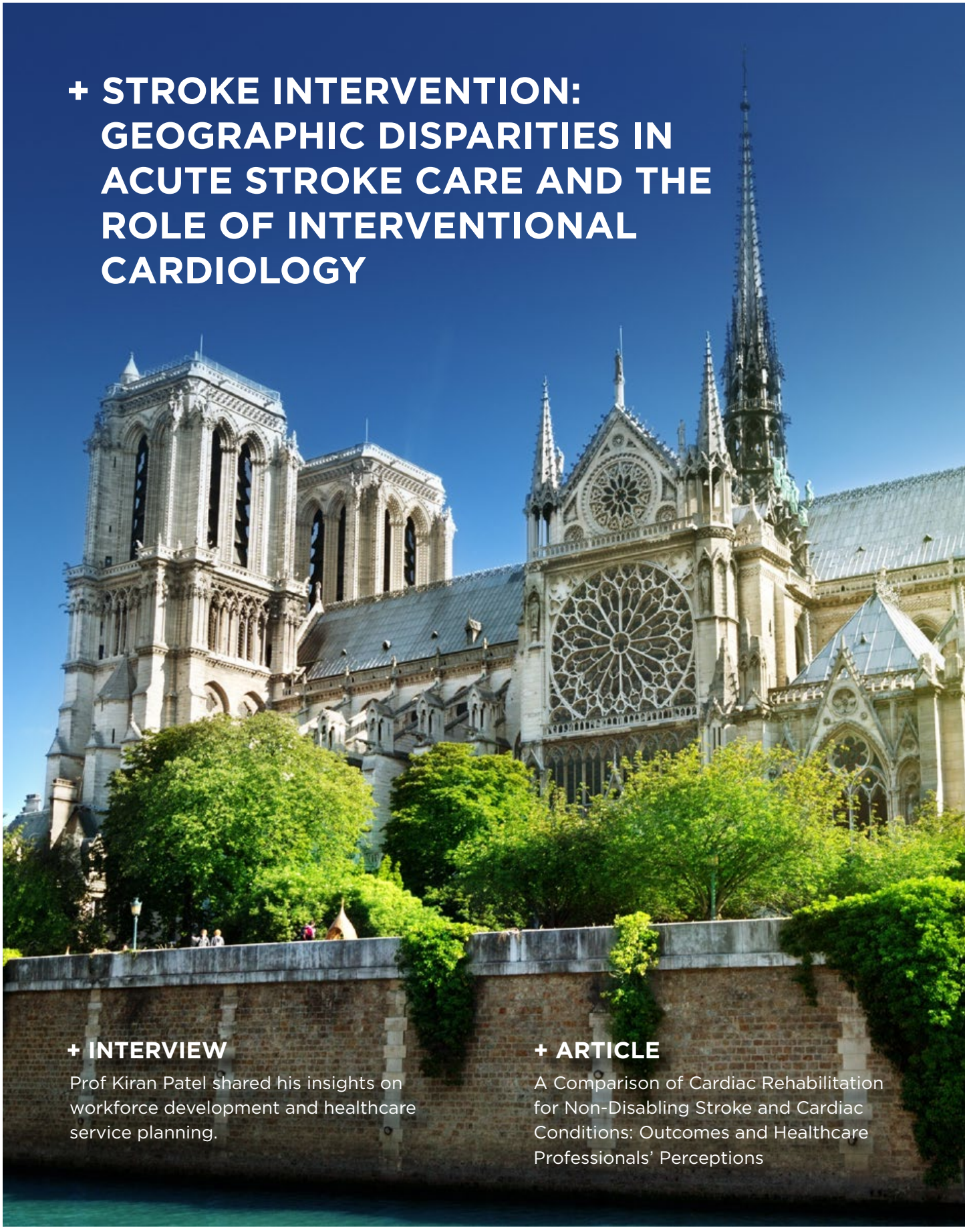
EMJ INTERVENTIONAL CARDIOLOGY

European Edition — Vol. 8.1 November 2020 emjreviews.com

+ STROKE INTERVENTION: GEOGRAPHIC DISPARITIES IN ACUTE STROKE CARE AND THE ROLE OF INTERVENTIONAL CARDIOLOGY



+ INTERVIEW

Prof Kiran Patel shared his insights on workforce development and healthcare service planning.

+ ARTICLE

A Comparison of Cardiac Rehabilitation for Non-Disabling Stroke and Cardiac Conditions: Outcomes and Healthcare Professionals' Perceptions

Contents

Podcast with Prof. Nick Curzen and Dr. Rasha Al-Lamee

How physiology guidance can help treat patients right first time

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This Publication

ISSN 2053-423X

EMJ Interventional Cardiology is published once a year. For subscription details please visit: www.emjreviews.com

Front cover and contents photograph: Paris, France.

EMJ Interventional Cardiology 8.1

Welcome

Dear Readers,

Welcome to the latest issue of *EMJ Interventional Cardiology*, an eJournal dedicated to facilitating the continual progression of the interventional cardiology field. Usually, we would bring you the highlights from the EuroPCR meeting; however, the event leaders made the difficult decision to cancel the meeting this year due to the ongoing coronavirus disease (COVID-19) pandemic. We look forward to bringing you highlights from next year's meeting in France and seeing you there too!

Included in the journal is an interview with Prof Kiran Patel, Chief Medical Officer and Consultant Cardiologist at University Hospitals Coventry and Warwickshire, Coventry, UK, who featured in the BBC Panorama documentary "On the NHS Frontline" earlier this year. During the interview, Prof Patel provided insights into his role as Chief Medical Officer, the importance of international scientific collaboration, and how the COVID-19 pandemic is affecting surgical procedures.

In the feature 'Percutaneous Transcatheter Metabolic Interventions: The Next Frontier?,' Kipshidze and Kipshidze impart their expert take on whether metabolic interventions are a feasible approach to tackling obesity and therefore the associated cardiovascular comorbidities.

This year's *EMJ Interventional Cardiology* eJournal is packed with articles discussing the latest developments in the field. In the Editor's Pick, White et al. delineate the geographic disparities in acute stroke care, while highlighting the role of interventional cardiology in the treatment pathway. Complementing this review is the article by Lennon et al., who report the findings from their study into stroke and cardiac outcomes following cardiac rehabilitation, and healthcare professionals' perceptions on the use of cardiac rehabilitation for transient ischaemic attack/nondisabling stroke. Further interesting reads can be found in the following pages, covering topics such as periprocedural stroke associated with transcatheter aortic valve implantation and a case of traumatic coronary artery dissection.

As always, I would like to thank all those who contributed to this issue, and I hope you find the following pages insightful and valuable.

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Dear Colleagues,

It is with great pleasure that I present to you this new issue of *EMJ Interventional Cardiology*. Normally at this time of year, EuroPCR would have finished and this issue would have been dedicated, as always, to highlighting the main advances and topics discussed. But these are not normal times. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease (COVID-19), has caused a global pandemic. With changing seasons and changing public health strategies, cases have risen and fallen across the world; some countries are slowly returning to normal, or a new normal, while in America we are still seeing 'hot spots' and curves showing infection and death rates still rising. At time of writing, there are 50.9 million confirmed cases and over 1.26 million deaths worldwide. Health systems on all continents have been pushed to the limit, several of them collapsed, with tragic consequences. Phrases like quarantine, social distancing, teleworking, screening, contact tracing, and opening economies, are in daily use everywhere.

Education has been particularly affected in these times. Closures of schools and universities have led to restructuring to distance learning and promoted innovation in the education arena. Continuing medical education has been no exception. Symposia and conferences are being held in an online format. As *EMJ Interventional Cardiology* is an eJournal, we have an even greater responsibility today to continue to bring our readers up-to-date information in the field.

I invite you to explore this issue, focussed on the treatment and rehabilitation of acute ischaemic stroke, particularly the use of mechanical thrombectomy, in which interventional cardiologists are called to play a more relevant role. Also included in this issue is an interesting article by Upadhyaya et al. that reaffirms the importance of noninvasive imaging for the diagnosis of coronary dissections.

I cannot finish these words without expressing my best wishes of wellbeing and gratitude to all those involved in the treatment and care of patients with COVID-19. It is in times like these, we as the medical community must rise and come together as one.

Dr Pablo Sepúlveda Varela

Division of Cardiovascular Diseases, Endovascular Therapy Center, Pontificia Universidad Católica de Chile, Santiago, Chile

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Interview

Professor Kiran Patel

Chief Medical Officer and Consultant Cardiologist at University Hospitals Coventry and Warwickshire, Coventry, UK

Q1 Having managed significant advancements in cardiac services, how have you seen complex cardiac devices develop during your career?

I guess there have been two significant advances in the field of device therapy while I have been practising. Firstly, the advent of complex device therapy (implantable cardioverter-defibrillator [ICD] and cardiac resynchronisation therapy [CRT]) which has really transformed the care of very sick patients. Secondly, the advent of remote monitoring has been, and will continue to be, a positive innovation in that we will now deliver more-frequent monitoring and commensurately improve patient safety, with better convenience for patients and commensurate economic and green benefits, including less time off work and less travel to hospitals.

Q2 How have you acquired the leadership skills to perform your role as Chief Medical Officer (CMO) at University Hospitals Coventry and Warwickshire? What, in your opinion, is the greatest challenge of this role?

There are no specific training courses or accreditation programmes which suddenly make one able to become a CMO. Personally, I think that becoming a CMO is a combination of opportunity, desire, and capability. All of the leadership roles I have had to date have been learning and developmental experiences which I use in my current role. I have held a few leadership roles within cardiology which have helped, and have also held regional clinical and medical director roles which helped me to gain experience strategically and in terms of policy. Overall, I have managed to gain experience in primary care, secondary care, and in the regulatory system, so all of that experience in combination is extremely helpful in my current University Hospitals Coventry and Warwickshire (UHCW) CMO role which also comes with a system leadership role of Sustainability and Transformation Plans (STP) clinical lead.

Q3 The work that you have carried out with UK universities to advise governments in Thailand and Indonesia has been extremely valuable in strengthening their healthcare systems. Why is it so important to drive international collaboration in this way, and why are you so passionate about this project?

In the UK, we are fortunate enough to have a universal healthcare system, free at the point of need. However, not all of the world's citizens are as fortunate.I believe we have a moral and ethical

responsibility to help develop health systems across the world and to share our challenges and experiences. International work is therefore important to me, as we are all more similar than we are different across the world, we just happen to have arrived in different places. At UHCW where I work, we have an ambition to be an international leader in healthcare and have partnerships across the globe so that we can share learning and develop together with other health systems.

Q4 Another project of yours is to improve workforce development in the UK's healthcare system. Currently, what are the most pressing issues for quality improvement in the National Health Service?

The main source of expenditure in the National Health Service (NHS) is on workforce, and it is the NHS workforce which is responsible for delivering excellent care. We therefore need to ensure we are a learning health system, which means that our workforce is also continually learning and developing to keep up with patient demand and to deliver care at the frontiers of medical innovation and development. We also need to transform in order to make healthcare more affordable, and innovate. One example I can give you is that in my last job I trained a nurse to implant pacemakers, thereby performing procedures which traditionally, and in most places, a doctor would do. I see no reason why role substitution like that cannot help us to deliver a safe and effective service, while at the same time release highly skilled and expensive medical staff to do the more complex things. Applying this across the workforce will enable us to deliver a greater breadth and depth of services which our patients deserve. There are many challenges in delivering a quality service and key to that is measurement, data, and feedback. We need to have a better and more real-time view on quality-related data so that we can measure what we do and then improve it. It's not ideal waiting over a year sometimes to see audit data to respond to; we can do better than that.

Q5 We saw you in the BBC Panorama documentary "On the NHS Frontline." What is the significance of documentaries such as these for raising awareness, particularly in this current crisis?

We were cautious about opening our doors to the outside world but, in hindsight, it served two purposes. For patients and carers, it was a window into seeing how we function as a hospital at a time of crisis, and I hope that viewers saw how organised and calm the organisation was while delivering a busy service which remained compassionate. Secondly, for our staff, it was great to be recognised for the great care we deliver. Everyone I have spoken to in the Trust has felt really proud of being in the public eye and I too think it's a great organisation to work in.

Q6 The NHS is focussed on combatting coronavirus and nonurgent procedures have been postponed or cancelled to maximise capacity for treating patients with COVID-19. What are the dangers of this?

So, we did have a pause on elective care for a few weeks, but we are rapidly starting to deliver elective care again based upon clinical need, as are most organisations across the NHS. We are delivering most of our cancer care now, and also starting cardiac surgery and cardiology procedures too. One concern we have is that the number of patients presenting with acute conditions such as heart attacks and strokes dropped off for several weeks, suggesting that patients were avoiding coming to hospital when they needed care. We have therefore undertaken a lot of public communication articulating that we are open for business as usual, to deliver care if patients need it and, fortunately, things are getting back to how they were. Yesterday we had returned to seeing the same number of ambulances as normal which is good news.

Q7 In the documentary, you stated that routine procedures which should take 15–20 minutes are now taking up to 1 hour to complete. How is this affecting workflow?

Having to don and doff personal protective equipment (PPE) for some cases now means that all staff, not just the operators, take longer

"I believe we have a moral and ethical responsibility to help develop health systems across the world"

"Teamwork has been key throughout the pandemic. We all need to support each other, both clinically and managerially."

to prepare for procedures, and after procedures sometimes the need for cleaning takes a while.

Therefore, overall productivity has decreased during the COVID-19 era. Now that we have 'green' pathways where, effectively, we have a hospital within a hospital, things are a lot more efficient as patients for elective procedures are screened for COVID-19 and, if negative, have an end-to-end pathway where risk of nosocomial exposure to COVID-19 is very low. Our hospital is effectively divided so that we have an entrance, corridor, ward, theatres, and cardiac catheterisation lab which are physically separate and staffed by COVID-negative staff. I think this complex era of operational management, for the benefit of patients until we are back in a safe era, will continue for several months yet.

Q8 What are your coping mechanisms for dealing with the magnitude of the crisis and how do you advise medical students and junior doctors to deal with this?

It is really important to maintain one's own physical and mental health. I tend to go for a long run once a week and use my home gym equipment. I try to have a separation of work and home so that I try not to get onto emails when I'm at home. That said, it has been an incredibly busy few months, preparing for and managing the impact of the pandemic. My advice to all staff is that this is a marathon not a sprint so, in addition to personal resilience, ensure you are part of a team which supports each other. Everyone will have ups and downs so mutual support is essential. Take regular breaks too. I have been fortunate in that I have a great clinical team in cardiology and a great executive team. One of the best things we have had here is a daily 8:30AM meeting of myself as CMO, the Chief Nursing Officer, Chief Operating Officer, and Chief Executive. A focussed half-hour (with plenty of caffeine) starts each day, which has been really important not just to focus and co-ordinate, but to support each other too. We then have the usual gold, silver, and bronze command management structure to manage the incident, so it has been an impressively slick machine in action since mid-January and a great experience.

Q9 The documentary highlighted the indispensable need for multidisciplinary units in the hospital. What more can be done to support the many key workers 'on the frontline'?

Teamwork has been key throughout the pandemic. We all need to support each other, both clinically and managerially. In addition, it has been fantastic to see how professional, flexible, and adaptable staff have been. We have had staff working in other teams and in other departments, with the appropriate training and induction of course. We have even had medical students working within our teams and overall, it has been a very positive experience for most staff.

Percutaneous Transcatheter Metabolic Interventions: The Next Frontier?

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Disclosure: Nicholas Kipshidze is the founder and a shareholder of Endobar Solutions, LLC., Orangeburg, New York, USA. Nodar Kipshidze is a consultant of Endobar Solutions, LLC., Orangeburg, New York, USA.

Keywords: Embolisation, obesity, transcatheter interventions.

Citation: EMJ Int Cardiol. 2020;8[1]:15-17.

INTRODUCTION

Obesity is a pandemic. The prevalence of obesity (BMI >30) and morbid obesity (BMI >40) among American adults is approximately 30% and 5%, respectively.[1] The condition is strongly associated with medical comorbidities (e.g., heart disease, Type 2 diabetes mellitus, stroke, obstructive sleep apnoea, certain types of cancer, and osteoarthritis) and mortality, and has begun to overtake infectious diseases as the most significant contributor to illness worldwide. Furthermore, it is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and considered one of the most serious public health problems of the 21st century.[2]

Currently, there are three clinically viable treatment options for obesity: surgery, pharmacologic intervention, and intragastric balloon administration. However, these methods have varying success rates and are not free of complications. There remains a critical need for a minimally invasive intervention that can target this growing population.

