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MINIREVIEWS

Transcatheter pulmonic valve implantation: Techniques, current roles, and future implications

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Abstract

Right ventricular outflow tract (RVOT) obstruction is present in a variety of congenital heart disease states including tetralogy of Fallot, pulmonary atresia/stenosis and other conotruncal abnormalities *etc.* After surgical repair, these patients develop RVOT residual abnormalities of pulmonic stenosis and/or insufficiency of their native outflow tract or right ventricle to pulmonary artery conduit. There are also sequelae of other surgeries like the Ross operation for aortic valve disease that lead to right ventricle to pulmonary artery conduit dysfunction. Surgical pulmonic valve replacement (SPVR) has been the mainstay for these patients and is considered standard of care. Transcatheter pulmonic valve implantation (TPVI) was first reported in 2000 and has made strides as a comparable alternative to SPVR, being approved in the United States in 2010. We provide a comprehensive review in this space–indications for TPVI, detailed procedural facets and up-to-date review of the literature regarding outcomes of TPVI. TPVI has been shown to have favorable medium-term outcomes free of re-interventions especially after the adoption of the practice of pre-stenting the RVOT. Procedural mortality and complications are uncommon. With more experience, recognition of risk of dreaded outcomes like coronary compression has improved. Also, conduit rupture is increasingly being managed with transcatheter tools. Questions over endocarditis risk still prevail in the TPVI population. Head-to-head comparisons to SPVR are still limited but available data suggests equivalence. We also discuss newer valve technologies that have limited data currently and may have more applicability for treatment of native dysfunctional RVOT substrates.

Key Words: Pulmonary valve; Congenital heart defects; Heart valve prosthesis implant; Pulmonary valve insufficiency; Pulmonary atresia; Pulmonary valve stenosis

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Core Tip: As patients with congenital heart defects continue to survive well into adult life, right ventricular function preservation and management of the right ventricular outflow tract has become increasingly important and sophisticated. As an alternative to surgical pulmonary valve replacement (PVR), the advent of transcatheter pulmonic valve therapy has offered a less invasive approach for many patients. Improved techniques and technologies have rapidly expanded its use in increasingly complex anatomy. In this review we summarize the indications for PVR, transcatheter pulmonic valve implantation techniques, clinical outcomes and also future directions of this treatment.

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INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease occurring in approximately 3 *per* 10000 live births[1]. This defect is comprised of the following four components: Ventricular septal defect (VSD), aortic override, right ventricular hypertrophy, and right ventricular outflow tract (OT) obstruction in the form of infundibular stenosis/pulmonary valve stenosis/pulmonary artery stenosis. Correction of this heart defect involves patch closure of the VSD and relief of the right ventricular outflow tract (RVOT) obstruction. The end result uniformly leaves the patient with residual OT dysfunction with some form of pulmonic stenosis (PS)[2] and/or pulmonary valve insufficiency (PI) leading to deleterious effects over the long-term[3,4]. The chronic effects of pressure and volume loading on the right ventricular (RV) ultimately lead to symptomatic ventricular dysfunction and arrhythmia[2,3].

While TOF is the stereotypic diagnosis for the management of residual RVOT disease, other congenital heart defects are managed similarly. Conotruncal defects such as truncus arteriosus, d-transposition of the great arteries with a VSD and pulmonary stenosis, double outlet right ventricle can be repaired with a VSD closure to the aortic valve and placement of a RV to pulmonary artery conduit. Another common example is the Ross operation for aortic valve stenosis which leaves the patient with a reconstructed RV to pulmonary artery connection. These surgically reconstructed outflows all universally fail over time leading to the same long-term deleterious effect on the RV.

Until recently, surgical pulmonic valve replacement (SPVR) was utilized universally for pulmonary valve replacement (PVR) and relief of RVOT dysfunction. In 2000, Bonhoeffer *et al*[5] implanted the first transcatheter valve into a human[5]. This led to the development of Melody Transcatheter Pulmonary Valve (Medtronic Inc, Minneapolis, MN), receiving Humanitarian Device Exemption (HDE) Food and Drug approval (FDA) for commercial use in dysfunctional RV to pulmonary conduits in the United States in 2010. Subsequent studies allowed for approval of the Sapien XT valve (Edwards Lifesciences LLC, Irvine, California) as transcatheter PVR in failed RV to pulmonary conduits[6].

In the following review we will review the indications for transcatheter pulmonic valve implantation (TPVI), discuss procedural considerations, techniques, outcomes as well as future considerations.

INDICATIONS FOR INTERVENTION

The indications for PVR, especially *via* transcatheter means are gradually evolving. Most clinical societies agree with need for PVR in symptomatic patients in the TOF spectrum with moderate to severe PS or PI (Table 1). However, the question of asymptomatic PI persists. The deleterious effects of progressive RV dilation with

Table 1 Comparison of American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for pulmonic valve placement

Indication	Recommendation		Level of evidence	
	ACC/AHA 2018	ESC 2010	ACC/AHA 2018	ESC 2010
Symptomatic with moderate/severe PR	I	I	B	C
Asymptomatic with moderate/severe PR and RV dilation	IIa	IIa	B	C
Asymptomatic with moderate/severe PR and ventricular arrhythmias	IIb	IIa	C	C

ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; PR: Pulmonary regurgitation; RV: Right ventricle

respect to increased mortality are well known, however it has not been convincingly proven that SPVR improves mortality or the incidence of ventricular arrhythmias[7]. There have been multiple studies to investigate what threshold of RV dilation should be used to pursue PVR in an asymptomatic patient which allows a reasonable chance of reversal of structural abnormalities[8]. However, surgical PVR for asymptomatic patients with lesser degrees of RV dilation has also been shown to increase chances of heart failure, atrial arrhythmias or ventricular tachycardia[9]. Thus, the need to balance the deleterious effects of progressive RV dilation with those of repeated operations and cardiopulmonary bypass need to be weighed together. With the increase in use of TPVI, the latter can be circumvented and with solutions for native RVOT also on horizon, it is likely that more asymptomatic patients may benefit from the procedure. Currently, generally accepted indications for TPVI in asymptomatic patients are the following[3]: (1) RV indexed end diastolic volume > 160 mL/m^2 or RV indexed end systolic volume > 80 mL/m^2; (2) RV end diastolic volume > 2 times of left ventricular end diastolic volume; (3) Significant RV dysfunction (RV ejection fraction < 45%); (4) Progressive tricuspid regurgitation in the setting of a dilated RV; and (5) Ventricular arrhythmias with a dilated RV.

PROCEDURE

Generally multidisciplinary discussion with different cardiology subspecialties (almost always with adult congenital specialists), congenital cardiac surgery and cardiac anesthesia is recommended to determine best strategy for each individual patient. Multi-modality imaging review and good understanding of prior operations is essential. It is of vital importance to understand the nominal size of RV to pulmonary artery conduits and bioprosthetic pulmonary valves as well as any known coronary artery anomalies.

General anesthesia is usually preferred[10]. Biplane fluoroscopy is most often employed to understand the RVOT and pulmonary artery anatomy in two views and requires patient positioning with the arms elevated in a non-stretched position to avoid brachial plexus injury[11]. Most patients have had multiple catheterizations/surgeries and may have unique vascular access considerations. While femoral venous access is often the first choice, the jugular (ideally right) can offer advantages for valve delivery as well for flexing of Edwards Sapien delivery systems[12].

Baseline data

A baseline right and left heart catheterization hemodynamic assessment is performed as well as RVOT, pulmonary artery, and aorta/coronary angiography. From this data, a plan for conduit rehabilitation and final balloon sizing is developed as well as ascertaining risk for conduit rupture and coronary artery compression. It also identifies other pulmonary artery stenosis that might need to be intervened upon during the procedure. After baseline data is obtained a stiff wire [Lunderquist Extra Stiff Guidewire (Cook Medical, Bloomington, IN), Amplatz Superstiff Guidewire (Boston Scientific, Boston, MA)] is positioned into the distal lower lobe of right or left pulmonary artery.

Conduit preparation-balloon/stent

Many dysfunctional RVOTs involve significant conduit stenosis. This requires conduit rehabilitation and stenting to achieve acceptable post procedure RV pressure. Serial balloon dilation with high pressure balloon angioplasty is often necessary. This places the conduit at risk for rupture necessitating covered stent angioplasty with a Cheatham-platinum covered stent (Numed, Hopkinton, New York, United States) (Figure 1)[13]. Once assured that an adequate final diameter can be achieved, bare metal stent angioplasty with large bore hand mounted stainless-steel stents [Palmaz XL (Cordis, Milpitas, CA, United States), InstraStent Max LD (EV3, Plymouth, MN, United States)] are implanted. Because of stent fracture risk of the Melody valve, multiple stents might be necessary to avoid recoil and limit metal fatigue[14]. Ideally, for an adult, the final diameter of the conduit should be at least 20-22 mm, otherwise, a residual RVOT gradient will persist.

Coronary artery and aorta testing

Prior to initial stenting of the conduit, assessment for risk of coronary artery obstruction is necessary. A variety of coronary artery anomalies can be at risk including a left anterior descending from the right coronary artery, ostial stenosis, abnormal location secondary to reimplantation. Coronary artery testing is performed with either aortic root angiography and/or selective coronary angiography. This is performed with the Anteroposterior tube angled caudal to perform and "down the barrel" assessment (Figure 2). If the coronary artery flow is compromised during balloon testing, this is considered a contraindication to proceeding with stent or PVI. While less commonly a problem, aortic root distortion causing aortic valve insufficiency has also been demonstrated[15].

Valve implant

Once the conduit is adequately prepared-the Melody valve is hand crimped onto the balloon Ensemble system (Medtronic, Minneapolis, MN, United States) (Figure 3). Balloons range from 18-22 mm and there are descriptions of maintained valve competency even when mounted on a 24 mm balloon[16]. The outer diameter of the valve is approximately 2 mm larger than the balloon diameter. The Edwards XT valve is crimped onto the Novaflex delivery system using the proprietary process (Figure 4).

After delivery system preparation, the delivery system is advanced into the appropriate position. Numerous techniques can be used to aid in delivery system advancement such as balloon assisted or a buddy wire methods[17]. Secondary to the stiffness of the delivery system, Edwards Sapien XT valve is more difficult to pass into the OT. Use of the Sapien S3 and the smaller delivery system is more amenable to traversing the RVOT. Use of the Edwards XT or Sapien S3 through a long (65 cm) large bore Gore sheath (Flagstaff, AZ) into position has mitigated some of the difficulty[18]. While the valve implant is typically stable, rapid pacing at 140-160 beats per minute can be performed to aid in valve positioning. Following valve implant, post implant hemodynamic data are obtained, and an angiogram is performed to evaluate for perivalvar leak and valve competence. Some have advocated for intracardiac echocardiogram imaging post implant to evaluate the implant and have a reference for the future[19]. Typically for hemostasis post procedure a figure of 8 stitch is sufficient[20].

Special considerations–valve in valve

Valve in bioprosthetic valve implantation tends to be a less complex procedure. The risk of coronary compression is less as the valve cannot be over-expanded at low pressure, and generally there is no need to pre-stent unless there is significant conduit stenosis separate from the valve. The type and size of bioprosthetic valve is of utmost importance as the inner diameter dictates the size of transcatheter valve. Many descriptions of valve fracture exist, expanding the valve to the size or just larger of the outer diameter with a high pressure True balloon (Atlas, Atlas Gold, or True Balloon, Bard Peripheral Vascular, Inc, Tempe, AZ) (Figure 5)[21]. This avoids future development of valve patient size mismatch. In the pulmonary system, fracture can be safely performed prior to valve implantation. One must be mindful of the coronary artery anatomy when considering valve fracture.

