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MINIREVIEWS

Same day discharge after structural heart disease interventions in the era of the coronavirus-19 pandemic and beyond

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Abstract

With recent advancements in imaging modalities and techniques and increased recognition of the long-term impact of several structural heart disease interventions, the number of procedures has significantly increased. With the increase in procedures, also comes an increase in cost. In view of this, efficient and cost-effective methods to facilitate and manage structural heart disease interventions are a necessity. Same-day discharge (SDD) after invasive cardiac procedures improves resource utilization and patient satisfaction. SDD in appropriately selected patients has become the standard of care for some invasive cardiac procedures such as percutaneous coronary interventions. This is not the case for the majority of structural heart procedures. With the coronavirus disease 2019 pandemic, safely reducing the duration of time spent within the hospital to prevent unnecessary exposure to pathogens has become a priority. In light of this, it is prudent to assess the feasibility of SDD in several structural heart procedures. In this review we highlight the feasibility of SDD in a carefully selected population, by reviewing and summarizing studies on SDD among patients undergoing left atrial appendage occlusion, patent foramen ovale/atrial septal defect closure, Mitra-clip, and trans-catheter aortic valve replacement procedures.

Key Words: Mitra-clip; Transcatheter aortic valve replacement; Same-day discharge; Atrial septal defect; Coronavirus

Core Tip: Same-day discharge can safely be done among a highly selected group of patients undergoing structural interventional cardiac procedures.

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INTRODUCTION

Same-day discharge (SDD) following percutaneous coronary interventions (PCI) in certain patient groups has been shown to have no increased risk of death, re-hospitalization, and has been associated with increased patient satisfaction[1-4]. According to the 2021 American College of Cardiology (ACC) SDD after PCI decision pathway, SDD is defined as a procedure that does not include supervised overnight monitoring in a facility or hospital after an elective procedure[5]. Several prerequisites have been postulated and the ACC consensus pathway provides a checklist that can be used to determine eligibility for SDD in patients undergoing PCI, however, no consensus has been formulated yet for patients undergoing structural interventional heart procedures[5]. Ideally, patients should be identified as candidates suitable for SDD before the procedure, have an uncomplicated procedure and recovery, be able to pick up required medications, be willing to depart on the same day, and have the means to care for themselves or have reliable caregivers to monitor them over the next 24 h. Most patients would be followed up on the same day *via* telephone-health and some are offered next day in-person visits to be assessed by the interventionalist[5,6]. This has now become important especially due to the current coronavirus disease 2019 (COVID-19) pandemic, as initially all elective procedures were recommended to be postponed by several leading health care authorities to prevent unnecessary exposure to patients and health care workers and to conserve personal protective equipment and bed availability. Delays in timely intervention among patients with structural/valvular heart disease place these patients at increased risk for adverse cardiovascular outcomes, including death[7]. A position statement from the ACC/Society for Cardiovascular Angiography and Interventions provides a framework to triage patients in need of structural heart interventions during the COVID-19 pandemic and discusses pre-procedural evaluation by a dedicated "heart team" and procedural indications[7]. In this manuscript, we aim to review and summarize the available literature on the safety of SDD among patients undergoing structural heart interventional procedures including, left atrial appendage occlusion (LAAO), patent foramen ovale (PFO)/atrial septal defect (ASD) closure, Mitra-clip, and Trans-catheter aortic valve replacement (TAVR) procedures.

SEARCH STRATEGY

We performed an extensive search of electronic databases including PubMed/Medline, Google Scholar, and ClinicalTrials.gov from inception till October 1st, 2021. We included studies that included structural intervention procedures and included patients who were discharged on the same day of the procedure. Eligible studies were reviewed and information was summarized by all authors.

LEFT ATRIAL APPENDAGE OCCLUSION DEVICE PROCEDURE

It was estimated that in the year 2010 around 9 million residents of the European Union were living with Atrial Fibrillation (AF). AF significantly increases the risk of embolic strokes and the postulated primary source of thrombus formation is the left atrial appendage[8]. Current ACC guidelines recommend the option of LAAO for patients with non-valvular AF at high risk for serious bleeding events or who have contraindications for long-term oral anticoagulation to reduce the risk of embolic

stroke[9]. Left atrial appendage occlusion can be achieved percutaneously by deploying the WATCHMAN device (Boston Scientific, Marlborough, MA, United States), at the left atrial appendage ostia *via* transseptal puncture using a 12 French sheath *via* trans-femoral venous access. In the PROTECT-AF and the PREVAIL trials, LAAO was found to be non-inferior to warfarin in the prevention of stroke, systemic embolization, and cardiovascular death[10,11]. The EWOLUTION study concluded that LAAO led to reduced incidence of stroke and non-procedural bleeding[12].

Traditional practice is to admit patients and observe them overnight after LAAO device procedures and to discharge them after around 24 h. Complications following LAAO procedures typically occur during or within a few hours after the procedure[13], hence certain groups created a clinical pathway for safe SDD after LAAO procedures. There have been four recently published studies with data regarding the feasibility of SDD among patients that underwent LAAO, with the vast majority being with the WATCHMAN device[13-16]. In a single-center, retrospective analysis of 190 successful LAAO device implantation using the WATCHMAN device, Tan *et al*[14] compared 7 and 45 d outcomes among SDD patients compared to non-SDD patients. In their study, 72 patients were discharged on the same day of the procedure compared to 118 patients that required at least one night of observation. In their study, pre-requisites for SDD were being able to ambulate two hours after the procedure to assess vascular integrity, anti-platelet and oral anticoagulant started or on hand, hemodynamic stability, no vascular access site complications, and some patients underwent a trans-thoracic echocardiogram (TTE) before discharge. The primary outcome of the study was a composite of stroke, systemic embolism, bleeding requiring blood transfusion, vascular access site complication, and death. The 7 d and 45 d primary outcomes were met by (1.2% *vs* 5.9% of SDD *vs* non-SDD patients) and (2.8% *vs* 9.3% of SDD *vs* non- SDD patients), respectively, $P = 0.26$ and $P = 0.14$. There was also no difference in re- admission or 45 d peri-device flow > 5 mm between SDD and non-SDD patients[14].

Several other smaller single-center studies reported on the feasibility of SDD among patients undergoing LAAO procedures. In a study by Gilhofer *et al*[13], 24 out of 78 patients were discharged on the same day of the LAAO procedure. Pre-requisites to SDD in their study were lack of significant frailty determined by a local scoring system, good home support, a TTE performed after 5 h of step-down observation revealing no significant pericardial effusion, and agreement to come in again the next morning for a repeat TTE and outpatient evaluation. They reported no significant events in either the SDD or non-SDD group[13]. In an effort to enhance SDD, Marmagkiolis *et al*[15] performed all WATCHMAN procedures under conscious sedation and were able to discharge 112 of their 178 patients within six hours after the procedure. They also required a TTE before discharge without evidence of significant pericardial effusion and a next-day follow-up TTE. They reported no complications in the SDD group. In another retrospective analysis of 177 LAAO procedures in the United Kingdom using various LAAO devices, 78 patients were discharged on the same day. Half of the patients had LAAO with the Amplatzer Cardiac Plug, 41% with the Amulet Occluder, and 2.5% with watchman. They reported that 1.7% of all their procedures suffered major in-hospital complications, hence were not suitable for SDD. They had required all patients to have a TTE on the day of the procedure without evidence of pericardial effusion, available transportation, and completion of the procedure before 4 pm to be considered eligible for SDD. In their study one patient from the SDD group was readmitted within 7 d, however, they concluded that it would have not been prevented by an overnight stay. Of note, all patients were discharged on DAPT for 28 d and then transitioned to SAPT thereafter, consistent with the European expert consensus statement[16,17].

MITRA-CLIP

Chronic systolic heart failure eventually leads to left ventricular dilatation and mitral regurgitation (MR) may develop secondary to ventricular remodeling and geometric dislocation of the mitral valve apparatus including the papillary muscles and chordae tendineae, impairing coaptation of the mitral leaflets[18]. In a recent meta-analysis of 45900 patients with secondary mitral regurgitation, secondary mitral regurgitation was associated with an increased risk of heart failure hospitalizations, cardiac mortality, and death[19]. The MITRA-FR study showed no difference in the primary outcome of death from any cause or hospitalization for heart failure (HF) at one year, while the COAPT trial showed a significant reduction in HF hospitalizations and all-cause mortality within 2 years[20,21]. The main reason for the observed differences was attributed to the enrollment in the COAPT trial requiring all patients to be on maximally tolerated guideline-directed medical therapy (GDMT) before enrollment, as compared with the MITRAFR trial[22]. The current 2021 ACC expert consensus HF guidelines recommend that GDMT should be optimized before percutaneous trans-catheter mitral valve repair based on evidence from previous randomized control trials[20,21,23]. The main reason for overnight observation in Mitra-clip procedures is usually to monitor for vascular access complications, as it requires a 24 French sheath introduced *via* the femoral vein, raising concern over possible bleeding complications.

In a single-center retrospective study by Marmagkiolis *et al*[24], 95 patients underwent Trans-catheter mitral valve repair, of which 82 were discharged on the same day of the procedure. In their study, 39

patients had primary MR and 43 had secondary/Functional MR due to heart failure. They included patients with a society of thoracic surgery (STS) score > 8% and deemed unsuitable for surgical mitral valve repair/replacement. The mean age of participants was 80.2 ± 2.5 years, mean EF = 45%, 20% with grade 3 MR, and 80% with grade 4 MR. They had a 100% procedure success rate and all procedures were performed under minimal conscious sedation or monitored anesthesia care and TEE guidance. All patients that had no intra-procedural complications and a stable course during observation for 6-8 h and were able to walk with no vascular access complications were considered for SDD. In their study, all patients underwent a figure of eight suture to the access site and only one patient had suffered from a minor bleeding event according to the valve academic research consortium-2 criteria[24].

In a case report by Chen *et al*[25], they describe an expedited Mitra-clip procedure for an 86-year-old patient with severe MR who was discharged on the same day during the COVID-19 pandemic. His STS risk score was 4.2%, with an EF of 40%, and NYHA III heart failure symptoms. Following the procedure, the patient was observed for four hours, a TTE showed no pericardial effusion, and confirmed the placement of the Mitraclips. The patient was sent home with a 7 d continuous rhythm-monitoring device without any documented arrhythmia and was seen on days 1 and 2 after the procedure *via* telephone-health calls[25]. These prior studies indicate that SDD is reasonable and possible for selected patients undergoing the Mitra-clip procedure without procedural complications and with adequate follow-up.

TAVR

Aortic stenosis (AS) is the most common type of valvular heart disease in the United States and is typically caused by calcific degeneration of a tri-leaflet aortic valve or stenosis of a congenital bicuspid aortic valve (AV)[26]. TAVR is an alternative to surgical aortic valve replacement for treating severe AS or Bio-prosthetic AV dysfunction in patients at high or intermediate surgical risk based on the STS score, frailty, and existing comorbidities[27]. Recently, the five-year outcomes from the PARTNER trial were published and showed no significant difference in the incidence of death or stroke in patients undergoing TAVR at intermediate surgical risk compared to SAVR[28]. Despite TAVR being a commonly performed interventional procedure in the current era, it does not come without the potential for serious procedural and post- procedural complications. As with any interventional procedure, TAVR has been associated with vascular access complications especially due to the large sheath introduced mainly *via* the femoral artery. Other complications include pericardial effusions and tamponade, peri-procedural stroke, and new conduction abnormalities such as high-grade atrioventricular block (AV) and complete heart block requiring permanent pacemaker (PPM) implantation[28,29]. Hence, the standard practice is to observe patients 24-48 h after the procedure for new or worsening conduction abnormalities[30]. However, with the COVID-19 pandemic and the patient population undergoing TAVR usually being elderly with multiple co-morbidities placing them at higher risk of COVID-19 related complications, several studies sought and reported on SDD following TAVR[6,31,32].

In a case series, three elderly patients with AS underwent TAVR and were discharged home on the same day with 7 d of continuous rhythm monitoring[31]. Authors hypothesized that SDD may be safe after TAVR in a pre-selected cohort of patients with AS and also help reduce the risk of unnecessary COVID-19 transmission, conserve hospital beds, and PPE. Since the authors recognized that the loss of a single patient secondary to preventable complications due to early discharge is a never event, they developed protocols and safety nets for their SDD protocol. They considered patients with no significant comorbidities such as end-stage kidney disease, hemoglobin < 9 mg/dL, NYHA ≥ 3 symptoms, EF < 30%, no significant pericardial effusion, new or worsening AV block, and no vascular access complications able to be discharged on the same day of the procedure after observation for 4-6 h. In order to minimize complications, they performed ultrasound-guided vascular access, performed a TTE immediately after device deployment and 4 h after deployment to detect complications, obtained serial electrocardiogram's to mainly assess QRS intervals, ambulated patients after 4 h, and performed serial lower extremity pulse checks. In their case series, there were no new conduction abnormalities detected and all patients were followed up on days 1 and 2 post-procedure. They had no deaths or re-admissions within 24 d of the procedure[31].

Rai *et al*[32] reported their experience of SDD based on 6 patients with severe symptomatic AS or bio-prosthetic valve dysfunction and proposed an SDD protocol. Since the major barrier to discharge patients after TAVR is related to new or worsening conduction abnormalities, they hypothesized that having a pre-procedure PPM or discharge with real-time continuous monitoring could allow for safe SDD. In their case series, they included patients that had predictors of next-day discharge after TAVR based on previous analyses[30]. In a recent study, rapid atrial pacing using the temporary pacing wire used for ventricular standstill during TAVR deployment while in the right atrium, had a 99% negative predictive value for pacemaker implantation after TAVR if no Wenckebach phenomenon developed at a heart rate of 120 bpm[33]. Rai *et al*[32] utilized this method in one of their patients and proposed its use prior to SDD in all patients without chronic AF, pre-existing PPM, or pre-existing AV block.

Additionally, all patients had pre-procedure and post-procedure ECGs performed and if there was a pre- existing right bundle branch block (RBBB) or new AV conduction disturbances, patients were admitted overnight for observation. Otherwise, if patients had a pre-procedure PPM, unchanged ECG from baseline, and no Wenckebach on rapid atrial pacing, they were considered for SDD after 4 h of observation given lack of vascular access site complications. Despite one of their patients developing Wenckebach at 110 bpm, he was discharged on the same day due to a low positive predictive value of the finding and the lack of other conduction abnormalities noted. All six patients were followed with continuous rhythm monitoring for seven days and followed up in person the next day. Based on their experience, they recommend patients with a baseline RBBB not be considered for SDD, as it is one of the strongest predictors for pacemaker need following TAVR[34], additionally, patients who develop a new left bundle branch block after TAVR should be kept overnight for monitoring. Of note, all 6 patients in their series underwent balloon-expandable valve replacements and these recommendations could not be generalized to patients undergoing TAVR utilizing a self-expandable system, as there has been evidence suggesting higher PPM implantation in these patients[35].

The largest study regarding SDD in TAVR was conducted by Perdoncin *et al*[6], in which they report on 29 consecutive SDD TAVR procedures at their center and compared outcomes to patients who underwent TAVR at their center that were non-SDD, who could have qualified for SDD based on their devised protocol. They considered patients with an EF > 30%, hemoglobin > 10, INR < 2, those who received a contrast load < 3 times the estimated Glomerular Filtration Rate (eGFR), without new or worsening conduction abnormalities, or hemodynamic instability for SDD. The primary outcome was to compare 30 d mortality, PPM implantation, stroke, and cardiovascular-related admissions in SDD patients and non-SDD patients. They compared 29 SDD patients to 128 patients that were non-SDD who currently met their protocol for SDD and were fairly similar with regards to baseline characteristics. Procedural characteristics were similar in both groups and all cases were performed *via* trans-femoral access under conscious sedation. Post-procedure, both groups had no in-hospital complications. At 30 d, there were no deaths, the rate of stroke was 0.6%, and delayed PPM implantation was also 0.6% in both groups combined. They noted a trend towards a higher rate of cardiovascular re-admissions in the non-SDD group compared to the SDD group. One patient in the non-SDD group was re-admitted for high-grade AV block requiring PPM implantation. Of note, both self-expanding and balloon expanding valves were used with a trend towards higher use of self-expanding valves in the SDD group. However, further studies are required to determine the feasibility of the use of self- expanding valves for SDD TAVR procedures given the potential concern of outward sub-annular radial force and risk of delayed conduction changes[36].

Overall, based on the prior studies the main concern for SDD in TAVR is related to new or worsening conduction abnormalities that could arise during or after the procedure. All patients considered being candidates for SDD should be identified early during a "heart team" multi-disciplinary discussion and deemed suitable based on pre-procedure pre- requisites. All patients with a baseline RBBB, new high-grade AV block after the procedure, new inter-ventricular conduction delay, or Wenckebach on right atrial pacing after valve deployment should be admitted overnight for inpatient observation. If considered for SDD, all patients must be willing to go home, have no vascular access complications after initial observation, have close follow-up arranged, and be sent home with a real-time rhythm monitor to detect arrhythmias. We present a proposed protocol for SDD following TAVR in Figure 1.

PFO/ASD CLOSURE

ASDs are one of the most common congenital heart defects found in the general population. Unrepaired ASDs can result in various cardiopulmonary adverse events such as arrhythmias, pulmonary hypertension, and paradoxical embolization. Current adult congenital heart disease guidelines recommend ASD closure in carefully selected patients with hemodynamic instability or clinical consequences resulting from their long- standing intra-cardiac shunting[37]. Additionally, up to 50% of patients with a cryptogenic stroke have been found to have an associated PFO[38]. The first three randomized controlled trials CLOSURE I, PC, and RESPECT failed to show any statistical significance in secondary stroke prevention[39-41]. More recent studies, however, have demonstrated that in carefully selected patients, PFO closure is preferable to medical therapy for secondary stroke prevention of cryptogenic strokes in patients with PFO[42,43]. In a review article published in the Journal of the American College of Cardiology, authors proposed a clinical pathway to aid in the appropriate selection of patients that should undergo PFO closure based on randomized trials showing benefit[38].

The PFO closure procedure is usually done as a day case procedure using one of only two FDA approved devices in the United States; the Gore Cardioform Septal Occluder (W.L. Gore and Associates, Inc, Newark, DE, United States) or the Amplatzer PFO Occluder (Abbott Structural, Santa Clara, CA, United States). The procedure is done under fluoroscopic and echocardiographic guidance in the form of TEE or intracardiac echocardiography (ICE) *via* femoral vein access.

In a single-center, retrospective study of 53 consecutive patients the safety and feasibility of SDD in PFO closure using ICE was evaluated[44]. In this study, a 12 Fr sheath for the occluder device and an 11

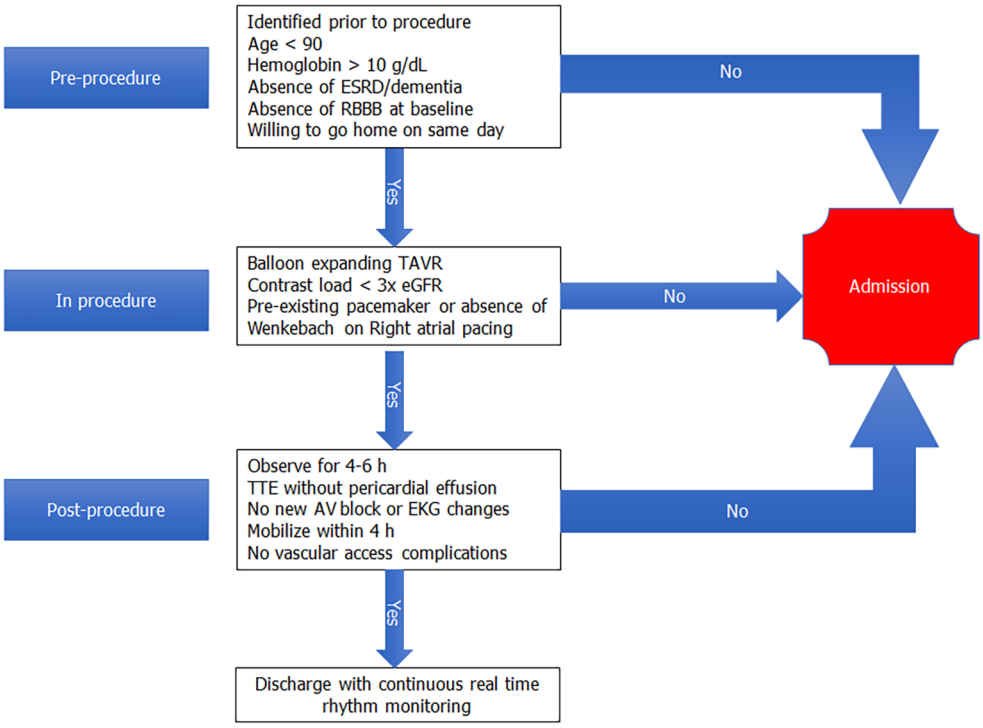

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Figure 1 Proposed algorithm for same day discharge for patients undergoing transcatheter aortic valve replacement. AV: Atrio-ventricular; eGFR: Estimated glomerular filtration rate; EKG: Electrocardiogram; ESRD: End stage renal disease; RBBB: Right bundle branch block; TAVR: Transcatheter aortic valve replacement; TTE: Transthoracic echocardiogram.