GASTROINTESTINAL HORMONES AND OBESITY

Obesity often presents as a combination of several component causes, including excessive caloric intake, a sedentary lifestyle, genetic susceptibility, or hormonal imbalances. There has been a growing understanding of the critical involvement of the stomach as an endocrine organ in the maintenance of energy homeostasis. Among more than 40 hormones that have been discovered to limit food intake, one hormone, ghrelin, is orexigenic (i.e., stimulates food intake). Ghrelin plays a role in both short-term and long-term food regulation. Cells producing ghrelin are predominantly located in the fundus of the stomach and directly fuel appetite and induce a positive energy balance, resulting in body weight gain.[3]

INTERVENTIONS TO MODULATE GHRELIN LEVELS

Varying attempts, whether mechanical or pharmaceutical, to modulate ghrelin production with the aim of food intake reduction have been undertaken, but significant clinical results have yet to be achieved. However, ghrelin is a promising target in both medical and surgical approaches to obesity. Recently, a number of animal studies have demonstrated that

embolising the arteries supplying the gastric fundus, a major source of ghrelin, can lead to a reduction in blood ghrelin levels and subsequently promote reduced food intake.[4-6] In 2012, the authors performed the first-in-human embolisation of the left gastric artery or transcatheter bariatric embolisation (TBE) in five obese patients using off-the-shelf equipment and 300–500 µm compressible microspheres (Biocompatibles UK Limited, Surrey, UK).[7] Based on the authors' previous animal studies (unpublished data), using particles with sizes ranging 300–500 µm is advantageous because smaller particles (e.g., 50–100 µm) can result in mucosal necrosis of the fundus and produce gastric ulcers. The first-in-human study demonstrated a mean weight reduction of 16% at 6-months follow-up. Blood ghrelin levels were significantly lower at 1- and 6-month follow-up (by 29% and 36% from baseline; $p<0.05$) and increased at 6-month follow-up compared with 3-month follow-up, while remaining 18% lower than the baseline ($p<0.05$).[7]

Following the first-in-human study, there have been several human clinical studies evaluating the effects of gastric embolisation for weight loss.[8,9] These studies have demonstrated clinically meaningful weight-loss results post-embolisation. They were, however, non-randomised, single-arm feasibility, safety, and efficacy trials, which come with inherent limitations. First, the absence of a control group does not allow definitive conclusions regarding efficacy. It is possible that the procedure and study participation led to a higher motivation for diet control and exercise. However, a decrease in plasma ghrelin levels should not be expected. Second, the intermediate-term follow-up is too short to allow conclusions regarding long-term weight loss. A rebound phenomenon with recurrent weight gain is conceivable. Third, in most of these studies there is a report of significant gastric ulcer formation, not attributed to the fundus but instead non-target embolisation. Using special antireflux microcatheters may limit antegrade and retrograde reflux and therefore minimise non-target embolisation: the current Achilles' heel of embolisation procedures performed in these highly collateralised tissues.

CARDIOVASCULAR COMORBIDITIES IN OBESE PATIENTS

In the landscape of approved obesity treatments, most, if not all, interventional approaches (surgical or pharmaceutical) require the presence of a comorbid condition. Numerous studies have indicated the correlation between obesity and heart disease or Type 2 diabetes mellitus. Obesity has also been linked to heart failure and atrial fibrillation (AF) and poorer prognosis in obese patients, with research demonstrating an association between increased visceral and epicardial fat depots. Recurrence rates following AF ablation are also higher in obese patients. A 5–10% weight loss has been associated with clinically meaningful reductions in HbA1c, triglycerides, low-density lipoprotein cholesterol, and as much as a 5–10 mmHg reduction in systolic blood pressure. The weight-loss targets are well within the weight loss achievable through TBE.

CONCLUSIONS

A randomised controlled trial with mid-term follow-up has recently demonstrated clinically significant weight loss in TBE over a sham group.[10] Further studies with larger patient numbers and long-term follow-up are needed to examine the utility of this procedure. Widened experience with this procedure will provide a refinement in procedural technique and use of dedicated antireflux devices to maximise the effect of weight loss but minimise the risk of mucosal injury and ulcer formation.

TBE may be utilised in the general population, however, a large proportion of patients who are in the catherisation lab for a percutaneous coronary, peripheral, structural, endovascular intervention, or AF ablation are also obese or overweight. These patients rarely visit specialised bariatric or weight-loss clinics. Therefore, percutaneous TBE could be a possible technique to add to the tool kit of the interventional cardiologist and radiologist who are already treating this patient population. As in structural heart disease, the authors recommend the creation of a weight-loss team consisting of a general cardiologist, interventional specialists, bariatric surgeon, registered dietitian, and endocrinologist or weight-loss specialist.

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Stroke Intervention: Geographic Disparities in Acute Stroke Care and the Role of Interventional Cardiology

EDITOR'S PICK

We have featured as our Editor's Pick for *Interventional Cardiology 8.1* this discussion by White et al. of disparities in acute stroke care delivery due to regional service differences. Randomised studies in acute ischaemic stroke have demonstrated the superiority of mechanical thrombectomy over systemic thrombolysis in achieving reperfusion of large vessel occlusion. For more than four decades, interventional cardiologists have accumulated experience in treating acute coronary syndromes, and integration into stroke teams may help to achieve timely reperfusion and solve the disparities in access to specialised stroke centres, as shown in this article.

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Disclosure: The authors have declared no conflicts of interest.

Received: 13.01.20

Accepted: 19.02.20

Keywords: Acute stroke intervention, carotid stent, disparities in care, interventional cardiology, mechanical thrombectomy (MT).

Citation: EMJ Int Cardiol. 2020;DOI/10.33590/emjintcardiol/20-00009

Abstract

Stroke is the second-leading cause of death and a major cause of disability worldwide. The majority of strokes are ischaemic, and effective therapy to achieve reperfusion includes intravenous thrombolysis and, for proximal large vessel occlusion strokes, endovascular mechanical thrombectomy (MT). There has been a paradigm shift in acute stroke care, driven by a series of randomised controlled trials demonstrating that timely reperfusion with MT results in superior outcomes compared to intravenous thrombolysis in patients with large vessel occlusion strokes. There are significant geographic disparities in delivering acute stroke care because of the maldistribution of neurointerventional specialists. There are now several case series demonstrating the feasibility and safety of first medical contact MT by carotid stent-capable interventional cardiologists and noninvasive neurologists working on stroke teams, which is a solution to the uneven distribution of neurointerventionalists and allows stroke interventions to be delivered in local communities.

INTRODUCTION

Stroke is the second-leading cause of death and a major cause of disability worldwide. Its incidence is increasing because the population is ageing.[1] Stroke rates in the young and in middle-aged adults are not decreasing and may even be increasing, likely because of the growing prevalence of atherosclerotic risk factors, including obesity and diabetes. In high-income countries, improvements in prevention, acute treatment, and neurorehabilitation have led to a substantial reduction in the burden of stroke. However, significant geographic disparities remain in delivering care for acute stroke because of the uneven distribution of neurointerventional specialists.

The causes of stroke include haemorrhage, thrombosis, and embolus. Embolic strokes may be from artery to artery or from a heart chamber (left atrium or ventricle) to an artery, particularly in patients with atrial fibrillation. A major tenet for the treatment of ischaemic stroke is that 'time is brain', and that earlier reperfusion is associated with better outcomes.

The extent of ischaemic brain injury is determined by the time from the onset of symptoms to reperfusion and is significantly affected by the presence of collateral circulation, including an intact Circle of Willis. The penumbra is the region of the brain surrounding the infarct area, where the blood supply is reduced but viability is maintained due to collateral flow. The viability of the penumbra depends on the severity and duration of ischaemia. If blood flow is rapidly restored, ischaemic brain tissue can be salvaged.

Treatment goals include preventing or limiting the mortality and morbidity of the acute event, and preventing recurrent events. The majority of strokes are ischaemic[2] and effective therapy to achieve reperfusion includes intravenous thrombolysis and, for proximal large vessel occlusion (LVO) strokes, endovascular mechanical thrombectomy (MT).[3]

STROKE THERAPY

Although rapid initiation of intravenous tissue-type plasminogen activator (IV tPA) with a door-to-needle time of less than 60 minGet With the Guidelines®-Stroke is important for a good outcome, the American Heart Association's (AHA) Get With the Guidelines® - Stroke national registry reported that fewer than one in three stroke patients are treated within 60 min of arrival at the hospital.[3,4] In the USA, a national heart attack quality initiative led interventional cardiologists to achieve dramatic reductions in door-to-balloon times for ST elevation myocardial infarctions;[5] however, acute stroke therapy remains without a workable national strategy to provide timely reperfusion.

Currently, there is no time-to-reperfusion goal for door-to-treatment time in the USA and it is not standard of care for stroke therapy as it is for heart attacks.[6]

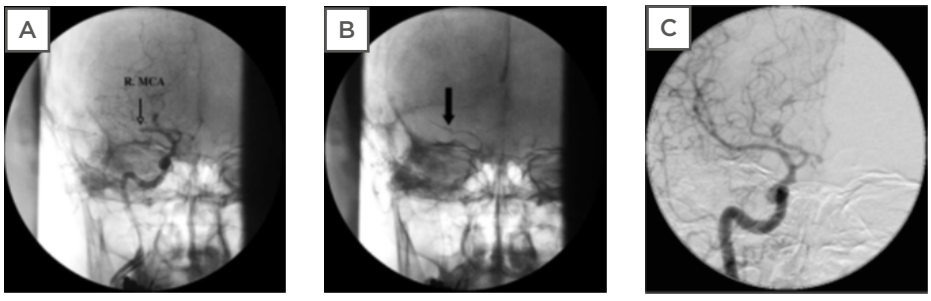

Figure 1: A) Patient with atrial fibrillation had an acute right middle cerebral artery occlusion; **B)** placement of the thrombectomy catheter (arrow) in the right middle cerebral artery; **C)** final result after thrombectomy of the right middle cerebral artery.

Adapted from Topol, Teirstein, 2019.[12]

Table 1: Skills needed to care for stroke patients.

Skill	Specialty	Description
Cognitive	Neurology	Knowledge of the natural history and pathophysiology of stroke, diagnostic methods, and treatment options.
Technical	IC, IR, NI, VS, VM	Competence to perform cerebrovascular angiography and interventions (e.g., vascular access, carotid stenting, MT).
Clinical	Neurology, NCC	The ability to care for acute stroke patients including managing complications, interpretation of diagnostic tests, hospital admitting privileges, and the ability to assess the risk to benefit ratio for treatment options.

IC: interventional cardiology; IR: interventional radiology; MT: mechanical thrombectomy; NCC: neurocritical care (anaesthesia, neurology, critical care); NI: neurointerventional (neuroradiology, neurosurgery, interventional neurology); VM: vascular medicine; VS: vascular surgery.

Unfortunately, because of a variety of issues including delayed time to presentation, lack of availability of rural (>1 hour by ground transportation) endovascular stroke programmes, and a lack of national focus on time-to-treatment, many patients with ischaemic stroke in the USA do not receive timely reperfusion therapy.[7]

There has been a paradigm shift in acute stroke care, driven by a series of randomised controlled trials demonstrating that timely reperfusion with MT results in superior outcomes compared to IV tPA in patients with LVO (Figure 1).[8-12]

There was a consistent favourable clinical outcome (defined as a modified Rankin Scale [mRS] of ≤2 at 90 days) for MT across all studies, with greater benefit seen with earlier intervention. When penumbral imaging with CT perfusion was used for patient selection, the advantage for MT was even more pronounced. Importantly, the use of MT added no additional risk of intracranial haemorrhage over standard management with IV tPA.

Although MT was associated with higher costs, it also resulted in better patient outcomes. Cost-effectiveness studies revealed that MT adds value when a standard threshold of $50,000 per quality-adjusted life year gained is adopted.[13]

In the USA, 10% of first-time ischaemic strokes have LVO and are potential candidates for MT. Minimising the delay to reperfusion is the key to optimising quality-of-life outcomes. It is estimated that every 10 min of delayed care reduces a patient's disability-free lifetime by approximately 40 days and reduces the net monetary benefit of MT by approximately $10,000.[14]

GEOGRAPHIC DISPARITIES IN STROKE CARE

There is a raging 'turf battle' between neurointerventionalists and non-neuroscience trained physicians who are capable of performing MT over who should be treating LVO acute strokes.[15-17] Neurointerventionalists are predominantly clustered in urban, academic medical centres because their routine day-to-day work is facilitated by a centralised referral model.[18,19] Endovascular stroke care, however, is time-sensitive, and many patients do not live close enough to the stroke centres to receive timely care. In the USA, only 50% of the

population has ≤1-hour access by ground transport to MT stroke treatment centres. In California, USA, only 39% of acute stroke patients live within 1 hour of hospitals performing 10 or more stroke interventions per year.[20]

POTENTIAL SOLUTIONS

One solution proposed by the neuro interventional community is the 'hub-and-spoke model' for transfer of stroke patients between hospitals. They suggest developing a national triage system to rapidly transfer stroke patients to highly specialised stroke centres. However, there is evidence that even a well-developed hub-and-spoke model is not an optimal solution for acute stroke therapy. An experienced European regional stroke centre initiated MT in 295 of 324 (91.0%) patients directly admitted to the hub hospital, but initiated MT in only 63 of 91 (69.2%) patients transferred to the hub from a regional hospital ($p<0.001$).[21] One quarter (24.2%) of patients transferred became ineligible for MT during transfer. There was a four-fold improvement in the odds for a good clinical outcome in transferred patients who received MT compared to those who became ineligible during transfer. The odds of a transferred patient receiving MT decreased by 2.5% for every minute of transfer time. The authors concluded that stroke intervention should be provided at first hospital contact whenever possible.

It has been suggested that training more neurointerventionalists would allow them to be deployed in rural areas to serve the needs of patients living more than 1 hour from stroke centres. Training more neurointerventionalists does not appear to be a practical solution as the volume of elective, daytime intracranial work in nonurban communities simply does not provide enough cases to support the additional neurointerventionalists needed to treat acute strokes or to maintain their skills. This uneven distribution of neurointerventionalists is manifested by efforts to reduce the number of their trainees because of oversupply.[22,23]

There has been a suggestion to offer practising non-invasive neurologists neurointerventional training whilst working in order to serve nonurban communities.[24]

Table 2: Results of interventional cardiology case series and neurointerventional randomised trials.

Author/ Study	N	Baseline NIHSS	30–90-day mortality (%)	mRS <2 90 Day (%)	ICH (%)	TICI flow 2b/3 (%)	DTB (min)
Htyte et al.,[26] 2014	54	15	16.0	45.0	7.4	78	152
Widimsky et al.,[27] 2015	84	18	11.0	36.0	3.6	72	205
Hornung et al.,[28] 2019	70	17	18.0	61.0	7.1	93	94
Guidera et al.,[29] 2018	40	19	15.0	55.0	15.0	80	108
IC (mean)		**17**	**15.0**	**49.0**	**8.0**	**81**	**140**
Mr Clean[8]	233	17	18.9	32.6	7.7	59	260
Escape[9]	165	16	10.4	53.0	3.6	72	241
Revascat[11]	103	17	18.4	43.7	1.9	66	355
Swift Prime[10]	98	17	9.0	60.0	0.0	88	252
NI (mean)		**17**	**14**	**47**	**3**	**71**	**277**

DTB: door-to-balloon (device) time; IC: interventional cardiology trials; ICH: intracranial haemorrhage; mRS: modified Rankin Scale; NI: neurointerventional trials; NIHSS: National Institute of Health Stroke Scale; TICI: thrombolysis in cerebral infarction flow grade.

The possibility of training a practising non-invasive neurologist to perform stroke interventions is challenging, if not unrealistic. Moreover, it is doubtful that there is a sufficient pool of non-invasive neurologists to train, given the small number of practising stroke neurologists outside of academic medical centres.

A multidisciplinary group performed a 'needs assessment' for stroke intervention, with representatives from neurology, cardiology, vascular medicine, radiology, and neurosurgery disciplines. The group concluded: "We suggest taking what has been learned in treating ST elevation myocardial infarctions and apply it to 'brain attacks' utilising a multidisciplinary approach" (Table 1).[25] This option would take advantage of currently available community-based, carotid artery stent-capable interventional cardiologists with a basic knowledge of the intracranial circulation, paired with non-invasive neurologists and radiologists capable of interpreting CT images, and nurses capable of caring for stroke patients, to provide timely reperfusion therapy at first medical contact. The neurology support and guidance could be offered via telemedicine.

In community hospitals without stroke neurologists, or those with a single neurologist for whom being the on-call doctor would be too burdensome, telemedicine support from a stroke neurologist at a remote centre would be a solution to guide patient selection and management alongside the interventional cardiologist. Reperfusion therapy at first medical contact would expedite early treatment and, if needed, a less time-sensitive transfer to the stroke centre could be performed.

CURRENT EVIDENCE

There are several reports demonstrating the feasibility of offering safe and effective first medical contact stroke therapy by stroke teams consisting of carotid stent-capable interventional cardiologists and non-invasive neurologists (Table 2).[26-29]

Htyte et al.[26] compared outcomes of interventional cardiologists versus neurointerventionalists in 124 consecutive acute stroke patients who received MT between 2006 and 2012.[26] The on-call interventional team (interventional cardiologists versus neurointerventionalists) rotated responsibility for stroke calls. The interventional cardiologists had extensive carotid stenting experience and teamed with a non-invasive stroke neurologist who was responsible for pre- and post-management decisions. Interventional cardiologists treated 58 of 124 (47%) patients and neurointerventionalists treated 66 of 124 (53%) patients. There were no significant differences between the two groups in age, baseline National Institute of Health Stroke Scale (NIHSS), 30-day mortality, or a good clinical outcome (mRS ≤2) at 90 days (Table 2).