Special consideration–native OT

The OT after transannular patch repair for TOF can be quite complex. Many times, it lacks a tubular landing zone and can have a funnel shape from the RV out to the pulmonary arteries. However, some native OTs have anatomy suitable for currently available valve to be used off-label. Balloon sizing with a large diameter (> 35 mm)

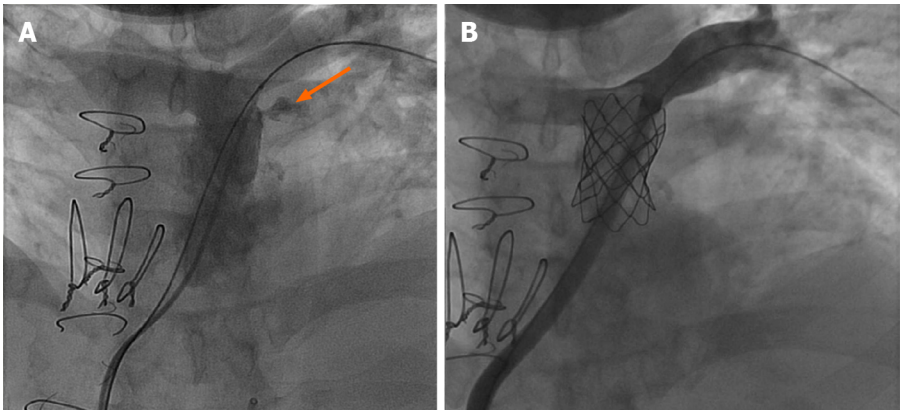

Figure 1 Covered Cheatham Platinum stent placement after conduit disruption. 23 years old patient with truncus arteriosus status post repair with a 20 mm homograft. A: With high pressure dilation at 22 mm, disruption of wall of conduit is noted (orange arrow) but contained; B: Covered Cheatham Platinum stent placed with resolution of the extravasation.

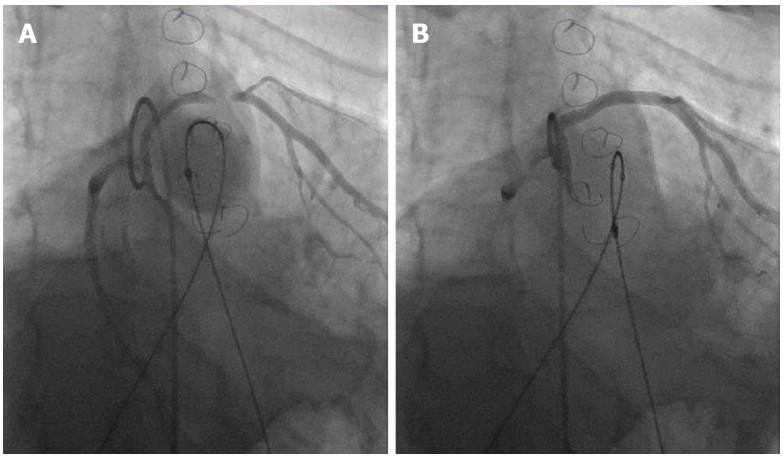

Figure 2 Tetralogy of Fallot full repair with 20 mm homograft. 28-year-old with tetralogy of Fallot status post repair with 20 mm homograft. A: Left anterior descending (LAD) arise from the right coronary coursing around the homograft. With inflation of a 22 mm balloon, the mid LAD is compressed; B: The coronary flow returns back to baseline upon balloon deflation.

compliant balloon can identify a suitable landing zone for a balloon expandable stent. In appropriate anatomic arrangements, this is reported with good short- and long-term success (Figure 6)[22]. Valve implant into one or both of the proximal branch pulmonary arteries has also been shown to be effective in reducing the degree of PI[23].

The Medtronic Harmony Valve (Minneapolis, MN, United States) (Figure 7) is a self-expanding valve that can be used in native OT after three-dimensional sizing data has been obtained. Similarly, the Alterra pre-stent (Edwards Lifesciences LLC, Irvine, California) (Figure 8) allows for creation of a landing zone to allow for implantation of a 29 Sapien S3 valve. Both are currently under investigation at the time of writing this review[24,25].

AVAILABLE AND UPCOMING VALVE SYSTEMS

The Melody valve (Medtronic Inc, Minneapolis, MN, United States) traces its origins to the implantation of an 18 mm bovine jugular vein mounted on a platinum stent in a 12 year old patient with conduit failure by Bonhoeffer *et at*[5]. In its current iteration, the Melody valve is a bovine jugular vein sutured inside of a Platinum Iridium stent, available in two sizes – 20 and 22 mm. The two sizes use 16 and 18 mm vein segments intended to be expanded up to 20 and 22 mm respectively. The valve is delivered *via* the Medtronic Ensemble delivery system which utilizes a "balloon-in-balloon" (NuMED Inc, Hopkinton, NY, United States). The delivery system is 22F and is available in 18, 20, and 22 mm sizes.

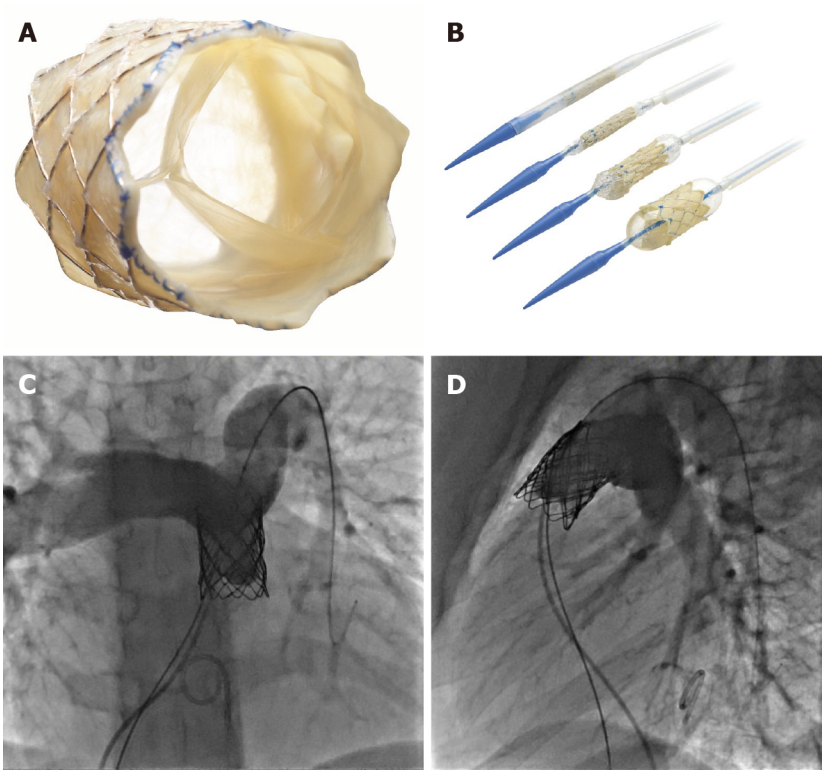

Figure 3 Melody transcatheter pulmonic valve. A: En-face view of Melody transcatheter pulmonic valve; B: Melody valve Ensemble with loaded valve demonstrating the two-stage balloon-in-balloon inflation (Reproduced with permission from Medtronic, Inc, Minneapolis, MN, United States); C: Angiogram after placement of a stainless steel pre-stent; D: 20 mm Melody valve in Antero-posterior and lateral projections.

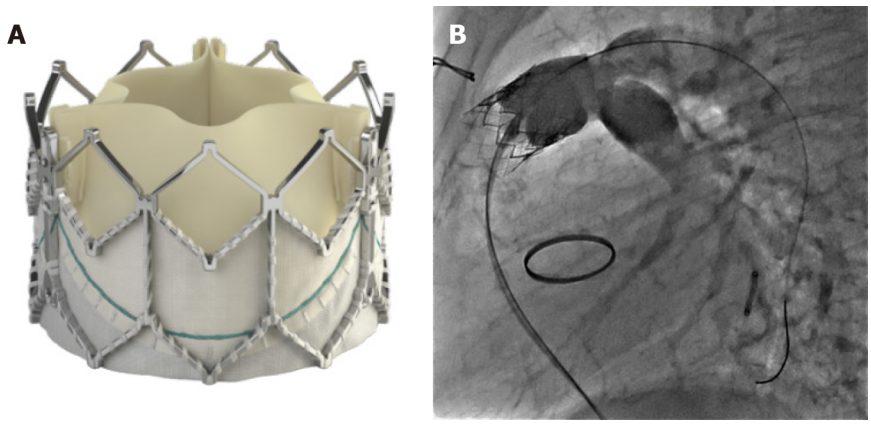

Figure 4 Edwards Sapien XT™. A: Edwards Sapien XT™ valve (Reproduced with permission of Edwards Lifesciences LLC, Irvine, CA, United States); B: Angiogram after placement of a 23 mm Edwards Sapien XT™ valve in a Contegra conduit stented with a stainless-steel stent up dilated up to 22 mm.

Experience from European centers with the Melody valve predates use in the United States–Lurz *et al*[26] reported their series of 155 implants with an excellent success rate of 96.7%, freedom from reoperation rates of 70% after 70 mo and lower re-operation rates with increasing familiarity/expertise with the valve system[26]. The United States Investigational Device Exemption trial reported its medium to long term results in 2015 enrolling a total of 171 patients with 148 successful implants and a re-intervention free rate of 76% at 5 years[27]. The Melody valve received Conformitè Europëenne Mark approval in 2006; the FDA granted HDE approval in 2010 and full post market approval in 2015. The United States post market approval study had 100 implants with 98% success rate and a 98% rate of freedom from catheter/surgical re-intervention[28].

The Edwards Sapien XT (Edwards Lifesciences, Irvine, CA, United States) transcatheter heart valve (THV) was approved by the FDA for use in the pulmonic position in 2016 (Figure 4). The valve is made of bovine pericardial tissue and

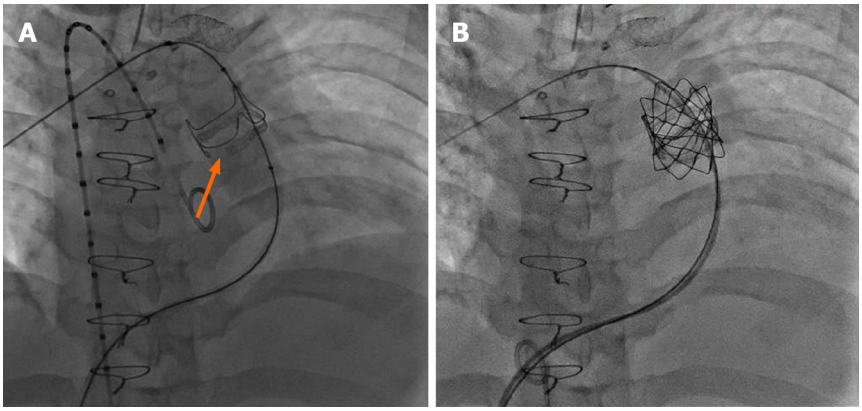

Figure 5 Transcatheter valve in valve with valve fracture: 21 years old with congenital pulmonary stenosis with a prior dysfunctional 21 mm Edwards Magna™ valve- 22 mm. A: Atlas balloon inflated to 20 ATM fractured the valve ring (orange arrow); B: placement of 22 mm Melody valve.

