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OPINION REVIEW

Redefying the therapeutic strategies against cardiorenal morbidity and mortality: Patient phenotypes

Dimitra Bacharaki, Ioannis Petrakis, Kostas Stylianou

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Dimitra Bacharaki, Nephrology Unit, 2nd Department of Internal Medicine, Attikon University Hospital, Chaidari 12462, Greece

Ioannis Petrakis, Kostas Stylianou, Department of Nephrology, Heraklion University Hospital, University of Crete, Heraklion 71500, Greece

Corresponding author: Dimitra Bacharaki, MD, PhD, Consultant Physician-Scientist, Nephrology Unit, 2nd Department of Internal Medicine, Attikon University Hospital, Rimini 1, Chaidari 12462, Greece. bacharaki@gmail.com

Abstract

Chronic kidney disease (CKD) patients face an unacceptably high morbidity and mortality, mainly from cardiovascular diseases. Diabetes mellitus, arterial hypertension and dyslipidemia are highly prevalent in CKD patients. Established therapeutic protocols for the treatment of diabetes mellitus, arterial hypertension, and dyslipidemia are not as effective in CKD patients as in the general population. The role of non-traditional risk factors (RF) has gained interest in the last decades. These entail the deranged clinical spectrum of secondary hyperparathyroidism involving vascular and valvular calcification, under the term "CKD-mineral and bone disorder" (CKD-MBD), uremia *per se*, inflammation and oxidative stress. Each one of these non-traditional RF have been addressed in various study designs, but the results do not exhibit any applied clinical benefit for CKD-patients. The "crusade" against cardiorenal morbidity and mortality in CKD-patients is in some instances, derailed. We propose a therapeutic paradigm advancing from isolated treatment targets, as practiced today, to precision medicine involving patient phenotypes with distinct underlying pathophysiology. In this regard we propose two steps, based on current stratification management of corona virus disease-19 and sepsis. First, select patients who are expected to have a high mortality, *i.e.*, a prognostic enrichment. Second, select patients who are likely to respond to a specific therapy, *i.e.*, a predictive enrichment.

Key Words: Cardiorenal; Morbidity; Mortality; Phenotype; Precision medicine; Personalized medicine

Core Tip: Stagnation in the Nephrology field has to be overcome with a new perspective. This new vision takes lessons from the past as personalized medicine, adapts precision medicine from today's lessons from corona virus disease-19 and sepsis and looks into the future with the aid of the big data. Our proposal is that cardiorenal management should be stratified according to patient phenotypes and not as an assembly of individual targets.

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INTRODUCTION

Cardiovascular (CV) disease is a major contributor of mortality in chronic kidney disease (CKD) patients, especially in the late stage 5 on dialysis (5D), mounting up to 58% of causes[1,2]. Aside traditional CV risk factors (RF), as diabetes and arterial hypertension, non-traditional RF related to kidney disease *per se* seem to play a pivotal role in the complex interaction between the kidney and the heart[3]. Non-traditional RF include secondary hyperparathyroidism resulting in vascular and valvular calcification, collectively termed as CKD-mineral and bone disorder (CKD-MBD)[4], uremia *per se*, inflammation, oxidative stress and dysbiotic gut microbiota[5].

THE PROBLEM

CKD patients have long been excluded from cardiovascular clinical trials, for various reasons: (1) Inadequate surrogate outcomes and low event rate, especially in end stage renal disease, demand a prohibitory large sample size and an extensive follow up[6]; and (2) fear for negative results or adverse events, since the aforementioned non-traditional risk factors are recognized as potential disease modifiers[7]. Nephrology practice could be characterized as "low evidence" medicine, which pursues targeting traditional RF with data originating from the general, non-CKD-population[8].

Major clinical problems, such as the choice of treatment for non-valvular atrial fibrillation in dialysis patients, remain unsolved and clinical nephrologists "navigate through darkness" regarding therapeutic strategy[9]. In the case of hyperphosphatemia although there is numerous scientific evidence that "phosphate is a cardiovascular toxin"[10], there has been no randomized control trial (RCT) providing evidence that "correction" will translate into tangible cardiovascular benefit, set the optimal timing of intervention, the different means or the optimal serum phosphate target[11]. Yet the patients endure an overwhelming phosphate binder pills consumption[12] with enormous economic implications for healthcare[13].

A LIGHT IN THE TUNNEL

Sodium-glucose cotransporter-2 inhibitors (SGLT2i), initially marketed as glucose lowering drugs in diabetes mellitus type2, are a game changer in the field of cardiorenal protection[14]. Their beneficial effects, regarding reduction in CV morbidity and mortality and renal function preservation, have been assessed by RCTs across CKD stages 1-3, notably with empagliflozin (EMPA REG OUTCOME)[15] and dapagliflozin (CAPA-CKD)[16]. The unprecedented success of this novel treatment stems from the pleiotropic effects of SGLT2i, targeting multiple intra-extrarenal pathways[17].

Another promising therapeutic tool is Mediterranean Diet (Med Diet) that has a pivotal role for cardiorenal protection[18]. Targeting all traditional and multiple non-traditional RF of cardiovascular morbidity and mortality along with exercise, Med Diet confers to an anti- inflammatory and anti-oxidative metabolic profile[19]. The level of adherence has been recently linked in an observational study with left ventricular geometry patterns in dialysis patients, a powerful independent risk factor of CV mortality in this particularly vulnerable population[20].

In clinical practice SGLT2i are currently tested as real world experience in advanced stages of CKD [21]. On the other hand nephrologists are still reluctant to prescribe vegetable based diets, as Med Diet, mostly for the fear or ignorance of handling potassium and/or provoking malnutrition[22].