Interventional cardiologists from three European centres without neurointerventional services treated 84 consecutive acute stroke patients (NIHSS ≥6) with MT in partnership with non-invasive neurologists.[27] Angiographic success (Thrombolysis in Cerebral Infarction [TICI] Grade 2b or 3) was achieved in 72% of patients. A good neurological outcome (mRS ≤2 at 90 days) was achieved in 42% (35 of 84) of patients, with 24 patients (29%) discharged directly home. In patients treated within 3 hours of stroke onset, a good neurological outcome (mRS ≤2) was obtained in 54% compared to 31% (p=0.031) in patients treated later than 3 hours. These acute stroke interventions by interventional cardiologists achieved results comparable to those from neurointerventional centres, suggesting that where local neurointerventional services are unavailable, emergent revascularisation by a carotid stent-capable interventional cardiologist, in partnership with a neurologist, is a reasonable option.

A multidisciplinary group from a community hospital located in Doylestown, Pennsylvania, USA (≥1 hour from the nearest stroke centre in Philadelphia, Pennsylvania, USA), without the services of a neurointerventionalist, determined that local acute stroke care was needed.[29] They formed a stroke team with carotid stent-capable interventional cardiologists, non-invasive neurologists, and a neuroradiology technician with interventional stroke experience. They treated 40 LVO stroke patients with MT after the neurologist reviewed their clinical and imaging data. The median NIHSS on presentation

was 19 (severe disability). The average time from presentation in the emergency department to MT was 108 min. TICI Grade 2b or 3 flow was achieved in 80% (32 of 40). Symptomatic intracranial haemorrhage occurred in 15% (6 of 40), with an in-hospital mortality of 13% (5 of 40). At 90 days, 55% of these severely affected patients were functioning independently (mRS ≤2).

A recently published report from Frankfurt, Germany, reported the experience of a carotid stent-capable interventional cardiology group working with stroke neurologists to treat 70 consecutive LVO ischaemic strokes.[28] The majority (90%) of patients were admitted from their emergency department and 10% were transferred from local hospitals. On presentation to the emergency department, the average NIHSS was 17. The mean door-to-MT time was 94 min. Successful reperfusion (TICI 2b or 3 flow) was achieved in 90% (65 of 70), with a 30-day mortality of 18% (13 of 70). At 90 days, 61% of their patients were functioning independently (mRS ≤2).

These two recent reports from hospitals without neurointerventional availability, one from the USA and one from Germany, add to the growing body of evidence that carotid stent-capable interventional cardiologists can achieve excellent outcomes for acute stroke intervention in partnership with non-invasive neurologists.[28,29]

SUMMARY

There are now convincing data that carotid stent-capable interventional cardiologists, working in multidisciplinary stroke teams with neurology guidance, can achieve results in LVO acute stroke patients comparable to the landmark neurointerventional-driven MT trials (Table 2). This is even more remarkable given that randomised trials have strict selection criteria that exclude high-risk patients, while the interventional cardiology case series are real-world patients that include higher risk patients.

In major metropolitan medical centres, acute stroke intervention should be performed by neurointerventionalists. Given that a large percentage of acute stroke patients live long distances from these medical centres, and that time-to-reperfusion is critical to achieving good outcomes, a patient-centred solution that brings stroke care to these geographically disadvantaged patients is needed. Encouraging carotid stent-capable interventionalists to provide that care seems reasonable, and the safety and efficacy of this strategy is supported by a growing evidence base.

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A Comparison of Cardiac Rehabilitation for Non-Disabling Stroke and Cardiac Conditions: Outcomes and Healthcare Professionals' Perceptions

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Disclosure: The authors have declared no conflicts of interest.

Received: 17.01.20

Accepted: 19.03.20

Keywords: Cardiac rehabilitation, coronary artery disease, stroke.

Citation: EMJ Int Cardiol. 2020;8[1]:26-38.

Abstract

Purpose: Emerging evidence supports cardiac rehabilitation for transient ischaemic attack (TIA)/non-disabling stroke secondary prevention. This study compares stroke and cardiac participant outcomes following cardiac rehabilitation and examines healthcare professionals' perspectives of cardiac rehabilitation for TIA/non-disabling stroke.

Methods: (1) Retrospective chart review of stroke patients (n=100) referred to cardiac rehabilitation and a matched cardiac group. (2) Semi-structured focus group with healthcare professionals. Independent-t, Mann-Whitney-U, and chi-squared tests explored between-group differences. Qualitative data were analysed thematically.

Results: Compared to cardiac counterparts, programme enrolment among stroke patients was lower (57% versus 97%) and dropout rates were higher (39% versus 15%), p<0.001. Healthcare professionals largely attributed this to perceived cognitive impairment. No significant changes were observed between groups in cardiovascular fitness (modified Bruce protocol metabolic equivalent of task [MET] and duration), blood pressure, Hospital Anxiety and Depression Scale, or fasting cholesterol levels, except low-density lipoproteins which reduced more in stroke participants (p<0.005). Both groups made significant improvements post-cardiac rehabilitation in MET (stroke: 2.0±1.9; p<0.001), (cardiac: 2.2±1.6; p<0.001); stress test duration (stroke: 2 min±2.2; p<0.001), (cardiac: 2.1 min±2.3; p<0.001); systolic blood pressure (stroke: -16.1 mmHg±20.2; p<0.001), (cardiac: -11.1±18.0; p<0.001); low-density lipoprotein (stroke: -1.2 mmol/L±1.0; p<0.001), (cardiac: -0.7±0.9; p<0.001); and triglycerides (stroke: -0.6 mmol/L±0.9; p<0.001), (cardiac: -0.3±0.9; p=0.002). Significant within-group reductions in total cholesterol were observed in stroke only (-1.3 mmol/L±1.2; p<0.001). Reductions in anxiety scores in the Hospital Anxiety and Depression Scale (-0.9; p=0.01) in cardiac participants were not replicated in stroke. Qualitative data identified similar exercise ability in both groups but noted individuals with stroke engaged less in education sessions.

Conclusion: TIA/non-disabling stroke and cardiac patients made similar physiological and cardiovascular fitness improvements following cardiac rehabilitation. Poor uptake/adherence rates and healthcare professionals' concerns about cognition and engagement warrant investigation.

INTRODUCTION

Globally, stroke is a leading cause of death and disability.[1] Recurrence rates are high, with a cumulative 10-year risk of 39%,[2,3] constituting 25–30% of all strokes and typically associated with greater severity and disability burden.[4,5] Current secondary prevention strategies for stroke patients remain largely reliant upon pharmacological therapies[6,7] for managing cardiovascular disease which are largely attributable to lifestyle risk factors.[8,9] The INTERSTROKE study identified hypertension and physical inactivity as the top two risk factors for stroke, highlighting important targets for stroke secondary prevention.[8] The prespecified secondary analysis of the medical arm of the SAMMPRIS trial identified physical activity as an independent predictor for decreasing the likelihood of recurrent strokes, myocardial infarction, or vascular death at 3 years following stroke.[10] In addition, greater efforts at preventing sedentary behaviour and physical inactivity while promoting exercise training and improving levels of cardiorespiratory fitness have been called for throughout the healthcare system on a worldwide basis to tackle noncommunicable diseases, including cardiovascular disease.[11]

While best practice guidelines in stroke secondary prevention suggest the implementation of multimodal lifestyle interventions for recurrent stroke prevention, the level of evidence to support these recommendations remains limited.[6,12] Recent research has considered the utility for the cardiac rehabilitation model as a secondary prevention strategy for ischaemic stroke and transient ischaemic attack (TIA), given its proven efficacy in reducing both all cause and cardiac mortality in the coronary artery disease population.[13] Cardiac rehabilitation has additional proven beneficial effects on lipids, blood pressure, smoking, inflammation, and on psychological risk factors such as depression, anxiety, hostility, and total levels of psychological stress. These benefits have now been extended to heart failure and peripheral arterial disease.[14] Evidence from emerging randomised[15-17] and nonrandomised[18-21] controlled trials of cardiac rehabilitation and other exercise-based intervention studies broadly modelled on the paradigm[22-24] indicate that cardiac rehabilitation is feasible and safe for the stroke population and associated with benefits in risk profiles,[15-18] mortality,[25] recurrent cardiovascular events,[25] and hospital readmissions.[25]

However, results from clinical trials do not always translate well to clinical practice.[26] Challenges to routine implementation, as identified in the literature, include the current adaptability of traditional cardiac rehabilitation programmes to accommodate participants with stroke and its associated sequalae.[27] Lastly, partnerships between traditional stroke rehabilitation services and cardiac rehabilitation need to be built to operationalise the referral processes required to promote a continuum of care after stroke, inclusive of comprehensive secondary prevention.[27] This study has two elements aiming to bring new insight to this field by using a mixed methods convergent design to evaluate real world implementation of cardiac rehabilitation after stroke: 1) using retrospective data from a cardiac rehabilitation programme that has piloted referral to cardiac rehabilitation after TIA/non-disabling stroke at the Mater Misericordiae University Hospital (MMUH), it aims to compare the short-term outcomes following cardiac rehabilitation between individuals with TIA/mild non-disabling stroke and a matched comparator group with cardiac aetiology to establish if comparable changes are made between these groups in routine clinical care; and 2) a focus group from the perspective of healthcare professionals engaged in cardiac rehabilitation assessed the challenges and differences encountered when delivering cardiac rehabilitation to individuals after stroke alongside cardiac counterparts.

METHODS

Study Design

A convergent design with a multistage mixed methods framework was implemented utilising both quantitative and qualitative methodologies. Study 1 consisted of a quantitative, retrospective chart review of data from stroke and cardiac cohorts pre- and post-participation in the cardiac rehabilitation programme. Study 2 was a qualitative semi-structured focus group of healthcare professional stakeholders in cardiac rehabilitation following mild non-disabling stroke. The cardiac rehabilitation programme ran over an 8-week period and participants attended 16 supervised exercise sessions and eight educational and support sessions addressing risk factor reduction and pharmacological compliance as standard.

Ethics

Ethical approval was granted by the MMUH Ethics Committee (Institutional Review Board Reference: 1/378/2006) and by the Human Research Ethics Committee, University College Dublin (LS-E-18-176-Lennon Exemption). All participants provided written informed consent.

Procedure

In Study 1, a retrospective chart review was conducted during October and November 2018 for 100 patients with TIA/non-disabling stroke who had been referred to an 8-week cardiac rehabilitation programme at the MMUH over the previous 5-year period (2013–2018). Cardiac patients (n=100) matched by age, sex, and the same time period were randomly selected for similar chart review. Baseline data including age, sex, cardiovascular diagnosis, time from cardiovascular event, diagnosis of diabetes, hypertension, family history, alcohol consumption levels, smoking status, physical activity levels, and BMI were extracted. Outcomes extracted pre- and post-cardiac rehabilitation included systolic and diastolic blood pressure, aerobic capacity (MET and duration of a modified Bruce protocol stress test), blood lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein cholesterol, triglycerides), fasting glucose, and Hospital Anxiety and Depression Scale scores. Programme uptake following referral, dropout rates, and number of exercise and educational classes attended during cardiac rehabilitation were extracted.

Study 2 comprised a focus group, conducted after Study 1 completion. Participants were healthcare professionals affiliated with the cardiac rehabilitation service at the MMUH. Potential participants were volunteers by self-selection, recruited by an information letter sent to relevant staff. Following written consent, each participant provided basic demographic details. The focus group lasted 1 hour and was facilitated by a researcher experienced in qualitative methodologies. The discussion was recorded electronically and an assistant moderator took field notes and recorded nonverbal or emotive responses, or responses generating high agreement. A predesigned question schedule employing introductory, transition, and key questions was employed to guide discussions (*adapted from Kreuger*).[28] In conclusion, the moderators provided an oral summary of the discussion content, and participants were provided with the opportunity to respond to and verify these summaries. Focus group transcripts were subsequently sent to participants.

Data Analysis

The quantitative data from Study 1 were entered on to the Statistical Package for the Social Sciences (SPSS) Version 24.0. Baseline descriptive statistics were summarised. Programme uptake and attendance and dropout rates were compared between stroke and cardiac patients using chi-squared tests. Differences between groups in the number of classes and talks attended were analysed using independent t-tests.

Baseline and change scores pre- and post-cardiac rehabilitation were compared between stroke and cardiac groups using independent t-tests for interval or ratio data, Mann-Whitney U tests for nonparametric data, and chi-squared tests for categorical variables. Adjustments for multiple comparisons were made and the significance value was set at $p<0.01$. Subanalysis employed paired t-tests, Wilcoxon signed ranks tests, and chi-squared tests, as appropriate to the data, to identify intragroup changes or explore sex differences.

Analysis was re-run based on five multiple imputed datasets and missing data post-intervention was imputed with Markov Chain Monte Carlo simulations using a fully conditional specification to account for missing items from chart review.

Study 2 recordings were anonymised and transcribed verbatim. Transcripts were reviewed by two independent researchers and thematic analysis conducted utilising transcripts and field notes. Analysis proceeded through stages of familiarisation, thematic framework identification, indexing, charting, mapping, and interpretation, as guided by Pope et al.[29]

Intracoding and intercoding percentage agreement rates were established within and between reviewers. Findings from the qualitative analysis were embedded with the quantitative data using a narrative weaved approach.[30]

RESULTS

Study 1: Retrospective Chart Review

A total of 100 TIA/non-disabling stroke patients (modified Rankin score ≤2) were referred to cardiac rehabilitation at the time of data collection (October 2018). A corresponding number (n=100) of cardiac referrals were randomly drawn from the same time period. Ten charts were unavailable at the time of the review with a net total of 94 stroke referrals and 96 cardiac referrals reviewed. Baseline descriptive statistics from both groups are presented in Table 1. No statistical differences in baseline characteristics between stroke and TIA populations were identified, except for current alcohol consumption, where the proportion was higher in cardiac participants in comparison to stroke participants (p=0.04). Higher numbers of missing data items in stroke charts in comparison to their cardiac counterparts were identified.

Table 2 summarises programme uptake, dropout, and attendance rates for stroke and cardiac programme participants following referral. A significantly higher proportion of stroke patients did not attend the cardiac rehabilitation service following referral (p<0.001). Similarly, a greater proportion of stroke patients failed to complete the programme (p=0.002), and of those who completed the programme stroke patients attended fewer of the educational support sessions (p<0.001) compared to cardiac patients. No proportional sex differences were identified in programme uptake, dropout rates, or in attendance.

Outcome data pre- and post-cardiac rehabilitation and associated change scores are presented in Table 3. Using the data directly available from chart review, no significant group differences in change scores were noted in outcomes of interest, with the exception of LDL cholesterol which decreased more in the stroke group upon programme completion. The effect size related to this is small (Cohen's d=0.11). Pooled analysis from the five multiple imputed datasets to account for missing data items identified significant decreases in systolic blood pressure, LDL cholesterol, and triglycerides in the stroke participants when compared to the cardiac group, and again small effect sizes were noted for all these variables (Cohen's d=0.18–0.40). Cardiac participants in contrast demonstrated significantly greater improvements in diastolic blood pressure, stress test duration, and anxiety reduction, again with small effect sizes noted (Cohen's d=0.17–0.18).

Intragroup analysis identified significant and beneficial changes in systolic blood pressure, aerobic capacity (MET and stress test duration), total cholesterol, and LDL and triglyceride profiles in both patient cohorts. Diastolic blood pressure and the anxiety subscale of the Hospital Anxiety and Depression Scale both improved significantly in cardiac participants, a finding which was not replicated within the stroke group.

Study 2: Focus Group

Multidisciplinary team members (two cardiac rehabilitation nurses, one clinical psychologist, and one medical consultant) participated in the qualitative focus group discussion. Thematic analysis of their perspectives of cardiac rehabilitation in TIA/non-disabling stroke identified three primary level themes: 1) programme suitability, 2) cognition and mood profiles, and 3) tailoring intervention for stroke. Second level coding identified a further five subcategories under these headings. Intercoding and intracoding percentage agreement were 96% and 98%, respectively.

Table 1: Participant descriptive statistics.

Descriptive	Stroke N=94	Cardiac N=96
	Mean (SD)	Mean (SD)
Age (years)	59.4±11.2	60.5±11.9
Time since event	125.4±50.4	118.6±98.2
	n (%)	n (%)
Male	70 (74.5%)	65 (67.7%)
Female	24 (25.5%)	31 (32.3%)
Risk factor		
Family history		
Stroke	2 (5.6%)	4 (5.3%)
Cardiac	17 (47.2%)	53 (70.7%)
Both	7 (19.4%)	8 (10.7%)
None	10 (27.8%)	10 (13.3%)
Missing items	58	21
Hypertension		
Yes	24 (49.0%)	42 (50.0%)
No	25 (51.0%)	42 (50.0%)
Missing	45	12
Alcohol consumption*		
Current	25 (51.0%)	56 (66.7%)
Previous	19 (38.8%)	16 (16.7%)
Never	5 (10.2%)	12 (12.5%)
Missing items	45	12
Smoking*		
Current	18 (27.3%)	15 (16.7%)
Previous	32 (48.5%)	53 (58.9%)
Never	16 (24.2%)	22 (24.4%)
Missing items	28	6
Physical activity levels*		
Meeting guidelines	30 (69.8%)	47 (56.6%)
Not meeting guidelines	13 (30.2%)	36 (43.4%)
N/D	51	13
Diabetes		
Yes	13 (18.3%)	16 (26.2%)
No	58 (81.7%)	45 (73.8%)
Missing items	23	35
BMI		
<18.5	0 (0.0%)	0 (0.0%)
18.5–24.9	4 (8.0%)	18 (19.8%)
25.0–29.9	25 (50.0%)	31 (34.1%)
>30	21 (42.0%)	42 (46.2%)
N/D	44	5

*Self-reported results.

N/D: not documented; SD: standard deviation.