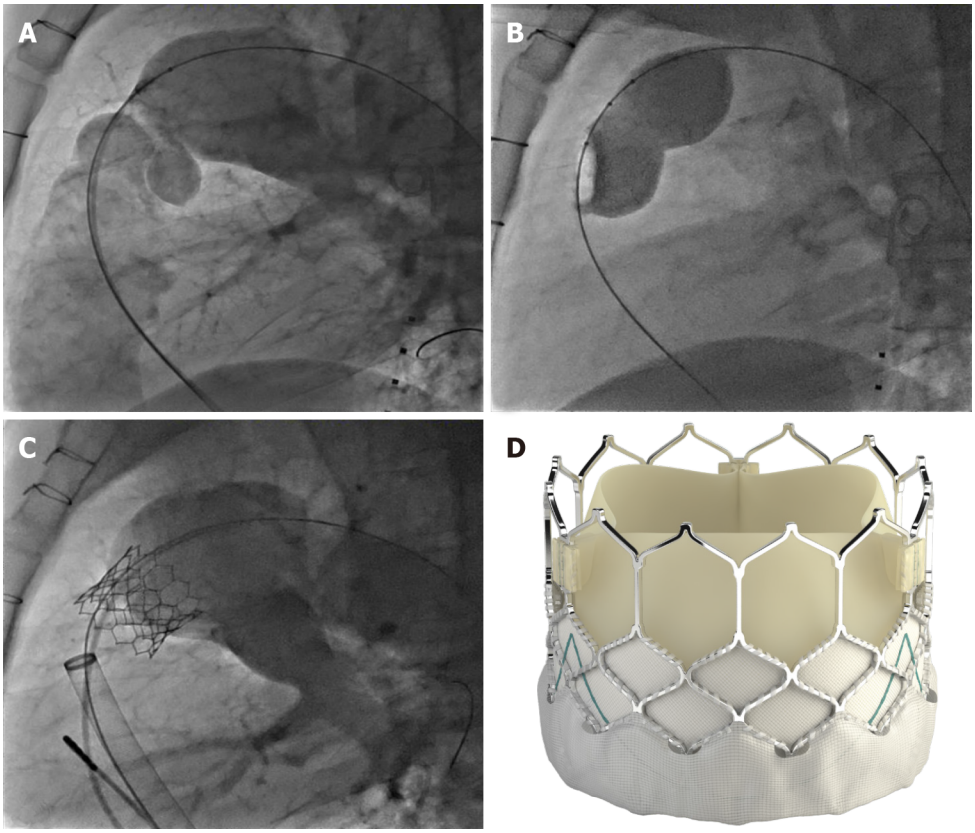

Figure 6 Native transcatheter pulmonary valve implantation. A and B: 46 years old with prior surgical pulmonary valvotomy as a child presenting with severe insufficiency (A), balloon sizing performed with 40 mm Numed sizing balloon demonstrated a narrowed landing zone of 27 mm (B); C: Native implant with a 29 mm Sapien 3™ valve was feasible through a 26 F 65 cm Gore DrySeal sheath; D: Edwards Sapien 3™ valve (reproduced with permission from Edwards Lifesciences LLC, Irvine, CA, United States).

mounted on a cobalt chromium stent with a fabric skirt on the outside lower part of the stent to minimize perivalvular regurgitation. The valve sizes are 23, 26 and 29 mm and delivered *via* the Edwards Novaflex delivery system. The COMPASSION clinical trial enrolled 81 patients and implanted the Sapien XT THV in 69 with a 93.7% freedom from re-intervention at 3 years[6]. There are ongoing clinical trials, for post market approval surveillance of the use of this valve and also for the evaluation of the Edwards Sapien 3 THV (Figure 4). The Sapien 3 expands the valve sizes with a 20 mm option–the Commander valve delivery system is also believed to be better suited for delivery into the RVOT. Data from a series of 56 patients from Germany suggests excellent procedural success and no reinterventions were needed up to 2 years of follow up[29].

Figure 7 Medtronic Harmony transcatheter pulmonic valve (Reproduced with permission from Medtronic, Inc, Minneapolis, MN, United States).

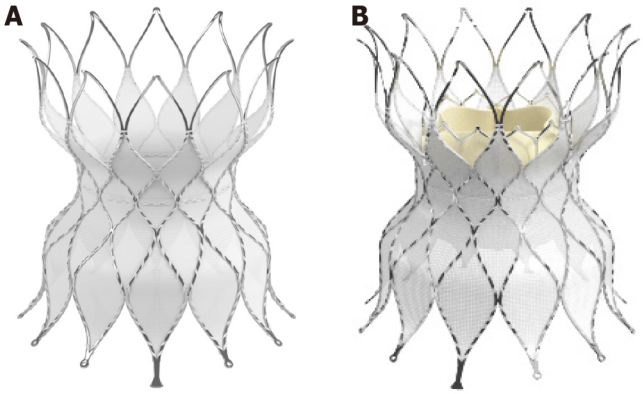

Figure 8 Edwards native outflow tract prestent. A: Alterra Adaptive Prestent™; B: Edwards Sapien 3™ valve implanted inside the Alterra prestent (Reproduced with permission from Edwards Lifesciences LLC, Irvine, CA, United States).

The venus *P* valve (Venus Medtech, Hangzhou, China) is a newer generation valve using porcine pericardium leaflets mounted inside the middle segment of a self-expanding nitinol stent. The middle segment measures 22-36 mm in diameter and 20-35 mm in length. The proximal and distal ends are flared to provide an hourglass shape that helps with anchoring in the RVOT and main pulmonary artery. The delivery system consists of a 19-24F capsule which houses the crimped stent valve and a 15F shaft. This system is designed keeping in mind the unmet need of treating PI in native RVOT which in most circumstances sizes out of approved valve systems' range in adults. Multiple small series report favorable outcomes with the venus *P* valve–in a 38-patient retrospective multi center report, 37 implantations were successful; 1 patient subsequently required surgical repositioning. With a median follow up of 25 mo, no significant valve dysfunction was reported. Stent fractures were reported in 27% patients but the significance of those with this valve system is not yet known[30].

Another valve system with a similar concept is the Pulsta valve (TaeWoong Medical Co, Gyeonggi-do, South Korea). It also has a knitted double strand Nitinol wire frame which is self-expanding with treated porcine pericardial tissue leaflets sutured on. The valve is available in 18-28 mm sizes (2 mm increments). The length of the stent frame is 28-38 mm depending on the valve size and the ends are flared 4 mm wider than the outer diameter for anchoring. The diameter of the "valve loading zone" is 18F while the shaft of the delivery system is 12F in caliber. There is a "hook block" to minimize chances of abrupt delivery and migration. In a Korean feasibility study, ten TOF patients with PR were treated with the Pulsta valve–five with 26 mm and other five with 28 mm valve. There were no major complications with all 10 implants showing good valve function and significant reduction in RV volumes[31].

OUTCOMES OF TPVI

Procedural success and complications

With growing experience, procedural success has improved remarkably–in a prior meta-analysis, we reported a success rate of 96.2% using observational reports, which is consistent with the 98% success rate reported in the Melody United States post market approval surveillance study[28,32]. The most dreaded complications for TPVI are conduit rupture and coronary compression. Conduit rupture is estimated in about 4.1% patients–more so in homografts[32,33]. In recent years, the practice of performing TPVI off label in conduits sized < 16 mm has increased, and the rate of conduit rupture is much more in this population. Varied estimates from 16% to 50% have been reported-however most of these ruptures are limited and can usually be managed with a covered stent implant[34,35].

Coronary compression was reported more frequently in the earlier TPVI experience and led to procedural mortality. In our pooled analysis of 1044 attempted TPVI, there were a total of five coronary complications. There were only two deaths in elective cases, and both were attributed to coronary compression[32]. However, with more experience and careful testing prior to stent/valve implant, these have become extremely rare. In the United States post market approval study, only 1 out of 100 implants had coronary compression was reported which required conversion to surgery. Five other patients out of the originally considered 120 patients had evidence of coronary compression on balloon testing[28]. It should especially be noted that anomalous origin of coronaries especially left coronary artery arising from the right cusp is a strong predictor of coronary compression[36].

Re-interventions

The issue of needing frequent re-interventions or re-operations has largely been deemed secondary to stent fractures of the Melody valve and the rates for same have vastly improved since the adoption of pre-stenting. The United States Investigational Device Exemption trial for example had only 10% pre-stenting in the first tertile of the study and reported a freedom from re-intervention rate of 76% after 5 years. The other factors leading to re-interventions were found to be implant in a homograft, a higher post implant gradient (> 25 mmHg) and pre-existing significant tricuspid regurgitation[27]. Conversely, in a French registry study with 96.9% pre-stenting only 3/62 (4.8%) patients needed re-operation for conduit re-stenosis at a median follow up of 4.6 years[37]. The other common cause for re-operation is endocarditis, which is discussed separately. The issue of re-operation/intervention has not been adequately answered for the Edwards Sapien THV because of smaller number of studies. The COMPASSION trial reported a freedom from re-intervention rate of 93.7% after 3 years with seven re-interventions in four patients[6].

Endocarditis

Endocarditis/blood stream infection has been described as a late complication after TPVI. There have been variable reports of endocarditis after Melody and Sapien valve implants, more for the former. McElhinney *et al*[38] used three patient cohorts in North America and Europe with a cumulative sample of 309 patients and a follow up of 5.1 years–Endocarditis was diagnosed in 46 patients with TPV related endocarditis occurring in 35 patients[38]. Median time to endocarditis was 3.1 years. At 5 years, 89% patients were free of endocarditis. However widely variable reports of endocarditis rates exist-Abdelghani *et al*[39] in their systematic review reported cumulative incidence ranging from 3.2%-25% with the median time from TPVI to onset of endocarditis being 18 mo[39]. 79% of these patients had evidence of RVOT obstruction with vegetations detected in 34% cases. They also did a patient level pooled analysis from 69 case reports, 8.7% patients died and 52% required surgical or transcatheter re-intervention. Less data exists for Edwards Sapien THV–97.1% freedom from endocarditis was reported in the COMPASSION study at 3 years[6]. There are also multiple reports with no endocarditis in the medium term after TPVI with Sapien THV. In a French cohort of 79 patients with a median follow up of 1.8 years, 8/32 Melody valve patients developed endocarditis compared to none for the 47 Sapien XT THV[40].

It is also interesting to note that there are differences in endocarditis rates amongst surgical PVR recipients–rates are much higher in patients receiving bovine jugular vein conduits as compared to homografts–20.4% *vs* 2.4%[41].

Comparison to surgical PVR

Very few head-to-head comparisons of SPVR and TPVI exist. Caughron *et al*[42] reported a study of 66 patients (SPVR 36; TPVI 30) and found no differences in mortality, cardiovascular re-admissions or repeat interventions in the two groups[42]. A recent meta-analysis of 1132 TPVI and 4939 SPVR patients also did not show any difference in mortality or repeat interventions. However, there were fewer procedure related complications and higher rate of endocarditis with TPVI[43]. A study using the Nationwide Inpatient Sample database also suggested the same–comparing an estimated 8449 SPVR and 555 TPVI admissions, it showed a higher in-hospital mortality with SPVR along with other iatrogenic cardiac complications. Also, TPVI predictably had less hospital length of stay decreasing the impact on societal loss of wages for patients/care givers[44].

CONCLUSION

TPVI has dramatically evolved over that past decade and has become a common procedure to manage many patients with dysfunctional RVOT. The short and midterm results are overall quite favorable with a low and acceptable morbidity and mortality. Ideally in the future, smaller and more flexible delivery systems will be developed. With native OTs, intervention becomes quite appealing if a new valve can be placed inside indefinitely thus avoiding surgery except for at the time of initial repair. As all the existing valves have been implanted for a short time with limited follow up, future data is necessary to understand their overall longevity and types of valve failure. Furthermore, as many patients have smaller and stenotic conduits even in a growing child, adoption of new surgical techniques to allow for further expansion of small and stenotic conduits could be of significant clinical benefit.

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ORIGINAL ARTICLE

Case Control Study

Correlation between soluble receptor for advanced glycation end products levels and coronary artery disease in postmenopausal nondiabetic women

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Abstract

BACKGROUND

The established cardiovascular risk factors cannot explain the overall risk of coronary artery disease (CAD), especially in women. Therefore, there is a growing need for the assessment of novel biomarkers to identify women at risk. The receptor for advanced glycation end products (RAGE) and its interaction with the advanced glycation end product (AGE) ligand have been associated with atherogenesis. The soluble fraction of RAGE (sRAGE) antagonizes RAGE signaling and exerts an antiatherogenic effect.

AIM

The study aim was to explore the association between plasma levels of sRAGE and CAD in nondiabetic postmenopausal women.

METHODS

This case-control study included 110 nondiabetic postmenopausal women who were enrolled in two groups. Group I included 55 angiographically proven CAD subjects with > 50% stenosis in at least one of the major coronary arteries and Group II included 55 healthy control women who did not have CAD or had < 50% stenosis of the coronary arteries. Stenosis was confirmed by invasive angiography. Plasma sRAGE was determined by an enzyme-linked immunosorbent assay.

RESULTS

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We observed significantly lower plasma sRAGE concentrations in subjects with CAD *vs* healthy controls ($P < 0.05$). Univariate and multivariate logistic regression analysis also revealed a significant correlation between plasma sRAGE levels and CAD ($P = 0.01$). Multivariate odds ratios for CAD revealed that subjects with sRAGE concentrations below 225 pg/mL (lowest quartile) had a 6-fold increase in CAD prevalence independent of other risk factors.