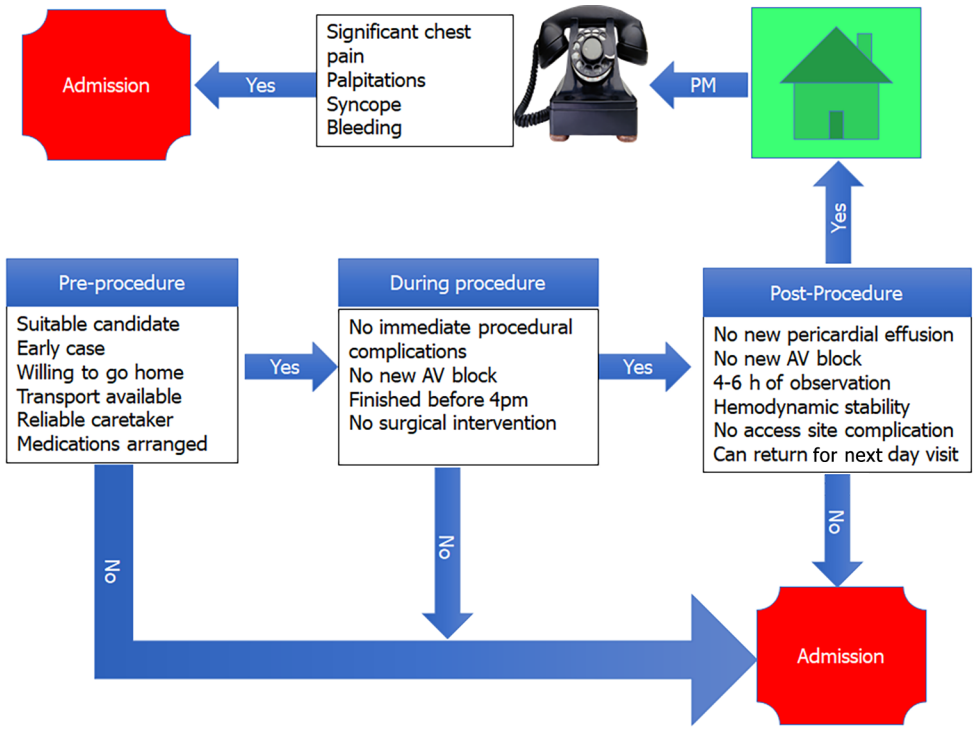

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Figure 2 Proposed algorithm for same day discharge for patients undergoing structural interventional procedures. AV: Atrio-ventricular.

Fr sheath for the ICE probe were inserted into the femoral vein using only local anesthetic and light sedation. In this study 5 of the 53 patients were found to not have PFO by ICE. The remaining 48 patients underwent successful PFO closure with the HELEX occluder (GORE, Flagstaff, AZ, *n* = 47) and the Amplatzer device (AGA medical corporation, Golden Valley, MN, *n* = 1). SDD candidates had to

Table 1 Proposed pre-requisites for same day discharge in structural cardiac procedures

Pre-procedure
Administrative buy-in
Experienced operator
Same day discharge multi-disciplinary team including social workers and nursing
Elective procedure
Reliable means for follow-up
Patient without significant co-morbidities
Willing to depart on the same day
Adequate social support
During procedure
Intra-Procedural monitoring without significant hemodynamic compromise
Successful vascular access without immediate complications
Successful deployment of device
Right atrial pacing for TAVR without wenkebach
Post-procedure
Hemodynamic monitoring for 4-6 h without instability
Able to mobilize without assistance
Vascular access site integrity
TTE without significant pericardial effusion
No new AV block or inter-ventricular conduction delays
Prescriptions arranged
Evening phone call from provider
Next day in-person follow up for imaging and laboratory investigations

AV: Atrioventricular; TAVR: Transcatheter aortic valve replacement; TTE: Transthoracic echocardiogram.

ambulate successfully following the procedure and undergo TTE prior to discharge to confirm appropriate device placement. Appropriate device positioning was confirmed on all 48 patients. Only 1 patient failed SDD due to groin hematoma requiring observation overnight and was discharged the following day. No other complications were reported. Patients were scheduled for a three-month TTE follow-up to assess for any residual shunting. At three months follow up, 45/48 (94%) had no residual shunt.

In a nonrandomized, retrospective, single-center observational study Barker *et al*[45] analyzed peri-procedural outcomes of 467 patients undergoing PFO closure. All patients underwent closure with the Amplatzer PFO Occluder; 381 patients underwent fluoroscopy-only occlusion and 86 patients with ICE guidance. ICE guidance was used as a backup modality and limited to complex atrial septal anatomy as seen on TEE. There was no significant difference in periprocedural complications between the fluoroscopy-only and ICE group. SDD occurred in 97.6% of all patients; 98.2% and 95.3% in the fluoroscopy and ICE group respectively (P = 0.246). Complete closure was seen in 94.6% of patients at the three-month TTE follow-up. There was no significant difference in death, 30-day readmission, device thrombosis, and stroke/TIA between the fluoroscopy-only and ICE group. As of the writing of this article, the literature review reveals only one prospective case series proposing a SDD clinical pathway for patients undergoing ASD/PFO closure[46]. Prerequisites for SDD following PFO closure in their study includes hemodynamic stability and the ability to ambulate 2 h post- procedure. Patients are permitted to go home 1-hour post mobilization with a 6-month TEE follow-up and 6 months of antithrombotic therapy based on the device placed. In their study of 187 patients that underwent PFO/ASD closure (PFO = 117, ASD = 70); SDD occurred in 99.4% of cases. There were no major complications, and a 6-month TEE revealed no residual shunt in 96% of patients[46].

Table 2 Summary of Studies with same day discharges for structural heart disease procedures

Ref.	Year	Procedure	Same day discharge, *n*	Outcome
Gilhofer *et al*[13]	2020	LAAO	24	No significant difference in overall events between SDD and non SDD
Tan *et al*[14]	2021	LAAO	72	No significant difference in 7 and 45 d outcomes between SDD and non SDD
Marmagkiolis *et al*[15]	2021	LAAO	112	No complications among patients that underwent SDD
Williams *et al*[16]	2018	LAAO	78	1 patient from the SDD group was readmitted within 7 d
Marmagkiolis *et al*[24]	2021	Mitra-clip	82	No intra-procedure complications, only 1 patient had minor access site hematoma
Chen *et al*[25]	2020	Mitra-clip	1	No post procedure complication
Perdoncin *et al*[6]	2021	TAVR	29	No in hospital complications, no 30 d deaths
Russo *et al*[31]	2020	TAVR	3	No deaths or re-admissions within 24 d of procedure
Rai *et al*[32]	2021	TAVR	6	No immediate complications or events on 7 d rhythm monitor
Ponnuthurai *et al*[44]	2009	PFO/ASD	48	One Patient with groin hematoma immediately after procedure
Barker *et al*[45]	2020	PFO/ASD	455	No significant difference in death, 30 d readmission, device thrombosis, and stroke/TIA

ASD: Atrial septal defect; LAAO: Left atrial appendage occlusion; PFO: Patent foramen ovale; SDD: Same day discharge; TAVR: Transcatheter aortic valve replacement; TIA: Transient ischemic attack.

FUTURE SCOPE

Adopting a standardized method for same-day discharges will help reduce adverse events. However, as most of the evidence available to date comes from case series and retrospective studies, there is a need for larger prospective studies to be undertaken to validate the safety of SDD across a greater cohort of patients undergoing structural intervention cardiac procedures, to be reflected in the guidelines, before it becomes the standard of care.

CONCLUSION

Same-day discharge appears to be feasible in appropriately selected patients undergoing TAVR, Mitra-clip, LAA, ASD/PFO closure. Safe same-day discharge has the potential to not only reduce hospital costs but also improve patient satisfaction. The availability of a "heart team" consisting of a multi-disciplinary group of providers to identify suitable patients for SDD is prudent. Additionally, only centers with significant volume and experience performing complex structural procedures should consider SDD in their pre-selected suitable patients. We propose an algorithm to facilitate SDD following structural intervention procedures based on the review of available literature (Figure 2, central figure). We also provide a framework checklist to consider when adopting a SDD approach at centers performing structural intervention procedures along with a summary of previous studies with SDD with structural heart procedures (Tables 1 and 2).

FOOTNOTES

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ORIGINAL ARTICLE

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Bioinformatics prediction of potential mechanisms and biomarkers underlying dilated cardiomyopathy

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Abstract

BACKGROUND

Heart failure is a health burden responsible for high morbidity and mortality worldwide, and dilated cardiomyopathy (DCM) is one of the most common causes of heart failure. DCM is a disease of the heart muscle and is characterized by enlargement and dilation of at least one ventricle alongside impaired contractility with left ventricular ejection fraction < 40%. It is also associated with abnormalities in cytoskeletal proteins, mitochondrial ATP transporter, microvasculature, and fibrosis. However, the pathogenesis and potential biomarkers of DCM remain to be investigated.

AIM

To investigate the candidate genes and pathways involved in DCM patients.

METHODS

Two expression datasets (GSE3585 and GSE5406) were downloaded from the Gene Expression Omnibus database. The differentially expressed genes (DEGs) between the DCM patients and healthy individuals were identified using the R package "linear models for microarray data." The pathways with common DEGs were analyzed *via* Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and gene set enrichment analyses. Moreover, a protein-protein interaction network (PPI) was constructed to identify the hub genes and modules. The MicroRNA Database was applied to predict the microRNAs (miRNAs) targeting the hub genes. Additionally, immune cell infiltration in DCM was

analyzed using CIBERSORT.

RESULTS

In total, 97 DEGs (47 upregulated and 50 downregulated) were identified. GO analysis showed that the DEGs were mainly enriched in "response to growth factor," "extracellular matrix," and "extracellular matrix structural constituent." KEGG pathway analysis indicated that the DEGs were mainly enriched in "protein digestion and absorption" and "interleukin 17 (IL-17) signaling pathway." The PPI network suggested that collagen type III alpha 1 chain (COL3A1) and COL1A2 contribute to the pathogenesis of DCM. Additionally, visualization of the interactions between miRNAs and the hub genes revealed that hsa-miR-5682 and hsa-miR-4500 interacted with both COL3A1 and COL1A2, and thus these miRNAs might play roles in DCM. Immune cell infiltration analysis revealed that DCM patients had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting dendritic cells.

CONCLUSION

COL1A2 and COL3A1 and their targeting miRNAs, hsa-miR-5682 and hsa-miR-4500, may play critical roles in the pathogenesis of DCM, which are closely related to the IL-17 signaling pathway and acute inflammatory response. These results may provide useful clues for the diagnosis and treatment of DCM.

Key Words: Dilated cardiomyopathy; Bioinformatics; Differentially expressed genes; Function enrichment analysis; Protein-protein interaction network; Immune cell infiltration

Core Tip: As the most common cause of heart failure, the diagnosis and therapy for dilated cardiomyopathy (DCM) are still unsatisfactory because of its indistinct pathogenesis and specific biomarkers. Thus, we comprehensively utilized the microarray data from the Gene Expression Omnibus database to uncover the biomarker and mechanisms underlying DCM development. Collagen type III alpha 1 chain and collagen type I alpha 2 chain, which are regulated by hsa-miR-5682 and hsa-miR-4500, may play critical roles in the pathogenesis of DCM through the acute inflammatory response and interleukin 17 signaling pathway. These biomarkers and mechanisms need to be further studied.

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INTRODUCTION

Dilated cardiomyopathy (DCM) is a progressive myocardial disease. It accounts for 30%–40% of heart failure cases and leads to high mortality worldwide[1]. DCM is characterized by biventricular dilatation, cardiac systolic dysfunction, and ventricular remodeling[2]. Recently, several studies have reported that mutations, myocarditis, hypertension, and ischemia are the induction factors of DCM[3,4]. Increasing evidence shows that various gene mutations and biomarkers are associated with DCM[5-7]. Mutations in cytoskeletal proteins, including dystrophin[8] and desmin[9], impair muscular force transmission and thereby contribute to the development of DCM. Mutations in lamin A/C, a nuclear membrane protein, usually cause DCM with atrioventricular block and atrial fibrillation[10]. Li *et al*[11] reported that mutation of aryl hydrocarbon receptor nuclear translocator-like protein 1 (known as BMAL1) plays a critical role in the development of DCM through the regulation of mitochondrial fission and mitophagy *via* mitochondrial protein B cell leukemia/lymphoma 2 interacting protein 3. Mutations in thin filament regulatory proteins including cardiac troponin T, cardiac troponin I, and α-tropomyosin can cause DCM with systolic dysfunction by reducing fractional shortening and systolic calcium level[12]. Moreover, some biomarkers associated with the development of DCM have been reported. For example, syndecan-1 and syndecan-4 may serve as useful biomarkers for predicting adverse cardiovascular events in DCM patients[13,14]. Carbonic anhydrase 2 and 3 are associated with heart failure and are potential risk biomarkers for DCM[15], and serum fibroblast growth factor 21 level is linked to the prognosis of DCM [16].

Several studies have sought DCM-related genes and mechanisms *via* bioinformatic methods and found some meaningful results. Huang *et al*[17] found that Fos proto-oncogene, AP-1 transcription factor subunit, tissue inhibitor of metalloprotease-1, and serpin family E member 1 may serve as therapeutic targets in DCM. Zhao *et al*[18] identified 89 differentially expressed genes (DEGs), mainly enriched in the extracellular matrix and biological adhesion signaling pathways, which may play significant roles in the development of DCM. However, the main cause(s) and pathogenic mechanism(s) underlying DCM are still unknown; thus, DCM is mostly diagnosed late, which causes a poor prognosis in turn. More studies are urgently needed to improve the diagnostic and therapeutic efficiency in DCM. The Gene Expression Omnibus (GEO) database includes many DCM-related microarray data, which have not been fully utilized. These data can be used to identify additional candidate biomarkers and pathways to further explore the cause(s) of DCM. To investigate the candidate genes and pathways involved in DCM patients, we analyzed the two gene expression data sets GSE3585 and GSE5406. Using the "linear models for microarray data" (limma) method, we identified 97 DEGs between healthy individuals and DCM patients. In addition, we identified the mechanisms commonly regulated by the DEGs *via* Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses, and gene set enrichment analyses (GSEA). Moreover, a protein-protein interaction network (PPI) network was applied to identify the hub genes that may contribute to the pathogenesis of DCM and predict the microRNAs (miRNAs) targeting the hub genes. Furthermore, we investigated the pattern of immune cell infiltration in DCM.

MATERIALS AND METHODS

Microarray data extraction from the GEO database

The mRNA expression profiles GSE3585 and GSE5406 in the GEO database (http://www.ncbi.nlm.nih.gov/geo/), which is a shared platform in which researchers deposit their microarray data related to various diseases, were downloaded. The GSE3585 dataset, generated by Barth *et al*[19], and the GSE5406 dataset, generated by Hannenhalli *et al*[20], consisted of 7 DCM patients and 5 healthy individuals, and 86 DCM patients and 16 healthy individuals, respectively. In total, 114 samples of the left ventricular myocardium, consisting of 93 DCM and 21 healthy samples (control group), were included in this study.

Data processing and DEGs identification

The two datasets GSE3585 and GSE5406 were loaded onto the GPL96 platform (Affymetrix Human Genome U133A Array [HG-U133A]). Additionally, the series matrix and platform annotation for the two databases were downloaded from the GEO database. The probe identity documents were transformed into gene symbols. Then, *via* the R package "Surrogate Variable Analysis," the two databases were merged, and any batch effect was removed using the "Empirical Bayes" method[21]. The R package "limma" was applied to identify the DEGs between the DCM and healthy myocardium tissues[22]. The screening criteria were set as $P < 0.05$ and $|\log \text{fold change (FC)}| > 0.589$ (FC > 1.5). Volcano and heat maps were generated using R software.

Gene expression enrichment analysis

The gene expression enrichment analysis in this study included GO analysis (https://www.geneontology.org)[23], KEGG (https://www.genome.jp/kegg)[24] pathway analysis, and GSEA (https://www.gsea-msigdb.org/gsea) analysis[25]. The DEGs were inputted into Metascape (https://metascape.org)[26]: The species was selected as *Homo sapiens*; The screening standard was set as $P < 0.05$; and The GO terms of biological process (BP), cellular component (CC), and molecular function (MF) were analyzed and KEGG pathway analysis was performed with the criteria of $P < 0.05$. GSEA interprets the biological function of the expression dataset. The expression dataset in the DCM cases *vs* healthy tissues was loaded into GSEA 4.0.3 software, set gene sets database as GO gene set (c5.all.v7.1.symbols.gmt), set number of permutations as 1000, set phenotype labels as control *vs* DCM, set collapse/remap to gene symbols as no collapse, set permutation type as phenotype, and the other parameters were set at default parameters. Then the GSEA software was used to obtain the enrichment results. The enriched terms were defined as significant with nominal $P < 0.05$.

PPI network construction and hub gene identification

The PPI network was constructed with the online website Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, https://stringdb.org/cgi/input.pl)[27] to contribute to the understanding of the interactive relationship among DEGs. The DEGs were inputted into this website, species of *Homo sapiens* was selected, and the identification criterion was set as combined score > 0.4 (medium confidence). Then the profile of interacting node pairs was imported into Cytoscape (https://cytoscape.org)[28] to visualize the PPI network. The top 10 hub genes were identified with the standard of connectivity degree by using the CytoHubba plugin. The plugin Molecular Complex

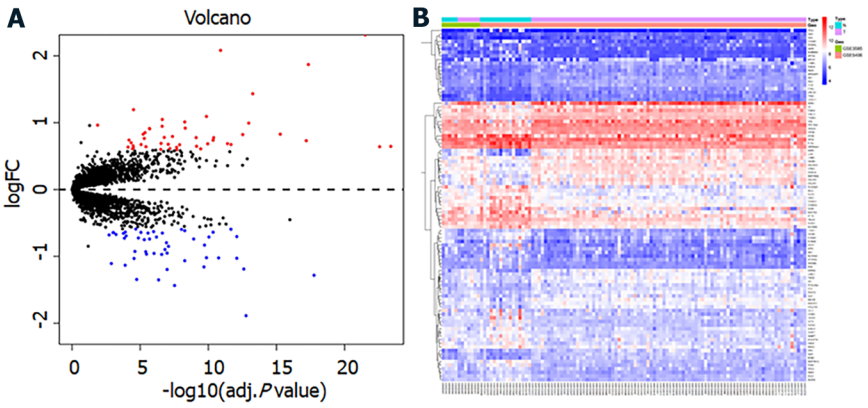

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Figure 1 Identification of differentially expressed genes. A: Volcano map, in which the red node represents the upregulated differentially expressed genes (DEGs) and the blue node represents the downregulated DEGs; B: Heatmap of DEGs.

Detection (MCODE) was applied to identify the essential module within the PPI network in Cytoscape with the default parameters (degree cutoff, 2; node score cutoff, 0.2; kcore, 2; and maximum depth, 100).

Construction of the miRNA-mRNA interaction network

miRNAs, a class of small non-coding RNAs, regulate the expression of various genes by binding to their transcripts and play critical roles in DCM progression[29]. By using the MicroRNA Database (miRDB) [30] (http://mirdb.org/), we predicted miRNAs targeting any of the top 10 hub genes. Then, we sorted these miRNAs according to their prediction scores and selected the top 10 miRNAs. The mRNA-miRNA pairs were imported into Cytoscape to visualize the miRNA-mRNA network.

Immune cell infiltration analysis

The CIBERSORT (cibersort.stanford.edu) algorithm was applied to analyze the normalized gene expression data, and the proportions of 22 types of immune cells in each sample were analyzed[31]. The gene expression data were normalized *via* "limma" and transformed into the 22 types of immune cell expression data through the source of CIBERSORT[32] *via* R. Then the results were filtered out *via* Perl (https://www.perl.org) with $P < 0.05$, and the immune cell infiltration matrix was obtained. Next, the "vioplot" package was used to draw violin diagrams to visualize the difference in immune cell infiltration between the DCM and healthy groups in detail. The "ggplot2"[33] package was applied to perform principal component analysis (PCA) and draw a PCA clustering map. The "corrplot" package was used to analyze the correlation among immune cell infiltration and draw a correlation heatmap.

RESULTS

Identification of DEGs

After merging the two datasets, 97 DEGs, including 47 upregulated and 50 downregulated genes, were obtained in the DCM group compared with the control group. Figure 1 shows the volcano map and heatmap of the 97 DEGs. The details of the top 10 upregulated or downregulated genes are shown in Table 1.