Table 2: Programme uptake and participation levels.

Referred to cardiac rehabilitation	Stroke (N=94)	Cardiac (N=96)	Between group analysis	
	n (%)	n (%)	p-value	95% CI
Enrolled in the service	54 (57.4%)	93 (96.9%)	<0.001	0.5, 0.7
Completed the programme	33 (61.1%)	79 (84.9%)	0.002	0.6, 0.9
	Mean (SD)	Mean (SD)		
Number of exercise classes attended	9.2±4.9	10.1±3.9	0.24	-2.3, 0.6
Number of education sessions attended	4.1±2.1	5.7±2.1	<0.001	-2.2, -0.8

*Self-reported results.

CI: confidence interval; SD: standard deviation.

Table 3: Pre- and post-cardiac rehabilitation outcomes for stroke and cardiac groups.

	Stroke				Cardiac				Analysis of intergroup change		
	n	Pre-cardiac rehabilitation	Post-cardiac rehabilitation	Change	n	Pre-cardiac rehabilitation	Post-cardiac rehabilitation	Change	p-value	95% CI	Effect size
Physiological											
Systolic BP (mmHg)	n=44	140.7±20.9	124.7±15.5	-16.1*	n=90	134.9±19.8	123.8±16.6	-11.1*	0.651	-1.8, 11.8	
Imputed systolic BP	n=54	141.5	125.9	-15.6*	n=93	135.0	123.9	-11.2**	<0.001**	-2.1, -6.9	0.22
Diastolic BP (mmHg)	n=45	73.9±11.9	71.3±8.9	-2.6	n=90	73.4±11.4	68.7±9.0	-4.7*	0.368	-6.6, 2.4	
Imputed diastolic BP	n=54	74.7	72.6	-2.1	n=93	73.1	68.6	-4.5**	0.003**	-4.0, -0.1	0.18
Aerobic capacity											
MET[a]	n=30	6.9±2.2	8.9±2.3	2.0*	n=74	7.3±2.8	9.5±3.1	2.2*	0.983	-0.7, 0.7	
Imputed MET	n=54	7.5	9.4	1.8**	n=93	7.4	9.6	2.2**	0.031	0.02, 0.51	
Stress test duration (mins)	n=30	5.5±2.3	7.5±2.5	2.0*	n=74	6.1±2.8	8.2±2.7	2.1*	0.861	-0.9, 1.1	
Imputed stress test duration	n=54	6.3	8.0	1.7*	n=93	6.1	8.2	2.1**	0.006**	0.13, 0.76	0.17
Lipids (mmol/L)											

Table 3 continued.

	Stroke				Cardiac				Analysis of intergroup change		
	n	Pre-cardiac rehabilitation	Post-cardiac rehabilitation	Change	n	Pre-cardiac rehabilitation	Post-cardiac rehabilitation	Change	p-value	95% CI	Effect size
TC	n=41	4.9±1.0	3.6±0.6	-1.3*	n=71	5.2±5.2	3.8±1.0	-1.4	0.889	-1.7, 1.5	
Imputed TC	n=54	4.6	3.7	-0.9	n=93	4.8	3.7	-1.1	0.427	-0.7, 0.3	
LDL	n=40	3.1±1.0	1.9±0.5	-1.2*	n=70	2.7±0.9	2.0±0.8	-0.7*	0.005*	-0.2, -0.9	0.11
Imputed LDL	n=54	2.9	2.0	-0.9**	n=93	2.6	2.0	-0.5**	<0.01**	-2.3, -0.5	0.4
HDL	n=40	1.0±0.3	1.1±0.3	0.6	n=71	1.1±0.4	1.2±0.4	0.1	0.857	-0.1, 0.1	
Imputed HDL	n=54	1.1	1.2	0.1*	n=93	1.1	1.2	0.1	0.01	0.1, 0.0	
Triglycerides	n=40	2.0±1.4	1.4±1.0	-0.6*	n=70	1.8±1.3	1.4±0.9	-0.3*	0.119	-0.1, 0.6	
Imputed triglycerides	n=54	1.9	1.4	-0.5*	n=93	1.6	1.4	-0.3*	0.003**	-0.1, -0.3	0.19
Fasting glucose (mmol/L)	n=18	7.5±8.2	9.3±11.1	1.7	n=34	5.6±1.6	5.6±1.2	-0.1	0.182	-4.5, 0.9	
Imputed fasting glucose	n=54	7.1	8.3	1.2	n=93	5.7	6.2	0.5	0.066	-1.6, 0.1	
HADS anxiety	n=21	6.0±4.2	5.9±4.4	0.2	n=65	6.8±4.4	5.9±4.0	-0.9~	0.127	-0.5, 2.8	
Imputed HADS anxiety	n=54	6.2	6.4	0.2	n=93	6.8	6.2	-0.6	0.002*-	1.3, 0.3	0.18
HADS depression	n=22	4.8±3.8	3.4±3.2	-0.7	n=66	4.4±3.1	3.7±3.6	-0.7	0.93	-1.5, 1.5	
Imputed HADS depression	n=54	5.1	4.2	-0.8	n=93	4.3	3.8	-0.5	0.152	-0.2, 0.8	

BP: blood pressure; CI: confidence interval; HADS: Hospital Anxiety and Depression Scale; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MET: metabolic equivalent of task; TC: total cholesterol.

[a] Indicates energy expenditure as a multiple of resting metabolic rate.

* Paired t-test for within group differences p<0.01.

~ Wilcox signed-rank test for intragroup differences p<0.01.

** Independent t-test p<0.01.

*- Mann–Whitney U test p<0.01.

Theme 1: Programme suitability

As identified in the quantitative data, healthcare professionals noted decreased attendance rates for participants after stroke as well as higher dropout rates and poorer programme compliance.

Participant 1 (cardiac rehabilitation nurse): "They didn't always show up [...] they didn't finish. They were the most likely not to turn up for a stress test at the end."

There was an overall consensus that individuals with non-disabling stroke made suitable candidates for cardiac rehabilitation.

Participant 4 (medical consultant): "Well I believe the cardiac rehab model is equally applicable to stroke patients as it is to coronary heart disease patients, because so many of the risk factors are shared."

The exercise component was highlighted as beneficial for all patients.

Participant 1 (cardiac rehabilitation nurse): "I would see that (exercise) as a similarity across cardiac and stroke patients. You can really see how somebody can really get into tunnel vision, so I think the exercise is getting them out of that, breaking that, getting them into social interaction, seeing themselves, monitoring it, improving it [...]."

No difficulty or differences in exercise intensity levels between the two participant groups were observed.

Participant 2 (cardiac rehabilitation nurse): "Are they able to keep up in the same way with their [cardiac] peers? Yes absolutely. No problem."

Theme 2: Cognition and mood profiles

Cognition was a recurrent theme during the focus group and contrasts between stroke and cardiac patient profiles were stressed.

Participant 1 (cardiac rehabilitation nurse): "I feel very strongly that their cognitive profile is different. They are not as able. I just worry that they're [stroke patients] not keeping up."

Participant 3 (clinical psychologist): "For them to cognitively get what you're saying, it's different to the cardiac group."

Specific cognitive issues identified included poor recall.

Participant 4 (medical consultant): "I wonder about capacity to take it in [...] they do not remember what you say to them."

Reduced processing capability was also mentioned.

Participant 3 (clinical psychologist): "I think with some of the stroke patients [...] there's less awareness, there's less insight, there's more cognitive damage. There's kind of a slower processing."

These issues were thought to affect stroke participants' abilities to participate in the cardiac rehabilitation educational and support components.

Participant 3 (clinical psychologist): "Even in the stress talk they [stroke patients] are not keeping up, and you can't go at that pace necessarily for the wider group. And I have no way of checking in with them without singling them out and saying, 'can you follow what I'm saying'."

Health professionals identified that individuals with stroke considered themselves as being different to their cardiac peers.

Participant 1 (cardiac rehabilitation nurse): "I do wonder whether they feel like there's a difference, they'll often identify themselves as a stroke anytime they'll speak [...] you know there's a bit of 'since I've had the stroke I'll [...]' whereas you know nobody else [cardiac patients] will necessarily mention [their illness] because they'll assume the group is the same."

Differences in mood profiles between stroke and cardiac participants were identified with general agreement that stroke participants tended to be more emotional, frustrated, and have decreased coping abilities, whereas cardiac participants were described as being more anxious in general. Quantitative data support a higher anxiety profile in the cardiac participants on programme commencement but not in depression profiles between the cohorts.

Participant 1 (cardiac rehabilitation nurse): "[Stroke patients are] not necessarily that kind of high-level anxiety, that cardiac patient type. More almost [...] kind of tearfully, emotionally overwhelmed, and not sure how to cope."

Theme 3: Tailoring the cardiac rehabilitation stroke service

Health professionals in the focus group agreed that the existing service could be better tailored physically to individuals with non-disabling stroke.

Participant 1 (cardiac rehabilitation nurse): "You'd have the same exercise piece, but [...] the information [...] you'd be delivering it at a slower pace [for the stroke patients]."

They highlighted that because of the perceived differences in mood and cognitive ability, group-based sessions were not always optimal.

Participant 3 (clinical psychologist): "I think what would work better in terms of the stress talk piece would be an ability to check in [one to one with stroke patients]."

It was discussed that in order to open participation in cardiac rehabilitation to a wider profile of stroke patients, including those with physical disability, additional resources would be required. The limited involvement of therapy professionals in the current programme was considered a barrier to widening participation.

Participant 2 (cardiac rehabilitation nurse): "There isn't occupational therapist involvement and there isn't physiotherapy involvement."

More staff, wheelchair accessibility, different/adaptive equipment, and varying degrees of rehabilitation would be required to cater for more diverse needs of this stroke population. Programme changes and additional supports were identified.

Participant 1 (cardiac rehabilitation nurse): 'More individualised, supported [...] with appropriate equipment and appropriate layers of people."

DISCUSSION

This is the first study, to the authors' knowledge, to perform an upfront comparison of outcomes between stroke and cardiac patients after a cardiac rehabilitation programme. Results show that compared to cardiac participants, individuals with TIA/non-disabling stroke acquire similar physiological and physical benefits. Cardiac rehabilitation reduces cardiovascular mortality and morbidity and is cost effective in coronary heart disease treatment.[13] The parallels in improvement in physiological and aerobic fitness markers between stroke and cardiac patients in this current study show promise for accruing similar benefits for stroke survivors. In a recently published definitive trial in TIA and minor stroke, a support programme using motivational interviewing (without an active exercise component) in comparison to usual care was associated with improved secondary prevention targets at 1 year, but not significant reductions in major vascular events, total vascular events, or all-cause mortality at 3.6 years follow-up.[31] Long-term data from similar well conducted multimodal stroke clinical trials including exercise are required.

Aerobic capacity improved in individuals with TIA/non-disabling stroke following 8 weeks of cardiac rehabilitation in this study and the health professionals associated with the programme identified no difficulty with the exercise delivery component. These findings are replicated and extend to those with stroke-related mobility impairments in the literature. A recent systematic review of aerobic programmes for stroke survivors, similar in design to cardiac rehabilitation, identified a small effect size for improved composite aerobic capacity (0.38; confidence interval: 0.27–0.49) following intervention.[32] Similarly, individuals with mild and moderate stroke-related motor impairments met or exceeded the minimal recommended exercise targets of intensity, duration, and energy expenditure during aerobic and resistance training sessions in cardiac rehabilitation.[33] Trials of cardiac rehabilitation after stroke in comparison to usual care identified not only significant improvements in aerobic capacity but also in physical activity participation in both stroke and TIA participants.[15,17,22] Noncontrolled studies have identified positive and significant

changes in aerobic capacity, functional capacity[34] and in the proportion of individuals categorised in the lowest mortality risk category by stress test result.[18] In this study both groups made improvements of approximately two MET on fitness testing and this warrants specific comment in secondary prevention strategies. Improvement in cardiorespiratory fitness is noted to be a better prognostic predictor than PA alone[11] and, albeit in healthy participants, meta-analysis has identified that every one MET increase in cardiorespiratory fitness is associated with a 13% and 15% reduction in all-cause and cardiovascular disease/coronary heart disease mortality, respectively.[35]

In the focus group with health professionals, the decreased programme uptake, higher dropout rates, and lower attendance at educational and support sessions by stroke patients were largely attributed to cognitive issues. In acute stroke care a positive correlation was previously identified between attendance rates at an aerobic exercise programme and Functional Independence Measure (FIM) cognitive rating[36] and severe cognitive deficits identified as a primary cause of ineligibility for cardiac rehabilitation after stroke.[37] Accommodations for cognitive impairments are not routinely factored into the delivery of the cardiac rehabilitation programmes and cardiac patients are noted to develop only mild cognitive decline 6 years after the event.[38] However, it is estimated that cognitive impairment occurs in up to 64% of people who have had a stroke[39] and even in cases of excellent clinical recovery, high levels of cognitive impairment at 3 months remain.[40] Furthermore, progressive cognitive decline is described in the years following stroke.[41] No baseline cognitive screening protocol existed in the cardiac rehabilitation programme reported in this study and confirmation of the cognitive impairment perceived by health professionals is not possible. In future delivery of cardiac rehabilitation after stroke, the inclusion of cognitive screening is recommended to gauge individual capacity and to tailor psychological and education supports appropriately. It is interesting to note in this context, exercise and resistance training for 6 months after stroke has been shown to result in a significant reduction in the proportion of patients meeting the threshold criteria for mild cognitive impairment post-training (65.9% versus 36.6%; p<0.001) and cardiac rehabilitation may have merit as a cognitive intervention after stroke.[42]

In studies where participants were actively recruited, cardiac rehabilitation completion rates reported were higher (80–100%)[17,22] in comparison to the 61% identified in this translational study. Recently published enrolment and completion rates for cardiac rehabilitation after stroke confirm similar completion rates to this study (67%) when individuals are referred to routine cardiac rehabilitation, but in contrast identified 90% completion rates when referred to stroke-adapted cardiac rehabilitation programmes.[37] This warrants future consideration in service development and delivery, given that health professionals in this study considered that individuals with stroke have different profiles to cardiac patients, the stroke survivors self-identify themselves as different to their cardiac counterparts and delivery of educational and support components for stroke was currently deemed suboptimal. Qualitative data from TIA patients who attended conventional cardiac rehabilitation previously identified a downward comparison with individuals who had a cardiovascular event, a need for improved information delivery specific to their risk factors, and addressing the psychological impact of stroke as unmet needs.[43] Barriers to cardiac rehabilitation attendance by stroke survivors identified in the literature include weather, transport, health issues, and travel distance,[44] but with many of these issues echoed in cardiac populations.[45]

Mood and emotional disturbances are common in both stroke[46] and cardiac conditions[47] and cardiac rehabilitation has established efficacy in reducing the prevalence of anxiety and depression in cardiac participants.[48,49] Prevalence rates of anxiety and depression in TIA/non-disabling stroke attending cardiac rehabilitation were previously reported in a prospective cohort trial as 39.2% and 6.5%, respectively and, in line with the findings from this study, the trial identified that completing a cardiac rehabilitation programme was not independently associated with improvement in these domains in stroke.[19] Conflicting results from previous stroke and cardiac studies identify intragroup reductions in depressive symptoms following cardiac rehabilitation[15,49] and while reductions in

depression scores were observed for both groups in the current study, these were not statistically significant.

The health professionals who contributed to the focus group considered cardiac patients to have higher anxiety profiles in comparison to stroke; previously described prevalence rates of anxiety (27%) and high anxiety (13%) in cardiac patients attending cardiac rehabilitation match those published for stroke participants.[19,48] This current study in line with the literature notes significant intragroup reductions in anxiety in cardiac patients following cardiac rehabilitation, but these findings were not replicated in stroke, suggesting there may be subtle differences between the anxiety profiles of both groups or that their responsiveness to group-based management differs. Furthermore, analysis of the imputed dataset identified the reduction in anxiety in cardiac participants to be significantly more than that of participants with stroke. This warrants further investigation.

The high number of missing data items in stroke participants is a noteworthy finding and a limitation in the current study. Several items may have contributed to this finding. The first relates to the differing referral pathways. Cardiac patients are referred either by a structured discharge pathway administered by cardiac rehabilitation staff following surgical intervention or by an online referral mechanism from the acute services hospital information system for nonsurgical patients. Both have a standard proforma and recent test results are available. A small number of cardiac patients from other hospitals and all stroke patients were referred by letter, where the content of the letter was directed by the referring physician. Data routinely collected during the cardiac rehabilitation programme was phased over the initial assessment/orientation appointment and the subsequent cardiac rehabilitation appointment to minimise burden of assessment. The lower attendance rates noted in stroke participants in comparison to cardiac counterparts may have contributed to the higher missing data items noted in this group as a result. Where participants were required to attend phlebotomy services for blood glucose and fasting lipid testing, stroke participants were less likely to follow through with these additional hospital appointments, as noted by health professionals in the focus group conducted who largely attributed this issue to cognitive difficulties. Better integration of individuals with stroke into cardiac rehabilitation has been called for[27] and a previous out-patient stroke rehabilitation and cardiac rehabilitation partnership proven to be an effective continuum of care.[37] However, greater understanding of the reasons underpinning poor programme adherence, the support structures required for individuals after stroke in cardiac rehabilitation, and the optimal referral and assessment pathways is still required.