CONCLUSION

Our findings indicated that low sRAGE levels were independently associated with CAD in nondiabetic postmenopausal women. Risk assessment of CAD in postmenopausal women can be improved by including sRAGE along with other risk factors.

Key Words: Coronary artery disease; Soluble receptor for advanced glycation end products; Postmenopausal status; Nondiabetic females; Correlation; Regression

Core Tip: The growing need for the assessment of novel biomarkers led us to identify the risk in women. The receptor for advanced glycation end products (RAGE) and its interaction with the AGE ligand have been shown to play an important role in promoting atherosclerosis. The soluble fraction of RAGE (sRAGE) binds to ligands and antagonizes RAGE signaling, thereby exerting an antiatherogenic effect. This study established that low levels of sRAGE in plasma are independently associated with the presence of coronary artery disease in nondiabetic postmenopausal females.

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of morbidity and mortality throughout the world. The incidence of CAD is rising rapidly in India, and it is projected that more than 50% of CAD cases in the world will in from India by 2025[1]. Atherosclerosis is the most common cause of CAD. It causes luminal narrowing, which creates an imbalance between supply and demand, thereby impairing the coronary reserve. The etiology of CAD is multifactorial. Traditional risk factors include diabetes, hypertension (HTN), hyperlipidemia, smoking, family history, physical inactivity, obesity, and others. Along with the classical risk factors, oxidative stress and inflammation are now considered as significant risk factors of CAD. Evidence in the literature supports significant positive correlations between various inflammatory mediators including high-sensitivity C-reactive protein (hsCRP), homocysteine, lipoprotein (Lp)-a, matrix metalloproteinases, and tissue inhibitor of matrix metalloproteinase and development of CAD[2]. Postmenopausal status is an important risk factor of CAD, and cardiovascular disease is more common in postmenopausal than in premenopausal women because of decreased endogenous estradiol in that age group[3]. Postmenopausal status is the strongest predictor in women, but it is the least studied factor compared with other traditional risk factors.

Numerous reports in the literature state that CAD occurs in the absence of major risk factors in about one-third of patients in India[4]. Therefore, the overall risk of CAD cannot be explained by traditional and established cardiovascular risk factors[4-6]. The elucidation of novel biomarkers is the need of the hour to identify women at risk. One of the candidate genes that potentially accounts for an inherited predisposition to CAD is receptor for advanced glycation end products (RAGE) together with its soluble circulating form, sRAGE, and an endogenous secretory form

called esRAGE.

RAGE is a transmembrane receptor of the immunoglobulin superfamily, and it is located in the major histocompatibility complex (gene 6 p21.3)[7]. It can interact with various ligands involved in inflammation, atherosclerosis, and vasoconstriction[8] and is highly expressed at the site of vascular pathology[9]. Activation of the RAGE-dependent pathway is followed by many deleterious effects occur like activation of nuclear factor-B, increased cytokines, and induction of oxidative stress[10,11]. Advanced glycation end products (AGEs) are RAGE ligands for RAGE and their interaction results in coronary atherosclerosis[12]. AGE-RAGE interaction and the subsequent effects are also of great importance in diabetic vasculopathy. Recent studies have shown the key role of this signaling pathway in nondiabetic atherosclerosis[13].

sRAGE is produced by the cleavage of membrane-bound RAGE. It consists of the extracellular ligand-binding domain only and lacks both cytoplasmic and transmembrane domains[14]. It circulates abundantly in blood and antagonizes RAGE signaling[15]. There are two schools of thoughts regarding the association of sRAGE and CAD. Some investigators believe that decreased levels of sRAGE increase the risk of CAD; others believe that increased levels of sRAGE increase the risk of CAD. Many experimental and clinical studies have assessed the association and correlation of the plasma levels of sRAGE and CAD, but whether increased or decreased levels of sRAGE are associated with CAD remains controversial. Moreover, very few of those studies were carried out in Indian populations, especially in postmenopausal women. In this study, we aimed to assess the correlation between plasma levels of sRAGE and CAD in postmenopausal women.

MATERIALS AND METHODS

Study design

This case-control prospective observational study was conducted at the Advanced Cardiac Center of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. After screening, we enrolled 110 nondiabetic postmenopausal women and assigned them to two groups. Group I included women with CAD and > 50% stenosis in at least one of the major coronary arteries (n = 55). and Group II included healthy women without CAD and with < 50% stenosis in the coronary arteries. Each study subject underwent coronary angiography following the cardiac center protocol. The indications for angiography were suspicion of CAD or preoperative screening for CAD in subjects with valvular disease. Exclusion criteria were patients with diabetes, premenopausal female, surgery or trauma during the month preceding the study, known cardiomyopathy, known malignant diseases, known febrile conditions, subjects using lipid lowering agents, acute or chronic inflammatory disease, connective tissue disorder, renal insufficiency (creatinine > 1.5 mg/dL), abnormal liver function, patients with heart failure or cardiogenic shock, refusal to give informed consent and patient with any neoplasm. Subjects having a concentration of hsCRP > 10 mg/L, a level considered to be indicative of clinically relevant inflammatory conditions, were also excluded from the study[16].

Ethical approval and informed consent: The study was conducted following the ethical standards detailed in the Declaration of Helsinki[17] and was approved by the Institute ethical committee. Informed consent was obtained from all the patients after explaining the protocol prior to their enrolment in the study.

Clinical examination and parameters

All participants underwent a standard clinical examination. All cardioactive drugs used by the patients were registered, with particular regard to beta-blockers, calcium-antagonists, ACE inhibitors, antiplatelet drugs, statins, and nitrates. Clinical characteristics including height, weight, smoking status, blood pressure (BP), waist circumference, family history of CAD, and body mass index (BMI, kg/m^2) were documented. According to the Asian classification, a BMI of < 18.5 kg/m^2 is underweight, 18.5-22.99 kg/m^2 is normal, 23.0-27.49 kg/m^2 is overweight and > 27.5 kg/m^2 is obese[18]. A waist circumference cutoff of 80 cm as applied for women[19]. Cigarette smoking was dichotomized into ever *vs* never, with ever smoking defined as having smoked daily for 1 year or more. Many patients had quit after the onset of CAD, hence the designation as ever smoking rather than current and former. HTN was defined as a systolic BP of > 140 and/or a diastolic BP of > 90 and/or on treatment with antihyper-

tensives, following the eighth Joint National Committee guidelines[20]. American Diabetes Association guidelines, diabetes was taken as either fasting blood sugar (FBS) > 126 mg/dL, 2 h postprandial glucose > 200 mg/dL, glycosylated hemoglobin (HbA1c) > 6.5% or Rutherford backscattering spectroscopy > 200 mg/dL, with symptoms of hyperglycemia in an oral glucose tolerance test[21]. The study protocol excluded subjects with diabetes.

Laboratory methods

All laboratory determinations were performed in a blinded fashion. Before angiography, A 14 mL blood sample was collected from antecubital vein after an overnight fast, and 10 mL were immediately sent to different laboratories in PGIMER for testing as described below. The remaining 4 mL was collected in ethylenediaminetetraacetic acid vials and was centrifuged at 1000 *g* for 30 min for collection of plasma and immediately divided into aliquots. Plasma was stored at −80°C until performing the Lp(a) and sRAGE assays.

Lipid profile: All components of the lipid profile were measured in an autoanalyzer. Subjects were classified as dyslipidemic if they had levels of low-density lipoprotein cholesterol (LDL-C) > 100 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 50 mg/dL, triglycerides > 150 mg/dL or total cholesterol > 200 mg/dL[22].

Blood sugar: Plasma FBS and postprandial blood sugar (PPBS) were estimated by the glucose oxidase method. HbA1c was estimated by high-performance liquid chromatography.

hsCRP: hsCRP levels were estimated in samples of plasma containing suspensions of latex particles coated with monoclonal/polyclonal antibodies to human CRP. The plane polarized light passing through the solution was scattered in a manner proportional to the CRP concentration. The intensity of the scattered light was measured against a standard curve prepared using known concentrations of the CRP antigen.

Plasma homocysteine: Plasma homocysteine levels were determined in heparinized blood samples with an enzyme cycling assay.

Renal function tests: For renal function tests, urea levels were measured by Fearon reaction and creatinine levels were measured by Jaffe's alkaline picrate method in an autoanalyzer.

Lp(a): Lp(a) levels were estimated using a commercially available enzyme-linked immunosorbent assay kit (Assay Max Human Lp(a), Assaypro Catalog no: EL3001-1). This assay employed a quantitative sandwich enzyme immunoassay technique that measured human Lp(a) in less than 4 h. The normal Lp(a) value with this kit was 60-180 µg/mL.

sRAGE: Plasma sRAGE levels were determined using a commercially available enzyme-linked immunosorbent assay kit (BioVendor, Catalog No: RD191116200R) following the manufacturer's protocol. Briefly, a monoclonal antibody against sRAGE was used to capture sRAGE from plasma. Captured sRAGE was detected with a polyclonal anti-human sRAGE antibody. After washing, plates incubated with streptavidin-horseradish peroxidase, were developed with the appropriate substrate, and the OD_{450} was determined using an enzyme-linked immunosorbent assay plate reader. Measurements were performed in duplicate and the results were averaged and reported as pg/mL.

Coronary angiography

Coronary angiography was carried out in all the patients using a standard protocol. The catheter was inserted through femoral or radial artery and moved up to the coronary arteries. Radiocontrast was injected into the coronary arteries under X-ray guidance in order to display the coronary anatomy and possible luminal obstruction. Existing significant CAD was defined as stenosis in the major epicardial coronary arteries that reduced the lumen diameter by 50%.

Statistical analysis

The sample size of 55 in each group had a power of more than 90% and confidence intervals (CI) of 95%. The statistical analysis was carried out using the Statistical Package for Social Sciences version 20 (IBM Corp.) All quantitative variables were estimated using measures of central location (mean) and measures of dispersion

(standard deviation). Normality of data was checked by measures of skewness and Kolmogorov–Smirnov tests of normality. Normally distributed data in groups was expressed as means ± SD. For normally distributed data, differences of the case and control mean values were compared using Student's *t*-tests. Qualitative or categorical variables like smoking history, HTN, and family history of CAD were reported as frequencies and percentages. Frequencies were compared using χ^2 or Fisher's exact tests, whichever was applicable. Pearson's correlation was used to find the associations of variables like serum triglycerides, HDL-C, LDL-C, total cholesterol, Lp(a), and sRAGE. The CAD patients and controls were categorized in quartiles of the plasma sRAGE concentration in the entire study cohort. The interquartile cutoffs of sRAGE concentration were categorized into four categories: I < 225 pg/mL, II = ³225 to < 397.5 pg/mL, III = ³397.5 to < 730 pg/mL, and IV ³730 pg/mL. To evaluate the risk associated with decreasing levels of sRAGE, odds ratio (ORs) for each quartile in the entire study cohort relative to the fourth quartile were calculated. To determine independent predictors of CAD, univariate and multivariate logistic regression were performed for categorical variables like age, HTN, and family history of CAD, and for continuous variables like waist circumference, total cholesterol, triglycerides, LDL-C, HDL-C, Lp(a), hsCRP, and sRAGE. Lastly, Pearson's correlation was used to find any correlation between sRAGE levels and other biochemical parameters. All baseline variables related to CAD with $P < 0.01$ and $P < 0.05$ in simple logistic regression analysis were included in the multivariate model. Crude and multivariate adjusted ORs were reported with their 95%CIs. Values were considered statistically significant at the $P < 0.01$ and $P < 0.05$ levels.

RESULTS

Subject characteristics

The clinical and biochemical characteristics of the study subjects (Group I: Cases; Group II: Controls) are shown in Table 1. All the participants were postmenopausal women and with a similar socioeconomic status. All were never-smokers, 30 patients and 24 control subjects had HTN, and 26 patients and 14 control subjects had family histories of CAD. Student's *t*-tests found no significant differences in age, BMI, waist circumference, lipid profile, FBS, PPBS, HbA1c, creatinine, hsCRP, homocysteine, Lp(a), and sRAGE. Chi-square tests found no significant differences in HTN or family history of CAD. No significant differences in age, BMI, waist circumference, HTN, low physical activity, total cholesterol, LDL-C, HDL-C, sugar profile (FBS/ PPBS/ HbA1c), creatinine, and Lp(a) ($P > 0.05$) were observed among the study groups. Study subjects in Group I had significantly higher levels of triglycerides (TG), hsCRP, and homocysteine along with a significant factor, *i.e.* family history of CAD, than those in Group II ($P < 0.05$). However, sRAGE levels were significantly lower in Group I (subjects with CAD) compared with Group II (subjects without CAD, $P < 0.05$).

