL cholesterol is usually calculated by the Freidewald equation,[13] LDL cholesterol levels, determined on the basis of the newer HDL cholesterol method, will be of the order of 0.25 mmol/l lower than when calculated by the older method. All the LDL and HDL cholesterol values involved in this effort were based on analyses by the older precipitation method and are therefore uniform and accurate with regard to their arteriography correlations.

CONCLUSION

In summary, in POSCH the partial ileal bypass-induced alterations of the LDL cholesterol, HDL cholesterol, and CRF support the LRH and are highly correlated with the sequential CA changes of atheromatous plaque progression and non-progression (stabilisation/regression). Since the POSCH sequential arteriograms have been documented to be accurate surrogates for clinical ATD events and overall mortality, this study affirms that individual patient prognosis can be predicted by the magnitude of response to lipid interventional therapy, especially as reflected by the CRF.

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HOW I TREAT: CORONARY HEART DISEASE: THE PLEIOTROPIC EFFECTS OF STATINS

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Cardiovascular (CV) diseases currently represent the first cause of death in industrialised countries with coronary heart disease (CHD) corresponding to the zenith of the phenomenon being responsible either for acute CV events or chronic heart failure (HF). Over 7 million people every year die from CHD, accounting for 12.8% of all deaths. Dyslipidaemias undeniably play a pivotal role in the pathogenesis and progression of atherosclerosis, and lipid lowering with statins is an essential and integral part of CHD prevention and management. Statins are the most widely prescribed drugs worldwide for lowering blood cholesterol levels. They have been used for over 20 years, and have been found to be effective, safe, and well tolerated over a broad range of patients.

Statins reduce synthesis of cholesterol in the liver by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. A number of large-scale clinical trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and secondary prevention. Statins at doses that effectively reduce low-density lipoprotein cholesterol (LDL-C) by 50% also slow progression or even promote the regression of coronary atherosclerosis. Current available evidence suggests that the clinical benefit is largely independent of the type of statin while it is reliant on the extent of LDL-C lowering; therefore, the type of statin used should reflect the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient.

Besides the reduction of LDL, statins have been demonstrated to accomplish a number of other effects, known as 'pleiotropic effects'. These effects are due to cholesterol-independent mechanisms and include improvement of endothelial dysfunction, inhibition of inflammatory responses, decreased oxidative stress, stabilisation of atherosclerotic plaque, modulation of platelet function, and smooth muscle cell proliferation. Statins exert their effect by upregulating the expression of endothelial nitric oxide synthase, increasing the expression of tissue-type plasminogen activator, decreasing the expression of endothelin-1, reducing the production of thromboxane A2 and high-sensitivity C-reactive protein levels, inhibiting the lymphocyte function-associated antigen 1/intercellular adhesion molecule 1 interaction. Furthermore, statins are able to inhibit the expression of metalloproteinases and tissue factor with cholesterol-dependent and independent mechanisms, and to induce angiogenesis by promoting proliferation, migration, and survival of circulating endothelial progenitor cells. Many of these pleiotropic effects are mediated by inhibition of isoprenoids, which serve as lipid attachments for intracellular signalling molecules.

The benefits in terms of primary and secondary prevention of acute CV events are highlighted by more than 27 trials. Statin therapy reduces the 5-year incidence of major CV events by 20% per mmol/L reduction in LDL-C regardless of initial LDL-C or other baseline characteristics. Specific trials have demonstrated the benefit of early and intensive statin therapy in patients with acute coronary syndromes in terms of reduction of the risk of CV death, non-fatal myocardial infarction (MI), and coronary revascularisation.[1] Moreover, a meta-analysis performed on 13 randomised clinical trials with 3,341 patients with high-dose statin pre-treatment showed a significant reduction in periprocedural MI and 30-day adverse events in patients undergoing percutaneous coronary intervention (PCI).[2]

Furthermore, numerous large observational studies demonstrated that statin therapy was associated with decreased development of HF after MI and improved outcomes in patients with HF. A meta-analysis with data from 10 randomised trials (10,192 patients with HF) compared statins to placebo showing that statins did not affect CV mortality but significantly decreased hospitalisation rate for HF worsening, with a significant 4.2% increase in left ventricular ejection fraction.[3] These clinical benefits may be related to pleiotropic effects of statins such as a beneficial modulation of endothelial function as well as a reduction of oxidative stress and inflammation. On this basis, the pleiotropic effects of statins may also reduce the risk of iodinated contrast-induced nephropathy (CIN), which is an important cause of hospital-acquired acute renal injury in patients undergoing PCI.

The pathophysiological mechanism responsible for CIN may be related to direct renal tubular toxicity, vasoconstriction, and high levels of oxidative stress. A recent meta-analysis compared the effects of statins to placebo or standard therapies for the prevention of CIN, showing that atorvastatin and rosuvastatin administered at high doses before iodinated contrast administration have a consistent and beneficial preventive effect on CIN, with no difference between these two agents.[4] All these current evidences show that statins exert multiple nonlipid lowering (i.e. pleiotropic) effects including several mechanisms involving the positive modulation of inflammation and endothelial function, and the reduction of oxidative stress and of apoptopic pathways. These new emerging data have obvious and non-negligible theoretical and applicative implications. Taken together, the key effects of statins are significant at different levels, and implications identifying novel potential therapeutic mechanisms or suggesting new clinical indications for statin therapy broadening in this way underline the drug's range of action as the term pleiotropy refers to.

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