This study as a retrospective chart review, supported by qualitative data representing health professionals' opinions, represents a true depiction of cardiac rehabilitation delivered after TIA/non-disabling stroke in clinical practice. However, a number of limitations must be noted. Both quantitative and qualitative data are drawn from one service and this limits its generalisability. Of note, data collection and analysis were conducted by neutral, independent researchers which limits inherent bias in interpretation of the findings. Similarly, as only individuals with TIA/non-disabling stroke were referred to this service, results cannot be extrapolated to the broader stroke population, encompassing many with stroke related physical disability. A higher proportion of stroke patients than anticipated did not attend the cardiac rehabilitation programme and this, when coupled with missing data items at chart review, limits the interpretation of the findings. While data imputation was conducted to minimise this, further studies with larger numbers are required to support these preliminary findings.

CONCLUSION

In routine clinical practice, cardiac rehabilitation for individuals with TIA/non-disabling stroke is associated with many of the same fitness and physiological improvements as those in cardiac patients; however, stroke patients are less likely to enrol, complete, or engage with the educational and support components in the programme and do not achieve the same anxiety reduction. Awareness of and screening for cognitive issues after stroke may be required to gauge capacity and tailor interventions appropriately in stroke. Adequately resourced stroke-adapted cardiac rehabilitation may allow wider participation in cardiac rehabilitation and may result in higher enrolment and attendance rates.

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Traumatic Coronary Artery Dissection Diagnosed Immediately with Cardiac CT

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Disclosure: The authors have declared no conflicts of interest. The patient provided consent for publication.

Received: 26.03.20

Accepted: 01.05.20

Keywords: Coronary angiography, CT fractional flow reserve (FFR_{CT}), myocardial infarction, spiral dissection.

Citation: EMJ Int Cardiol. 2020;DOI/10.33590/emjintcardiol/20-00069

Abstract

A young male presented with chest pain after blunt chest wall trauma. Immediate CT coronary angiography demonstrated a spiral dissection of the right coronary artery. CT fractional flow reserve confirmed modest flow limitation so the patient was treated medically. At follow-up CT the vessel had healed and CT fractional flow reserve had normalised.

BACKGROUND

The incidence of traumatic coronary artery dissection is rare, but it can be life-threatening. It is underdiagnosed because the chest pain following a physical injury is often attributed to the musculoskeletal bruising resulting from the impact itself. In some cases, ECG helps to make a diagnosis of myocardial infarction but in the absence of ECG changes, a high index of suspicion is required to pursue cardiac-specific investigations such as high-sensitivity troponin.

This paper presents a young male with chest trauma during martial arts practice presenting with right coronary artery (RCA) dissection, diagnosed on immediate CT coronary angiography (CTCA). Using the novel technique of CT fractional flow reserve (FFR_{CT}), this was shown to be only minimally flow-limiting and he was managed medically with antiplatelet agents rather than stenting. A follow-up CTCA at 2 months confirmed the complete healing of the artery with normal flow on FFR_{CT}.

CASE

A 30-year-old male developed sudden-onset chest heaviness, radiating to his left shoulder, after being punched in the chest during a competitive karate match. He presented to hospital with excruciating chest pain. Clinical examination and a chest X-ray were normal. ECG confirmed early repolarisation changes but was otherwise normal.

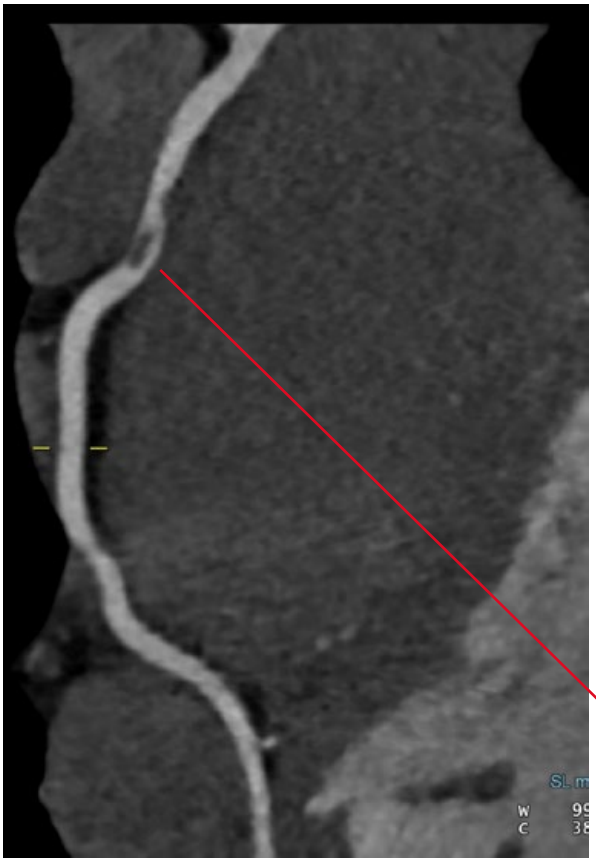

Figure 1: Index scan of reconstructed right coronary artery from CT coronary angiography.

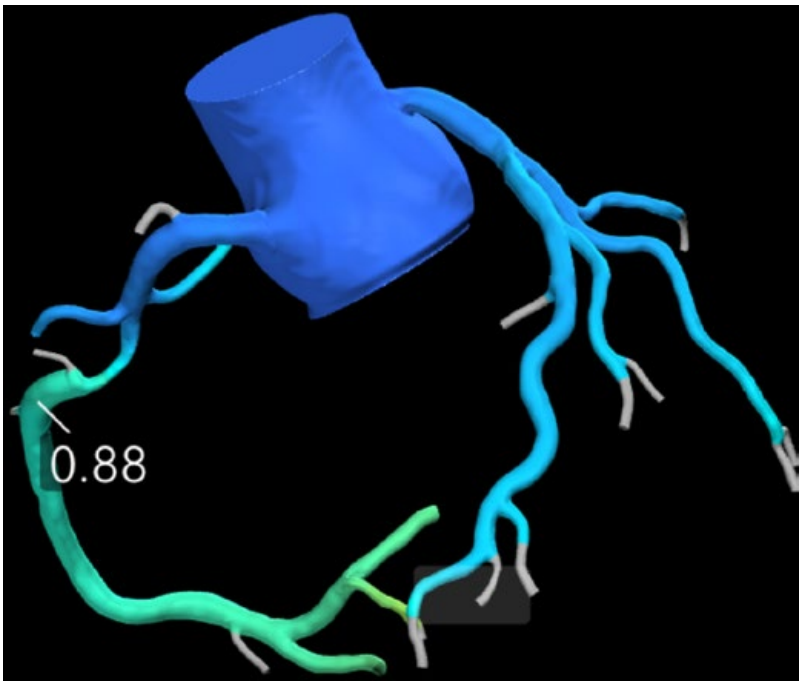

Figure 2: CT fractional flow reserve on admission.

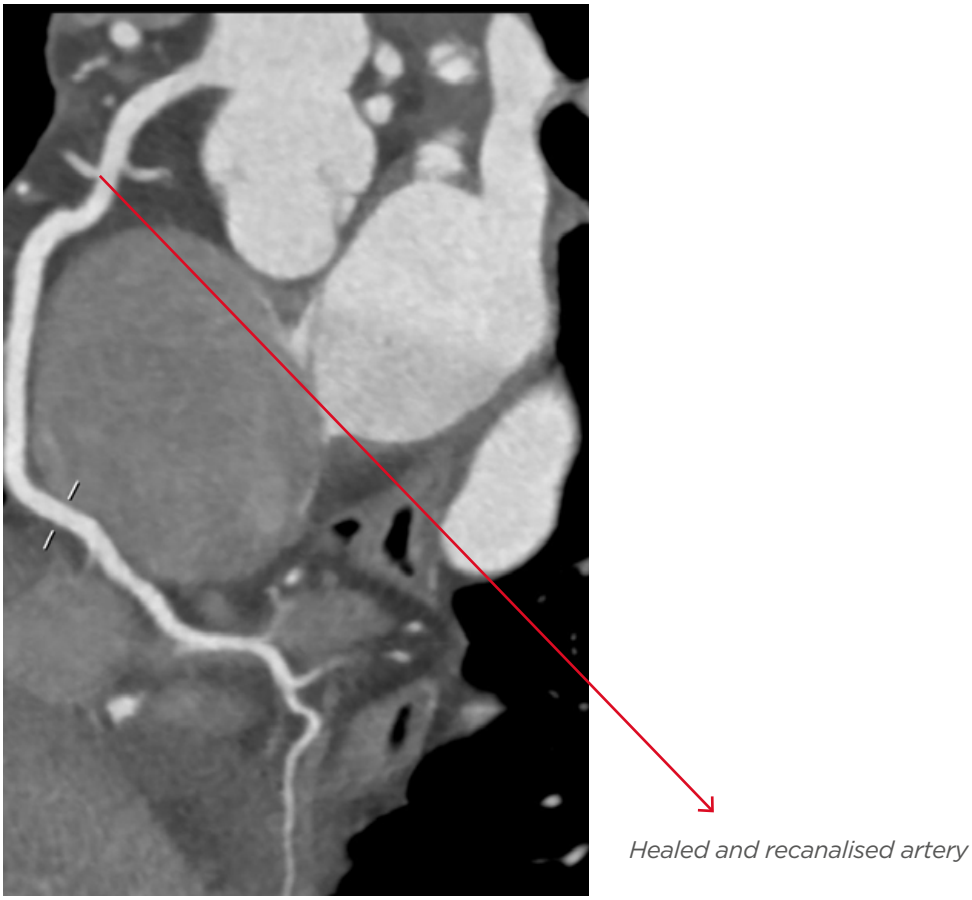

Figure 3: Follow-up study of reconstructed right coronary artery from CT coronary angiography.

Serial troponins were, retrospectively, elevated at 99 and 199 at 3 and 6 hours post-event, where the normal range is <15; the rest of the blood tests were normal. An initial diagnosis of probable acute coronary syndrome was made, and the patient was treated with dual antiplatelet, anticoagulant, and statin therapies as per the local protocol. Given the potential delay in interhospital transfer for invasive cardiac catheterisation at a nearby centre, immediate CTCA was performed locally. The CTCA revealed a spiral filling defect (Figure 1) in the proximal RCA, highly suggestive of spiral dissection. Given the uncertainty about the flow, noninvasive assessment of coronary physiology using the new technique of FFR_{CT} was performed. This confirmed a slightly reduced FFR_{CT} of the proximal lesion of the RCA at 0.88 (Figure 2). Generally, stents are not inserted unless the FFR_{CT} is <0.80.

After discussion at a multidisciplinary meeting, it was deemed appropriate to perform the traditional 'gold standard' invasive coronary angiogram to confirm the diagnosis of coronary dissection. Invasive coronary angiography confirmed spiral dissection of the proximal RCA with normal blood flow distally, and intravascular ultrasound confirmed this was due to a limited spiral dissection. Transthoracic echocardiography confirmed normal left ventricular systolic function without any evidence of wall motion abnormality.

The final diagnosis of coronary artery dissection secondary to the blunt chest wall trauma was reached and managed medically with dual antiplatelet and statin therapies. A follow-up CTCA 8 weeks later confirmed the RCA dissection had healed anatomically (Figure 3) and repeat FFR_{CT} was increased with now completely normal flow. There was no coronary artery disease visible, so the statin was stopped and dual antiplatelet therapy reduced to aspirin alone.

CONCLUSION

Coronary artery dissection secondary to blunt trauma is rare but can lead to myocardial infarction[1-3] and can be fatal.[4] The involvement of the RCA is extremely unusual, with very few cases having been reported in the literature.[5,6]

In this case, the diagnosis was made on immediate CTCA.[7] Coronary dissection without any associated atherosclerotic plaque disease on CTCA, and lack of significant impairment to coronary blood flow on the novel technique of FFR_{CT}, allowed for conservative management as opposed to stent implantation.[8] This has not previously been reported and may allow many patients to have rapid non-invasive diagnosis without the need for invasive coronary angiography. In this case, invasive coronary angiography was performed to confirm the diagnosis, but it added nothing to the CTCA information and could potentially have extended the dissection. This case demonstrates that utilisation of noninvasive CTCA and FFR_{CT} in acute situations could help direct appropriate management of the patient. This case also demonstrated the utilisation of noninvasive CTCA for follow-up to ensure the complete recanalisation of the artery.

LEARNING POINTS

1. Blunt chest wall injury during sport can cause traumatic coronary dissection and should be considered in patients with severe chest pain.

2. CTCA and FFR_{CT} can be utilised as first-line investigations in suspected traumatic coronary artery dissection for both anatomical diagnosis and to confirm the physiological significance.

3. Follow-up CTCA should be considered to ensure the complete recanalisation of the artery.

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Percutaneous Coronary Intervention of a Diffusely Degenerated Saphenous Vein Graft: A Road Less Taken

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Disclosure: The authors have declared no conflicts of interest.

Received: 14.04.20

Accepted: 07.08.20

Keywords: Coronary artery bypass graft (CABG), degeneration, percutaneous coronary intervention, saphenous vein graft (SVG).

Citation: EMJ Int Cardiol. 2020;8[1]:43-53.

Abstract

Years after coronary artery bypass graft surgery, plaque formation or graft degeneration is a major concern. Saphenous vein grafts (SVG) are vulnerable to degeneration and occlusion, leading to poorer long-term disease because of atherosclerotic degeneration. The main mechanism responsible for SVG failure is neointimal hyperplasia and the occluded SVG is treated with percutaneous coronary intervention, mostly with the use of additional protection devices. Graft intervention for the diffuse degeneration of SVG can be performed with the use of suitable hardware without the distal protection device being required.

The authors herein report the case of a 63-year-old female who presented with degenerated SVG to the left anterior descending artery with anastomotic stenosis, 6 years after coronary artery bypass graft surgery. She was successfully treated with three ultra-thin sirolimus-eluting stents in SVG to the left anterior descending artery, without the use of any embolic protection device.

Learning Objectives

1. Coronary intervention for the diffuse degeneration of the SVG can be contemplated when there is a 'no-option' clinical situation.

2. Intervention of this unusual form of degeneration of venous graft has not previously been mentioned in the literature.

3. Diffusely degenerated venous graft intervention requires the same approaches as chronic total occlusion intervention, such as the use of Gaia-2 (Asahi Intecc, Aichi, Japan) and the support of the microcatheter, multiple balloons for sequential predilatation, and longer length stents.

INTRODUCTION

Treatment of degenerated saphenous vein grafts (SVG) has been challenging, even in the era of escalating advancements in technology. SVG are more vulnerable to high-grade stenosis and occlusion, secondary to venous graft degeneration (VGD), as compared to native coronary arteries, such that within 10 years post coronary artery bypass graft (CABG) surgery only about 60% of SVG remain patent. VGD differs from coronary artery disease, which involves the native coronaries in morphology, as it comprises foam cells, cholesterol crystals, blood elements, and necrotic debris, and less fibrocollagenous tissue and calcification, with softer, friable, and larger plaque. However, uniquely, there can be diffuse degeneration processes that can include the entire length of the SVG, including anastomotic location. In these cases, the process of pathophysiology primarily involves the increased neointimal hyperplasia and extensive atherosclerosis, which contributes to diffuse long segment VGD and has been correlated with plaque embolisation and the occurrence of no-reflow.

All these characteristics lead to challenging interventional procedures in SVG.[1] In addition, patients undergoing SVG percutaneous coronary intervention (PCI) are found to be at elevated procedural risk and in-hospital mortality relative to patients undergoing PCI of native coronary arteries. Herein, the authors present the case of a female with a diffuse, long segment of VGD with chronic total occlusion (CTO) of the anastomotic site to the left anterior descending artery (LAD). She was successfully treated in the SVG-LAD vessel with three ultra-thin sirolimus-eluting stents (SES), without using any embolic protective device (EPD).

CASE PRESENTATION

A 63-year-female presented with complaints of shortness of breath on exertion, New York Heart association (NYHA) Class III in the previous week, and bilateral pedal oedema for the past 3 days. Six years ago, she had undergone CABG with SVG grafts to her LAD and left circumflex (LCX) arteries at another hospital. Ten years previously, she had also undergone PCI to the mid-segment of the LAD using bare-metal stent. She had a known history of hypertension and bronchial asthma.

Upon examination at admission, her pulse rate was 80 bpm and her blood pressure was 120/80 mmHg. An electrocardiograph showed 2 mm downsloping ST-segment depressions in leads I, aVL, and V1-4, suggestive of antero-lateral wall ischaemia. Echocardiography demonstrated mild left ventricular dysfunction with regional motion abnormalities of the anterior wall, distal interventricular septum, and apex, and moderate mitral regurgitation (jet area: 8 cm^2). Biochemical and haematological reports were normal, including cardiac enzymes. A clinical diagnosis of unstable angina was made. After therapeutic stabilisation using dual antiplatelet agents ticagrelor and aspirin, nitrates, β-blockers, and high-dose statins, angiography of the native coronary arteries showed severe stenosis of the distal left main coronary artery with multiple bridging collaterals across the in-stent occlusion of the ostial-proximal segment of the LAD (Figure 1A and 1B). The LCX was nondominant, with proximal mild disease, and was followed by total occlusion of the major obtuse marginal branch. The right coronary artery (RCA) was the dominant artery, with 50% stenosis of the distal segment with retrograde collaterals that could visualise the distal segment of the LAD (Figure 1C and 1D). The angiography of the SVG revealed streaky, thinned out, diffusely degenerated SVG to LAD, with sluggish flow and stasis of contrast at the site of anastomosis. The LAD was caused by occlusion and there was no visualisation of the distal segment of LAD beyond it (Figure 1E and 1F). The SVG to LCX was patent, with some features of VGD. The patient was advised to undergo PCI to treat the SVG graft lesion, as intervention of the native LAD–CTO (Japanese-CTO score: 2) was thought to be more complex.