GO and KEGG enrichment analyses

Next, the DEGs were used to perform enrichment analysis for BP, CC, MF, and KEGG pathways. By using the Metascape website, the BP of GO was found to be significantly enriched in "response to growth factor," "blood vessel development," "regulation of smooth muscle cell proliferation," "muscle tissue development," and "acute inflammatory response" (Figure 2A). The DEGs in CC were mainly enriched in "extracellular matrix," "cytoplasmic vesicle lumen," "collagen trimer," and "sarcoplasm" (Figure 2B). Regarding MF, the DEGs were mainly enriched in "extracellular matrix structural constituent," "growth factor binding," "alpha-actinin binding," and "calcium ion binding" (Figure 2C). KEGG pathway analysis revealed significant pathway enrichment of DEGs in "protein digestion and absorption," "interleukin 17 (IL-17) signaling pathway," "advanced glycation end products-receptor for advanced glycation end products signaling pathway in diabetic complications," "complement," and "coagulation cascades" (Figure 2D).

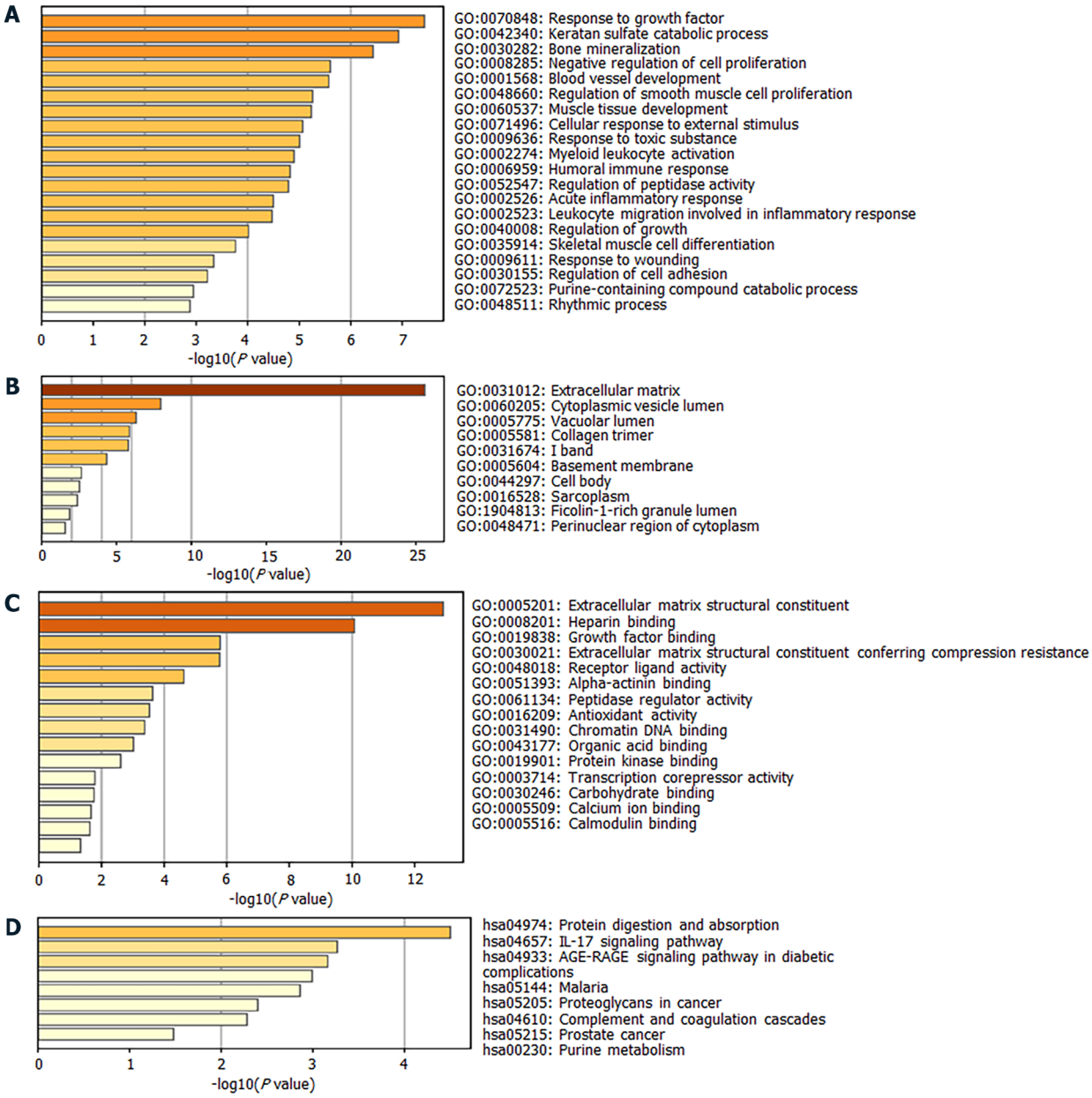

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Figure 2 Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analysis of enrichment for differentially expressed genes. A: Biological process; B: Cellular component; C: Molecular function; D: Kyoto Encyclopedia of Genes and Genomes.

GSEA analysis

GSEA analysis results revealed that, compared with the control group, the DCM group was significantly enriched in GO terms "heart development," "response to ischemia," "vascular smooth muscle cell differentiation," "response to transforming growth factor beta," "stem cell proliferation," and "regulation of mitochondrial fission" (Figure 3).

PPI network and identification of hub genes

To further explore the relationship among the DEGs at the protein level, the PPI network of the 97 DEGs was constructed using STRING with the criterion of combined score > 0.4 and visualized using Cytoscape. The PPI network consisted of 77 nodes and 145 edges (Figure 4A). The top 10 hub genes included collagen type III alpha 1 chain (COL3A1), COL1A2, signal transducer and activator of transcription 3 (STAT3), C-C motif chemokine ligand 2 (CCL2), fibromodulin (FMOD), asporin (ASPN), C-X-C motif chemokine ligand 12 (CXCL12), lumican (LUM), heat shock protein 90 alpha family class A member 1 (HSP90AA1), and osteoglycin (OGN) (Figure 4B). The detailed information of these hub genes is provided in Table 2. MCODE analysis identified five essential modules, and COL3A1, myosin heavy chain 6, activating transcription factor 3, B cell leukemia/lymphoma 6 transcription repressor,

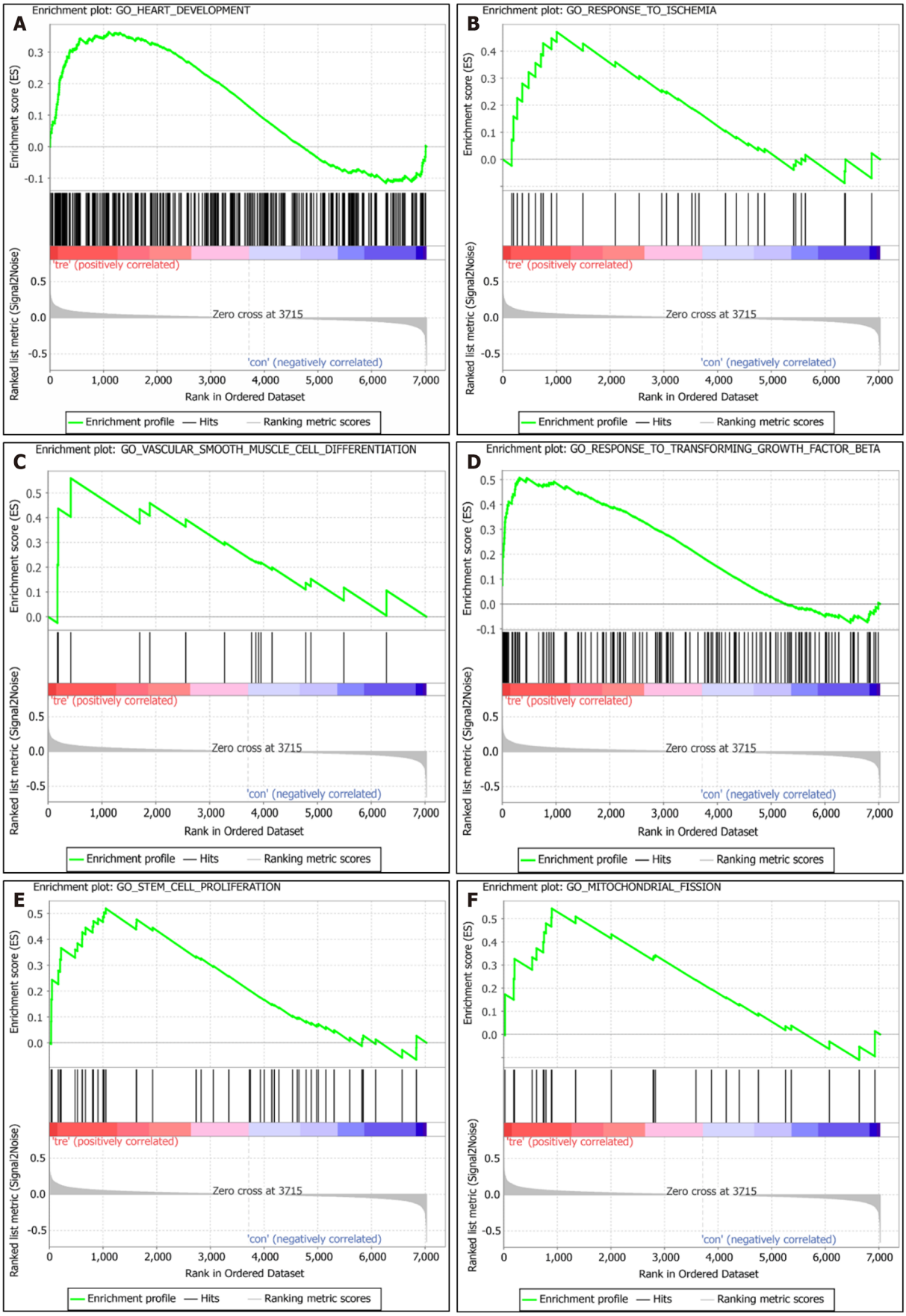

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Figure 3 Gene set enrichment analyses of enrichment of differentially expressed genes. A: Heart development; B: Response to ischemia; C: Vascular smooth muscle cell differentiation; D: Response to transforming growth factor beta; E: Stem cell proliferation; F: Regulation of mitochondrial fission.

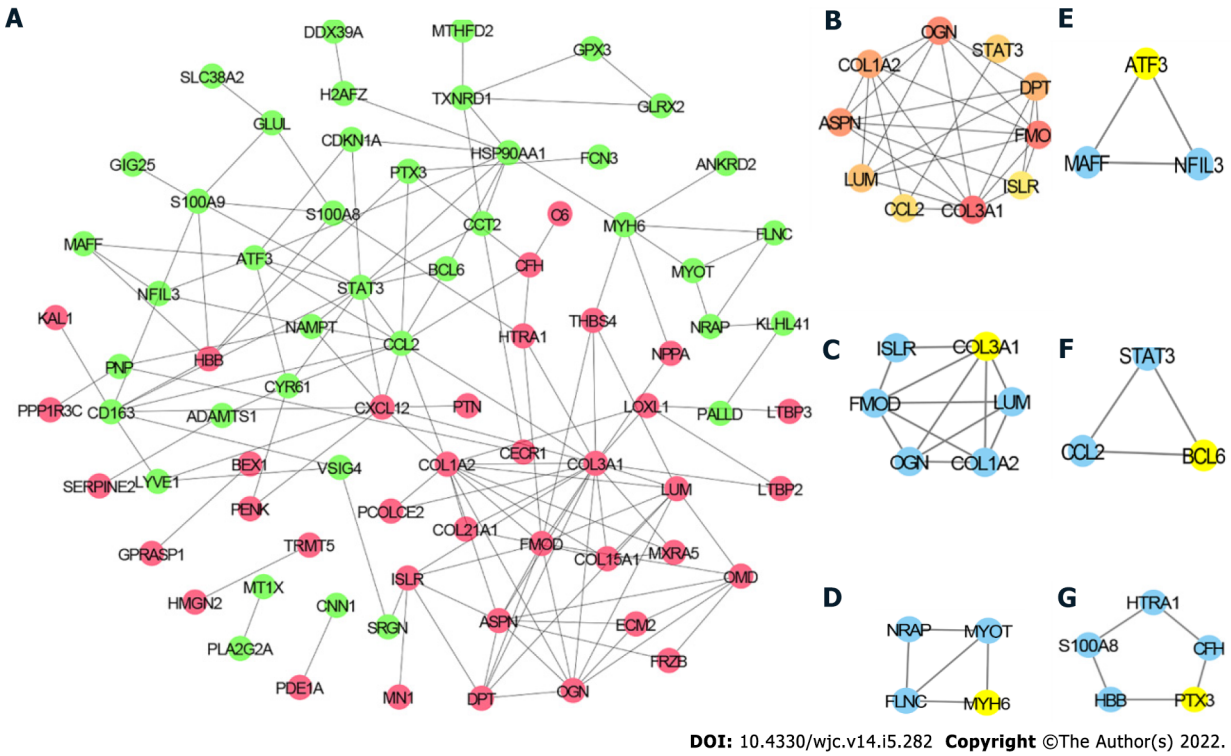

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Figure 4 Protein-protein interaction network. A: Protein-protein interaction (PPI) network of differentially expressed genes (DEGs), in which the red node represents upregulated DEGs and the green node represents the downregulated DEGs; B: Top 10 hub genes; C: Module 1; D: Module 2; E: Module 3; F: Module 4; G: Module 5. Yellow node represents the Seed gene of each module.

and pentraxin 3 were the seeds of clusters 1, 2, 3, 4, and 5, respectively (Figure 4C–G).

miRNA–mRNA interaction network

Increasing evidence shows that miRNAs play important roles in the development and progression of DCM. By using the miRDB database, we predicted miRNAs targeting any of the top 10 hub genes. Then we sorted these miRNAs according to their prediction scores and selected the top 10 miRNAs. Additionally, the top 100 miRNA–mRNA pairs were visualized using Cytoscape (Figure 5). Consequently, hsa-miR-5682, hsa-miR-4500, hsa-miR-32-3p, and hsa-miR-374a-3p were each found to target ≥ 2 hub genes.

Immune cell infiltration in DCM

Immune cells infiltrate into the myocardium upon myocardial injury[28]. Thus, a violin plot was constructed to investigate the difference in immune-cell infiltration between the DCM and control groups (Figure 6A). Compared with the control group, the DCM group had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting dendritic cells (DCs), whereas there was no significant difference in the remaining 18 types of immune cells. However, the PCA results showed that the control and DCM groups could not be well distinguished according to the infiltration patterns of the 22 types of immune cells (Figure 6B). We generated a correlation heatmap to assess the correlation among the 19 immune cells that were found infiltrated in the DCM or control group. As shown in Figure 6C, the number of infiltrated B memory cells was positively correlated with that of the infiltrated resting DCs, activated natural killer (NK) cells and T follicular helper cells, the number of infiltrated activated NK cells was negatively correlated with that of infiltrated resting NK cells, and the number of infiltrated resting memory CD4 T cells was negatively associated with that of infiltrated B memory cells and regulatory T cells.

DISCUSSION

DCM is one of the main reasons of sudden cardiac death and heart failure. It is a heterogeneous disease caused by various types of pathogenic factors including genetic, infectious, hormonal, and environmental factors[34]. The causes of DCM should be explored in depth to improve the diagnosis, treatment, and prognosis of DCM patients. Therefore, it is of great significance to elucidate the genetic mechanisms involved in DCM.

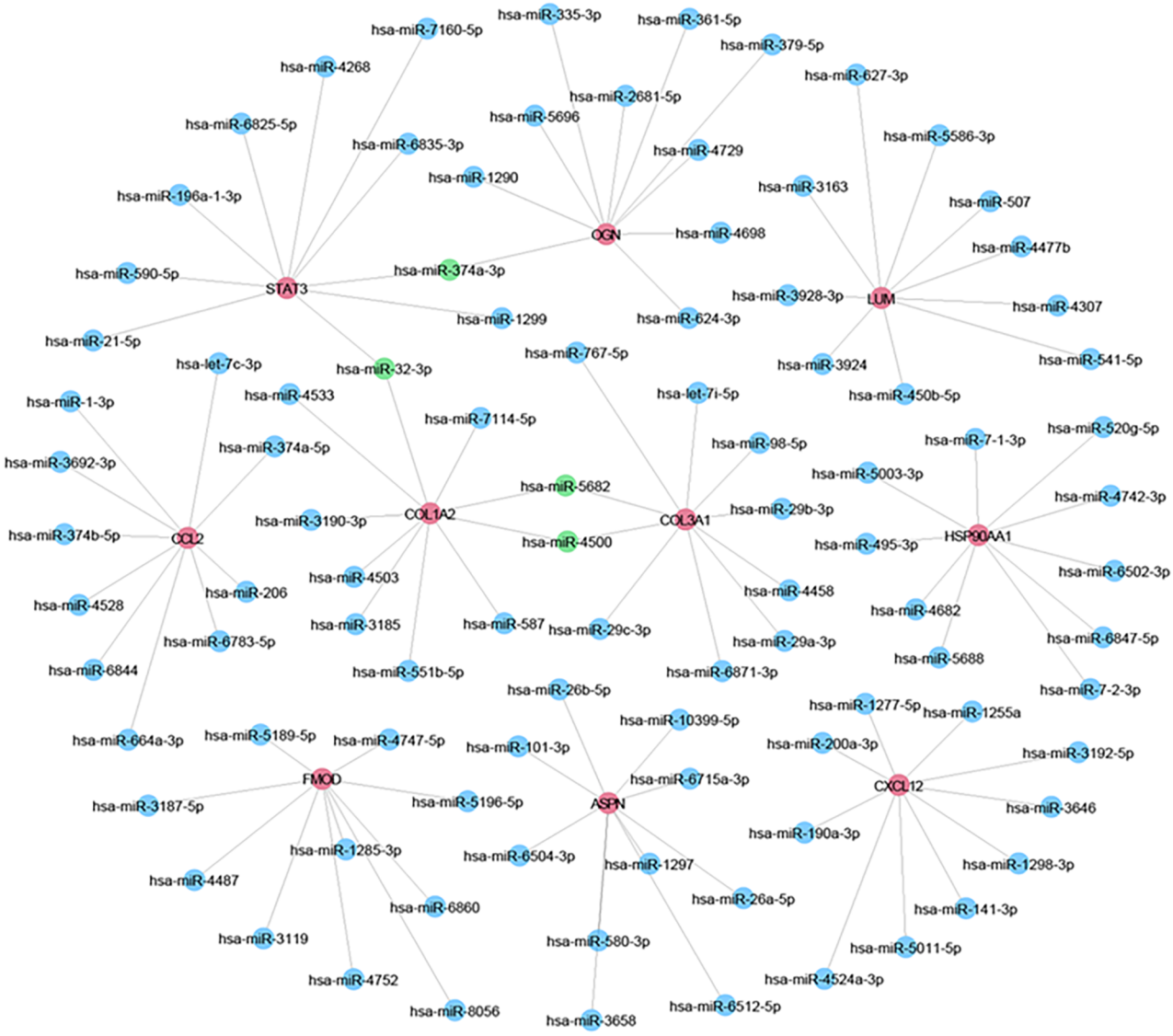

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Figure 5 MicroRNA-mRNA network. Red node represents the Hub genes; blue node represents the Targeted microRNAs; green node represents the mutual targeted miRNAs of ≥ 2 hub genes.

In this study, 97 DEGs, consisting of 47 upregulated and 50 downregulated genes, were identified between the DCM and control groups. GO of BP and GSEA analysis revealed that the DEGs were not only enriched in the development of the cardiovascular system, such as in the development of the muscle tissue, heart, and blood vessels, but also in the etiology of DCM, such as in acute inflammatory response and mitochondrial fission (Figures 2 and 3). Growing evidence shows that infiltration of inflammatory cells is associated with the pathogenesis of DCM[35-37], and prelamin A accumulation [38] and myosin binding protein C3 mutation[39] can promote DCM pathogenesis *via* regulation of inflammation. Xia *et al*[40] reported that dynamin-related protein 1 (Drp1, myocardial fission protein) is significantly upregulated in DCM patients. Moreover, Sacubitril (known as LCZ696), a novel inhibitor of the angiotensin receptor neprilysin, can alleviate the cardiac dysfunction in doxorubicin-induced DCM and reduce apoptosis by inhibiting mitochondrial fission *via* the Drp1-mediated pathway.