Logistic regression

Univariate logistic regression analysis: To evaluate the significance of each factor in Table 1, univariate logistic regression analysis was performed. We observed significant differences in family history of CAD, serum cholesterol, LDL-C, homocysteine, Lp(a), hsCRP, and plasma sRAGE levels in the two groups. The results are shown in Table 2.

Multivariate logistic regression analysis: After controlling for family history of CAD, serum cholesterol, LDL-C, homocysteine, Lp(a), hsCRP and plasma sRAGE, multivariate logistic regression analysis revealed significant differences in the two groups, thus indicating them as independent predictor of CAD ($P < 0.05$). However, no significant differences in association w observed with other parameters such as HTN, HDL-C and triglycerides. The results are shown in Table 3.

Quartiles of sRAGE and CAD

The plasma sRAGE concentration [mean: 474.89 (range: 30-4350) pg/mL] was significantly lower ($P < 0.02$) in CAD cases (Group I) compared with control subjects (Group II) [mean: 725.73 (range: 90-4800) pg/mL]. The study subjects were further categorized in quartiles of sRAGE concentration, which were found to be significantly different in the multivariate analysis. The interquartile sRAGE concentration cutoffs were Category I: < 225; Category II: ≥ 225 to < 397.5; Category III: ≥ 397.5 to < 730 and Category IV: ≥ 730. The numbers and percentages of subjects in each quartile of plasma sRAGE concentration, are shown in Table 4 and Figure 1. The number of CAD

Table 1 Baseline characteristics of the study subjects

Variable	Group I (*n* = 55)	Group II (*n* = 55)	*P* value
Age (yr)	57.58 ± 7.75	56.29 ± 7.69	0.38
BMI (kg/m²)	25.41 ± 3.05	24.81 ± 3.79	0.35
WC (cm)	83.02 ± 5.17	81.42 ± 6.11	0.14
Serum CHOL (mg/dL)	175.33 ± 40.68	180.12 ± 37.12	0.52
Serum TG (mg/dL)	175.16 ± 48.67	150.09 ± 42.67	0.05
Serum HDL-C (mg/dL)	38.57 ± 6.89	40.59 ± 8.17	0.16
Serum LDL-C (mg/dL)	123.68 ± 27.73	113.17 ± 31.58	0.06
FBS (mg/dL)	92.89 ± 8.81	95.71 ± 10.14	0.12
PPBS (mg/dL)	133.33 ± 5.53	133.15 ± 3.76	0.84
HbA1c (%)	5.24 ± 0.19	5.28 ± 0.14	0.14
Serum creatinine (mg/dL)	0.79 ± 0.16	0.85 ± 0.23	0.09
Serum hsCRP (μg/mL)	5.26 ± 1.94	1.41 ± 0.44	0.00[b]
Plasma HC (μmol/L)	18.13 ± 5.39	12.83 ± 3.99	0.00[b]
Lp(a) (μg/mL)	294.36 ± 202.22	251.22 ± 221.42	0.28
sRAGE (pg/mL)	285 (30-2490)	540 (90-3450)	0.02[a]
Category 1 (< 225)	24	4	0.00[b]
Category 2 (≥ 225-< 397.5)	8	19	0.01[a]
Category 3 (≥ 397.5-< 730)	13	15	0.66
Category 4 (≥ 730)	10	17	0.12
Hypertension	30	24	0.25
Family history	26	14	0.01[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
Data are means ± SD, median (interquartile range), or frequency counts, as appropriate. BMI: Body Mass Index; CHOL: Cholesterol; FBS: Fasting blood sugar; HbA1c: Glycosylated hemoglobin; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitivity C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein (a); PPBS: Post prandial blood sugar; sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides; WC: Waist circumference.

cases was 6-fold higher in the first quartile (plasma sRAGE < 225 pg/mL), than in the control subjects ($P = 0.00$). In the second (sRAGE ≥ 225-< 397.5), third (sRAGE ≥ 397.5-< 730) and fourth (sRAGE ≥ 730) quartiles, the number of control subjects was 2.38 ($P = 0.01$), 1.15 ($P = 0.66$), and 1.7-fold higher ($P = 0.12$), respectively than the number of CAD patients.

Univariate and multivariate ORs

To evaluate the risk associated with decreasing levels of sRAGE, ORs for each quartile in all of the study groups relative to fourth quartile was calculated. As shown in Tables 5 and 6, the ORs of CAD was significantly higher in the first quartile of sRAGE level compared with the fourth quartile ($P = 0.001$), but no significant differences were observed between second and fourth and third and fourth quartiles.

Pearson's correlation

Pearson's correlation was used to evaluate the significance of the relationships between sRAGE levels and other biochemical parameters. We found no significant correlations between sRAGE levels and total cholesterol, triglycerides, HDL-C, LDL-C, hsCRP, homocysteine, or Lp(a) levels (Table 7).

Table 2 Univariate logistic regression analysis

Parameter	SE	*P* value	OR	95%CI for OR	
				Lower	Upper
Age (yr)	0.038	0.374	1.034	0.960	1.115
HTN	0.598	0.742	0.821	0.254	2.651
BMI (kg/m²)	0.202	0.354	1.206	0.812	1.791
WC (cm)	0.126	0.152	0.835	0.653	1.069
FH CAD	0.668	0.011[a]	0.184	0.050	0.680
S. CHOL (mg/dl)	0.017	0.001[b]	1.060	1.025	1.096
S.LDL-C (mg/dl)	0.024	0.008[b]	0.938	0.895	0.983
S.HDL-C (mg/dl)	0.041	0.963	1.002	0.924	1.087
S.TG (mg/dl)	0.008	0.350	0.993	0.978	1.008
HC (μmol/L)	0.079	0.00[b]	0.725	0.621	0.847
Lp(a) (μg/mL)	0.002	0.041[a]	0.996	0.993	0.999
sRAGE (pg/mL)	0.001	0.010[a]	1.002	1.001	1.003
hsCRP (μg/mL)	1.037	0.00[b]	0.023	1.001	0.178

[a]$P < 0.05$.
[b]$P < 0.01$.
BMI: Body mass index; CAD: Coronary artery disease; CHOL: Cholesterol; CI: Confidence interval; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitive C-reactive protein. HTN: Hypertension; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); OR: Odds ratio; SE: Standard error; sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides; WC: Waist circumference.

Table 3 Multivariate logistic regression analysis

Parameter	SE	*P* value	OR	95%CI for OR	
				Lower	Upper
FH CAD	0.639	0.014[a]	4.827	1.379	16.904
S. CHOL (mg/dL)	0.017	0.002[b]	1.055	1.020	1.091
LDL-C (mg/dL)	0.024	0.011[a]	0.941	0.898	0.986
HC (mg/dL)	0.074	0.00[b]	0.734	0.635	0.848
sRAGE (pg/mL)	0.001	0.011[a]	1.001	1.0001	1.003
Lp(a) (μg/mL)	0.001	0.052	0.997	0.994	1.000
HTN	0.571	0.755	1.195	0.390	3.662
HDL-C (mg/dL)	0.040	0.853	0.993	0.918	1.073
TG (mg/dL)	0.008	0.265	0.991	0.976	1.007
hsCRP (μg/mL)	1.037	0.00[b]	0.023	0.003	0.178

[a]$P < 0.05$.
[b]$P < 0.01$.
CAD: Coronary artery disease; CHOL: Cholesterol; CI: Confidence interval; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitive C-reactive protein; HTN: Hypertension; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); OR: Odds ratio; SE: Standard error; sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides.

DISCUSSION

CAD is a major cause of morbidity and mortality worldwide, and a large proportion of the cases of CAD occur in India. CAD mortality is declining in developed nations, but it is increasing in developing countries. In India, CAD prevalence has increased 4-fold over past two decades[23], and postmenopausal women are major contributors.

Table 4 Quartiles of soluble receptor for advanced glycation end products

Frequency distribution of CAD and control in sRAGE quartile categories					
sRAGE (pg/mL)		Group		Total	*P* value
		Case	Control		
< 225	*n*	24	4	28	19.16/0.00[b]
	%	43.6	7.3	25.5	
≥ 225-< 397.5	*n*	8	19	27	5.9/0.01[a]
	%	14.5	34.5	24.5	
≥ 397.5-< 730	*n*	13	15	28	0.19/0.66
	%	23.6	27.3	25.5	
≥ 730	*n*	10	17	27	2.4/0.12
	%	18.2	30.9	24.5	
Total	*n*	55	55	110	
	%	100.0	100.0	100.0	

[a]$P < 0.05$.
[b]$P < 0.01$ (χ^2 test).
CAD: Coronary artery disease; sRAGE: Soluble receptor for advanced glycation end products.

Table 5 Univariate odd ratios for prevalence of coronary artery disease in each category of soluble receptor for advanced glycation end products relative to category 4

Category	*P* value	OR	95%CI	
			Lower	Upper
Category 1 *vs* 4	0.001	0.098	0.026	0.365
Category 2 *vs* 4	0.564	1.397	0.448	4.355
Category 3 *vs* 4	0.481	0.679	0.231	1.994

CI: Confidence interval; OR: Odds ratio.

Table 6 Multivariate odd ratios for prevalence of coronary artery disease in each category of soluble receptor for advanced glycation end products relative to category 4

Category	*P* value	OR	95%CI	
			Lower	Upper
Category 1 *vs* 4	0.001	0.065	0.014	0.308
Category 2 *vs* 4	0.533	1.555	0.387	6.243
Category 3 *vs* 4	0.096	0.325	0.087	1.221

CI: Confidence interval; OR: Odds ratio.

Traditional risk factors like diabetes, HTN, hyperlipidemia and others cannot fully explain the occurrence of CAD in this population. Many studies have been done worldwide to find a correlation between emerging inflammatory risk factors like sRAGE and CAD. Such studies are lacking in India, especially in postmenopausal women. Postmenopausal women are more prone to CAD than premenopausal women because of decreased levels of protective estrogen[24]. Therefore, this study was undertaken in postmenopausal females to understand whether sRAGE, an emerging inflammatory risk factor, was independently correlated with CAD in postmenopausal women. To the best of our knowledge, our study is the first to demonstrate a

Table 7 Pearson's correlation

Parameter	CHOL	LDL-C	HDL-C	TG	hsCRP	HC	sRAGE	Lp (a)
CHOL	1	0.865[b]	−0.616[b]	0.491[b]	0.052	0.090	−0.179	0.227
LDL−C	0.865[b]	1	−0.606[b]	0.646[b]	0.082	0.094	−0.197	0.205
HDL−C	−0.616[b]	−0.606[b]	1	−0.529[b]	−0.157	−0.164	0.245	−0.169
TG	0.491[b]	0.646[b]	−0.529[b]	1	−0.182	−0.002	−0.127	0.174
hsCRP	0.052	0.082	−0.157	−0.182	1	0.761[b]	0.011	−0.235
HC	0.090	0.094	−0.164	−0.002	0.761[b]	1	0.067	−0.226
sRAGE	−0.179	−0.197	0.245	−0.127	0.011	0.067	1	0.158
Lp(a)	0.227	0.205	−0.169	0.174	−0.235	−0.226	0.158	1

[a]$P < 0.05$.
[b]$P < 0.01$.
CHOL: Cholesterol; HC: Homocysteine; HDL-C: High-density lipoprotein cholesterol; hsCRP: High-sensitive C-reactive protein; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein (a); sRAGE: Soluble receptor for advanced glycation end products; TG: Triglycerides.