After administration of 100 units/kg of unfractionated heparin, the SVG graft was cannulated with a 6 Fr Amplatz™ Left (AL)-2 (Boston Scientific, Marlborough, Massachusetts, USA) guide catheter through the right femoral approach. At the very first attempt, the SVG-LAD graft lesion was successfully crossed using a 0.014-inch Gaia-2 (Asahi Intecc, Aichi, Japan) guidewire with the support of a FineCross® microcatheter (Terumo Corporation, Tokyo, Japan) and a wire tip was placed in the distal LAD (Figure 2A).

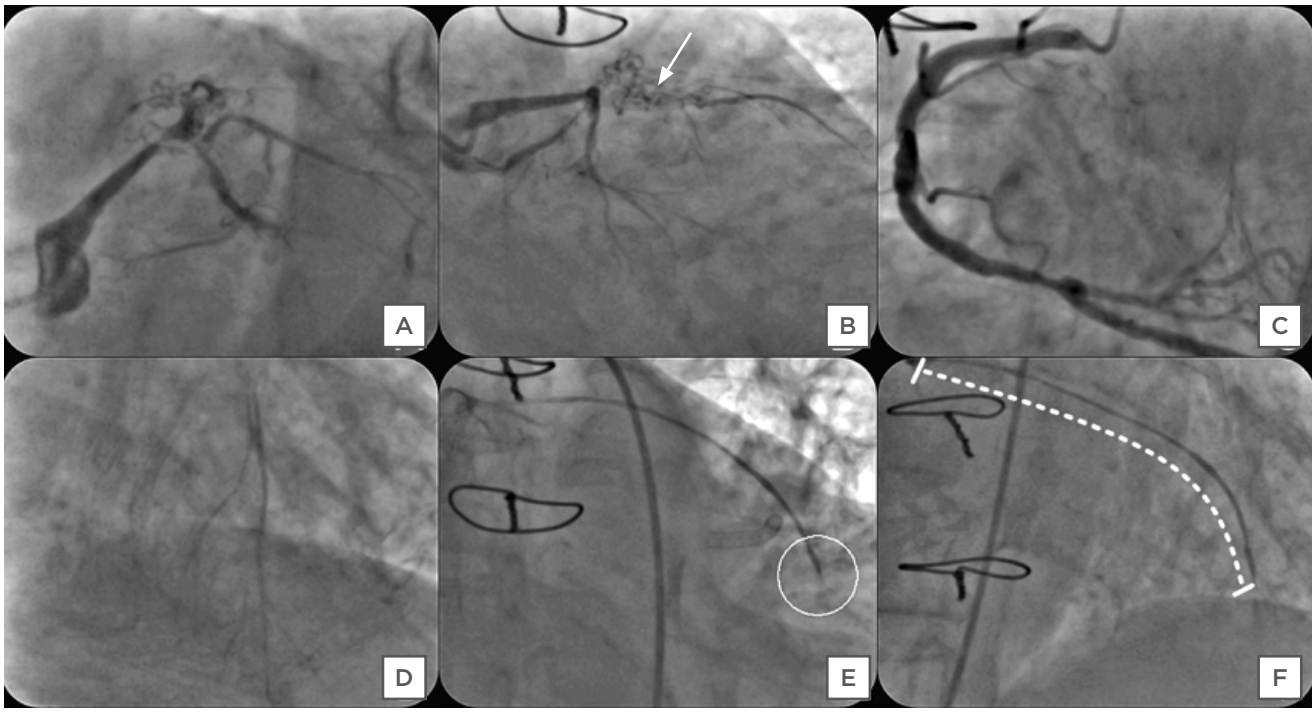

Figure 1: A–F) Angiography of the native coronary arteries in the left anterior oblique caudal **(Panel A)** and the right anterior oblique caudal **(Panel B)**, showing critical stenosis of the distal segment of the left main coronary artery with ostio-proximal in-stent chronic total occlusion (CTO) of the left anterior descending artery (LAD) with multiple bridging collaterals (solid white arrow), leading to thrombolysis in myocardial infarction II flow into its distal bed (Japanese-CTO score: 2). The left circumflex artery had CTO of the obtuse marginal branch with patent saphenous vein graft supplying its territory (not shown). The right coronary angiography in the anterior-posterior cranial view demonstrated nonobstructive plaques **(Panel C)** with retrograde inadequate filling of LAD up to its mid segment through collaterals **(Panel D)**. Angiography of saphenous vein graft to the left anterior descending artery in the right anterior oblique caudal, and cranial views showing diffusely degenerated graft with the slow, streaky flow and its occlusion **(white circle, Panel E)** at the anastomosis with mid segment of the left anterior descending artery. The venous graft degeneration involved the entire length, and the calculated saphenous vein graft degeneration score was 100% **(dashed curved white line, Panel F)**.

The LAD lesion was predilated with 1.2x8 mm and 2.0x12 mm Tazuna® balloons (Terumo Corporation, Tokyo, Japan) at 12 atm for 15 seconds (Figure 2B).

The 0.014-inch Gaia-2 guidewire was exchanged for a Runthrough® guidewire (Terumo Corporation, Tokyo, Japan) (Figure 2B). Initially the Distal SVG-LAD graft lesion was stented with 2.25x44 mm Supralimus Grace (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) SES, deployed at 12 atm for 20 seconds (Figure 2C). Subsequently, proximal SVG-LAD graft lesion was stented with 2.5x48 mmm SES, deployed at 12 atm for 20 seconds (Figure 2D and 2E). Another overlapping 2.5x20 mm SES was placed using StentBoost subtract visualisation software (Koninklijke Philips N.V, Amsterdam, the Netherlands) in the mid segment of the SVG-LAD graft (Figure 2F). StentBoost subtract image-guided segmental post-dilation of underexpanded portions of the deployed stents was done with 2.5x15 mm noncompliant balloons at nominal pressure of 10–12 atm. A post-procedural angiogram demonstrated no residual stenosis/dissection, with brisk thrombolysis in myocardial infarction (TIMI) III flow in the SVG-LAD graft, filling the antegrade limb of LAD beyond its mid segment, as well as multiple septal and diagonal branches (Figure 2G). Echocardiography demonstrated improvement in mitral valve regurgitation (jet area: 5.0 cm^2) and left ventricular function.

The patient was discharged in a haemodynamically stable condition. She was still in a favourable condition, without any related complaints, at the 9-month follow-up post PCI procedure.

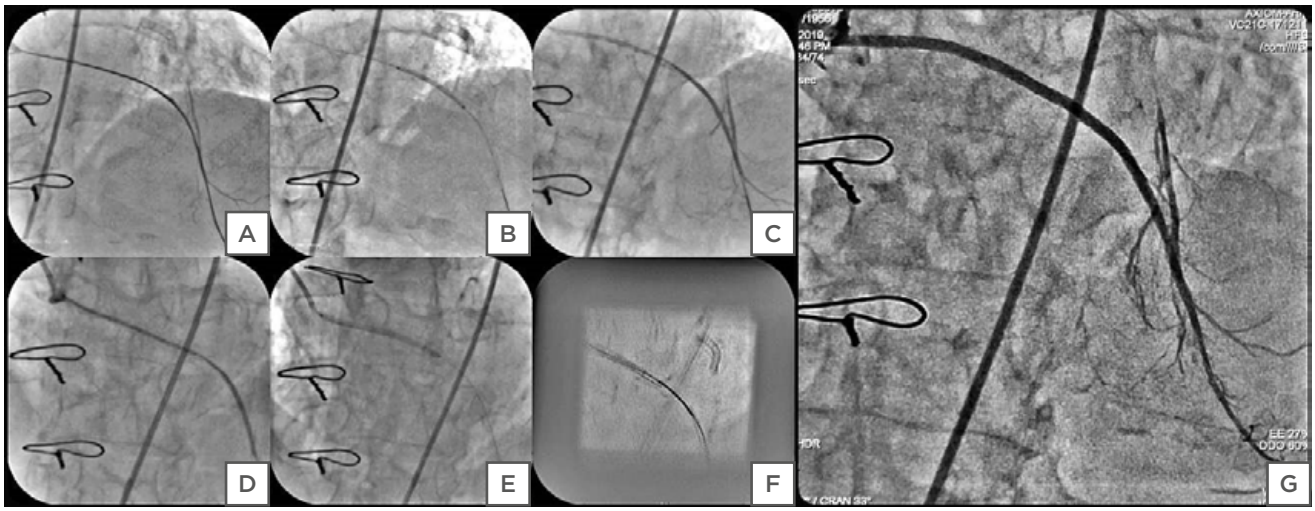

Figure 2: A–G) The percutaneous coronary intervention of the diffusely degenerated saphenous vein graft (SVG) to the left anterior descending artery (LAD). A Gaia-2 (Asahi Intecc, Aichi, Japan) wire tip was placed in the distal LAD with support of the FineCross® microcatheter (Terumo Corporation, Tokyo, Japan) **(Panel A)**. The lesion was predilated with Tazuna® balloons (Terumo Corporation, Tokyo, Japan) of 1.2x8.0 mm and 2.0x12.0 mm at 12 atm for 15 seconds **(Panel B)** after the Gaia-2 wire was exchanged with the Runthrough® guidewire (Terumo Corporation, Tokyo, Japan). The distal SVG-LAD graft deployed with 2.25x44.0 mm Supralimus Grace (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) at 12 atm for 20 seconds **(Panel C)**. The proximal SVG-LAD graft deployed with 2.5x48.0 mm Supralimus Grace at 12 atm for 20 seconds **(Panel D, E)**. Stent boost image of Supralimus Grace (2.5x20.0 mm) in the mid SVG-LAD graft, overlapping proximal and distal stents **(Panel F)**. Post-percutaneous coronary intervention final angiography showing thrombolysis in myocardial infarction III flow in the saphenous vein graft-left anterior descending artery graft, with filling of the mid and distal segments of the left anterior descending artery and its branches **(Panel G)**.

DISCUSSION

With increasing numbers of CABG surgeries being performed worldwide, incidence of VGD has also been amplified, especially after >5 years post-CABG.

This has, in turn, resulted in an increase of complex SVG interventions, made more complex because SVG anastomosis to a native vessel is a predisposition to vessel occlusion, leading to development of a CTO, as in this case. However, PCI in SVG interventions are more difficult than native coronary arteries and are indicated in patients who are not candidates for redo-CABG or who have only one SVG lesion, combined with the native coronary artery lesion supplying the same territory, as in this case. There was a nondiscrete diffuse degeneration spanning the entire length of the SVG. Usually interventions for diffuse VGD are not attempted and typically aggressive medical treatment is recommended in the event of complex lesion characteristics.[2]

AETIOPATHOLOGY OF VENOUS GRAFT DEGENERATION

Intimal hyperplasia and advanced atherosclerosis contribute over 10–20 years to a cumulative occlusion of SVG.[3] In the early phase, the technique of graft handling during cardiac surgery, including high-pressure leakage tests and exposure to the arterial circulation, leads to the venous graft distention. This leads to development of an inward remodelling, characterised by intimal hyperplasia, and a reduced lumen remodelling, characterised by mild intimal hyperplasia, depending on local and systemic influences such as inflammatory factors. In the late phase, the study of human vein grafts extracted at autopsy has also shown that coronary vein grafts undergo rapid development of atherosclerotic lesions. Lesions in coronary vein graft have a more dispersed and diffuse appearance than native lesions. Furthermore, these vein grafts have a very high propensity to rupture and occlude because of thrombosis.

This may lead to focal or diffuse degeneration of the SVG. Angiographically, there can be either singular or multiple focal stenotic lesions, with or without areas of ectasia, which are more common compared to diffuse narrowing, as seen in this case.[3,4]

Complexities of Saphenous Vein Graft-Venous Graft Degeneration Interventions

Because of the difference in morphology and physiology of SVG grafts, proper selection of stents and EPD with the right application of good procedural techniques are required to deal with complexities, in order to reduce complications.

Firstly, the recommendation for the PCI of SVG interventions should be based primarily on patient symptoms and documentation of myocardial ischaemia in the territory supplied by the SVG. Secondly, suitable catheter selection for angiography can also reduce complications and procedural time. In the present case, upon selection of the appropriate catheter, the authors were able to cross the lesion at first attempt. Thirdly, imaging techniques such as intravascular ultrasound (IVUS) are used to assess the extent of SVG degeneration as positive remodelling on IVUS is a strong predictor of no-reflow post-intervention. In addition, the relevance of IVUS in SVG interventions is addressed below.

Role of Intravascular Ultrasound in Saphenous Vein Graft Intervention

IVUS has not been sufficiently studied in prospective SVG intervention studies to endorse intervention based on IVUS findings alone.[5] Nevertheless, grey-scale IVUS has drawbacks when it comes to distinguishing between fibrous plaques and fatty plaques. This technique is less sensitive in detecting small pieces of fatty plaque, and is likely to miss them.[6] Virtual histology-IVUS is used to provide quantitative assessment of both plaque composition and morphological characteristics, but there is presently no research investigating the correlation between virtual histology IVUS-identified atherosclerotic plaque components and patient outcomes in patients undergoing PCI of SVG.

IVUS can be used for the proper sizing and positioning of the stent, which is important to ensure long-term durability and patency. One study has examined the idea of undersized stenting to decrease distal embolism.[7] The effects of SVG intervention using drug-eluting stents (DES) were evaluated by Hong et al.[7] in three groups, using ratio of the stent diameter to the average IVUS reference lumen diameter (Group I: <0.89 mm; Group II: 0.9–1.0 mm; Group III: >1.0 mm). The elevation of cardiac enzymes more than three-times the normal was 6%, 9%, and 19%, respectively, among the three groups, without further increases in clinical adverse events. The reduction of distal embolism and periprocedural myocardial infarction with undersized stenting has to be balanced against the possible risk of increased long-term in-stent restenosis (ISR).[5] Considering all these odds, the authors did not advocate the use of IVUS as there was diffuse degeneration of the graft, secondary to neointimal hyperplasia.

Selection and Technique of Implantation of Stents for Venous Graft Degeneration

The authors opted for the implantation of the undersized, latest generation DES. The latest generation DES inherently had good deliverability and crossability that posed to be of additional help towards successful graft intervention in this case. Inflation at high pressure is discouraged to minimise a 'cheese grater' effect, which may increase the risk of distal embolisation. It is also necessary to reduce post-stent manipulation to reduce embolisation.[8]

Hence, in this case, only under expanded segments of the deployed stents, detected with the help of the StentBoost subtraction imaging technique, were post-dilated, sufficiently sized, noncomplaint balloons recommended at nominal pressure.

Correlation Degree of Venous Graft Degeneration Failure-Saphenous Vein Graft Degeneration

Measurements of angiographic variables like angiographic evidence of thrombus, lesion length, vessel angulation>450°, and novel parameters like the SVG degeneration score, enabled estimation of plaque volume, which was associated with 30-day major adverse cardiac events (MACE). This included composite of

death, myocardial infarction, and target vessel revascularisation.[9] In this case, as the whole length of the SVG was degenerated, the calculated SVG degeneration score was 100%. The estimated plaque volume could not be calculated as there was no normal segment of the SVG to measure the reference vessel diameter.

Data relating to sex differences is controversial. Some suggest male patients are prone to poorer outcomes, while some studies quote vice versa. However, in many studies, female patients have been inclined towards considerably higher rates of vascular complications and post-procedural acute renal failure compared to male patients.[5]

Guideline-Based Therapies Intervention and Role of Embolic Protective Device in Saphenous Vein Graft Interventions

The current guidelines include a Class I recommendation for the use of EPD for the intervention of SVG. While Coolong et al.[10] identified 30-day MACE predictors in patients treated with EPD, their effectiveness in routine practice is questionable; several recent studies, including the National Cardiovascular Data Registry (NCDR) CathPCI Registry, showed no advantage of routine EPD use. Comparing all-cause mortality, MACE, myocardial infarction, or target vessel revascularisation in SVG intervention with and without EPD, in a meta-analysis by Paul et al.[11] which involved 52,893 patients, indicated no obvious advantage in the regular use of EPD in contemporary real-world practice during SVG interventions. Sometimes interventions of SVG are technically demanding because of an inability to track hardware because there could be inadequate proximal support and long diffuse lesions without a sufficient landing zone that precludes the use of EPD.[12]

The intervention of long segment, diffuse VGD with occlusion at site of anastomosis is a Class III recommendation, according to the current recommendations of the guidelines, but there are numerous publications in the literature regarding effective SVG–CTO interventions, as in this case. Debski et al.[13] reported a case of refractory angina in a post-CABG patient who had patent left internal mammary artery to LAD, but occluded SVG to RCA, with CTO of the native RCA. Initial antegrade and retrograde approaches could not cross the native RCA-CTO. Hence, during a second attempt, they could cross SVG to RCA with CTO using retrograde approaches across the septal collaterals but could not use EPD because of an insufficient landing zone, as in this case.[13] Garg et al.[14] registered a success rate of 79% in their retrospective analysis of PCI for SVG-CTO. The authors suggest that SVG intervention should be attempted whenever there are technical difficulties in re-canalising the native vessel.