Regarding CC, the DEGs were enriched in sarcoplasm. Previous studies have reported that mutations in phospholamban (related to abnormal contractility)[41] and B-cell lymphoma 2-associated athanogene 3 (alter the cardiac response)[42] are closely associated with DCM in the sarcoplasmic reticulum. GO analysis of MF indicated that the DEGs were enriched in alpha-actinin binding and calcium ion binding. Alpha-actinin and calcium ion are critical for myocardial contraction[43,44]. Other studies have demonstrated that most DCM patients exhibit abnormalities related to calcium ion and α-actinin, which cause decreased heart contractility[45-47]. Cardiac troponin contributes to myocardial contraction[48]. Mutations in cardiac troponin T, troponin C, and troponin I are mainly related to DCM pathogenesis[49, 50]

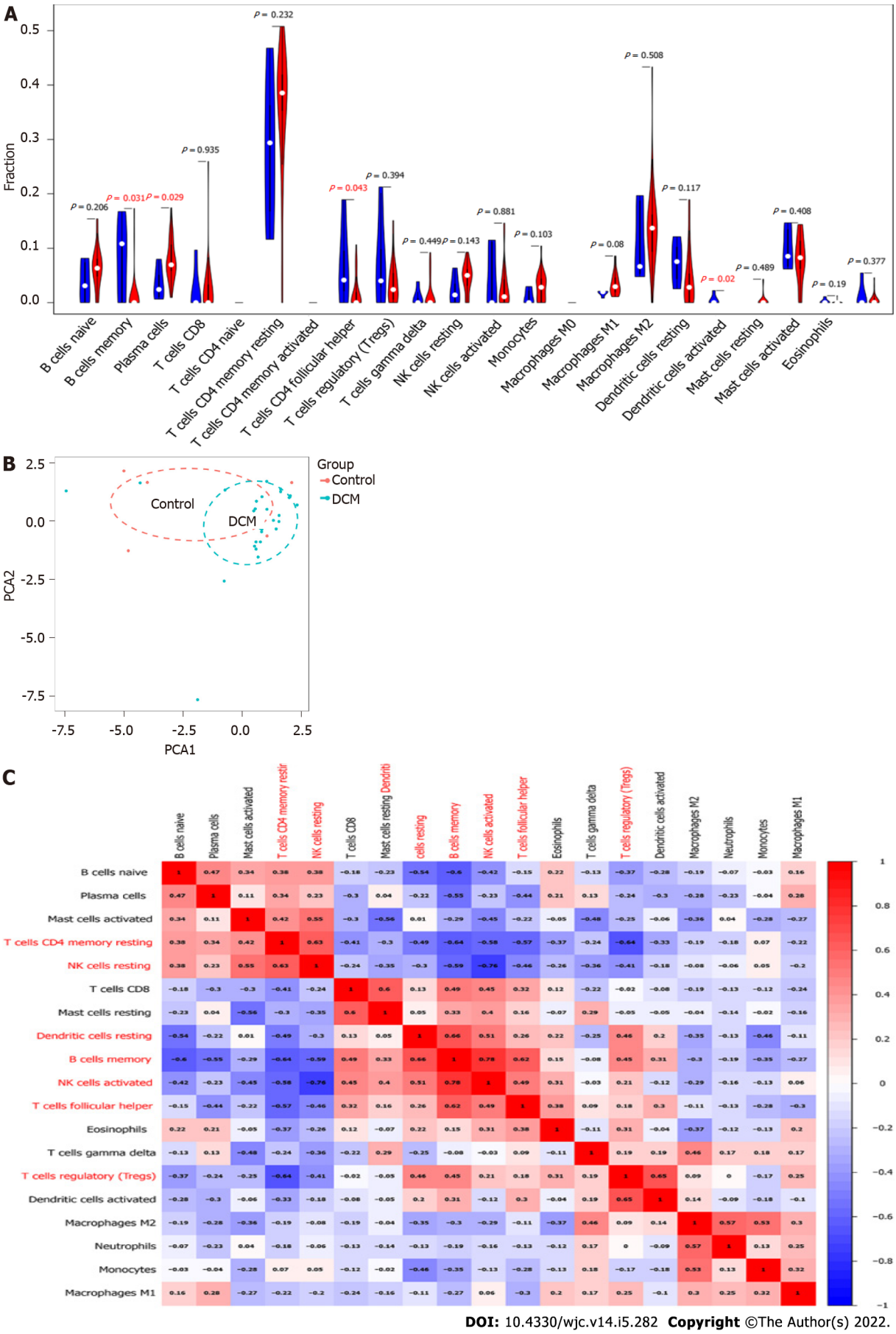

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Figure 6 Immune cell infiltration analyses of differentially expressed genes. A: Violin plot, in which red represents dilated cardiomyopathy group and blue represents the normal group; B: Principal component analysis; C: Correlation heatmap.

Table 1 Top 10 differentially expressed genes in the dilated cardiomyopathy group *vs* normal group

Expression	Gene symbol	Description	logFC	adj. *P* value
	ASPN	Asporin	2.31	3.05E-22
	NPPA	Natriuretic peptide A	2.08	1.26E-11
	LUM	Lumican	1.87	4.56E-18
	MXRA5	Matrix remodeling associated 5	1.43	5.47E-14
UP	*HBB*	Hemoglobin subunit beta	1.20	3.08E-05
	COL1A2	Collagen type I alpha 2 chain	1.09	1.37E-10
	COL3A1	Collagen type III alpha 1 chain	1.05	2.39E-07
	OGN	Osteoglycin	1.01	5.38E-09
	FRZB	Frizzled related protein	0.99	1.08E-13
	EIF1AY	Eukaryotic translation initiation factor 1A Y-linked	0.96	1.33E-02
	MYOT	Myotilin	-1.89	1.70E-13
	ANKRD2	Ankyrin repeat domain 2	-1.44	3.00E-08
	PLA2G2A	Phospholipase A2 group IIA	-1.35	4.43E-07
	MYH6	Myosin heavy chain 6	-1.35	1.80E-05
	SERPINA3	Serpin family A member 3	-1.28	1.75E-18
Down	*CYP4B1*	Cytochrome P450 family 4 subfamily B member 1	-1.20	1.06E-07
	FCN3	Ficolin 3	-1.19	2.48E-13
	CNN1	Calponin 1	-1.16	2.09E-10
	PTX3	Pentraxin 3	-1.13	1.27E-04
	NRAP	Nebulin related anchoring protein	-1.11	1.30E-03

Table 2 Top 10 hub genes in the protein-protein interaction network

Gene symbol	Description	Rank	Degree
COL3A1	Collagen type III alpha 1 chain	1	18
COL1A2	Collagen type I alpha 2 chain	2	12
STAT3	Signal transducer and activator of transcription 3	3	11
CCL2	C-C motif chemokine ligand 2	3	11
FMOD	Fibromodulin	5	10
ASPN	Asporin	6	9
CXCL12	C-X-C motif chemokine ligand 12	6	9
LUM	Lumican	8	8
HSP90AA1	Heat shock protein 90 alpha family class A member 1	8	8
OGN	Osteoglycin	8	8

KEGG pathway analysis showed that the DEGs were significantly enriched in the IL-17 signaling pathway. DCM is induced by viral myocarditis, accompanying autoimmune dysfunction, affecting the secretion of IL-17 cytokine by T helper 17 cells, and IL-17 itself promotes myocardial cell injury[51]. Wang *et al*[52] reported that elevated IL-17 levels are significantly associated with DCM incidence and progression. Additionally, the serum levels of other inflammatory factors such as IL-6, tumor necrosis factor-α, and IL-21 are significantly increased in DCM patients[53]. Thus, the IL-17 signaling pathway may be one of the major signaling pathways involved in the development of DCM.

Through construction of PPI and miRNA-mRNA interaction networks, we identified the hub genes and the miRNAs targeting them. The hub genes, COL1A2 and COL3A1, encode the pro-alpha2/1 chains of type I and III collagens, respectively. Collagens I and III, the main collagens of cardiac extracellular

matrix, are classical biomarkers of cardiac fibrosis in DCM[54]. Mihailovici *et al*[55] reported that collagens I and III are upregulated in DCM patients compared with matched healthy controls. Additionally, Zhao *et al*[18] reported that COL1A2 may participate in DCM pathogenesis by regulating the cardiac remodeling characterized by collagen deposition in the extracellular matrix[56]. Consistent with our results, Liu *et al*[53] identified STAT3 as a hub gene in DCM *via* bioinformatic analysis. Other studies have also indicated a role of STAT3 in DCM. Podewski *et al*[57] showed that STAT3 protein level is significantly decreased in the cardiomyocytes of patients with end-stage DCM. Moreover, inhibition of the IL-6–mediated STAT3 signaling pathway can improve myocardial remodeling through reducing myocardial apoptosis in a mouse model of DCM[58]. Thus, the roles of COL1A2, COL3A1, and STAT3 in DCM should be further investigated. Moreover, the identified miRNAs hsa-miR-5682, hsa-miR-4500, hsa-miR-32-3p, and hsa-miR-374a-3p may participate in DCM pathogenesis through their interaction with ≥ two hub genes. Previous studies have also suggested that miRNAs play significant roles in DCM. It has been found that miR-21, miR-29a, and miR-133b are differentially expressed in DCM patients[59]. miR-133a expression is associated with fibrosis, myocyte necrosis, left ventricular function, and clinical outcome in patients with inflammatory DCM[60]. Moreover, Satoh *et al*[61] showed that a low let-7i level can serve as an independent predictor of cardiac death and heart failure (relative risk = 3.76).

Immune cells commonly infiltrate into the myocardium upon various types of cardiac damage[49, 62]. Overactivation of immune cells could be investigated in pathological examination about cardiac biopsy specimens in DCM patients. Noutsias *et al*[63] reported that the upregulation of genes associated with T cells exacerbates DCM progression. Therefore, our study also assessed the correlation between DEGs and immune cell infiltration. The results indicated infiltration of 19 types of immune cells in DCM pathogenesis. Notably, compared with the control group, the DCM group had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting DCs. However, Liu *et al* [53] have demonstrated that, compared with healthy controls, DCM patients have more infiltrated T follicular helper cells and fewer T follicular regulatory cells, and infiltration of T follicular regulatory cells is positively correlated with left ventricular ejection fraction.

Our study had some limitations. First, the gene expression data were acquired from a public database. Moreover, we did not experimentally verify the relevance of the identified DEGs with DCM and their enriched functions or hub genes. Likewise, we did not verify the predicted miRNA-mRNA interactions and their relevance.

CONCLUSION

In summary, we first identified that COL1A2 and COL3A1 may be both presumably regulated by hsa-miR-5682 and hsa-miR-4500, and play significant roles in the pathogenesis of DCM through acute inflammatory response and IL-17 signaling pathway. These results may provide useful biomarkers for the diagnosis and treatment of DCM, but further research is needed to clarify the roles of the predicted genes and pathways.

ARTICLE HIGHLIGHTS

Research background

Dilated cardiomyopathy (DCM), a disease of the heart muscle, is one of the most common causes of heart failure. However, the original cause and pathogenesis in development of DCM are still remain elusive.

Research motivation

The early diagnosis and prognosis of DCM patients are unsatisfactory because of DCM main cause and pathogenesis are still unclear. Increasing DCM datasets were provided online but little was been explored. Bioinformatics could further investigate the DCM mechanism and biomarkers for improving the diagnostic and therapeutic efficiency.

Research objectives

This study investigated the candidate genes and pathways involved in DCM patients.

Research methods

Expression datasets were downloaded from the Gene Expression Omnibus database. Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and gene set enrichment analyses investigated the key pathway in differentially expressed genes (DEGs) between the DCM patients and healthy individuals. Protein-protein interaction network identified the hub genes and modules in DCM. MicroRNA Database predicted the microRNAs which targeting the hub genes. CIBERSORT analyzed the immune-

ell infiltration in DCM.

Research results

Ninety-seven DEGs mainly enriched in "response to growth factor," "extracellular matrix," and "extracellular matrix structural constituent." Moreover, the top two pathways were "protein digestion and absorption" and "interleukin 17 signaling pathway." Collagen type III alpha 1 chain (COL3A1) and COL1A2, whose were regulated by hsa-miR-5682 and hsa-miR-4500, mainly contributed to the pathogenesis of DCM. Compared with the control group, DCM patients had more infiltrated plasma cells and fewer infiltrated B memory cells, T follicular helper cells, and resting dendritic cells.

Research conclusions

DCM progression closely related to IL-17 signaling pathway and acute inflammatory response. COL1A2 and COL3A1 and their targeting miRNAs, hsa-miR-5682 and hsa-miR-4500, are the potential biomarkers of DCM.

Research perspectives

This study may provide valuable pathways and biomarkers for the diagnosis or treatment of DCM. Further studies should investigate the functions of the predicted genes and pathways.

FOOTNOTES

Author contributions: Liu Z and Song YN designed this study; Chen KY collected the relevant data; Liu Z analyzed the data; Liu Z and Gao WL drafted the manuscript; Chen HJ and Liang GY reviewed and supervised this manuscript; All authors approved the final version of the article.

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ORIGINAL ARTICLE

Retrospective Study

Pledget-assisted hemostasis to fix residual access-site bleedings after double pre-closure technique

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Abstract

BACKGROUND

The use of pre-closure suture-based devices represents a widely access-site hemostasis technique in percutaneous transfemoral transcatheter-aortic-valve-replacement (TF-TAVR); yet this technique is associated with the risk of a device failure that may result in clinically relevant residual bleeding. Thus, a bailout intervention is needed. So far, the best management of pre-closure device failure has not been recognized.

AIM

To report the first clinical results obtained using a novel bailout hemostasis technique for patients with double suture-based vascular closure device failure in the setting of TF-TAVR.

METHODS

We developed a "pledget-assisted hemostasis" technique to manage residual access-site bleeding. This consists of the insertion of a surgical, non-absorbable, polytetrafluoroethylene pledget over the sutures of the two ProGlide (Abbott Vascular, CA, United States). The ProGlide's knot-pushers are used to push down the pledget and the hand-made slipknot to seal the femoral artery leak. This technique was used as a bailout strategy in patients undergoing TF-TAVR with a

systematic double pre-closure technique. Post-procedural access-site angiography was systematically performed. In-hospital complications were systematically detected and classified according to Valve Academic Research Consortium-2 criteria.

RESULTS

Out of 136 consecutive patients who underwent TF-TAVR, 15 patients (mean age 80.0 ± 7.2 years, 66.7% female) with access-site bleeding after double pre-closure technique failure were treated by pledget-assisted hemostasis. In the majority of patients, 16F sheath was used (n = 12; 80%). In 2 cases (13%), a peripheral balloon was also inflated in the iliac artery to limit blood loss during pledget preparation. Angiography-confirmed hemostasis (primary efficacy endpoint) was achieved in all patients. After the procedure, 1 patient required blood transfusion (2 units), and no other bleeding or major ischemic complication was noticed.

CONCLUSION

The "pledget assisted hemostasis" might be considered as a possible bailout technique to treat patients with residual access site bleeding. Further studies are needed to compare this approach with other bail-out techniques.

Key Words: Transcatheter aortic valve replacement; Transcatheter aortic valve implantation; Vascular complications; Preclosure device; Pledget; Hemostasis; Personalized medicine

Core Tip: This is a retrospective pilot study to report the first clinical results obtained using a novel bailout hemostasis technique for patients with double suture-based vascular closure device failure in the setting of trans-femoral transcatheter-aortic-valve-replacement. The "pledget-assisted hemostasis" technique consists of the insertion of a surgical, non-absorbable, polytetrafluoroethylene pledget over the sutures of two ProGlide (Abbott Vascular, CA, United States). The ProGlide's knot-pushers are used to push down the pledget and the hand-made slipknot to seal the femoral artery leak. This technique was used as a bailout strategy in patients undergoing trans-femoral transcatheter aortic valve replacement with systematic double preclosure technique.

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INTRODUCTION

Despite increased operator experience and device improvement, access site complications still pose a significant concern regarding procedural safety of trans-femoral transcatheter aortic valve replacement (TF-TAVR)[1]. Accordingly, strategies to minimize the occurrence and the clinical sequelae of access-site complications are continuously investigated.

When practicing percutaneous TF-TAVR, in addition to proper access site selection and precise puncture of common femoral artery (CFA)[2], the use of vascular closure devices (VCD) is actually widely adopted. Within different VCD-based technical options, pre-implantation of suture-based closure devices has gained popularity. However, vascular complications are not abolished, and residual access site bleeding is often detected (in up to one-third of patients)[3-5] due to significant blood leakage at the level of arterial entry site. Thus, as a part of TF-TAVR procedures, strategies to bailout manage VCD failures are applied daily according to various local expertise. The best technique to manage residual bleeding after suture-based VCD failure has not yet been recognized. Thus, we herein report the description and the results obtained in the early clinical practice of a novel "pledget-assisted hemostasis" technique.

MATERIALS AND METHODS

Technique description

According to our local practice, TF-TAVR is systematically performed under conscious sedation according to the previously described "less-invasive totally-endovascular" (LITE) technique[6]. Briefly, the LITE technique combines a series of technical solutions aimed to minimize vascular complications and includes radial approach as the "secondary access" (to guide valve positioning, to check femoral-access hemostasis, and to manage eventual access-site complications) and precise CFA puncture using angiographic-guidewire-ultrasound guidance[7]. Femoral hemostasis was systematically attempted using a double pre-closure technique with two suture devices (ProGlide, Abbott Vascular, CA, United States). After prosthesis implantation and TAVR sheath removal, hemostasis with parallel double ProGlide sutures was done[8].

At this stage, before the suture threads of the ProGlide device were cut down, hemostasis was checked by selective iliac-femoral angiography performed by radial access with a multipurpose guiding catheter[6]. Digital subtraction angiography of the iliac-femoral arteries allowed to assess vascular integrity or to diagnose the occurrence of vascular damages or bleeding complications. At this stage, when significant residual bleeding at the site of femoral entry was recognized, a new "pledget-assisted hemostasis" technique was applied (Figure 1A). It consists of the application of a surgical non-absorbable polytetrafluoroethylene 6.5 mm x 4 mm x 1.5 mm pledget over the two ProGlide sutures (one of each device). The steps practiced to mount the pledget over the suture threads are depicted in Figure 2. Then, the pledget was pushed down over the two sutures using the ProGlide knot-pusher, and tied with a hand-made sliding knot to achieve a stable approximation to the surface of the vessel wall.

After pledget application, selective iliac-femoral digital subtraction angiography was repeated to check for hemostasis achievement (Figure 1B).

When massive bleeding was noticed at the first angiographic check such that manual compression was considered insufficient, a peripheral balloon was advanced and inflated in the iliac-femoral artery by radial route to prevent significant blood loss during pledget-assisted hemostasis performance.

Study population

According to the standard practice of our center, all patients were referred for TAVR based on formal, multidisciplinary, heart-team discussion. For each patient, the peripheral computed tomography was revised by at least two operators to assess the feasibility of TF approach. Clinical data and procedure details were prospectively entered into a dedicated database that allowed to assess previously the impact of EuroSCORE on coronary interventions[9] and the safety of transradial procedures[10]. At the time of heart-team consultation, patients' surgical risk was graded according to the Society of Thoracic Surgeons (STS) predicted operative mortality[11]. TAVR risk was graded according to the STS-American College of Cardiology Transcatheter Valve Therapy (STS-ACC TVT)[12] using the online TAVR in-hospital mortality risk calculator (https://tools.acc.org/tavrrisk/#!/content/evaluate/).

The antiplatelet/anticoagulant regimen was individualized according to the patient's characteristics, and no standardized protocol was available. As a general approach, most of the patients received double antiplatelet therapy, while the patients with the need for anticoagulation were kept on anticoagulant therapy plus 1 mo of single antiplatelet therapy. All procedures were performed under systemic anticoagulation with unfractionated heparin (70 UI/kg, reversed with protamine sulfate at the end of the procedure, before hemostasis).

In-hospital clinical outcomes were prospectively recorded, since the continuous monitoring of in-hospital clinical outcomes for TAVR is part of the Institutional clinical pathway dedicated to patients with heart valve diseases (http://www.policlinicogemelli.it/Policlinico_Gemelli.aspx?p=21C1F922-73FF-4B2F-A2FF-022DE91A6586) according to the European recommendations[13]. Bleeding or vascular complications were defined according to Valve Academic Research Consortium-2 (VARC-2) criteria[14].

Out of consecutive patients who underwent TF-TAVR from October 2019 to September 2020, we selected all patients with residual access site bleeding who underwent pledget-assisted hemostasis attempt after the failure of double pre-closure technique with ProGlide suture. These patients constituted the study population of the present pilot study[15].

Study endpoints

The primary efficacy end-point was the achievement of angiographically-confirmed hemostasis in the operative room without the need for further bail-out interventions (surgery or endovascular).

The primary safety end-point was the occurrence of life-threatening bleedings, major bleedings, or major vascular complications as defined according to VARC-2 classification[14].