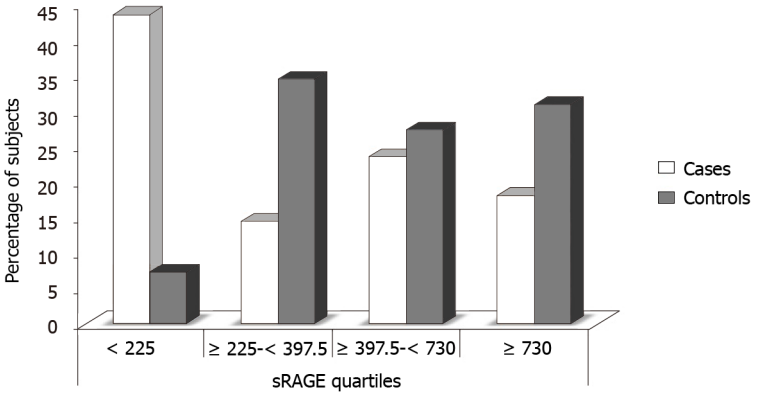

Figure 1 Plasma concentrations (pg/mL) of soluble receptor for advanced glycation end products. Group I included coronary artery disease cases and Group II included healthy controls. sRAGE: Soluble receptor for advanced glycation end products.

correlation between plasma sRAGE levels and CAD in nondiabetic postmenopausal women.

Amino groups of proteins bind non-enzymatically to carbonyl groups of reducing sugars to form glycated proteins known as AGEs. The altered proteins lose their normal functions. AGEs increase with ageing, but production is markedly accelerated in diabetes and with oxidative stress[26]. AGEs are associated with atherosclerosis in both diabetic and nondiabetic subjects and increases in the concentration of circulating AGEs are associated with the severity of CAD and adverse clinical outcomes[27]. In addition to extracellular interactions, some AGEs are as specific ligands RAGE, which is a membrane-bound receptor. It is a transmembrane receptor of the immunoglobulin superfamily and is expressed in endothelial, neuronal, smooth muscles, mesangial and mononuclear cells[7]. Bucciarelli *et al*[13] and Kislinger *et al*[28] demonstrated that even in the absence of diabetes, the ligand-RAGE axis plays an important role in vascular pathology and the development of atherosclerosis[28]. Again plaque instability and rupture occur when there is over-expression of RAGE and plaque stabilization can be achieved by blocking RAGE[29]. EsRAGE and sRAGE are soluble forms of RAGE that are abundantly present in the circulation. EsRAGE is produced by alternative splicing of the gene for RAGE and sRAGE is produced by cleavage of membrane-bound RAGE[15]. They competitively inhibit the ligand-RAGE interaction and subsequent downstream signaling. sRAGE also serves as a scavenger receptor for circulating AGEs and other RAGE ligands[29]. Park *et al*[30] and Bucciarelli *et al*[13] infused sRAGE in a mouse model and demonstrated that it retarded the development of atherosclerosis[30]. To date, few studies have been performed to evaluate the role of sRAGE in human atherosclerosis. In a pioneer study, Falcone *et al*[31] first demon-

strated an inverse association between levels of sRAGE and atherosclerosis in humans. In their case-control study, involving nondiabetic Italian men, plasma sRAGE levels were lower in subjects with CAD than in subjects without CAD. In addition, Kucukhuseyin *et al*[32] demonstrated that the sRAGE concentration was significantly associated with the presence and severity of CAD in nondiabetic Japanese subjects[32]. All those studies found an inverse association of sRAGE level and CAD. In this study, we investigated the correlation between sRAGE and CAD in postmenopausal nondiabetic Indian women. The study results are consistent with the earlier observations that decreased levels of sRAGE were significantly and independently associated with CAD.

The study included 110 nondiabetic postmenopausal women, 55 of whom had angiographically proven CAD (Group I) and 55 control subjects (Group II) who were proven by invasive angiography not to have CAD. Blood samples were collected and processed as described in the materials and methods and the results were systematically analyzed. Student *t*-tests and χ^2 tests were performed for continuous variables and categorical variables respectively. When compared with subjects without CAD, those with proven CAD had a significantly higher serum TG, hsCRP, and homocysteine levels and a significant family history of CAD. However, the opposite was found to be true for plasma sRAGE levels, which were found to be significantly lower in subjects with CAD compared with those without CAD ($P < 0.05$). Univariate and multivariate logistic regression analysis also revealed a significant correlation between plasma sRAGE levels and CAD ($P = 0.01$). Multivariate ORs for CAD revealed that the study subjects with sRAGE concentrations below 225 pg/mL had a 6-fold increase in CAD prevalence, independent of other risk factors. That finding is consistent with a study carried out by Falcone *et al*[31] that evaluated the correlation between sRAGE levels and CAD in Italian men, and found that low sRAGE levels (< 776 pg/mL, the first quartile) were associated with a 6.719-fold increase in CAD prevalence, independent of the other risk factors[16]. Similar results were obtained by Mahajan *et al*[2], who reported in 2009, that subjects with low sRAGE levels (< 607 pg/mL, the first quartile) were associated with a 13.6-fold increase in CAD prevalence, independent of other risk factors[2].

Pearson's correlation failed to find any significant correlations between sRAGE levels and other biochemical parameters like total cholesterol, triglycerides, HDL-C, LDL-C, hsCRP, homocysteine, or Lp(a) levels. That finding is in contrast to a report by Basta *et al*[33], who demonstrated a positive correlation between sRAGE and HDL levels in an Italian population[33]. Our finding that no correlation existed between sRAGE levels and HTN contradicts a study by Geroldi *et al*[34] finding that hypertensive subjects had lower levels of sRAGE compared with normotensive CAD subjects[34]. The cause for this discrepancy is not clear, but it could be explained by differences in the ethnicity and sex of the two studies. Our subjects were all postmenopausal Indian women. We also found that sRAGE levels were lower in women. A 2005 study in nondiabetic Italian men by Falcone *et al*[31] reported mean sRAGE levels of 966 pg/mL in cases and 1335 pg/mL in controls[16]. In our study population the means were 474.89 in cases and 725.73 pg/mL in controls. The observed differences could have resulted from different study populations and small sample size in our study.

In our study, we found a significant correlation between CAD and some biochemical parameters. Univariate and multivariate analysis revealed a significant correlation between hsCRP and CAD. ($P = 0.00$) Our finding is consistent with Mahajan *et al*[2] and Haidari *et al*[35], who reported a positive correlation between increased sRAGE level and severity of CAD. Pearson's correlation analysis found a strong positive correlation between hsCRP and homocysteine levels ($r = 0.76$, $P = 0.00$), which supports the observations of Liu and Ding[36], who also observed a positive correlation between serum homocysteine and hsCRP levels in CAD subjects. In our study, homocysteine emerged as an independent risk factor of CAD ($P = 0.00$), which supports the data of Schaffer *et al*[37] who also found a strong positive correlation between CAD and homocysteine levels[37].

Multivariate analysis revealed that a family history of CAD was an independent risk factor of CAD ($P = 0.014$). Our findings support Bachmann *et al*[38] reported in 2012 that a family history of CAD was associated with a persistent increase in CAD and related mortality across a long-term follow-up[38]. Our study also revealed a significant positive correlations of CAD and total cholesterol ($P = 0.002$) and CAD and LDL-C levels ($P = 0.011$) It is clear that high hsCRP, homocysteine, Lp(a) levels and decreased sRAGE levels, when considered together, are the best predictor of development and progression of CAD.

Our study has some limitations. First, the study population included only women from northern India. The results might not be obtained in other ethnic groups. Second, we determined only total sRAGE levels and not individual isoforms of sRAGE. Thus, it is possible that the observed reduction in sRAGE levels may reflect a reduction in a distinct circulating sRAGE isoform. Third, follow-up of the study subjects were not done. Therefore, the effects of drugs on the variables under consideration are not known. Last but not the least, the study sample size was small and might thus have been underpowered. Therefore, further studies in a larger number of subjects with CAD are warranted.

CONCLUSION

In conclusion, CAD in postmenopausal women cannot be fully explained by traditional risk factors. RAGE and its ligand, sRAGE play an important role in the development of atherosclerosis and CAD. Despite the limitations mentioned above, ours is the first study that included only postmenopausal nondiabetic women to demonstrate the correlation of decreased level of sRAGE with CAD. Our findings corroborate existing evidence that the pathogenesis of CAD involves many aspects of inflammation. Risk assessment for CAD in postmenopausal women can be further improved by considering sRAGE with other risk factors. Further studies in a large number of postmenopausal nondiabetic women from different geographical areas are needed to show that its correlation with the development of CAD is applicable to other ethnic groups.

ARTICLE HIGHLIGHTS

Research background

The overall risk assessment for coronary artery disease (CAD) in postmenopausal women cannot rely on traditional risk factors. Thus, assessment of novel markers is needed. Receptor for advanced glycation end products (RAGE) interaction is of great importance in diabetic vasculopathy and plays a key role in atherosclerosis.

Research motivation

The motivation was to add to what is known of the role of soluble fraction of RAGE (sRAGE**)** in Indian postmenopausal women.

Research objectives

The objective was to investigate the association and correlation between plasma levels of sRAGE and CAD in nondiabetic postmenopausal women.

Research methods

This case-control study included 55 angiographically proven CAD subjects with > 50% stenosis of at least one of the major coronary arteries and 55 healthy control women. Plasma sRAGE was determined with an enzyme-linked immunosorbent assay.

Research results

Plasma sRAGE concentrations were significantly lower in subjects with CAD than it was in healthy controls. A significant correlation between plasma sRAGE levels and CAD was observed using univariate and multivariate analysis.

Research conclusions

sRAGE was positively correlated with CAD independent of other traditional risk factors.

Research perspectives

sRAGE can be included in the assessment of CAD-risk in postmenopausal women.

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SYSTEMATIC REVIEWS

Efficacy and safety of distal radial approach for cardiac catheterization: A systematic review and meta-analysis

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Abstract

BACKGROUND

The traditional radial approach (RA) is recommended as the standard method for coronary angiography (CAG), while a distal RA (DRA) has been recently used for CAG.

AIM

To assess the efficacy and safety of the DRA *vs* RA during CAG.

METHODS

The following databases were searched through December 2020: MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, the World Health Organization International Clinical Trials Platform Search Portal, and Clinical-Trials.gov. Individual randomized-controlled trials for adult patients undergoing cardiac catheterization were included. The primary outcomes were the successful cannulation rate and the incidence of radial artery spasm (RAS) and radial artery occlusion (RAO). Study selection, data abstraction and quality assessment were independently performed using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

RESULTS

Three randomized control trials and 13 registered trials were identified. The two approaches showed similar successful cannulation rates [risk ratio (RR) 0.90, 95% confidence interval (CI): 0.72-1.13]. The DRA did not decrease RAS (RR 0.43, 95%CI: 0.08-2.49) and RAO (RR 0.48, 95%CI: 0.18-1.29). Patients with the DRA had a shorter hemostasis time in comparison to those with the RA (mean difference -

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6.64, 95%CI: -10.37 to -2.90). The evidence of certainty was low.

CONCLUSION
For CAG, the DRA would be safer than the RA with comparable cannulation rates. Given the limited data, additional research, including studies with standard protocols, is necessary.

Key Words: Radial artery; Cardiac catheterization; Coronary angiography; Snuff box; Systematic review; Meta-analysis

Core Tip: No consensus is available in the literature about which technique for coronary angiography—distal radial approach (DRA) or radial approach (RA)—is more beneficial to patients. This is the first systematic review and meta-analysis to compare clinical data on the DRA and RA. We investigated the successful cannulation rate, the incidence of radial artery spasm and radial artery occlusion, the mean number of punctures, and the mean time for hemostasis with the two approaches. The present study indicated the DRA to be safer than the RA, with comparable procedure rates. Further research, including studies with standard protocols, is required to establish clinical practice using the DRA.

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INTRODUCTION

Coronary angiography (CAG) is an invasive but essential part of the diagnosis and treatment for coronary artery disease (CAD). Annually, it is estimated that 1016000 inpatient diagnostic CAG and 480000 inpatient percutaneous coronary intervention (PCI) procedures are performed in the United States[1]. In European countries, it is estimated that 4500 diagnostic coronary angiograms per million people and 2000 PCI procedures per million people are performed each year[2]. Interventional cardiologists gain access *via* a peripheral artery, and the latest guidelines from the European Society of Cardiology, National Institute for Health and Care Excellence, and American College of Cardiology/American Heart Association recommended the radial approach (RA) over the transfemoral, transbrachial, and transulnar approaches, because it is associated with a reduced risk of cardiac death, all-cause mortality, bleeding, and access site complications[3-5].