In view of the aforementioned statements by the literature, this case appears to be interesting as it constitutes most predictors for adverse events, i.e., acute coronary syndrome, diffuse long-segment VGD, anastomotic site occlusion, complex CTO of native coronary artery, significant ischaemic mitral regurgitation, and female sex. Despite presence of various adverse predictors, the case was dealt with successfully without use of any distal embolic devices, occurrence of any post-procedural complications, or MACE at 9-month follow-up.

FUTURE RESEARCH DIRECTIONS

Strategies to Prevent or Impede Venous Graft Degeneration

Constrictive remodelling, intimal hyperplasia development, dysfunctional atherosclerotic lesions, and local and systemic inflammation are the key causes of VGD. In addition to the reduction of cholesterol and the pleotropic effects of statins, the specific targets of the different inflammatory factors have great potential to prevent VGD in future.[3] While hyperplasia in the smooth muscle cell (SMC) is a characteristic of VGD, therapies to inhibit various cell-cycle interactions may be an important method of suppressing smooth proliferation of muscle cells in VGD, and knowledge may also be learnt from previous investigations of DES. Cancer research has also identified several important therapeutic inhibitors such as verteporfin, a tyrosine kinase inhibitor.[15]

The proinflammatory cytokine interleukin-1β also plays various roles in atherothrombotic plaque formation by promoting monocyte and leukocyte adhesion to endothelial vascular cells (VEC), as well as vascular SMC proliferation. Anti-inflammatory therapy targeted with

canakinumab resulted in a significantly lower risk of cardiovascular event recurrence than placebo in the CANTOS study; this was shown to be irrespective of the reduction in lipid levels in patients with elevated C-reactive proteins >2 mg/L and atherosclerotic cardiovascular diseases, which can also help to reduce inflammation in VGD.[16]

A recent solution to preventing VGD is the use of extravascular support. The extravascular support acts as a protective outer layer of SVG, which minimises wall stress and reduces activation of SMC and VEC by a stretch mechanism. Upon external stenting, the VEST trial showed a decline in lumen irregularity 4.5 years after CABG, as it reduced the remodelling of the SVG and greatly decreased the diffuse intimal hyperplasia. A significant factor appears to be close approximation of the external stent to the wall of the SVG. Further large randomised controlled trials are needed to refine the principle of extravascular graft support to boost the long-term patency of SVG.[17]

In-Stent Restenosis and Saphenous Vein Graft-Venous Graft Degeneration Intervention

Mechanisms of in-stent restenosis

Restenosis is a pathophysiological form of reaction to injury which triggers the narrowing of the vessel because of negative vascular remodelling or neointimal hyperplasia. Similarly, balloon dilatation and deployment of the stent leads to damage to the vessel wall and triggers a healing response consisting of inflammation and proliferation of the VEC and SMC. A maladaptive healing response from the vessel wall leads to the development of various forms of ISR.[18] Various stent designs and materials have proved to have a beneficial impact on the endothelial and medial layer damage caused by stenting. The higher the artery expansion achieved during balloon inflation, the greater the damage sustained on the media layer, leading to a greater ISR rate. Therefore, the production of ISR during stent deployment is directly related to the magnitude of artery expansion.[19] He et al.[19] created a tissue-growth model, which compares the stent-induced tissue damage with the ISR and using the finite-element method to simulate ISR creation after PCI.

Techniques to tackle in-stent restenosis

Various stent designs and materials have proved to have a beneficial impact on the endothelial and medial layer damage caused by stenting. With respect to the materials used to make stents, the ISR was lower for softer materials than for harder ones. However, for polymeric stents, the need of bulkier stent design to satisfy the strength requirements may cancel out such gains. A newer-generation, ultrathin (60 µm) DES-biodegradable polymer-coated SES has been designed to substantially minimise the ISR and MACE, including composite of cardiac death, myocardial infarction, and target-lesion revascularisation.[20]

Another possible cause for ISR is the premature, untimely release of cytostatic drugs, which contribute to overdose and further delay the restoration of the endothelium.[21] The antiproliferative drugs have no specificity, which not only inhibits the proliferation of vascular SMC, but also blocks the proliferation of VEC and slows the endothelialisation in an inverse relationship.

Techniques for optimising drug dissolution

The pattern of drug release has a significant effect on its retention in the arterial wall, which can affect healing of the blood vessels and therapeutic effects. Various other novel strategies for regulating the rate of drug release leading to controlled delivery, as well as other, newer stent platforms, are summarised in Figure 3 and discussed below.

Polymers

Permanent and biodegradable polymers are commonly used in present generation DES, which could result in ISR and late stent thrombosis. Polymer-free DES have better drug delivery methods and effectively prevent ISR.[22] DES without a polymer can minimise the risk of polymer-induced late-stage thrombosis, which also has promising drug dissolution rate and effectively prevents ISR.

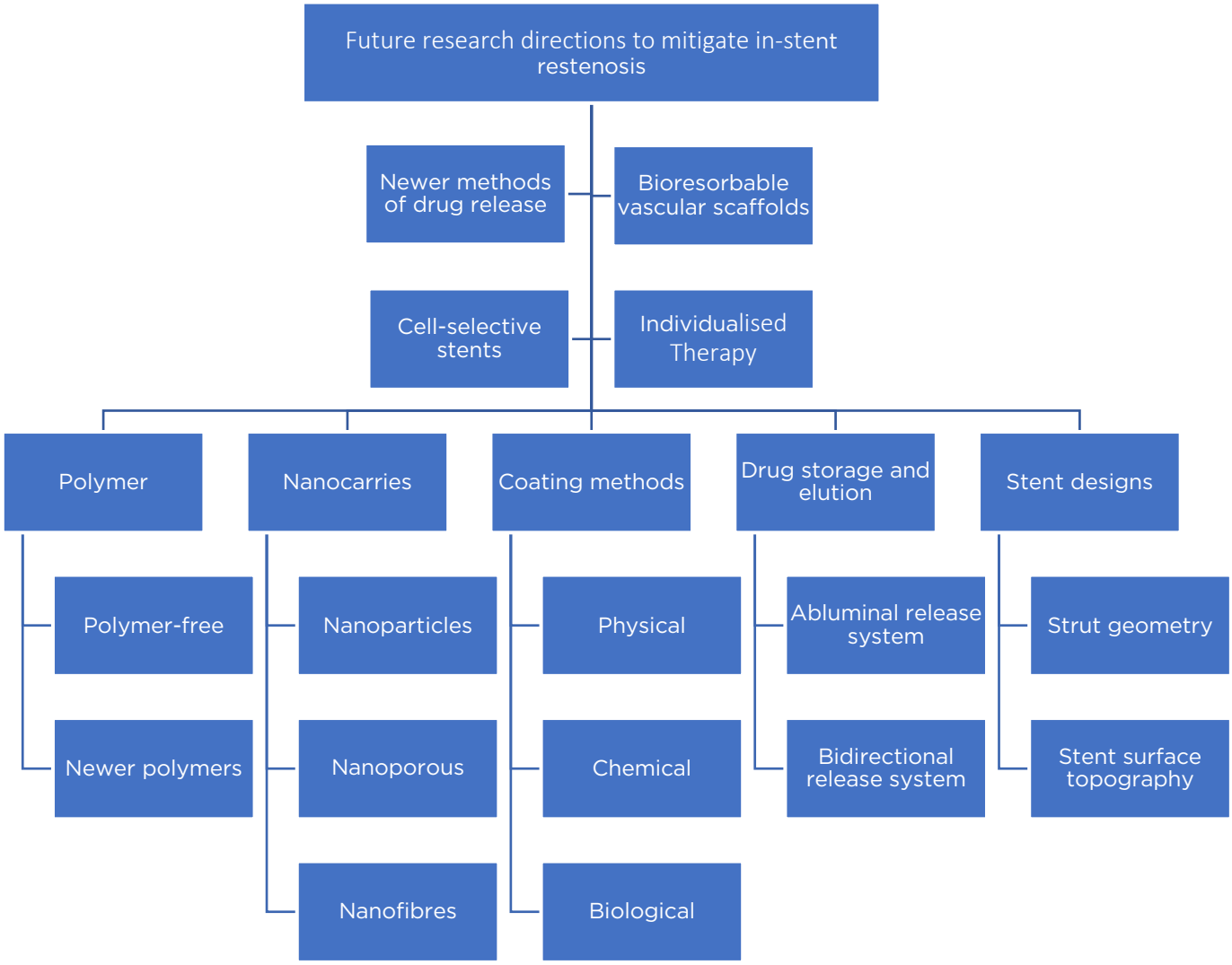

Figure 3: Flow chart summarising the future research strategies to mitigate in-stent restenosis.

New polymers have effective drug dissolution mechanisms that match physiological properties such as temperature and bioactive surfaces, and mechanical properties such as alternating multiblock structure.[23] Nanostructured hybrid polymers, called polyhedral oligosilsesquioxane thermoplastic polyurethanes, control the release of drug and can be effective. Nanocomposite polymers include polyhedral oligomeric silsesquioxane poly (carbonate-urea) urethane, which serves as a framework for the attachment of biologically active compounds, used for DES coating materials with covalently linked anti-cluster of differentiation (CD)34 antibodies.

Nanocarrier technology

Because of their special biochemical properties, nanocarriers can deliver drugs inside the cells of the vessel wall. These nanoscale carriers store drugs using the core-shell technique, which releases drug in two phases: earlier immediate-release and later slow-release, combining new biologically absorbable stent materials.[22,24,25] A substantial number of studies have shown nanoparticles are able to carry different drugs or biomolecules to achieve the effects of a predictable controlled release of drugs. Additionally, nanoporous materials enable drug dissolution by altering nanopore or nanotube structures and regulating microporous openings. Currently, nanotubular titanium and nanoporous anodic alumina are used as nanopores because of their exceptional inert, nontoxic properties. Nanofibers are another material that has unique characteristics, including small pores, high porosity, and a large

surface area because the polymer nanofibers are electrospun into ultrafine fibres. Their high volume-to-surface ratio can boost drug loading abilities, cell attachment, and mass transfer.

Coating technologies

Appropriate surface transformation of the stent should prevent immune processes, the development of thrombosis, and intimal hyperplasia, and accelerate endothelialisation to form a continuous endothelium coating on the stent surface within the first month. There are various physical, chemical, and biological methods developed for the surface modification, including the preparation of stent grooves; the use of nanoscale carriers, which store drugs using the core-shell technique and leads to earlier immediate-release and later slow-release; and the combination of new, biologically absorbable stent material.[22]

Much of the development of new polymers and the advancement of coating technology has tried to capture molecules to trap the stem cells as a stent coating.[23] Physical methods include electrostatic dry powder deposition technology, used to embed sirolimus in polyethylene-co-vinyl acetate (PEVA)/polybutyl methacrylate (PBMA) polymer microparticles, with an average diameter of 3 µm. Once these microparticles have been applied, they begin to melt on the stent surfaces to produce a homogeneous continuous film that displays continuous release over 25 days.[26]

Specific chemical methods include acid/alkaline anodic oxidation, often used for biphasic release processes in which firmly linked compounds are delivered from DES at a sustained rate along with the drug, while the weakly bound molecules are liberated in smaller spurts. The coating of polydopamine (PDA) exhibits a significant specificity for different substrates leading to secondary reactions such as different cell–material interactions that enhance endothelial cell proliferation and reduce SMC proliferation. It offers DES with a tangible and enticing surface-modifying approach.[22,27] Another novel technique for improving stent surface haemocompatibility is the phosphorylcholine (PC)-based stent coating. Lewis et al.[28] demonstrated that the PC-coated device supports its nonthrombogenic purpose and exceptional tolerance of the arterial wall, as well as the ability to activate a variety of therapeutic agents.

Many of the biological methods used are based on the basic surface markers of stem cells, which are not completely known, and how the stem cells differentiate directly into specific cells and the transformation pathways remain unclear; this is one of the major hurdles in further developing this technology.[29]

For the effective release of antiproliferative drugs to reduce ISR, various directive delivery systems methods have been established.[30,31] The abluminal release system involves the antiproliferative drug being only coated on the abluminal or external surface of the stent to allow the luminal or internal surface to be a bare-metal surface (also called a mural-release system). It aids reduction of polymer exposure to the luminal area of the blood vessel, which allows the drug–polymer matrix to interact only with the blood vessel wall. A bidirectional release system is a two-sided coating method in which the antithrombotic/endothelisation-promoting drug can be layered on the luminal surface and the antiproliferative drug can be instilled on the abluminal surface.

STENT DESIGN

Advances in strut structure and topography of the stent surface have resulted in improvements in the cross-sectional design, influencing the consistency of the flow pattern and thus reducing the deposition of prothrombotic fibrin and promoting the production of endothelial anticoagulant thrombomodulin, which prevents late stent thrombosis.[32]

Progress in micro- and nanotechnology has made it possible to produce fine configurations on metal and polymeric biomimetic coatings that are simple and cost-effective. Polymer-free DES uses techniques of multiple reservoirs, grooves, or micropores in the stent struts to load the drug, which is released directly to the arterial wall and would not get flushed away by the circulation.[33]

The various nanotopography geometries, such as nano-gratings, nano-post arrays, nano-islands, and nano-pits, modify the surface of the stent physically. These grooves and cavities are crafted on the stent struts by laser engraving. In this situation, the stent must have excellent

biocompatibility and mechanical properties, with sufficient compressive strength and adaptability.[22]

Bioresorbable Scaffold

Long-term follow-up evidence from the leading bioresorbable scaffold (BRS) has raised concerns about its efficacy and safety because of the relatively high incidence of scaffold thrombosis. Clinical studies on bioresorbable metal scaffolds include the use of magnesium and its alloys.[34] Magnesium metal is commonly used in coronary stents because of its excellent properties, including high resistance, outstanding reverberation and impact resistance, and good thermal and electrical conductivity.[35] Research in this field is promising, as different improvised next-generation European Conformity (CE) mark-approved BRS have been designed and their implantation techniques further refined. The thinner strut is the latest generation of BRS and is the most innovative technology with the potential for overcoming the current limitations.[36]

Cell-selective antirestenosis-prohealing drug-eluting stents

As the mechanisms of action of the drugs eluted from the DES are nonselective, available therapies are not adequate for preventing ISR. To date, there are no cell-selective drugs available which could differentiate between inflammatory and prohealing components. Canfield et al.[37] demonstrated the effects of the experimental microRNA-based cell-selective strategy in their preclinical studies, showing inhibition of vascular SMC proliferation while promoting EC antithrombotic and anti-inflammatory functions.[37,38] Such strategy forms the framework for developing innovative cell-selective DES, designed to eliminate the need for extended dual antiplatelet medication regimens.

Individualised Treatment for Coronary Artery Disease

The Human Genome Project (HGP) established the foundation for the development of precision medicine, also known as personalised medicine.[37] Genome-wide association studies have identified a wide range of single nucleotide polymorphisms that significantly raise an individual's predisposition to coronary artery disease, ISR, and antiplatelet therapy response.[39] Consequently, genetic screening can predict the PCI-related outcomes in patients, which could further individualise the therapy.[40]

CONCLUSIONS

Though SVG intervention itself is a complicated event, especially if it occurs many years after the CABG procedure, if the interventional procedure is performed with the use of appropriate hardware and with the necessary expertise, it can be easily intervened without any further complications or events. Accordingly, in this case, the patient was treated successfully with the use of the potent antiplatelet agent ticagrelor and the latest generation stent, without use of any additional protective devices. There are no case studies documenting the intervention of diffuse VGD in the literature. Newer therapies targeting the pathways of inflammation and cell cycle may improve the long-term patency of SVG and DES/scaffolds.

Declaration of Patient Consent

The authors certify that they have obtained appropriate patient consent. In the form the patient gave her consent for her images and other clinical information to be reported on and published. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Mechanical Thrombectomy for Transcatheter Aortic Valve Insertion (TAVI)-Related Periprocedural Stroke: Current Literature and Future Directions

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Disclosure: The authors have declared no conflicts of interest.

Received: 03.03.20

Accepted: 14.04.20

Keywords: Acute ischaemic stroke, aortic valve implantation, embolic debris, endovascular revascularisation, periprocedural, stroke, thrombolysis, transcatheter aortic valve implantation (TAVI), transcatheter aortic valve replacement (TAVR), transcatheter mechanical thrombectomy.

Citation: EMJ Int Cardiol. 2020;DOI/10.33590/emjintcardiol/20-00054.

Abstract

Transcatheter aortic valve implantation (TAVI) has dramatically altered the treatment of high-risk patients with symptomatic, severe aortic stenosis. Its utilisation has also begun to extend into intermediate- and low-surgical risk patients. Despite major advancements in the field of TAVI, stroke remains a significant complication because of its high mortality and morbidity rate . This article reviews the role of mechanical thrombectomy (MT) in the management of TAVI-related periprocedural stroke. A comprehensive literature search was performed for studies to include in this systematic review of MT in periprocedural and post-TAVI stroke patients. The search identified 11 case reports in which MT was utilised to treat periprocedural stroke successfully. MT without thrombolysis has several potential benefits for TAVI-related periprocedural stroke because a large proportion of strokes are secondary to nonthrombotic emboli and there is a high bleeding risk associated with patients undergoing TAVI. The authors propose that centres undertaking TAVI procedures have dedicated thrombolysis and thrombectomy pathways for patients who experience a TAVI-related periprocedural stroke.