RESULTS

During the study period, 136 patients underwent TF-TAVR. The TAVR systems used included Medtronic Evolute R (n = 40, 29%), Medtronic Evolut Pro (n = 81, 60%), Edwards Sapien3 (n = 10, 7.3%),

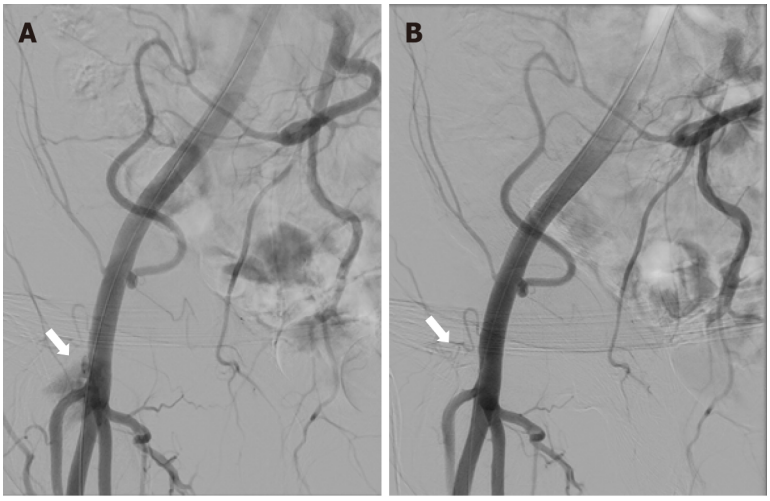

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Figure 1 Angiography before and after pledget-assisted hemostasis. A: Residual bleeding at the transcatheter-aortic-valve-replacement access site (white arrow) after double ProGlide preclosure; B: Absence of residual bleeding (white arrow) after pledget assisted hemostasis.

and Abbott Portico (n = 5, 3.7 %).

A total of 15 patients (mean age 80.0 ± 7.2 years, 66.7% female) with residual access site bleeding after double pre-closure in TF-TAVR were prospectively included in the pilot study. The main characteristics of the study population are summarized in Table 1. The average STS mortality score was 3.7 ± 2.5, and TAVR score was 2.69 ± 0.7. In the majority of patients, 16F sheath was used (n = 12; 80%), while 14F sheath was used in 2 patients (6.7%) and 18F in 1 patient (6.7%). Direct valve implantation was done only in 1 patient. In 6 (40.0%) patients, valve post-dilatation was done. Balloon inflation in the iliac artery was performed in 2 cases (13.3%) to limit blood loss during pledget preparation and in 2 cases (13.3%) to treat an intimal flap (Table 2).

Angiographically-confirmed hemostasis was achieved in all patients (100%).

After TAVR, 1 patient required blood transfusion (2 units) (Table 2), and no other bleeding or vascular complication were noticed (Table 2). All patients were discharged after 7 ± 5 d.

DISCUSSION

The complete percutaneous approach in TF-TAVR represents a less invasive technique to treat patients with aortic valve stenosis. Suture-based VCD use according to pre-closure technique is actually widely adopted to achieve arterial haemostasis but is associated with the possibility of residual blood leakage. Thus, as a part of TF-TAVR procedures, strategies to bailout manage VCD failures are daily applied according to various local expertise.

In the present study: (1) We describe a novel technique (based on "pledget" use) to manage double suture-based device failure; and (2) We report the efficacy and safety observed in a pilot clinical observational study.

According to VARC-2 position paper, "access-related" complications are defined as any adverse clinical event possibly associated with any of the access sites used during the procedure[14]. Across the literature, wide variations regarding the occurrence of vascular complications and their impact on clinical outcomes exist[16-18]. Different sizes of the valve delivery systems used over time, evolving closure techniques, and operator experience might play a major role. In such context, the occurrence of VCD failure might determine different clinical consequences ranging from life-threatening bleedings to the absence of any significant blood loss. According to recent studies[16-18], up to 70% of VARC-2 major vascular complications were related to VCD failure. Puncture site optimization and VCD selection might modulate VCD failure occurrence. Regarding entry-site optimization, the "perfect puncture" of CFA within spots free from calcium and above the bifurcation may be pivotal in reducing complications. To select a proper puncture site, either ultrasound guidance[19] or angio-guidewire-ultrasound technique[7] might be considered. Furthermore, different vascular closure devices (VCD) are available to diminish bleeding complications and to make TF-TAVR totally percutaneous. Percutaneous haemostasis of the large-bore devices used during TAVR, requires the "preclosure" technique, which is based on the deployment of the sutures before the introduction of the large sheaths. Then, after the valve implantation at the end of the procedure, sutures are tied by pushing down the knots after introducer removal.

Table 1 Main characteristics of study population

	Patients
Patient number	15
Age, yr (mean ± SD)	80.0 ± 7.2
Female gender	10 (66.7%)
BMI, kg/m^2 (mean ± SD)	27.41 ± 3.6
Risk factors	
Diabetes	2 (13.3%)
Hypertension	13 (86.7%)
Dyslipidemia	6 (40.0%)
Smoking	0
Medical history/comorbidities	
Chronic kidney disease (not on dialysis)	3 (20.0%)
Chronic dialysis	0
Peripheral artery disease	2 (13.3%)
Atrial Fibrillation	8 (53.3%)
Previous stroke	2 (13.3%)
Chronic pulmonary disease	2 (13.3%)
Previous myocardial infarction	2 (13.3%)
Previous PCI	4 (26.7%)
Previous CABG	1 (6.7%)
STS mortality	3.7 ± 2.5
TAVR score	2.69 ± 0.7
Anticoagulant and antiplatelet therapy	
Anticoagulants	7 (46.6%)
Dual antiplatelet therapy	6 (40%)
Clopidogrel	11 (73.3%)
Acetyl salicylic acid	8 (53.3%)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; STS: Society of Thoracic Surgeons; TAVR: Transcatheter-aortic-valve-replacement; SD: Standard deviation.

Regarding VCD selection, several devices entered the clinical practice and include suture-based closure devices such as 6F ProGlide, 10 F Prostar XL (both Abbott Vascular Inc, Santa Clara, CA, United States), and plug-based 14 F or 18 F MANTA (Essential Medical Inc., Malvern, PA, United States). Among suture-based closure devices, Prostar XL is associated with a higher rate of major bleeding compared to Proglide, as demonstrated in previous studies[20-24] and meta-analysis[25]. The novel collagen-based MANTA (14 and 18F) appears to be an effective and safe device for large-bore access closure, reporting only 4% of major and 5.6% of minor access site complications in the prospective MARVEL registry[5]. Initial data comparing MANTA with Proglide did not show clear advantages for MANTA device in the terms of access site bleeding complications[26-29]. Thus, the preclosure technique with ProGlide is still popular, and prompt hemostasis failure recognition and effective bailout management strategies might be pivotal to limit the clinical impact of VCD failure. Depending on the characteristics of the access site complications, different methods and materials for bailout endovascular interventions are proposed[2], mainly to avoid the risk of urgent vascular surgery. One possible solution is the crossover balloon occlusion technique (CBOT), which has been associated with a lower risk of VARC-2 major vascular bleeding complications[30]. Of note, CBOT might be effectively performed not only from the contralateral femoral artery, but it can be done ipsilaterally by superficial femoral artery access[31] or remotely by radial access[6].

Table 2 Bleeding and vascular adverse events according to the updated standardized endpoint from Valve Academic Research Consortium-2

Adverse events	*n* (%)	Adverse event description and management
Bleeding complications		
Life-threatening bleeding (bleeding in a critical organ or causing hypovolemic shock or severe hypotension requiring vasopressors or surgery or overt source of bleeding with drop in hemoglobin ≥ 5 g/dL or transfusion ≥ 4 units)	0	
Major bleeding (bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2-3 units, or causing hospitalization or permanent injury, or requiring surgery but does not meet criteria of life-threatening or disabling bleeding)	1 (6.7%)	1 patient requiring post-operative blood transfusion (2 units) without further bleeding source
Minor bleeding (any bleeding worthy of clinical mention that does not qualify as life-threatening, disabling, or major)	0	
Vascular complications		
Major vascular complications	0	
Minor vascular complications	2 (13.3%)	
Access site or access-related vascular injury (not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment)	2 (13.3%)	Two femoral artery non-occlusive dissections successfully treated by balloon angioplasty during the index procedure
Distal embolization	0	
Any unplanned vascular intervention (endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication)		
Need for vascular repair (*via* surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)	0	
Primary safety end-point (life-threatening bleedings or major bleedings or major vascular complications)	1 (6.7%)	

When a failure of VCD is recognized and wire is still left through the arteriotomy, either a third ProGlide device or an Angio-Seal (Abbott Vascular, Redwood City, CA, United States) can be utilized with great effectiveness and safety[32,33]. Yet, if a wire is no longer available, only prolonged manual compression or endovascular techniques through other arterial accesses can be practiced. Thus, we introduced the novel option of using the Proglide's sutures to deliver a surgical pledget in order to seal residual leak. According to our experience, this "pledget-assisted hemostasis" was highly effective, allowing early achievement of complete hemostasis. This translated into the smooth clinical post-procedural course in all but 1 patient (who received blood transfusion in the absence of further blood loss source documentation).

Study limitations

The present paper should be regarded just as a pilot study for a novel technique practiced by experienced interventional cardiologists in a limited number of procedures. Important limitations are evident (beyond the sample size) in this study.

First, the long-term safety of this technique has still to be ascertained, since specific complications (like local infections) might theoretically be triggered by the use of additional devices and we limited our follow-up to the in-hospital period.

Second, the study lacked a comparative arm. Thus, it is not possible to speculate regarding the possible benefit as compared with other bailout management strategies.

CONCLUSION

We have proposed a novel strategy to guarantee post TF-TAVR access site hemostasis using the Proglide sutures to deliver a surgical pledget in order to seal residual leak. The "pledget assisted hemostasis" might be considered as a possible bailout technique to treat patients with residual access site bleeding. Further studies are needed to compare this approach with other bail-out techniques.

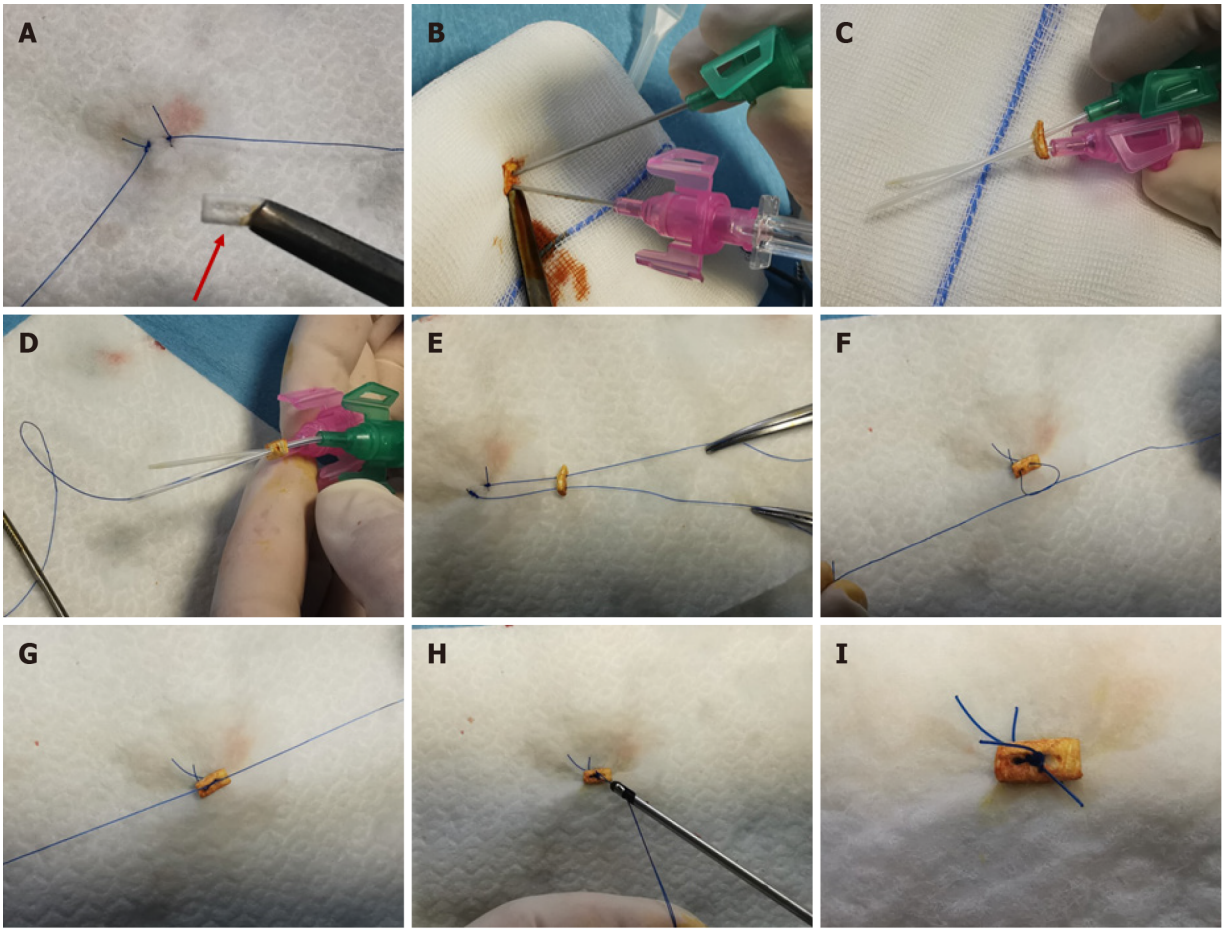

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Figure 2 Steps of pledget-assisted hemostasis. The technique is shown as practiced on a white drape in order to show the steps in the absence of blood. A: Double ProGlide suture after cutting one monofilament from each device and pledget (red arrow); B: Insertion of two cannulas through the pledget (colored by iodine solution to facilitate recognition); C: Steel needles removal from the cannulas; D: Insertion of ProGlide monofilaments through the cannulas; E: Cannulas removal leaving Proglide monofilaments inserted through the pledget; F: Realization of one of two knots; G: Pledget fixation on the artery wall tightening the knots; H: Cut of residual Proglide threads; I: Final configuration achieved with pledged tightened over the two ProGlide's sutures.

ARTICLE HIGHLIGHTS

Research background

The most common technique used for hemostasis in transfemoral transcatheter aortic valve replacement (TF-TAVR) is the use of pre-closure devices. Despite favorable results in terms of successful hemostasis, sometimes it can be followed by device failure and residual bleeding.

Research motivation

Although there are different possibilities to manage residual bleeding after hemostasis device failure, such as bailout additional closure device use, balloon-assisted hemostasis, or surgery, the best management is still unclear.

Research objectives

To describe and report the results of an original technique for managing residual access site bleeding after vascular closure devices failure.

Research methods

The authors developed a novel technique to resolve residual access-site bleeding named "pledget assisted hemostasis". If residual bleeding was noticed, "pledget assisted hemostasis" with surgical non-absorbable polytetrafluoroethylene 6.5 mm x 4 mm x 1.5 mm pledget was done on the top of double pre-closure device. Proper hemostasis without residual bleeding was confirmed with control angiography.

Research results

A total of 15 consecutive patients (mean age 80.0 ± 7.2 years, 66.7% female) with residual access site bleeding after double pre-closure in TF-TAVR were prospectively included in this pilot study. In the majority of patients 16F sheath was used (n = 12; 80%), 14F sheath was used in 2 patients (6.7%), and 18F in 1 patient (6.7%). Hemostasis with the pledget technique was achieved in all patients (100%) immediately after implantation. Major bleeding defined by Valve Academic Research Consortium-2 definition did not occur. No access site infection was observed in the follow-up period.

Research conclusions

"Pledget assisted hemostasis" after pre-closure vascular device failure might be considered as a possible bailout technique to treat patients with residual access site bleeding. Further studies are needed to compare this approach with other bail-out techniques.

Research perspectives

"Pledget assisted hemostasis" might be considered as a possible bailout technique for vascular closure device failure.

FOOTNOTES

Author contributions: Burzotta F conceived the study; Burzotta F and Aurigemma C extracted, analyzed, and interpreted the data and drafted and revised the final version of the manuscript; Kovacevic M collected the clinical data and drafted and revised the final version of the manuscript; Trani C, Burzotta F, Aurigemma C, and Romagnoli E performed the procedures; Bruno P, Nesta M, Romagnoli E, Bianchini F, and Cangemi S collected the clinical data and interpreted the data; Trani C helped interpret the data and critically reviewed the manuscript for important intellectual content.

Conflict-of-interest statement: Dr. Burzotta F, Trani C and Aurigemma C received speaker's fees from Abbott, Medtronic, and Abiomed. Other authors have no conflicts of interest.

Data sharing statement: Data are collected according to our institution center record of the activity of cath laboratory. Clinical data and procedure details were prospectively entered into a TAVI-dedicated section of an electronic database.

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ORIGINAL ARTICLE

Retrospective Study

Day-to-day blood pressure variability predicts poor outcomes following percutaneous coronary intervention: A retrospective study

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Abstract

BACKGROUND

For patients with cardiovascular disease, blood pressure variability (BPV), distinct from hypertension, is an important determinant of adverse cardiac events. Whether pre-operative BPV adversely affects outcomes after percutaneous coronary intervention (PCI) is to this point unclear.

AIM

To investigate the relationship between blood pressure variability and outcomes for patients post-PCI.

METHODS

Patients undergoing PCI in a single state in 2017 were studied (n = 647). Systolic and diastolic BPV, defined as both the largest change and standard deviation for the 3-60 mo prior to PCI was calculated and patients with more than ten blood pressure measurements in that time were included for analysis (n = 471). Adverse

outcomes were identified up to a year following the procedure, including major adverse cardiac events (MACE), myocardial infarction, cerebrovascular accident, death, and all-cause hospitalization.

RESULTS

Visit-to-visit systolic BPV, as measured by both standard deviation and largest change, was higher in patients who had myocardial infarction, were readmitted, or died within one year following PCI. Systolic BPV, as measured by largest change or standard deviation, was higher in patients who had MACE, or readmissions ($P < 0.05$). Diastolic BPV, as measured by largest change, was higher in patients with MACE and readmissions ($P < 0.05$).

CONCLUSION

As BPV is easily measured and captured in the electronic medical record, these findings describe a novel method of identifying at-risk patients who undergo PCI. Aggressive risk modification for patients with elevated BPV and known coronary artery disease is indicated.

Key Words: Blood pressure variability; Percutaneous coronary intervention; Angioplasty; Major adverse cardiac events

Core Tip: Pre-procedural visit-to-visit blood pressure variability, as measured by either standard deviation or largest change between two consecutive visits, is higher in patients who are readmitted, have complications, or die after percutaneous coronary intervention. Aggressive risk modification is indicated for patients with elevated blood pressure variability and known coronary artery disease.

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INTRODUCTION

Percutaneous coronary intervention (PCI) has long been established as an effective method of coronary revascularization for patients with coronary artery disease and is performed over 965000 times each year in the United States[1]. When patients present with acute coronary syndrome, it is estimated that approximately 60% will undergo PCI, 10%-15% will require surgical revascularization with coronary artery bypass graft (CABG), and the remainder are treated with medical therapy alone[2]. Although PCI is generally safe, known subsets of patients are at elevated risk for procedural complications after PCI. These include patients in shock, chronic heart failure, complex vascular anatomy, and diabetes mellitus, among others[3]. In addition to acute complications (such as bleeding at the entry site, vascular injuries, and arrythmias), patients may suffer from delayed complications after the procedure. Post-procedural additional major adverse cardiac events (MACE), include myocardial infarction (MI), cerebrovascular accident (CVA), hospitalization, or death. Risk factors for these delayed outcomes are less well understood. Aside from diabetes mellitus, relatively little is known about non-cardiac factors impacting outcomes after PCI.

In particular, whether preoperative blood pressure variability (BPV) affects outcomes after PCI is unclear. BPV, which is distinct from hypertension, is a measure of the degree of instability of a patient's blood pressure (BP) over time. BPV has been shown to be a risk factor for 90-day rates of complications after major surgical procedures, including coronary artery bypass graft (CABG)[4,5]. BPV may be calculated in a variety of ways, using standard deviation (SD), average change, or largest change between consecutive measurements (LC), and may be based upon either systolic or diastolic blood pressure readings[6]. BPV is most commonly reported in the literature by SD, but each method of reporting BPV may be similarly valid[7]. High outpatient BPV is associated with higher risk of all-cause hospitalization and death in ambulatory medical patients[8] and surgical patients[4], regardless of if the patient is hypertensive, normotensive, or hypotensive[9]. Indeed, BPV has recently been shown to predict cardiac events in patients with heart failure[10], and to be associated with development of end stage renal disease[11], and with cerebral small vessel disease leading to CVA[12]. The causes of BPV are likely highly multifactorial and may be due to physiological abnormalities (such as vascular wall

stiffness and hypertrophy), autonomic dysfunction, "white coat syndrome", and medication non-compliance[13,14]. For patients with cardiovascular disease, consistency of BP control has been shown to be an important determinant of adverse cardiac events[3,6,8]. BPV has also been shown to be associated with adverse outcomes in patients with cardiac failure[10], survivors of STEMI[15], in patients undergoing CABG[5], and other major surgical procedures[4]. We therefore sought to determine whether elevated BPV would be associated with adverse outcomes in patients undergoing less invasive cardiac procedures than CABG, such as PCI. In particular, we hypothesized that patients who had adverse outcomes would have higher mean BPV than those who did not have these outcomes, and that the likelihood of a poor outcome would be greater for patients with larger pre-procedural BPV.