The distal RA (DRA) was recently introduced, as this approach may have some potential advantages in comparison to the RA[6,7]. Previous observational studies showed that the two approaches were associated with similar successful cannulation rates[8], while the rates of vascular complications in the DRA, including radial artery occlusion (RAO) and radial artery spasm (RAS), were less frequent than the RA[9-16]. The DRA is assumed to be an alternative approach to the RA, but the efficacy of the two approaches has never been systematically reviewed and analyzed.

Therefore, the present study aimed to evaluate the efficacy and safety of the DRA in comparison to the RA. To achieve this aim, a systematic review and meta-analysis of only randomized-controlled trials (RCTs) were conducted to produce high-quality evidence that would inform clinical practice decisions for guidance of the cardiac catheterization procedures concerning these two approaches.

MATERIALS AND METHODS

Literature search

Our review protocol was registered in protocol.io (dx.doi.org/10.17504/protocols.io.bramm^{2}c6). Our study was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement[17].

Individual RCTs were included to evaluate the efficacy and safety of the RA *vs* DRA for cardiac catheterization. All papers, including published and unpublished articles, abstracts of conferences, and letters, were included, regardless of language, country restrictions, or publication year. Non-RCTs were excluded. The inclusion criteria were adult patients (≥ 18 years of age) undergoing diagnostic CAG and PCI for CAD. Patients for whom a > 7-Fr sheath was used were excluded (available on a commercial basis)[18]. The DRA is a method of puncturing distal radial arteries at the proximal part of the anatomical snuffbox or the first intermetacarpal space. After successful artery puncture, a guidewire is smoothly passed through the needle and used to guide the sheath through the artery. After introduction of the sheath, interventional cardiologists perform diagnostic CA and PCI with the coronary catheters through the sheath[19]. The RA is a method of puncturing radial artery at the forearm, a few centimeters above the wrist joint[20]. The primary outcomes were the successful cannulation rate and the incidence of RAS and RAO. The successful cannulation rate was defined as completion of the procedure without cross-over to another access site or as defined by practitioners. RAS was diagnosed by angiographic evaluation of the radial artery. RAO was diagnosed based on the absence of flow on color Doppler ultrasound. The secondary outcomes were the mean number of punctures per patient and the mean time for hemostasis. The success of hemostasis was defined as no bleeding or hematoma formation after release. The total time was defined as the time from when the sheath was removed to when successful hemostasis was confirmed. All outcomes included the definitions of the authors of original studies.

The following databases were searched through December 2020: MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE (Supplementary material, Appendix 1). The World Health Organization International Clinical Trials Platform Search Portal and ClinicalTrials.gov databases were also searched for ongoing or unpublished trials (Supplementary material, Appendix 2). The original authors were asked for unpublished or additional data if necessary. The reference lists of studies, including international guidelines published by the European Society of Cardiology, National Institute for Health and Care Excellence, and American College of Cardiology/American Heart Association[3-5], as well as the reference lists of eligible studies and articles citing eligible studies, were checked.

Study selection

Two independent reviewers (Izumida T and Yoshida R) screened the titles and abstracts, then assessed the eligibility based on the full text. We contacted the original authors when relevant data were missing. Disagreements between the two reviewers were resolved by discussion, and when this failed, a third reviewer acted as an arbiter (Watanabe J).

Data extraction

Two reviewers (Izumida T and Yoshida R) performed independent data extraction of the included studies using a standardized data collection form. The form included information on the study design, study population, interventions, and outcomes. Any disagreements were resolved by discussion, and when this failed, a third reviewer acted as an arbiter (Watanabe J).

Risk of bias

Two reviewers (Izumida T and Yoshida R) evaluated the risk of bias independently using the Risk of Bias 2[21]. Disagreements between the two reviewers were resolved by discussion, and when this failed, a third reviewer acted as an arbiter (Watanabe J).

Statistical analysis

We pooled the relative risk ratios (RRs) and 95% confidence intervals (CIs) for the following binary variables: Cannulation success, RAS, and RAO. We pooled the mean differences and the 95%CIs for the following continuous variables: Mean time for hemostasis. An intention-to-treat analysis was performed for all dichotomous data (to the extent that was possible). For continuous data, missing data were not imputed based on the recommendation of the Cochrane handbook[22]. A meta-analysis was

performed using the available data in the original study. The Review Manager software program (RevMan 5.4.1) was used to perform the meta-analysis. A random-effects model was used. The statistical heterogeneity was evaluated by a visual inspection of forest plots and calculation of the I^2 statistic (I^2 values of 0%-40%: Might not be important; 30%-60%: May represent moderate heterogeneity; 50%-90%: May represent substantial heterogeneity; 75%-100%: May represent considerable heterogeneity)[22]. When there was substantial heterogeneity (I^2 > 50%), the reason for heterogeneity was assessed. The Cochrane chi-squared test (Q-test) was performed for the I^2 statistic, and P values of < 0.10 were considered statistically significant. A funnel plot was not created and the Egger test was not performed because < 10 trials were included in our analysis[22]. The following subgroup analyses of the primary outcomes were performed when sufficient data were available: For participants, the young- to middle-age group (< 65 years of age) *vs* the elderly group (≥ 65 years of age) and for intervention, right-side approach *vs* left-side approach[23,24] and diagnostic CA *vs* PCI. For the sensitivity analyses of the primary outcomes, studies using imputed statistics were excluded and participants were only included if they completed the study and their data were complete.

RESULTS

Study selection

Figure 1 shows the flow of the study selection of studies comparing the DRA *vs* RA for cardiac catheterization. We identified a total 752 records (MEDLINE 63 records, EMBASE 150 records, CENTRAL 36 records, ClinicalTrials.gov 132 records, and ICTRP 371 records) published prior to December 7, 2020. After the initial screening, 16 trials met the inclusion criteria. Among these trials, we identified eight ongoing trials (NCT03611725, NCT03986151, NCT04171570, NCT04194606, NCT04211584, NCT04232488, NCT04318990, KCT0004537), five protocols without results (NCT03373565, NCT04001764, NCT04023838, NCT04125992, NCT04238026), and three clinical trials.

Table 1 summarizes the characteristics of eligible studies. Three studies included 519 participants[16,25,26]. Table 2 and Supplementary Tables 1-4 show the risk of bias in each study. The overall risk of bias for the successful cannulation rate was similar in the three studies.

Primary outcomes

Successful cannulation rate: Three studies were eligible for the evaluation of the successful cannulation rate[16,25,26]. In one study, the operators were specialists, and in the other two studies, the operators' skills were unknown. The DRA resulted in little to no difference in the successful cannulation rate in comparison to the RA (RR 0.90, 95%CI: 0.72-1.13; I^2 = 93%) (Figure 2A).

Incidence of RAS: The incidence of RAS was measured in two of three studies[16,25]. The two studies used verapamil and nitrate, respectively[16,25]. The DRA did not reduce the incidence of RAS (RR 0.43, 95%CI: 0.08-2.49; I^2 = 29%) (Figure 2B).

Incidence rate of RAO: Two of the three studies were eligible for the evaluation of incidence of RAO[25,26]. The DRA did not reduce the incidence of RAO (RR 0.48, 95%CI: 0.18-1.29; I^2 = 0%) (Figure 2C).

We could not perform a pre-specified subgroup analysis or sensitivity analyses for the successful cannulation rate, the incidence of RAS, or the incidence of RAO.

Secondary outcomes

Mean number of punctures: We included one RCT for the evaluation of mean number of punctures[25]. In the study, the mean number of punctures per patient was 2.4 with the DRA and 1.6 with the RA.

Mean time for hemostasis: Two of the three studies were eligible for the evaluation of the mean time for hemostasis[16,26]. In one study, hemostasis was performed only by manual compression without using a device[16], and in the other study, it was unclear whether a device was used[26]. The DRA reduced the mean time for hemostasis in comparison to the RA (mean difference -6.64, 95%CI: -10.37 to -2.90; I^2 = 88%) (Figure 3).

Table 1 Summary of the characteristics of the eligible studies

Ref.	Country	Subject No.	Mean age in yr	Male, %	Right arm/left arm, *n*	CAG/PCI (*n*)	5-Fr sheath/6-Fr sheath, *n*	Operators	Medications to prevent radial artery spasm	Approach to hemostasis	Timing of assessment of radial artery occlusion
Mokbel *et al*[26], 2018	Romania	200	63.4	NS	NS	NS	NS	NS	Nitrate	NS	At discharge
Koutouzis *et al*[25], 2019	Greece	205	63.3	75.5	152/48	200/0	0/200	Specialists	Verapamil	Manual compression	At discharge
Vefalı *et al*[16], 2020	Turkey	114	60.4	69.3	33/172	156/49	205/0	NS	NS	Manual compression	NS

CAG: Coronary angiography; NS: Not stated; PCI: Percutaneous coronary intervention.

Table 2 Quality scores for the studies eligible for the evaluation of the successful cannulation rate

Ref.	Risk of bias 2 tool assessment					
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
Mokbel *et al*[26]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Koutouzis *et al*[25]	Low	Low	Low	Low	Some concerns	Some concerns
Vefalı *et al*[16]	Some concerns	Low	Low	Low	Some concerns	Some concerns

Certainty of evidence

The certainty of the evidence was low for the successful cannulation rate because of inconsistency due to substantial heterogeneity and imprecision due to the small sample size. The certainty of evidence was low for RAS, RAO, and the mean number of punctures because of imprecision due to small sample size and the small number of participants. The certainty of the evidence was very low for the mean time for hemostasis because of substantial heterogeneity, imprecision, and a high risk of bias (Table 3).

DISCUSSION

In the present review, the rate of cannulation failure with the DRA was suggested to be similar to that with the RA. Furthermore, the DRA might reduce the incidence of RAS and RAO in comparison to the RA. Additionally, the DRA had a shorter hemostasis time. These findings indicate the safe clinical practice analyses of the DRA to guide cardiac catheterization procedures.

The puncture of the distal radial artery has some caveats because of anatomical features such as the superficial position of the artery and the bone basement. The puncture site in the DRA is either the distal radial artery of the anatomic snuffbox or the more distal radial artery, which is located on the vertex of the angle between the tendon of the extensor pollicis longus and the second metacarpal bone[7]. Some studies showed that the diameter of distal radial artery was smaller and might have the increased tortuosity and angulations in comparison to forearm radial artery[25,27,28]. However, considering the similar results of successful cannulation rates and puncture counts for DRA and RA arms in our review, these anatomical factors might have little effect on the efficacy of the procedure.

Table 3 Summary of findings (the efficacy and safety of the radial approach *vs* the distal radial approach for diagnostic coronary angiography and percutaneous coronary intervention)

Patient or population: Adults; Setting: Diagnostic coronary angiography and percutaneous coronary intervention; Intervention: Radial approach (RA); Comparison: Distal radial approach (DRA)

Outcomes	Anticipated absolute effects[1] (95%CI)		Relative effect (95%CI)	Patient number (studies)	Certainty of the evidence, GRADE	Comments
	Risk with RA	Risk with DRA				
Successful cannulation rates	950 per 1000	798 per 1000 (532-1000)	RR 0.90 [0.72-1.13]	519 (3 RCTs)	Low[2,3]	DRA resulted in little to no difference in successful cannulation rates
Radial artery spasm	39 per 1000	16 per 1000 (4-56)	RR 0.43 [0.08-2.49]	405 (2 RCTs)	Low[3]	DRA may reduce incidence of radial artery spasm
Radial artery occlusion	32 per 1000	14 per 1000 (5-41)	RR 0.48 [0.18-1.29]	314 (2 RCTs)	Low[3]	DRA may reduce the incidence of radial artery occlusion
Mean number of punctures per patient	The mean number of punctures per patient were 2.4 in DRA in comparison to 1.6 in RA			200 (1 RCT)	Low[3]	DRA may reduce the mean number of punctures per patient
Mean time for hemostasis	-	MD 6.64 min lower (10.37 lower to 2.9 lower)	-	405 (2 RCTs)	Very low[2,3,4]	DRA reduced mean time for hemostasis

[1]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval). GRADE Working Group grades of evidence: High certainty: Very confident that the true effect lies close to that of the estimated effect. Moderate certainty: Moderately confident in the estimated effect. The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the estimated effect is limited: The true effect may be substantially different from the estimated effect. Very low certainty: We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

[2]Downgraded because of inconsistency due to substantial heterogeneity.