INTRODUCTION

Transcatheter aortic valve insertion (TAVI) has dramatically altered the treatment of patients with symptomatic, severe aortic stenosis and is currently the treatment of choice for patients deemed high risk for surgical aortic valve replacement (SAVR).[1] With the results of recent trials, the use of TAVI has also begun to extend into intermediate- and low-surgical risk patients.[2-4] These encouraging results in low-risk patients will likely further increase the utilisation of TAVI in modern practice.

Stroke remains an important complication of TAVI and is associated with significant morbidity and mortality.[5] Thirty-day stroke rates in high- and intermediate-risk patients undergoing TAVI have been reported to range from 1.4–1.9%.[6-9] For TAVI-related periprocedural stroke, mechanical thrombectomy (MT) with retrievable stents may provide several advantages over thrombolysis alone. Concerns related to TAVI-

related periprocedural stroke management include: increased bleeding risk associated with thrombolysis in the elderly; contraindication to thrombolysis in heparinised patients; and concerns regarding the effectiveness of thrombolysis in the setting of stroke secondary to embolised nonthrombotic material.[10] This article reviews the role of mechanical thrombectomy in the management of TAVI-related periprocedural stroke.

BACKGROUND

Stroke Rate Post-Transcatheter Aortic Valve Implantation

Contemporary data in high- and intermediate-risk patients undergoing TAVI show a 30-day stroke rate ranging from 1.4–1.9%.[6-9] Most recently, the PARTNER 3 trial has shown superiority of TAVI for the composite endpoint of mortality, stroke, and hospital readmission at 1 year (hazard ratio [HR] 0.38; 95% confidence interval [CI] 0.15–1.00) in comparison to SAVR. The Evolut Low Risk trial consisted of a longer follow-up of 2 years and reported non-inferiority of TAVI compared to SAVR regarding the composite primary end point of death and stroke (5.3% versus 6.7%). However, stroke remains a significant complication of TAVI, and confers an increased risk of 30-day mortality (odds ratio [OR]: 6.45; 95% confidence interval [CI]: 3.9–10.6).[3-5]

Timing of Transcatheter Aortic Valve Insertion (TAVI)-Related Periprocedural Stroke

The temporal presentation of TAVI-related cerebrovascular events has been classified as bimodal with an early phase (≤24 h) and a late phase (>10 days). Up to 50% of events occur within the first 24 hours after TAVI.[11,12] Studies involving routine diffusion-weighted MRI (DW-MRI) post-TAVI demonstrate that 60–90% of post-TAVI patients have new silent cerebral emboli. This appears to be independent of the mode of access or valve type utilised.[13–15] The effect of these silent lesions on cognitive function after TAVI has been debated.[16]

Aetiology of Transcatheter Aortic Valve Insertion-Related Periprocedural Stroke

Most acute cerebrovascular events post-TAVI are classified as ischaemic, with <5% attributed to haemorrhage.[11] The aetiology and predictors of these strokes mainly relate to procedural factors. The aetiology of acute periprocedural strokes includes atheromatous and calcific emboli caused by wire, catheter, and valve manipulation, balloon aortic valvuloplasty, and valve deployment.[10,17] Other causes of acute stroke include air embolism and global cerebral hypoperfusion.[17]

The PARTNER trial established that minimal aortic valve area was a predictor of cerebrovascular insult in the initial course post-TAVI.[11] This was related to a higher degree of valve calcification, which in turn increased the likelihood of balloon post-dilation.[18] Other predictors of early phase cerebrovascular events included number of implantation attempts, valve embolisation, and need for second valve implantation.[12,19,20] Total time in the catheterisation laboratory, total time of delivery system in the body, and rapid pacing during valvuloplasty were also associated with increased rates of acute stroke.[21] Less experience in implantation was also associated with higher stroke rates, though this was very minimal (2.03% versus 1.66%, p=0.01).[22]

Strategies to Reduce Transcatheter Aortic Valve Insertion-Related Periprocedural Stroke

To attempt to reduce thrombotic events, the majority of centres utilise intravenous heparin to obtain anticoagulation throughout the procedure, although 27.6% of centres do not monitor activated clotting time to guide anticoagulation.[23,24] Cerebral embolic protection devices (CEPD) have been associated with a reduction in the volume of silent ischaemic emboli, however a recent meta-analysis was unsuccessful in establishing a decline in the number of single or multiple ischaemic lesions.[25,26] Though a significant reduction in 30-day stroke rate has been shown, CEPD had no effect on 30-day mortality.[25]

Histological Analysis of Emboli in Transcatheter Aortic Valve Insertion-Related Periprocedural Stroke

A study by Van Mieghem et al.[27] utilised a dual filter-based CEPD in 40 patients undergoing TAVI. Embolic debris bound for the cerebrum was caught in 75% of TAVI procedures. Tissue fragments compatible with aortic valve leaflet or aortic wall tissue were found in 52% (21 of 40) of patients; 20% consisted of thrombus alone and 25% had no debris identified.[27] This non-clot embolic debris can lead to immediate cerebral ischaemia or may subsequently provoke delayed thrombus development. This may explain why the clinical symptoms and diagnosis of early post-TAVI stroke can be delayed for up to 10 days.[10] This is crucial as this non-clot debris would not be amenable to thrombolysis. General anaesthesia and sedation can also delay diagnosis of periprocedural strokes.[10]

Management of Transcatheter Aortic Valve Insertion-Related Periprocedural Stroke

When stroke is suspected, rapid access to CT of the brain, CT cerebral angiography, and specialist review, ideally by a stroke team, have been recommended.[10] A Cochrane review comparing CT and MRI against the clinical diagnosis highlighted that DW-MRI was substantially more sensitive than CT imaging.[28] DW-MRI also has the advantage of precisely quantifying brain ischaemia. The authors did not specifically comment on thrombolysis, however, they suggest that MT may have a potential role in acute and late-presenting stroke following TAVI, based on anecdotal evidence in the literature.[29]

LITERATURE REVIEW

A comprehensive literature search was performed for studies to include in this systematic review of MT in patients with periprocedural or post-TAVI stroke. Databases including Medline, Pubmed, Embase, and the Cochrane Library were searched using the following terms: "stroke", "mechanical thrombectomy", "thrombectomy", "transcatheter aortic valve insertion", "transcatheter aortic valve replacement", "tavi", "tavr", "neurovascular rescue", and "stent retriever" in various combinations with Boolean operators "OR" and "AND". The literature search was not limited by year. One author performed the initial search to identify potential studies for inclusion (SS). These were subsequently reviewed by co-authors (JJC, RS) and a final decision regarding studies to be included in the final analysis was made.

Inclusion criteria for identified studies were: studies published in English, studies reporting patients receiving TAVI for aortic valve disease, studies reporting patients affected by TAVI-related periprocedural stroke, and studies reporting thrombectomy utilised with or without thrombolysis for the management of TAVI-related periprocedural stroke. Exclusion criteria included: studies not published in English, studies reporting noncerebral emboli, and studies reporting thrombolysis utilised without thrombectomy.

RESULTS

The search identified 11 case reports involving 11 patients (five male, six female), summarised in Table 1. Ages ranged from 73–98 years. Transfemoral approach was utilised in the majority of cases (90.9%). The prosthetic valve types implanted included six balloon-expandable valves (three Edwards SAPIEN 3, three Edwards SAPIEN XT) and two self-expanding valves (two Medtronic CoreValves™). In three case reports the valve type utilised was not disclosed. The timing of the stroke was acute in most cases: six patients had 'on the table' strokes during their procedure, four patients were diagnosed with stroke immediately post-extubation or reversal of anaesthesia, and one was a late stroke, occurring 10 days post-TAVI. The left middle cerebral artery (MCA) was most commonly involved, with eight of the patients experiencing either a partial or complete occlusion of the left MCA; the remaining three patients had right MCA occlusions. Of the 11 patients, nine underwent thrombectomy alone (81.8%) and two patients underwent combined thrombectomy and thrombolysis (18.2%). Histology of retrieved embolised material demonstrated either aortic wall or valvular tissue in 63.6% of patients (7 of 11). All patients demonstrated a significant reduction in National Institutes of Health Stroke Scale (NIHSS) score post-thrombectomy.

Table 1: Review of all published cases of mechanical thrombectomy for TAVI-related periprocedural stroke.

Author	TAVI access	Valve type	Age	Sex	Timing of stroke	Location of lesion	Thrombectomy/ thrombolysis	NIHSS or symptoms pre/ post	Embolic material histology	Bleeding complication
Coughlan et al.,[29] 2017	TF	Edwards Sapien 3	80	M	On table	Left MCA (M2)	Thrombectomy	19/5	Thrombus, calcified aortic valve fragment	Nil
D'Anna et al.,[30] 2019	TF	ND	98	M	On table	Left MCA	Thrombectomy	24/3	Thrombus	Nil
Matsuo et al.,[31] 2017	TF	Edwards Sapien XT	90	F	Day 10 post-TAVI	Left MCA	Thrombectomy	19/11	Thrombus	Nil
Wollenweber et al.,[32] 2016	TF	Edwards Sapien 3	80	F	On table	Left MCA	Thrombectomy	Global aphasia and severe right-sided hemiparesis/ mild expressive aphasia and a latent palsy of the right leg	Endothelial arterial vessel wall tissue	Nil
Alqahtani et al.,[33] 2018	ND	ND	80	F	On table	Left MCA (M1)	Thrombectomy	31/5	Fibrous stroma with a myxoid appearance	Nil
Gülker et al.,[34] 2015	TF	Edwards Sapien XT	78	F	On table	Left MCA	Thrombolysis, followed by thrombectomy	27/0*	Tissue fragment of degenerated Hancockä II bioprosthesis	Nil
Hamandi et al.,[35] 2018	TF	Edwards Sapien 3	73	M	After extubation	Left MCA	Thrombolysis, followed by thrombectomy	Decreased responsiveness, dysarthria, and right-sided hemiparesis/0	ND	Nil
Miura et al.,[36] 2017	TF	Edwards Sapien XT	82	M	After extubation	Right MCA (M1)	Thrombectomy	Disturbance of consciousness and paralysis of the left side of the body/0	Intimal fibrous plaque derived from aortic wall	Nil
Fassa et al.,[37] 2014	TF	CoreValveä	90	F	On table	Right MCA (M1-M2)	Thrombectomy	Unresponsive/ fully responsive and orientated with modified Rankin Scale score 0	Pure calcific fragment: likely native aortic valve or aortic wall	Nil
Anuwatworn et al.,[38] 2015	TF	CoreValve	78	M	On awakening from sedation	Left MCA (M1)	Thrombectomy	Right hemiplegia/ heart valve tissue		Nil
Salinas et al.[39] 2013	TF	ND	88	F	After prompt reversal of anesthesia	Right MCA (M1)	Thrombectomy	Complete left hemiparesis/ modified Rankin scale 1	Thrombus	Nil

*authors reported patient had a full recovery of symptoms; assumption of a NIHSS score of 0.

F: female; M: male; MCA: middle cerebral artery (M1 or M2 segments); ND: not disclosed; NIHSS: National Institutes of Health stroke scale; TAVI: transcatheter aortic valve insertion; TF: transfemoral.

DISCUSSION

TAVI-related periprocedural stroke is a catastrophic complication with a high risk of 30-day mortality.[5-9] >50% of strokes occur in the first 24 hours post-TAVI.[11,12] The management of acute ischaemic stroke (AIS) has been revolutionised in recent years with the widespread adoption of MT. MT is now considered the gold standard of care for all AIS with large vessel occlusions.[40]

It has been well established that MT paired with intravenous thrombolysis (IVT) demonstrates favourable outcomes for functional independence, health-related quality of life, and cognitive function at long-term follow-up for patients with AIS, when compared to standard medical therapy alone.[41-43] This article describes all published cases of MT post-TAVI. MT was utilised successfully in all 11 published cases, with a significant reduction in NIHSS score and no complications post-recanalisation. This suggests that MT represents a potentially efficacious and safe management strategy for TAVI-related periprocedural stroke.

Recent data from the DAWN and DIFFUSE-3 trials have highlighted that the time window for MT can be extended past the traditional 6 hours, to 24 hours.[44,45] This is important since the recognition and diagnosis of TAVI-related strokes may be delayed past the 4.5 hour thrombolysis window, because of factors including general anaesthesia and procedural sedation.[10]

Combined treatment with IVT prior to MT was utilised in two patients. There is ongoing debate in the literature as to whether IVT before MT is superior to MT alone in AIS.[46] The American Heart Association (AHA) post-hoc analysis of the ASTER trial demonstrated that AIS patients treated with combined IVT and MT had lower 90-day mortality compared with those undergoing MT alone.[47] There were no significant differences between the IVT with MT and MT-alone groups in 90-day favourable functional outcome, successful reperfusion rate, NIHSS score improvement at 24 hours, or haemorrhagic complication rate. However, many of the studies contained only direct MT patients who were ineligible for IVT or where IVT was contraindicated, establishing a bias in which the MT-alone arm represented a patient cohort with a potentially increased morbidity and associated poorer outcome.[48,49] Kaesmacher et al.[50] proposed that when analyses were limited to cohorts with a reduced risk of selection bias, the data implied that MT alone might deliver comparable safety and efficacy to combined therapy.[51]

It is also difficult to directly extrapolate the results of these studies to patients undergoing TAVI. TAVI patients differ from the patients in these trials in several regards: the AIS occurs in the setting of a procedure; the patients are usually therapeutically anticoagulated with heparin at the time of the AIS; and the patients are generally older than patients in the MT trials, with a higher pre-stroke modified Rankin Scale and more comorbidities.[50]

As determined in this review of MT post-TAVI, 63.6% of patients had embolic debris histologically consistent with valvular and aortic wall tissue. These emboli would not be expected to respond to thrombolysis. This was consistent with the literature highlighting that >50% of debris collected by CEPD was nonthrombotic.[27] This differs from published data analysing thrombus composition in traditional AIS treated with MT.[52] The use of thrombolysis would potentially be of no benefit in these circumstances and may increase the rate of bleeding complications.

In the SURTAVI trial, the PARTNER 2 trial, and the US CoreValve studies, life-threatening and major haemorrhagic complications within 30 days of TAVI were identified in 10.2% of patients.[53–56] A meta-analysis by Wang et al.[57] indicated that post-TAVI bleeding was associated with a 323% increase in 30-day postoperative mortality, and that these patients were 410% more likely to die than patients without bleeding.[58] Physicians must be extremely cautious when considering thrombolysis in TAVI patients. The use of IVT may be relatively or absolutely contraindicated because of concurrent anticoagulation, increased activated partial thromboplastin time or activated clotting time, and high HAS-BLED score or bleeding risk.

Transfemoral access is the most-adopted approach for TAVI as it has a 20% relative reduction in mortality compared with SAVR.[57] It is also the preferred access in MT.[59] This is advantageous for the treatment of periprocedural strokes as there is the benefit of established femoral access. There is an ongoing debate regarding the training of cardiologists in performing MT, which is currently most often performed by interventional radiologists.[60] Cardiologists have skills transferable to MT and extensive experience with emergency, time-constrained interventions for patients with ST-elevation myocardial infarction. In the future, appropriately trained cardiologists may be able to perform MT in the cardiac catheterisation laboratory for patients experiencing TAVI-related

periprocedural stroke.[61] However, this requires a significant skillset, thorough training, and the requirement for many cases to become proficient.

While analysis of the published literature on MT post-TAVI provides interesting information, the high risk of publication bias must be acknowledged. As a result, mechanical thrombectomy alone may be a viable option to manage on-table stroke post-TAVI on a case by case basis, with or without thrombolysis. The SWIFT Direct trial is an ongoing prospective randomised controlled trial attempting to ascertain whether patients with an AIS secondary to large intracranial vessel occlusion in the anterior circulation will have non-inferior functional outcome at 90 days when managed with direct MT, compared to patients treated with bridging IVT prior to MT.[62] This will hopefully shed further light on the optimal treatment strategies for AIS.

In the interim, the authors propose that centres undertaking TAVI procedures have dedicated thrombolysis and thrombectomy pathways for patients who experience a TAVI-related periprocedural stroke. This may be as elementary as stabilising the patient, rapid access to imaging, review by a stroke team, and possible commencement of thrombolysis, with subsequent transfer to a centre with the facilities to treat AIS with MT. Hopefully, by maximising the number of patients receiving these therapies, there can be a reduction in the associated stroke-related morbidity and mortality and an improvement in outcomes for patients.

Limitations of the Manuscript

As mentioned previously, there is a high risk of publication bias in reporting of MT post-TAVI-related stroke. It is possible that only successful cases would be submitted for publication, and this review was unable to identify any published manuscripts detailing cases where MT was unsuccessful in the treatment of AIS. Secondly, all cases identified were case reports and there are no prospective randomised controlled trials investigating the treatment of TAVI-related periprocedural stroke.

CONCLUSION

MT has been described as a potential treatment for TAVI-related periprocedural stroke. MT without thrombolysis may have several potential benefits for TAVI-related periprocedural stroke because a large proportion of these strokes are secondary to non-thrombotic emboli and there is a high bleeding risk associated with patients undergoing TAVI. However, further research is required on the optimum management of TAVI-related strokes. TAVI centres should have dedicated MT pathways for TAVI-related periprocedural stroke. The SWIFT Direct trial will further provide further data regarding the benefit of IVT prior to MT.[63]

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