Previously collected data was reviewed from a prospectively maintained registry of patients who underwent PCI at a single institution and whose outcomes were then prospectively tracked. Patients who had a minimum of 10 prior outpatient BP recordings 3 to 60 mo prior to the procedure were included in this study to assure accuracy of BPV calculation. Charts were retrospectively reviewed to calculate BPV as both standard deviation and largest change for both systolic and diastolic BPV. BPV in patients who had poor outcomes was compared to those who did not; logistic regressions were used to control for the indication of the procedure.

MATERIALS AND METHODS

This study was approved by the Institutional Review Boards of the University of North Dakota and the Sanford Medical Center. The subjects for this study were retrospectively drawn from a prospectively maintained database of all patients who underwent a PCI at Sanford Medical Center in Fargo, North Dakota in 2017 (n = 647). Patients within the reach of this system generally receive most of their healthcare, both inpatient and outpatient, at either the same or an affiliated institution. The electronic medical record was queried and BP recordings (n = 25844) both from within and outside the hospital from patients prior to PCI were identified. Only individuals who had a minimum of 10 BP recordings 3-60 mo before PCI (n = 471) were included for analysis. The remaining 176 patients were excluded from the study. Of these excluded, 2 were missing demographics, 75.29% were male, and the average age was 66.3

A total of 22,253 BP recordings were analyzed for 471 patients. BPV was defined as systolic and diastolic SD and largest change (LC, mmHg) between consecutive patient encounters. MACE outcomes of MI, CVA, death, and all-cause hospitalization were identified up to a year after PCI. Readmission was defined as a recurrent admission to the hospital within 1 year of discharge after hospitalization from PCI procedure. The procedural indication was categorized as staged PCI (n = 48), non-STEMI (n = 249) or other (n = 174). Other variables including demographics, prior diagnoses, and medication use were retrieved from the records.

Statistical analysis

BPV and BP characteristics along with demographics, diagnoses, medications, and indications were described for patients by MACE outcome status. Independent t-tests and chi-square analyses were used to determine any relationships between patients with or without an outcome of MACE. Logistic regressions of BPV predicting MACE, readmission, and MI outcomes after 1-year were done while controlling for age, sex, smoking status, diagnoses of hypertension or diabetes, prior cardiovascular disease, prior MI, prior PCI, prior CABG, pre-procedure creatine level, prior PCI left ventricular ejection fraction, anginal class (no symptoms as reference value, Canadian Cardiovascular Society I, II, III, or IV), on anti-anginal medications, and indication (staged PCI was used as the reference value). Although the registry data did not indicate which patients had pre-existing chronic kidney disease, we did analyze pre-procedural serum creatinine level. This was categorized as values of less than or equal to 2, 2-5, or greater than 5 mg/dL. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated. Receiving operator characteristic (ROC) analysis was done to determine the best cutoff values for the four measures of BPV in determining MACE, readmission, and MI. Two-way analysis of variance (ANOVA) with interaction was done for the BPV measures between MACE and the categorical variables age, anginal class, and indication to test if the relationships between the BPVs and MACE differed for levels of those variables. SAS v. 9.4 was used for the analysis and alpha was set to 0.05.

RESULTS

Four hundred and seventy-one patients who had undergone a PCI and had 10 or more blood pressure readings 3-60 mo prior to PCI were studied. Table 1 presents the demographics of this patient sample. The average age was 68.8 (SD 11.5, range 35-95) and 72.1% were male. Five types of adverse outcomes were identified: 147 (31.2%) of the patients had MACE, 131 (27.8%) were readmitted, 47 (10.0%) had MI, 21 (4.5%) died, and 6 (1.3%) had CVA. Patients who had a MACE were an average of 2 years older (P =

Table 1 Descriptive statistics of variables in data set by adverse event for 471 patients with percutaneous coronary intervention

	No MACE (*n* = 324)			Had MACE (*n* = 147)		
	n	**mean**	**SD**	***n***	**mean**	**SD**
Systolic SD	324	13.72	6.02	147	15.38	5.26
Diastolic SD	324	8.54	3.11	147	8.93	2.71
Systolic LC	324	37.11	14.79	147	44.31	15.42
Diastolic LC	324	23.60	7.78	147	26.37	9.09
Systolic average	324	131.83	11.47	147	132.20	11.63
Diastolic average	324	74.82	7.75	147	71.33	7.64
Number of BP readings	324	40.19	35.86	147	62.81	52.85
Mean days between readings	324	59.07	37.04	147	42.19	30.70
Age	322	67.87	11.21	147	70.69	11.86
Pre PCI LVEF	252	56.44	11.73	122	53.06	13.63
Pre creatinine	307	1.15	0.98	138	1.50	1.19
		n	%		*n*	%
Sex	469					
Male		110	74.83		228	70.37
Female		37	25.17		94	29.01
Race	469					
White		142	96.60		312	96.30
Other		5	3.40		10	3.09
Hispanic		1	0.68		4	1.23
Smokes	467	22	14.97		51	15.74
Has hypertension	469	135	91.84		266	82.10
Has diabetes	469	67	45.58		122	37.65
Had prior CVD	469	39	26.53		68	20.99
Had prior MI	470	106	32.72		63	42.86
Had prior PCI	470	125	38.58		67	45.58
Had prior CABG	470	53	16.36		41	27.89
Prior creatinine	445					
0 to 2		296	91.36		118	80.27
> 2 to 5		8	2.47		18	12.24
> 5		3	0.93		2	1.36
Anginal class	469					
No symptoms		33	22.45		24	7.41
CCS I		11	7.48		39	12.04
CCS II		27	18.37		87	26.85
CCS III		43	29.25		95	29.32
CCS IV		33	22.45		77	23.77
On anti-anginal medication	469	114	77.55		204	62.96
Beta-blockers		98	66.67		164	50.62
Calcium channel blockers		37	25.17		76	23.46
Long-acting nitrates		33	22.45		41	12.65

Ranolazine		3	2.04	2	0.62
Indication	471				
Non-STEMI		82	55.78	167	51.54
STEMI		9	6.12	39	12.04
Other stage		56	38.10	118	36.42
MACE within 1 yr	471				
Readmission				131	27.81
MI				47	9.98
Death				21	4.46
CVA				6	1.27

MACE: Major adverse cardiac events; SD: Standard deviation; LC: Largest change; BP: Blood pressure; PCI: Percutaneous coronary intervention; LVEF: Left ventricular ejection fraction; CVD: Cardiovascular disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; CCS: Canadian Cardiovascular Society; STEMI: ST-segment elevation myocardial infarction; CVA: Cerebrovascular accident.

0.016). Hypertension was very common in both groups, though more so in patients with no MACE (P = 0.013). 15% more of those with a MACE were on anti-anginal medication (P = 0.003), with the largest difference found in patients taking beta blockers (16%; P = 0.002) and long-acting nitrates (10%; P = 0.011). Patients with a MACE were 5% more likely to be in anginal class CSS I and 8% more in CSS II (P < 0.001). About half were non-STEMI but twice as many MACE patients were STEMI.

BPV was measured in two ways, SD of all patient BPs in the study period and the largest change (LC) between two consecutive outpatient BP measurements. Table 1 shows the average values for the four BPV measures by MACE category. Systolic SD measures were significantly higher for patients with MACE (mean 15.38 ± 5.26) than patients with no MACE (mean 13.72 ± 6.02; P = 0.004). The diastolic SD were less than the systolic (8.54 and 8.93) but not significantly different between MACE categories (P = 0.188). Like the systolic SD, the systolic LC was significantly higher in MACE group (P < 0.001). The diastolic LC was on average 3 points higher for the MACE group (P = 0.002). Average systolic measures were comparable in each group, mean 131.83 ± 11.47 and mean 132.20 ± 11.63 (P = 0.748). The average diastolic measures of the MACE patients (mean 71.33 ± 7.64) were significantly lower than patients with no MACE (mean 74.82 ± 7.75) (P < 0.001). We also tested the metrics for gathering the BPs and found that those with MACE had 12 more BP readings on average (P < 0.001) though this variable was badly skewed. MACE patients had 17 fewer days between readings on average than non-MACE patients (P < 0.001).

Logistic regressions (controlling for demographics and health status) were used to estimate the risk of higher BPV for adverse outcomes. Only the outcomes of MACE, all-cause hospitalization, and MI were used for these analyses due to relatively small number of patients who experienced the other specific outcomes. Figure 1 shows the ORs for BPV predicting the outcomes. No BPV measures significantly increased the risk of MI when controlling for demographics and health status. The risk of all-cause hospitalization was increased significantly by higher systolic BPV as calculated by both LC (OR = 1.024, 95%CI: 1.006-1.042) and SD (OR = 1.049, 95%CI: 1.000-1.099). The risk of MACE was also increased significantly by higher systolic BPV as calculated by LC (OR = 1.024, 95%CI: 1.007-1.042) and SD (OR = 1.049, 95%CI: 1.003-1.100). Although eight of the risks of these outcomes were not statistically significant, we noted a trend where patients with high BPV had increased risk of any outcome.

Receiving operator characteristic (ROC) curves were generated to determine cutoff values of the four BPV measures for predicting MACE, hospitalizations, and MI (Figure 2). The systolic BPVs appeared better at predicting outcomes. Table 2 shows the cutoff value used that maximized sensitivity and specificity, the area under the ROC curve (AUC) and corresponding 95% confidence intervals. The cutoff values for systolic SD determining MACE was 12.0, 14.0 for readmission, and 13.5 for MI. Diastolic SD ranged from 8 to 9, systolic LC was 33 to 48, and diastolic LC was 15 to 26. Sensitivities ranged from 45% to 82%, and specificities from 44% to 77%. All AUCs were significantly different from 50%.

The relationships between the four BPVs and MACE were tested with subgroups of age, anginal class, and indication. Significant interaction in a two-way ANOVA indicated the relationship may differ according to groups. There were no significant interactions with anginal class and indication, suggesting the relationships between the BPV and MACE did not differ by those subgroups. Age (Figure 3) had significant interactions for systolic SD (P = 0.0429) and systolic largest change (P < 0.001).

Table 2 Receiver operative characteristic analysis of cutoff values for four measures of blood pressure variability predicting adverse events

	Cutoff	Sensitivity	Specificity	AUC	95% confidence interval	
					Low level	Upper level
MACE						
Systolic SD	12.0	0.7755	0.4475	0.6300	0.5752	0.6792
Diastolic SD	8.0	0.6395	0.5216	0.5674	0.5102	0.6195
Systolic LC	33.0	0.7891	0.4414	0.6510	0.5957	0.7001
Diastolic LC	26.0	0.5102	0.6235	0.5837	0.5262	0.6359
Readmission						
Systolic SD	14.0	0.5573	0.6324	0.6348	0.5792	0.6846
Diastolic SD	8.0	0.6565	0.5206	0.5734	0.5149	0.6267
Systolic LC	33.0	0.8168	0.4412	0.6592	0.6039	0.7083
Diastolic LC	25.0	0.5573	0.6176	0.6018	0.5426	0.6549
MI						
Systolic SD	13.5	0.6596	0.5684	0.6234	0.5371	0.6967
Diastolic SD	9.0	0.4894	0.6604	0.5730	0.4800	0.6533
Systolic LC	48.0	0.4468	0.7665	0.6609	0.5649	0.7393
Diastolic LC	26.0	0.6170	0.6038	0.6255	0.5370	0.7004

AUC: Area under the ROC curve; MACE: Major adverse cardiac events; SD: Standard deviation; LC: Largest change; MI: Myocardial infarction.

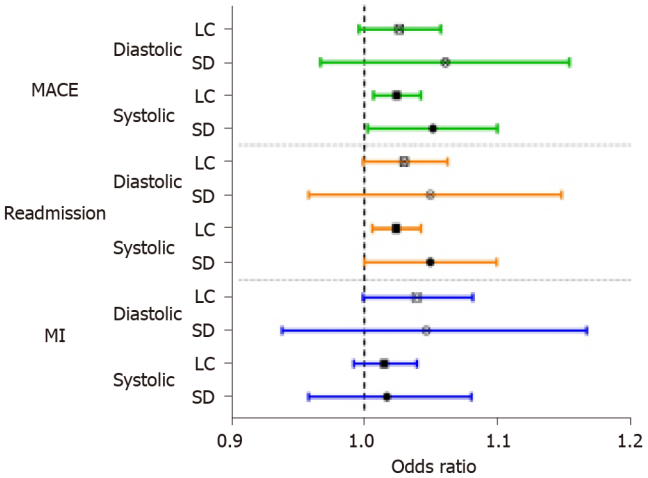

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Figure 1 Adjusted odds ratios with 95% confidence intervals from logistic regressions of preoperative blood pressure variability predicting outcomes after percutaneous coronary intervention. Odds ratios were controlled for age, sex, smoking status, diagnoses of hypertension or diabetes, prior cardiovascular disease, prior myocardial infarction, prior coronary artery bypass graft, prior percutaneous coronary intervention (PCI) left ventricular ejection fraction (LVEF), prior creatinine, anginal class, on anti-anginal medications, indication, and average systolic or diastolic blood pressure. Due to some missing values, myocardial infarction was not adjusted for PCI LVEF and creatinine. MACE: Major adverse cardiac events; MI: Myocardial infarction; LC: Largest change; SD: Standard deviation.

DISCUSSION

Chronic outpatient BPV, distinct from hypertension, has been shown to be associated with poor patient outcomes, not only in the general population, but in those who undergo surgical procedures[4] including CABG[5]. BPV can be studied as either systolic or diastolic variability, and each can be calculated by standard deviation as well as the largest change between two consecutive measurements.

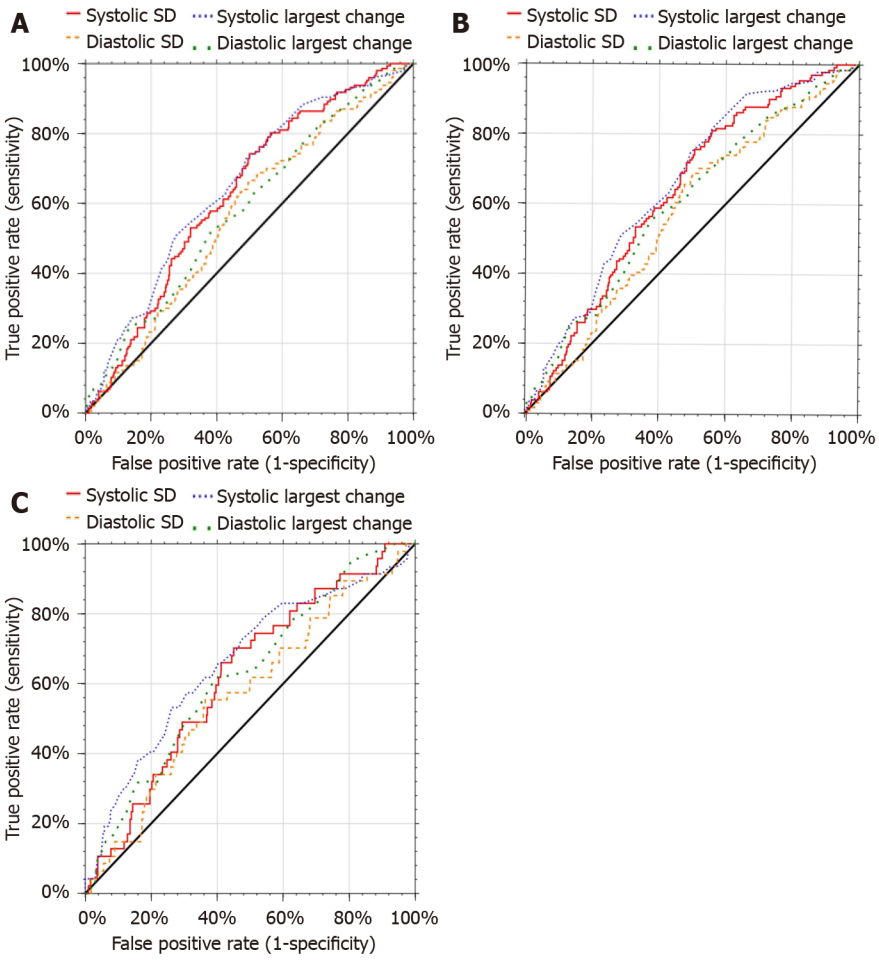

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Figure 2 Receiver operating characteristic curves for blood pressure variability predicting major adverse cardiac events, readmission, and myocardial infarction for patients one year after undergoing percutaneous coronary intervention. A: Major adverse cardiac events blood pressure variability (BPV); B: Readmission BPV; C: Myocardial infarction BPV. SD: Standard deviation.

A minimum of 10 outpatient BP recordings to measure BPV was previously used by other authors, ourselves included, because it was found to include enough measurements over a long enough timeframe to define BPV, yet short enough to be practical as patient physiology can drastically change with too large of a time interval[8]. Our key findings from this study were three. First, high pre-operative BPV gives patients elevated risk for poor outcomes following PCI. Second, systolic BPV may be a more sensitive indicator of adverse outcomes than diastolic BPV. Third, calculating BPV by LC seemed more indicative of adverse outcomes than calculating BPV by SD (following PCI).

While high BPV has been associated with worse post-operative outcomes after complex and highly invasive procedures such as CABG, colectomy, and total hip replacement[4,5], this is to our knowledge the first study investigating how BPV affects these outcomes after a much less invasive procedure such as PCI in patients who are known to have cardiac disease. This study confirms that patients with higher BPV are more likely to have poor outcomes after undergoing PCI. This is important because most patients who undergo PCI are already at higher baseline risk of adverse health outcomes, and thus preoperative BPV predisposes these individuals to an even higher risk. Patients who suffered from MI, all-cause hospitalization, and death within one year of the procedure had a significantly higher mean SD of their systolic BP. These patients also had a significantly larger mean greatest difference of both systolic and diastolic pressures. Moreover, when procedural indication was adjusted for, we found that risk for developing MI, all-cause hospitalization, and MACE was significantly increased when BPV was measured by LC.

Long term BPV has been shown to be a risk factor for MACE in several populations including type 2 diabetics, the elderly, younger populations, those with end stage renal disease, and post-operative patients[4,11,16-18]. Our results suggest that MACE occurs more frequently after PCI in patients with higher systolic BPV, and this remained true even when adjusted for indication. Regardless of how it is measured, even small changes in BPV can be clinically significant and associated with adverse outcomes for patients. Physicians should consider BPV while counseling patients who are considering elective PCI on the risks of the procedure. If a patient has high BPV, this may present an opportunity for physicians

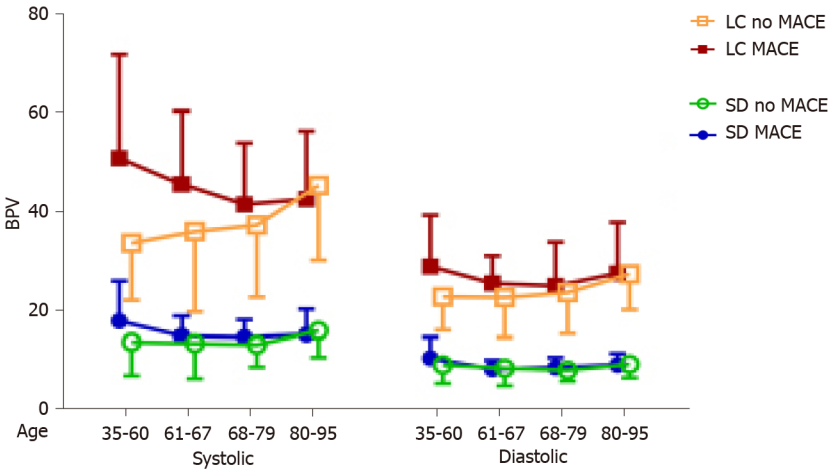

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Figure 3 Mean blood pressure variability by age and major adverse cardiac event status of patients one year after undergoing percutaneous coronary intervention. BPV: Blood pressure variability; LC: Largest change; MACE: Major adverse cardiac events; SD: Standard deviation.

to educate their patients on their other cardiac risk factors. Perhaps patients could be more motivated to modify controllable risk factors, such as smoking or a sedentary lifestyle, if they know that they have additional non-modifiable risk factors such as BPV. Moreover, although all patients are followed carefully, when a patient with high BPV undergoes PCI it may be vital to conduct additional thorough follow-up and vigilant surveillance to identify and intervene if such outcomes may occur.