[3]Downgraded because of imprecision due to small sample size and/or small number of participants.

[4]Downgraded due to imprecision because of high risk of bias.

CI: Confidence interval; MD: Mean difference; RCT: Randomized-controlled trial.

RAS is one of the most frequent complications in cardiac catheterization[29,30] and can be caused by mechanical stimulation by guide wires or catheters and increasing catecholamine levels, which are induced by pain and discomfort[28]. In previous systematic reviews, additional drugs, such as local anesthetics and vasodilatory medications, reduced RAS[31,32]. In the present review, the DRA arm was likely to reduce the incidence of RAS, despite the use of additional medications. Although the detailed mechanism remains unknown, a previous study reported that the DRA might be associated with more advantages in terms of patient satisfaction and the analgesic effect[16,33].

RAO is relatively common, with an incidence ranging from 0.6% to 2.2%; it occurs through the inflammation and endothelial dysfunction of the radial artery[34,35]. Regarding possible explanations for the lower incidence of RAO in the DRA arm, the first possibility seemed to be the anatomical features of the distal radial artery. The antegrade flow through the superficial palmar arch can be maintained during compression of the distal radial artery, resulting in a low risk of retrograde thrombus formation[6]. The second possibility was the shorter duration of hemostasis with the DRA[7], which appeared to be related to the structure of the anatomic snuffbox with a bony basement surrounded by tendons.

The mean number of punctures in the DRA could be mostly comparable to that in the RA. The operators were mainly specialists in the study setting; however, in the clinical setting, the DRA is associated with a learning curve because it involves the puncture of small and weak arteries[36]. Ultrasound is useful for increasing the rate of successful puncture and for reducing adverse events. The measurement of the diameter of the distal radial artery helps to select a suitable sheath, leading to reduced damage of the endothelium and reduced development of RAS and RAO[28]. The use of ultrasound may alter the results of similar studies in the future. Research is needed to evaluate the usefulness of ultrasound in the DRA.

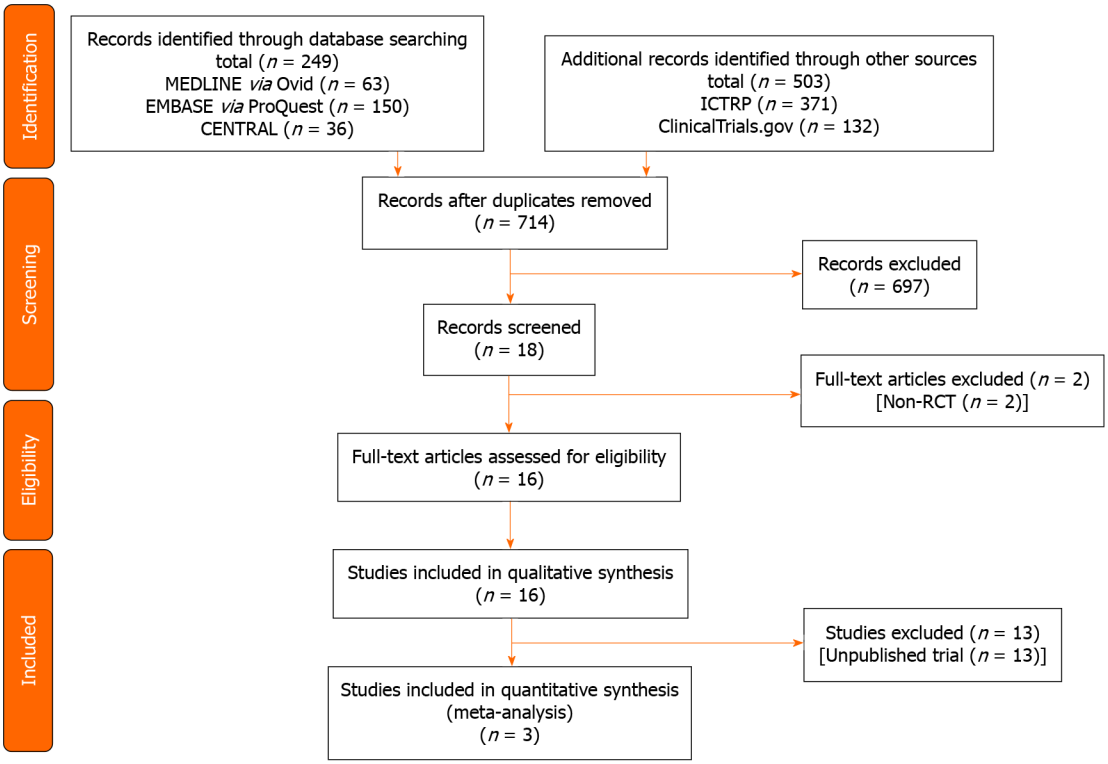

Figure 1 Study selection.

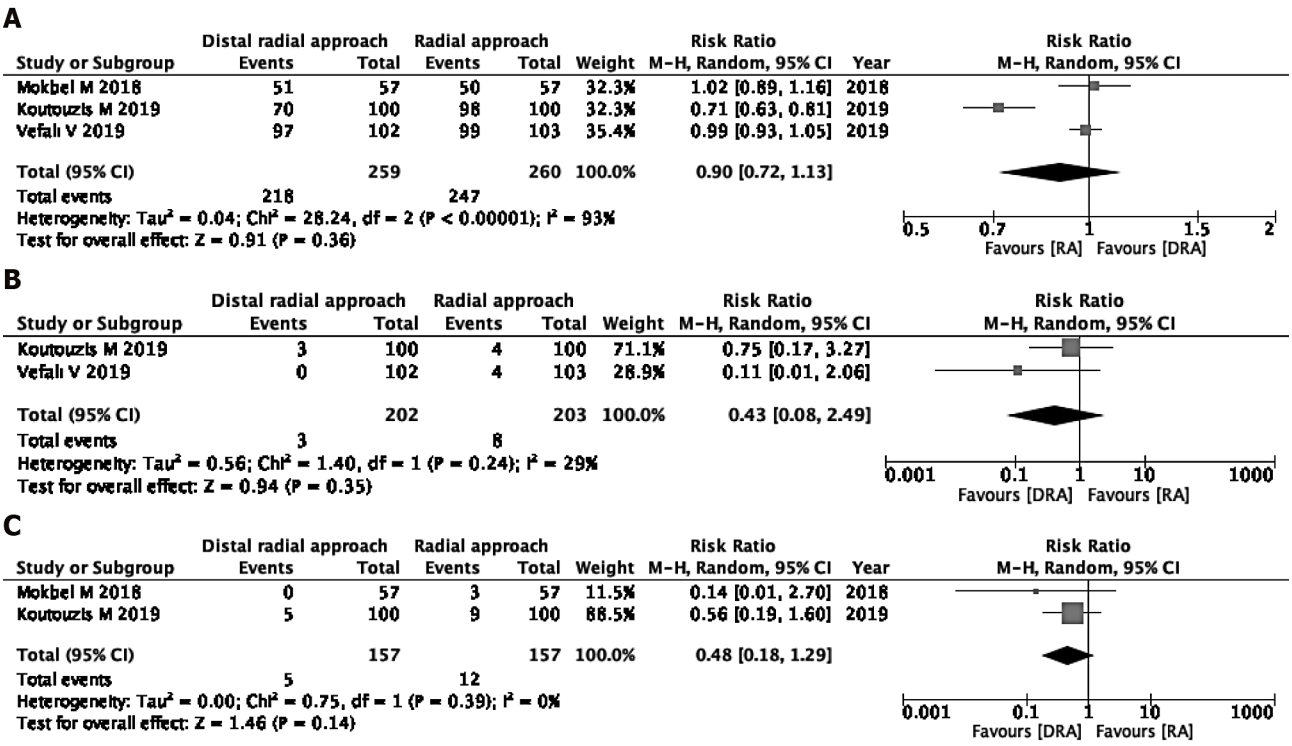

Figure 2 Forest plot. A: The successful cannulation rate; B: The rate of radial artery spasm; C: The rate of radial artery occlusion. CI: Confidence interval; RA: Radial approach; DRA: Distal radial approach.

The shorter time of hemostasis in the DRA, as found in the present review, is a useful aspect of this approach for the prevention of vascular damage. Due to the anatomical features of the distal radial artery, the DRA can reduce the hemostasis time. A new compression hemostasis device for the puncture site of the distal radial artery was also developed, and the safety and efficacy of the device were valida-

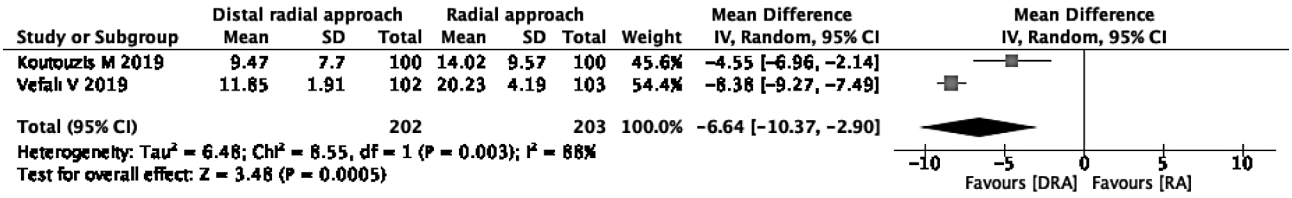

Figure 3 Forest plot of the mean time for hemostasis. CI: Confidence interval; RA: Radial approach; DRA: Distal radial approach.

ted[37]. Mechanical compression is more convenient and requires fewer human resources in comparison to manual compression[38]. In the present review, hemostasis was performed by manual compression. Further research is needed to evaluate the DRA using mechanical compression hemostasis.

The present review had some limitations. First, our review included a relatively small number of studies. Second, various definitions may have been applied for RAS, RAO, and hemostasis, because the protocols were not described. To improve the quality of evidence and draw convincing conclusions, it will be necessary to perform large cohort studies with standard protocols.

CONCLUSION

This first systematic review and meta-analysis to compare clinical data using the DRA and RA indicated that the DRA would be safer than the RA, with comparable procedure rates. Given the limited data, accumulating more knowledge by further research, including studies with standard protocols, is required to establish clinical practice using the DRA.

ARTICLE HIGHLIGHTS

Research background

While the traditional radial approach (RA) is the gold standard method for cardiac catheterization, a distal RA (DRA) has been recently introduced.

Research motivation

The DRA may have some advantages compared to RA; however, it is not fully understood as to which technique for coronary angiography—DRA or RA—is more beneficial to the patients.

Research objectives

Via the systematic review and meta-analysis, we compared clinical data using the DRA and RA.

Research methods

The databases MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, the World Health Organization International Clinical Trials Platform Search Portal and ClinicalTrials.gov were searched. All randomized-controlled trials for adult patients undergoing cardiac catheterization until December 2020 were included. The primary outcomes were the successful cannulation rate and the incidence of radial artery spasm (RAS) and radial artery occlusion (RAO). The statistical analysis was performed on a random-effect model to pool the relative risk ratios (RRs) and 95% confidence intervals (CIs) for the binary variables, such as cannulation success, RAS, and RAO.

Research results

Three randomized-control trials including 519 participants and 13 registered trials were identified. The two approaches showed similar successful cannulation rates (RR 0.90, 95%CI: 0.72-1.13). The DRA did not decrease RAS (RR 0.43, 95%CI: 0.08-2.49) and RAO (RR 0.48, 95%CI: 0.18-1.29). The evidence of certainty was low.

Research conclusions

The present study indicated the DRA to be safer than the RA, with comparable procedure rates. Importantly, there are limitations, including the limited study numbers and no studies with standard protocols, that prevent definitive conclusions.

Research perspectives

Further research, including studies with standard protocols, is required to establish clinical practice using the DRA.

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