The etiology of BPV is not well understood, although a couple hypotheses exist on what contributes to BPV. One hypothesis is that BPV is related to differing coronary physiology due to vascular wall stiffness, hypertrophy, and cardiovascular plaque stability among others. Greater BPV in young people with an absence of cardiovascular disease has been shown to be related to central aortic stiffness[18]. BPV is associated with unstable coronary plaques in patients with stable angina[14] and with carotid arterial stiffness in elderly patients[17]. Blood pressure control may facilitate the regression of left ventricular hypertrophy, and it has been suggested that increased blood pressure variability may be a contributing cause of idiopathic cardiac hypertrophy[19,20]. BPV has been shown to increase arthroscopic plaque vulnerability[14,21] which could be a factor in some of these adverse outcomes. Surgical risks could be directly affected by autonomic instability which has been indicated in patients with BPV [20]. Any of these could cause a different response to PCI as compared to patients who have better blood pressure stability.

Others have suggested that BPV may be a proxy for differences in inflammatory responses to the physiologic stressors and the acute coronary illness that follows[22]. Components of both the innate and adaptive immune system, specifically various cytokine differences, toll-like receptors, and inflammasomes, have been shown to play a role in pathogenesis of elevated blood pressure[23]. Although this relationship has not yet been specifically studied in blood pressure variability, it is possible that inflammatory changes that are associated with hypertension might also lead to BPV within that hypertension. Such differences could alter the acute response to the trauma caused by PCI, thus putting patients at a higher risk for later adverse outcomes. Although further extrapolation of the etiology of BPV is certainly warranted, it seems likely that both intrinsic baseline biology and anatomy and differences in patients' physiologic reactions to stress may all be associated with BPV in these patients and may contribute to their subsequent risk.

Although we[8] and others[7] have previously suggested that how BPV is calculated may be inconsequential, the results of this study seem to contrast with this idea. In this post-PCI population, systolic BPV seemed to be more sensitive of a predictor of adverse outcomes than diastolic BPV. Additionally, largest change may have been a more powerful predictor of adverse outcomes than standard deviation. This is potentially important because SD seems to be the most common way that BPV is analyzed in the literature. Increased systolic BPV showed statistical significance as a risk factor for each adverse outcome in this population as measured by LC. Systolic BPV as a more indicative measure of adverse outcomes after PCI may partially be due to the relatively high age of the patients who undergo this procedure. Systolic BP is known to have more use as a prognostic indicator with increasing age[22] and the average age of this population was 68.8 ± 11.5. Another factor to consider is that the association between elevated BPV and coronary atheroma progression was more strongly associated with systolic BPV[21].

Increased diastolic BPV also showed statistical significance for three outcomes but did not achieve statistical significance with any outcomes when calculated by SD. This suggests that diastolic BPV can also be a predictor of adverse outcomes when measured by LC. Although patients who experienced

adverse outcomes were not shown to be significantly different than those who did not have adverse outcomes when measuring diastolic BPV by SD, we did observe a trend in this direction and it is possible that this might have become statistically significant with a larger sample size since we did observe statistical significance when diastolic BPV was assessed using LC. Additionally, although six of the risks of the outcomes measured by logistic regression were not statistically significant, a general trend was noted in that patients with high BPV had elevated risk of any outcome occurring. Although age is a potential hypothesis for the differences between systolic and diastolic BPV as a risk factor for adverse outcomes, work remains to be done to determine the etiologic differences that exist between systolic and diastolic BPV.

Although it is possible that LC may be a more sensitive indicator of risk than SD in patients undergoing PCI, this may also be an artifact of this particular sample. Regardless, it seems clear that LC is at least as useful, if not more useful than SD in risk estimation. This is important because until electronic medical records are programmed to automatically calculate BPV for every patient, the average physician will find LC to be much easier to calculate, less time consuming, and more intuitive than attempting to determine SD. The physician may simply scan a list of blood pressure readings and find the largest change between consecutive encounters to rapidly screen patients for BPV prior to selection for PCI. Further studies need to be done to determine if LC could indeed be a stronger predictor of adverse outcomes than SD.

In cardiovascular trials, different authors use various defined composite clinical endpoints, one of which is commonly MACE. 3P MACE and 4P MACE exist depending on whether 3 or 4 individual event endpoints are used, with some variability of what these endpoints are 3 endpoint MACE are commonly defined to include MI, death, and CVA[24]. Although not commonly reported as a MACE, hospitalization is a commonly used endpoint related to heart failure or other post-operative trials, so we believe that it is appropriate to use all cause hospitalization as a composite endpoint for a major adverse cardiac event[24]. Therefore, we used a somewhat original 4P MACE for our study which we defined as all-cause hospitalization, MI, death, and CVA.

This study has limitations. 27% of the patients who underwent angioplasty during the study period were excluded *a priori* because they did not have 10 outpatient BP readings 3-60 mo prior to PCI. We had made this decision in advance of collecting our data because our previous analysis[8] suggested that BPV can be very accurately calculated with at least 10 readings. These 171 patients otherwise had remarkably similar demographics to the patients who were included in the study, making it less likely that selection bias has affected our results. Another potential concern is whether we missed complications in patients who may have gone to a separate healthcare system with their post-procedural complications. However, Sanford Health has a large catchment area and shares access to surrounding health systems' electronic records. Moreover, there seems no particular reason to postulate that patients with low or high BPV would have been more likely to seek attention at outside facilities which was indicative in that the outcomes we ascertained had 100% follow up prospectively. Another potential concern is that the BP readings that were used in this study were derived from chart review after routine clinical practice rather than being measured by pre-designed specified protocols. Clinical trials often utilize very precise practices to measure BP precisely because without such practices BP measurement may differ from how it is routinely measured in the clinical setting. Our BP measurements do lack standardization, which thus could be interpreted as a weakness in that measurements were not taken at fixed intervals with fixed protocols. However, the BP measurements used here do reflect how physicians would routinely assess patients' BPV in the clinic. Thus, one might conversely propose that this apparent limitation actually makes our study results more relevant to the real world. While considering kidney disease simply by pre-procedural serum creatinine levels is not ideal and represents a limitation to this study, the diagnosis of chronic renal failure was not included in the data available for analysis. While it would have been interesting to calculate a Kaplan-Meier survival curve for MACE, the specific dates for these key complications were unfortunately not included in the registry and so these data were unfortunately unavailable for analysis.

CONCLUSION

High outpatient BPV predicts adverse outcomes after PCI, including all-cause hospitalization, death, MI, and CVA, regardless of whether the patient is chronically hypertensive or normotensive. Calculating BPV by largest change was a stronger predictor than standard deviation for MACE within 1 year of the procedure. This was true for both systolic and diastolic BPV, although systolic BPV seemed to be a more sensitive indicator of poor outcomes. Prior to PCI, patients with high BPV should be counseled by their physician about their increased risk for adverse outcomes and should be followed more vigilantly after their procedure. Most percutaneous coronary interventions are relatively urgent and cannot be postponed for long periods of time for patients to attempt to modify risk factors prior to PCI. Furthermore, further research is still required to identify changes or pharmacologic interventions that patients may undertake to usefully reduce their BPV. However, patients with higher BPV who are about to undergo PCI can and should be counselled that they are at a higher risk of post-procedural

complications and that they should subsequently address any other modifiable risk factors that are also associated with poor post-operative outcomes to best optimize their individual post-procedural outcomes. Physicians performing PCI may also wish to consider BPV as they decide how aggressive to be in their procedures, while quality comparisons of PCI programs or research on future PCI interventions should consider as an additional risk factor in multivariate analyses of outcomes. Work remains to be done to discover the true etiology of BPV as well as why systolic and diastolic variability may have differing impacts on the patients' outcomes.

ARTICLE HIGHLIGHTS

Research background

Blood pressure variability (BPV), distinct from hypertension, is known to be a risk factor for long term complications, and has recently been shown to increase the acute risk of postoperative death, hospitalization, or other complications for patients undergoing major surgical procedures.

Research motivation

The impact of BPV on outcomes after the less invasive procedure of percutaneous coronary interventions (PCI) has not previously been explored despite the high risk nature of these patients.

Research objectives

To determine whether BPV represents an independent risk factor for poor outcomes after percutaneous coronary angioplasty.

Research methods

Six hundred and forty-seven patients undergoing PCI in a single state in 2017 were prospectively enrolled in a patient registry which was then retrospectively analyzed. Systolic and diastolic BPV were calculated as both the largest consecutive change between blood pressure measurements and the standard deviation of all blood pressure measurements for the 30-60 mo prior to PCI, considering only the 471 patients with more than ten blood pressure measurements for analysis. Other variables including demographics, prior diagnoses and medication use were retrieved. Procedural indications were categorized as staged PCI, non-STEMI, or other. Adverse outcomes were identified for up to a year following the procedure, including MACE, myocardial infarction, cerebrovascular accident, death, and all-cause hospitalization.

Research results

Even after taking into account other patient characteristics, visit-to-visit systolic BPV, as measured by both standard deviation and largest change, was higher in patients who had myocardial infarctions, were readmitted, or died within one year following PCI. Systolic BPV was higher in patients who had major adverse cardiac events (MACE), or readmissions ($P < 0.05$). Diastolic BPV, as measured by largest change, was higher in patients with MACE and readmissions ($P < 0.05$).

Research conclusions

BPV represents an independent risk factor for poor outcomes after PCI.

Research perspectives

BPV is easily measured and captured from the electronic medical record. Cardiologists performing PCI should consider high BPV in choosing among procedural outcomes or observation, and should follow patients with high BPV more closely after PCI. Patients with high BPV should be counseled about this risk factor in the informed consent process and should be counseled to work more aggressively to reduce other more modifiable risk factors after PCI in the face of their BPV.

FOOTNOTES

Author contributions: Weisel CL, Dyke CM, Haldis TA, and Basson MD designed the research study; Weisel CL, Dyke CM, Klug MG, Haldis TA, and Basson MD performed the research study; Klug MG contributed new analytic tools; Weisel CL, Klug MG, and Basson MD analyzed the data; Weisel CL, Dyke CM, Klug MG, Haldis TA, and Basson MD wrote the manuscript; and All authors have read and approved the final manuscript.

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META-ANALYSIS

Comparative efficacy and safety of adenosine and regadenoson for assessment of fractional flow reserve: A systematic review and meta-analysis

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Abstract

BACKGROUND

Adenosine is a coronary hyperemic agent used to measure invasive fractional flow reserve (FFR) of intermediate severity coronary stenosis.

AIM

To compare FFR assessment using adenosine with an alternate hyperemic agent, regadenoson.

METHODS

PubMed, Google Scholar, CINAHL and Cochrane databases were queried for studies comparing adenosine and regadenoson for assessment of FFR. Data on FFR, correlation coefficient and adverse events from the selected studies were extracted and analyzed by means of random effects model. Two tailed *P*-value less than 0.05 was considered significant. Heterogeneity was assessed using I^2 test.

RESULTS

Five studies with 248 patients were included in the final analysis. All included patients and coronary lesions underwent FFR assessment using both adenosine and regadenoson. There was no significant mean difference between FFR measurement by the two agents [odds ratio (OR) = -0.00; 95% confidence interval (CI): (-0.02)-0.01, $P = 0.88$]. The cumulative correlation coefficient was 0.98 (0.96-0.99, $P < 0.01$). Three of five studies reported time to FFR with cumulative results favoring regadenoson (mean difference 34.31 s; 25.14-43.48 s, $P < 0.01$). Risk of adverse events was higher with adenosine compared to regadenoson (OR = 2.39; 95%CI: 1.22-4.67, $P = 0.01$), which most commonly included bradycardia and hypotension. Vast majority of the adverse events associated with both agents were

transient.

CONCLUSION

The performance of regadenoson in inducing maximal hyperemia was comparable to that of adenosine. There was excellent correlation between the FFR measurements by both the agents. The use of adenosine, was however associated with higher risk of adverse events and longer time to FFR compared to regadenoson.

Key Words: Adenosine; Regadenoson; Fractional flow reserve; Meta-analysis

Core Tip: Regadenoson has comparable efficacy in inducing maximal coronary hyperemia in patients undergoing invasive coronary angiography with lower risk of side effects compared to adenosine. To compare fractional flow reserve (FFR) assessment using adenosine with an alternate hyperemic agent, regadenoson. PubMed, Google Scholar, CINAHL and Cochrane databases were queried for studies comparing adenosine and regadenoson for assessment of FFR. There was excellent correlation between the FFR measurements by both the agents. The use of adenosine, was however associated with higher risk of adverse events and longer time to FFR compared to regadenoson.

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INTRODUCTION

Coronary angiography has long been the gold standard for assessment of severity of coronary artery disease[1]. This modality is however limited to providing anatomic information with little physiologic and clinical correlation, and more notably has marked intra- and inter-observer variability with very little reproducibility[2,3]. Data has shown that reliability on angiography for assessment of stenosis to perform percutaneous coronary intervention may, in fact, result in higher rates of revascularization procedures without significant improvement in clinical outcomes[4]. Physiologic assessment of coronary stenosis is achieved through use of fractional flow reserve (FFR) which is the ratio of intracoronary pressures distal and proximal to the lesion. The distal pressure measurement can be recorded using a pressure wire sensor placed distal to the lesion and the proximal pressure can be recorded *via* the guide catheter. The resting FFR measurement may not unmask the true physiological significance of the lesion and is better unmasked under maximal coronary hyperemic conditions with the use of agents such as adenosine. This is especially useful in assessing hemodynamic significance of intermediate severity stenosis as shown by the FFR *vs* angiography for guiding percutaneous coronary intervention (FAME) and FFR-guided percutaneous coronary intervention plus optimal medical treatment *versus* optimal medical treatment alone in patients with stable coronary artery disease (FAME 2) trials[5,6].

Adenosine is the gold standard to achieve maximal hyperemia for adequate measurement of FFR, however due to non-selective receptor activation, it may cause transient shortness of breath, atrioventricular conduction blockade and chest pain. Regadenoson on the other hand is a selective A_{2A} receptor agonist and has a more favorable side effect profile and straightforward dosing (400 μg *vs* variable weight-based infusion dosing for adenosine, *i.e.*, 140 μg/kg/min for 2 min). Herein, we systematically reviewed published literature comparing the efficacy of regadenoson to adenosine for achieving maximal hyperemia, the correlation in FFR measurements, and the adverse effects to ascertain the safer and more cost-effective hyperemic agent.

MATERIALS AND METHODS

This investigation was conducted in accordance with the Cochrane collaboration guidelines and the results have been reported per the PRISMA statement[7]. Literature review was performed independently by two authors (Gill GS, Gadre A) in PubMed, Cochrane, CINAHL and Google Scholar

Table 1 Study characteristics of included investigations

Ref.	Country	Patients (*n*)	Population	Enrollment period	Adenosine dosing	Regadenoson dosing	Inclusion/exclusion criteria	Measured outcomes
Nair *et al* [10], 2011	United States	25	Prospective, single-center	July 2009-December 2010	IV adenosine infusion at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Elective angiography, intermediate stenosis (40%-70%), remainder per ADVANCE trial (2)	FFR correlation, flushing, dyspnea, headache, chest discomfort, nausea, diaphoresis, metallic taste
Arumugham *et al*[11], 2013	United States	20	Prospective, single-center	October 2009-September 2010	IV adenosine infusion at 175 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Intermediate stenosis (50%-80%). Exclusion: STEMI within 5 d, significant left main coronary artery stenosis, heart block, pregnancy, asthma or hypersensitive to either adenosine or regadenoson	FFR correlation, time to achieve FFR, effect on blood pressure and heart rate, heart block, bronchospasm, severe chest pain
Prasad *et al* [12], 2014	United States	57[1]	Prospective, multi-center	May 2011-November 2011	IV adenosine at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Intermediate stenosis (50%-70%). Exclusion: Age < 18 years old, 3-vessel CAD, ACS within 1 wk, prior MI in territory supplied by target lesion, hypersensitivity to adenosine or regadenoson, reactive airway disease, 2nd or 3rd heart block, currently receiving dipyridamole, hemodynamic instability	FFR correlation, blood pressure, change in heart rate, dizziness, shortness of breath, heart block, flushing, arrhythmias
Van Nunen *et al*[13], 2015	Netherlands	100	Prospective, single-center	NA	IV adenosine at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Ages 18-80 years old, lesions in proximal to mid coronary artery segments, at least 2 mm diameter, > 30% stenosis. Exclusion: Severe AS, 2nd-3rd heart block, acute MI within 5 d, bradycardia, severe hypotension, tortuous/calcified coronary vessels, severe asthma, pregnancy, inability to obtain femoral approach, dipyridamole within 48 h and methylxanthines within 12 h	FFR correlation, heart block, chest discomfort, blood pressure, heart rate, shortness of breath, nausea
Edward *et al* [14], 2018	United States	46	Prospective, single-center	April 2012-May 2014	IV adenosine at 140 μg/kg/min	IV regadenoson bolus 400 μg	Inclusion: Elective angiography, < 30%, >90% stenosis. Exclusion: Sinus node dysfunction, 2nd-3rd degree AV block without pacemaker, severe hypotension, acute MI within 30 d, severe AS, pregnancy, aberrant coronary anatomy or calcification	FFR correlation, time to reversal with aminophylline, side effects

[1]60 lesions from 57 patients were included in the analysis.

IV: Intra-venous; STEMI: ST-segment elevation myocardial infarction; FFR: Fractional flow reserve; CAD: Coronary artery disease; ACS: Acute coronary syndrome; MI: Myocardial infarction; AV: Atrioventricular; AS: Aortic stenosis; NA: Not available; IC: Intra-coronary.

databases using the keywords "adenosine", "regadenoson", "fractional flow reserve", "FFR" and "hyperemia" in different combinations. 836 titles and abstracts were found, of which 83 were removed as duplicate. Of the remaining 753 titles, 674 were excluded based on title and abstract. 79 abstracts, original investigations, editorials and review articles were screened to assess for inclusion and exclusion criteria. Eight articles and their references were manually screened for any additional studies that could qualify for inclusion, of which, three were excluded from final analysis (systemic review, retrospective and pooled analyses) (Figure 1). The five included studies met following criteria: (1) Published as full manuscripts in English; (2) Involved patients with angiographic evidence of coronary artery stenosis; and (3) Assessed and reported at least one of the outcomes (FFR correlation, time to achieve FFR, adverse effects) with both adenosine and regadenoson. The following studies were excluded: (1) Duplicates of previous publications; (2) Pooled studies and systematic reviews; (3) Studies that included comparison of adenosine or regadenoson with nicorandil; (4) Abstracts, editorials, reviews, and commentaries; and (5) Animal studies. Any disagreement during the study screening and selection

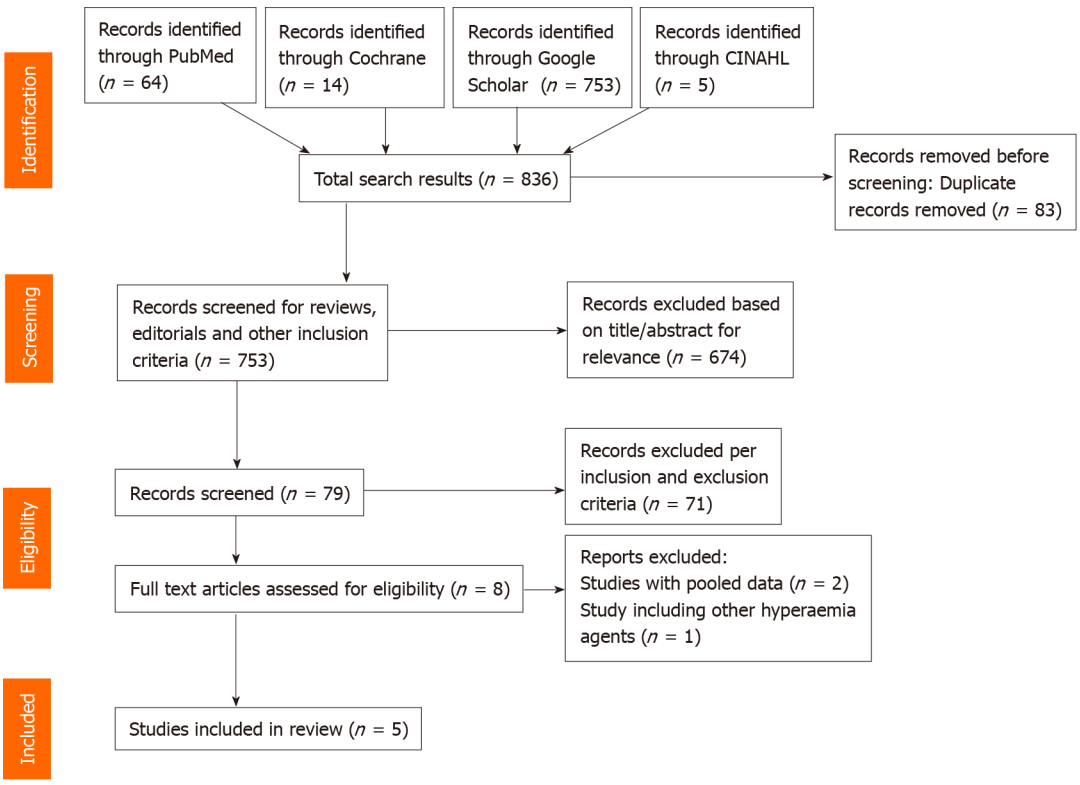

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Figure 1 Flowchart depicting study selection for inclusion in the meta-analysis.

process was resolved by consensus among all authors.

The primary outcome of interest was FFR correlation, and secondary outcomes were time to achieve FFR, and a composite of all reported adverse effects. Data extraction was performed using a standardized data extraction form by two independent authors (Gill GS, Gadre A). Any disagreement on data was resolved by consensus among all authors. For all outcomes in our analyses, pooled odds ratio (OR) with their corresponding 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel random-effects model for dichotomous variables and Inverse variance model for the continuous variables, and presented as Forest plots[8]. For the correlation coefficient Fisher's *Z* transformation was performed and reverse transformation with restricted maximum likelihood method to obtain meta-summary correlation coefficient. Heterogeneity across the studies was assessed using the chi-square-based Cochrane *Q* test and quantified using I^2 statistics. I^2 index values of < 25%, 25%-50% and > 50% were considered low, intermediate, and high heterogeneity, respectively[9]. Exclusion sensitivity analysis was performed by excluding one study at a time and repeating the analysis. Publication bias was assessed using Begg's dissemination selectivity test and visually inspected using funnel plots. All analyses were conducted using the Review Manager Version 5.4 software, STATA software version 16 (StataCorp 2019, College Station, TX, United States) and the IBM SPSS software Version 26 (IBM Corp, Armonk, NY, United States). There was no duplicate data within included studies. A two-sided *P* value of < 0.05 was considered statistically significant.

RESULTS

A total of eight investigations were reviewed to include five prospective studies involving 248 patients undergoing FFR analysis for 251 lesions in the final meta-analysis (Figure 1 and Table 1)[10-14]. A flowsheet of the study selection process in accordance with the PRISMA guidelines is shown in Figure 1. Study designs, infusion protocols, inclusion and exclusion criteria, and reported outcomes are represented in Table 1; and baseline characteristics of patients are reported in Table 2. Mean age of the study population was 63 years with women accounting for 25% of the participants. All studies were prospective with all 248 patients receiving both IV adenosine and IV regadenoson in a sequential manner.

FFR correlation was reported in all five studies. The cumulative correlation coefficient for FFR measurement was 0.98 (95%CI: 0.96-0.99) with I^2 estimate for heterogeneity at 93% (Figure 2A). Mean difference in measured FFR values with adenosine and regadenoson in pooled analysis was -0.00 [95%CI: (-0.02)-0.01; *P* = 0.88], with I^2 estimate for heterogeneity 0%. An exclusionary sensitivity analysis

Table 2 Baseline characteristics of patients from studies included in the meta-analysis

	Nair *et al*[10]	Arumugham *et al*[11]	Prasad *et al*[12]	van Nunen *et al*[13]	Edward *et al*[14]
Number	25	20	57 (60 lesions)	100	46
Age [yrs ± SD or yrs (CIs)]	63 ± 11	63.9 ± 9	57 ± 8	66 ± 8	63 ± 10
Women, *n* (%)	12 (48)	4 (20)	10 (18)	25 (25)	9 (20)
Body mass index (mean ± SD)	30.0 ± 5.7	NA	27.7 ± 4.1	26.7; H kg	33 ± 7
Hypertension, *n* (%)	21 (84)	NA	51 (90)	54	44 (96)
Diabetes mellitus, *n* (%)	6 (24)	NA	26 (46)	21	26 (57)
Hyperlipidemia, *n* (%)	21 (84)	NA	39 (68)	36	44 (96)
Tobacco use, *n* (%)	8 (32)	NA	24 (42)	20	7 (15)
CKD, *n* (%)	NA	NA	NA	NA	9 (20)
Prior MI, *n* (%)	5 (20)	NA	23 (40)	36	NA
Prior PCI, *n* (%)	8 (32)	NA	NA	43	NA

CI: Confidence interval; CKD: Chronic kidney disease; MI: Myocardial infarction; PCI: Percutaneous intervention; NA: Not available.

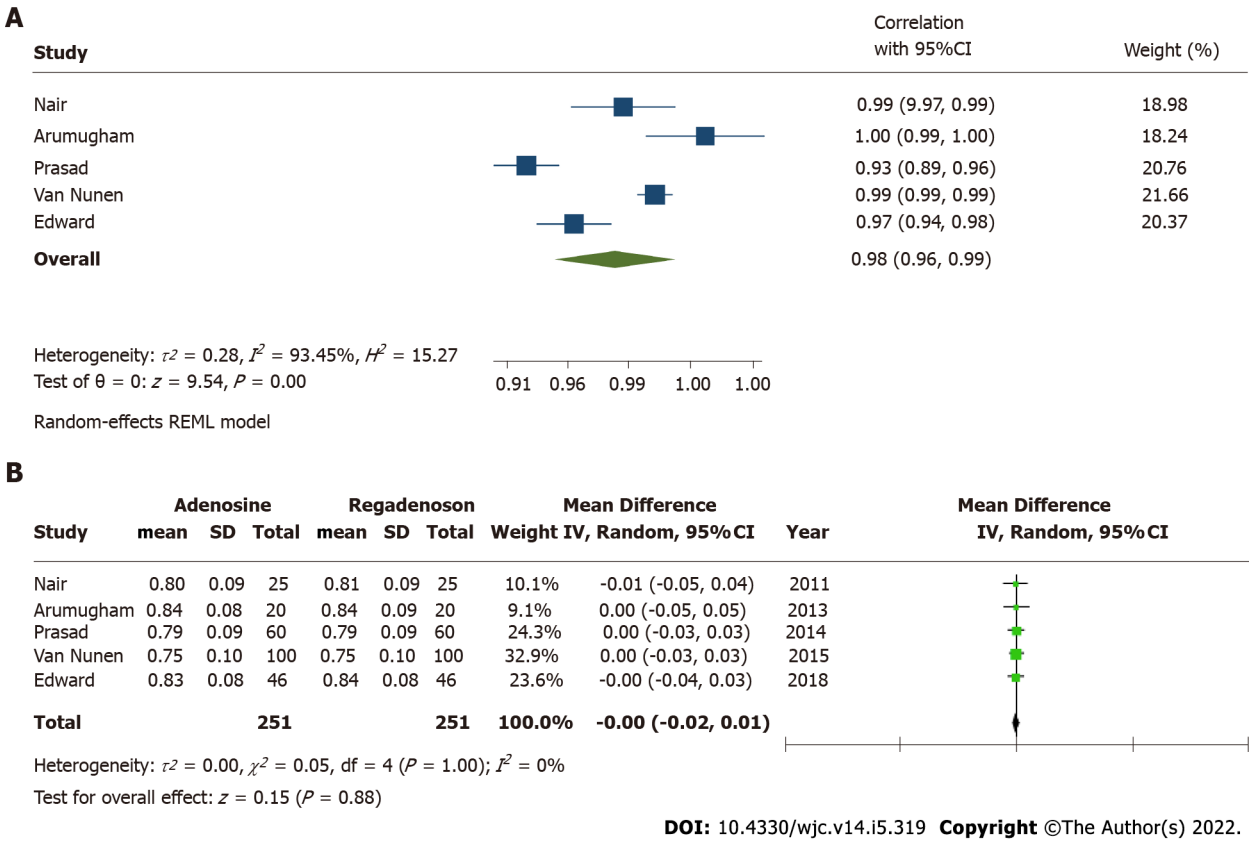

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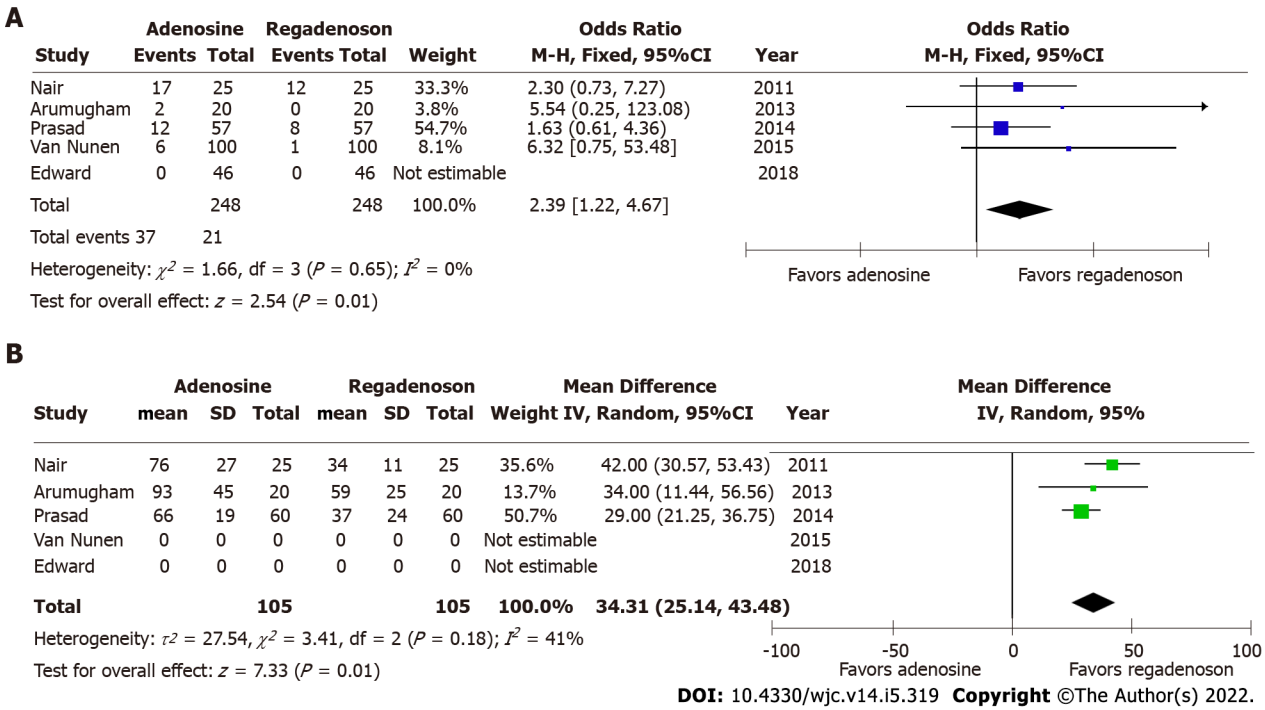
Figure 2 Primary outcomes – adenosine *versus* regadenoson cumulative. A: correlation coefficient for fractional flow reserve (FFR) measurements; B: Mean difference in FFR measures. CI: Confidence interval.

was performed with exclusion of studies with lesions including low- and high-grade stenosis (Van Nunen *et al*[13] and Edward *et al*[14]), where results remained consistent with mean difference -0.00 [(-0.03)-0.02; P = 0.92] (Figure 2B). Time to achieve FFR was reported in three of five studies, and was significantly lower with regadenoson with a mean difference of 34.31 s (95%CI: 25.14-43.48 s; P < 0.01) (Figure 3A). The degree of heterogeneity albeit higher than remainder results, was still moderate with I^2 index = 41% in this three-study analysis.



DOI: 10.4330/wjc.v14.i5.319

Figure 3 Secondary outcomes. A: Adverse event rates; B: Time to achieve fractional flow reserve (FFR) with adenosine versus regadenoson induced hyperemia for FFR measurement. CI: Confidence interval.

Pooled odds for any adverse effect were significantly higher for patients after administration of adenosine, than after receiving regadenoson (OR = 2.39, 95%CI: 1.22-4.67; P = 0.01) (Figure 3B). There was no evident heterogeneity among included studies with I^2 estimated at 0%. There was no evidence of dissemination bias on visual inspection of the funnel plot and Begg's test. There were no adverse effects reported in either arm of the study by Edward *et al*[14] among forty-six participants in the analysis where aminophylline were administered after regadenoson, while side effects reported in other studies were only transient and did not necessitate discontinuation of infusion or FFR measurement. In the study by Arumugham *et al*[11], a higher dose of IV adenosine was infused, while significant adverse event rates were not higher.

DISCUSSION

The major findings of this analysis are: (1) FFR correlation was excellent among both IV adenosine and IV regadenoson; (2) IV regadenoson achieved maximal hyperemia in a shorter interval; and (3) Adverse effects, including transient atrioventricular conduction block, chest pain, shortness of breath, hypotension, flushing and headache were higher with adenosine. Anatomic as well as physiologic assessment of coronary vasculature are integral elements to defining coronary artery disease in a patient. Over the past few decades, there have been advances in anatomic evaluation beyond traditional angiography, and have included developments in intravascular imaging, such as, intravascular ultrasound and optical coherence tomography. Studies comparing translation of anatomic *vs* physiologic assessment of coronary artery disease into clinical outcomes have concluded in comparable results[15]. Furthermore, investigations attempting to correlate optimum minimal lumen area to FFR values have concluded that their reciprocity may be vessel dependent[16]. This can be explained by the independent role of these modalities in assessing flow and identifying vulnerable plaques, respectively [17]. Due to easy availability and low cost, FFR based assessment of intermediate stenosis has been widely incorporated to practice.

Adenosine has traditionally been the gold standard for inducing maximal hyperemia while measuring FFR, although different agents have been investigated for efficacy and side effects with comparable results[10-14,18-22]. There is excellent correlation in FFR estimated by adenosine and regadenoson which is consistent with prior studies that have shown both agents achieve comparable hyperemia in animal as well as human models[23,24]. Adenosine is a non-selective activator of 4 receptors, A_1, A_{2A}, A_{2B} and A_3[25]. The activation of A_1 and A_3 receptor subtypes decreases cyclic adenosine monophosphate (cAMP) levels while activation of receptors A_{2A} and A_{2B} increases the cAMP levels[26]. cAMP is an important mediator of smooth muscle relaxation and therefore, activation of A_{2A} and A_{2B} receptors leads to coronary and peripheral arterial vasodilation and hyperemia. The non-

selective receptor activation by adenosine also causes bronchoconstriction and other side effects. Regadenoson, however, is a selective A_{2A} receptor agonist, and thus causes preferential coronary vasodilation with fewer side effects when compared to adenosine[27]. In cases where patients may experience adverse effects from regadenoson, they can be reversed using intravenous aminophylline[14, 28]. This easy reversibility makes physiologic evaluation feasible in patients with mild-to-moderate reactive airway disease and obstructive airway disease[27]. Another secondary outcome, time to FFR, was also shorter in patients who received regadenoson, thus favoring its use. This can potentially be explained by the non-weight-based bolus dosing of intravenous regadenoson, accommodated by the longer half-life (2-4 min) when compared to weight-based infusion of intravenous adenosine, which is administered preferably through central venous access due to its extremely short half-life (0.6-10 s). Because of its short half-life, administration of adenosine is challenging and could be time consuming. Our study results show that time to maximal hyperemia is shorter by about 30 s with the use of regadenoson. Further, this time does not take in to account the time taken for preparing the adenosine infusion which could take up to several minutes. This could potentially increase the duration of the procedure, and therefore, use of regadenoson may save valuable time for the catheterization laboratory and its staff while potentially leading to cost benefits despite the higher price of regadenoson.

As discussed above, our study demonstrates lower risk of adverse effects with regadenoson use. In study by Arumugham *et al*[11], a higher adenosine infusion rate was used (175 μg/kg/min), and to negate its effects, we conducted an exclusionary sensitivity analysis, where results remained similar (P = 0.02). We then conducted sensitivity analysis using jackknife approach for another secondary outcome, time to FFR, where heterogeneity was moderate with I^2 = 41% in the overall analysis. Here, we systematically excluded one study at a time, and noted a reduction in I^2 to 0% with exclusion of study by Nair *et al*[10], the oldest investigation. Outcome favoring regadenoson use remained unchanged (P < 0.01). Lastly, two of the five included studies did not limit the lesions to intermediate stenosis and a sensitivity analysis was conducted by excluding these investigations. The results remained unchanged with significant correlation between estimated FFRs (P = 0.92, I^2 = 0%).

The decision to use one agent over the other is further influenced by factors such as requirement of central venous access and cost. Although adenosine can be administered both *via* central or peripheral access, the onset of action is earlier and steady state hyperemia is more stable with central venous catheter. Regadenoson, on the other hand, has limitations including cost and unpredictability in the duration of hyperemia[13]. For this reason, regadenoson may not be the ideal agent, especially when evaluating multiple coronary arteries, and will require multiple dose administrations with incremental increase in the costs[29]. Regadenoson has near completely replaced adenosine for nuclear stress testing because of the ease of its administration and relatively fewer side effects and therefore is more appealing to be used for invasive FFR assessment. Our meta-analysis results clearly demonstrate that regadenoson is an acceptable alternative to adenosine for invasive FFR assessment of intermediate severity coronary stenosis.

Limitations and strengths

Our meta-analysis has inherent limitations as well as those inherited from the included studies. First, among the studies included in this meta-analysis, there is considerable variability in the definition of intermediate severity stenosis. Second, the study by Arumugham *et al*[11] used a higher adenosine infusion rate when compared to other investigations in an attempt to mitigate effects of deactivation of peripherally administered adenosine. This variability in dosing may have affected all outcomes, and potentially, strengthened the association between adenosine use and adverse effects. Third, the studies included in our analysis varied in drug infusion protocol in terms of peripheral *vs* central access which may be of importance when using an agent with short half-life, and investigating a time sensitive outcome, such as time to achieve FFR. Fourth, since these studies included patients undergoing elective angiography, these results may not be extrapolated to populations with unstable angina or other acute coronary syndromes. Lastly, in an attempt to conduct the analysis in consistency with PRISMA guidelines, this study may be subject to publication bias[30]. Inherently however, our investigation had limited risk of residual bias since all included studies had a prospective design with patients receiving both hyperemic agents. We performed several sensitivity analyses to document the consistency of our results despite the aforementioned limitations. We employed jackknife approach and excluded individual studies to investigate outcomes and re-calculate I^2. Given the lack of large multicenter studies addressing these differences in a well-designed prospective fashion, our analysis provides valuable insights into the differential outcomes of FFR measurement in patients with adenosine *vs* regadenoson use.

CONCLUSION

Our meta-analysis demonstrates that use of regadenoson for FFR measurement among patients undergoing elective angiography is associated with shorter time to achieve FFR, and lower risk of side effects while providing excellent correlation with the results obtained with adenosine and therefore may

be an acceptable alternative for FFR measurement in the cardiac catheterization laboratory. The ease of its use, and a relatively favorable side effect profile make regadenoson a very appealing alternative to adenosine.

ARTICLE HIGHLIGHTS

Research background

Regadenoson is a selective adenosine receptor agonist that causes coronary hyperemia and in limited studies has been shown to have comparative efficacy to adenosine in evaluating coronary fractional flow reserve (FFR).

Research motivation

Considering the evidence is limited in supporting the use of regadenoson as an alternative to adenosine in evaluating FFR, we hypothesized that using meta-analysis we can improve the strength of evidence comparing regadenoson *vs* adenosine in evaluating FFR in intermediate severity coronary stenosis.

Research objectives

To perform meta-analysis to evaluate regadenoson *vs* adenosine for efficacy and safety.

Research methods

Pooled meta-analysis of published studies. Comparing correlation coefficient and adverse events using random effects model. Visual inspection for bias and heterogeneity assessment using I^2 test.

Research results

The FFR correlation coefficient between regadenoson and adenosine was 0.98 [95% confidence interval (CI): 0.96-0.99, $P < 0.01$]. Time to achieve FFR was shorter by 34.31 s (95%CI: 25.14-43.48) in the regadenoson group. The risk of adverse events was higher with adenosine with odds ratio of 2.39 (95%CI: 1.22-4.67, $P = 0.01$).

Research conclusions

Regadenoson had comparable efficacy in obtaining FFR compared to adenosine and this was achieved in a shorter duration of time and with lower incidence of adverse effects.

Research perspectives

Regadenoson presents an alternative to adenosine in evaluating FFR in patients with intermediate severity coronary artery stenosis with lower risk of side effects and also saves time.

FOOTNOTES

Author contributions: Gill GS and Gadre A independently conducted literature search for studies to be included in the final analysis; all authors discussed disagreement in included studies; Gill GS prepared the first manuscript draft, tables and figures, conducted statistical analysis, and contributed to major revision; Gadre A contributed to revisions; Kanmanthareddy A conceptualized the study, performed independent statistical analysis, supervised methodology, made substantial changes to the manuscript, and contributed to major revision.

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