A KEY IN THE PUZZLE: CKD IS AN "INFLAMMAGING" CONDITION

The only positive RCT in the field of CV protection in CKD is the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcome Study)[23], where the inhibition of the pro- inflammatory IL-1β was more beneficial in post myocardial infarction patients with glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2. The concept of "inflammaging", introduced by Franceshi, unified all chronic degenerative conditions, in a common pathophysiology, which could be translated as a low grade sterile chronic inflammation resembling the natural course of ageing[24]. In observational studies IL-6 has been described as an independent predictor of outcome in pre-dialysis[25], hemodialysis[26] and peritoneal dialysis patients[27]. The association of inflammation and outcome seems so strong that a hypothesis proposal was made not to include inflamed and not inflamed patients in the same cohort in an RCT, since inflammation is powerful catalyst for other risk factors in CKD[28]. CKD patients are in a paradox state of both immune - paralysis (driving susceptibility to infections) and immune- activation (linked to CVD)[29].

THE SOLUTION: PRECISION AND PERSONALIZED MEDICINE

Treatment failure, targeting "traditional" RF and nontraditional RF (hyperphosphatemia, CKD- MBD parameters) stems probably from the fact that there is no stratification management that would guide a precision or personalized medicine. Nephrology practice seems to be in a state of involuntary blindness as the crowd that pretends to see the clothes of the naked Emperor in Hans Christian Andersen's tale [30]. In order to find a solution we propose the following 4 steps: (1) Gather the wisdom of the past in the form of personalized medicine; (2) adapt precision medicine from today's lessons from corona virus disease 19 (COVID-19); (3) sepsis; and (4) look into the future with the aid of the big data.

Personalized medicine negligence

Historically[31], the therapeutic practices have changed drastically from a "patient-centred" view to those of "evidence-based" medicine. "Germ theory of disease" in the 19th century, changed the "holistic view" perception of disease to a "specific cause for a specific disease". The treatment approach shifted therefore, to a narrow approach that targeted a specific cause. The patient's role diminished from an active contributor, through personal beliefs, adaptation and lifestyle choices, to a mere passive recipient of the treatment. Patients became "numbers" in any given trial, which will eventually provide the necessary information to form "therapeutic guidelines"[32]. Ironically and paradoxically, the contemporary nephrologist is called to manage CKD patients, who are at very high risk of cardiovascular morbidity and mortality, with guidelines based on weak evidence[6]. As mentioned Nephrology field lacks RCTs and the Cardiology field excludes CKD patients[7]. Furthermore, during the decision-making process the patient is a passive recipient of the diagnostic decision[32].

Precision medicine: Lessons from COVID-19

The pandemic of COVID-19 has taught us a great example of precision medicine. First it was discovered that patients respond differently to the "viral-intruder" and the host's immune response, whether regulated or dysregulated leads to a favorable or unfavorable outcome respectively[33]. Later on, two distinct pathways were revealed[34] as well as an early biomarker for disease prediction (SUPAR-Soluble urokinase plasminogen activator receptor)[35]. This approach led to precision guided therapy with anakinra that showed remarkable benefit regarding respiratory failure and mortality[36].

Lessons from sepsis

In many aspects "sepsis" and "CKD" have many similarities. Both are heterogeneous syndromes with underlying "inflammation". Sepsis is defined as "organ dysfunction caused by a dysregulated host response to infection"[37]. CKD is defined as kidney damage or GFR < 60 mL/min/1.73 m^2 for 3 mo or more, irrespective of cause[38]. Based on this definition half of people over 75 are "labelled" as CKD, but there is debate if they can be regarded as "same risk" for renal deterioration or CV morbidity and mortality as younger people with the same stage of CKD[39]. At the same time CKD has a "systemic nature"[40] affecting multiple organ pathways, on a specific epigenetic background. In parallel sepsis, despite all the achievements in understanding its pathophysiology, is now regarded as "a multifaceted disruption of the finely tuned immunological balance of inflammation and anti-inflammation"[41]. There is a trend to identify patient phenotypes in order to stratify an accurate management[42].

The promise of big data

The "big data" era of the last decade, a precious gift of the tremendous advances in computational technology has helped enormously diverse medical scientific fields, in terms of diagnosis, risk assessment and treatment, fueling precision medicine, but Nephrology field is lagging behind[43]. As an example, multi-omics data combined with clinical and demographic data helped to generate machine -

Table 1 Proposed Measures of prognostic enrichment

Category	Parameters	Evaluation method	
		Continuous	Discrete based on trials
Laboratory	eGFR	CKD-EPI (mL/min/1.73 $m^{2)}$	CKD stages 1,2,3a/b,4,5
	uACR	Mg albumin/g creatinine	Albuminuria stages A1,A2,A3
	hs-CRP		
	Serum magnesium		
	PTH	Intact PTH (pg/mL)	KDIGO < 150, 150-500, > 500 pg/mL
	Anemia variables	Ht/Hb/TSAT/Ferritin/Hepcidin	
Radiology	LVMI	LV mass indexed to body surface area (g/m^2)	Geometry types
	Lateral abdominal X-ray	Scale from 0-24	Leena Kaupilla Score ≤ 4 *vs* > 4
	Aortic stiffness	Pulse wave velocity carotid-femoral PWV (m/s)	CF-PWV < 8.8, 8.8-12, > 12 m/s
Clinical status	Frailty	Nine-point clinical frailty scale	
	Aortic stiffness	Pulse pressure (mmHg)	
	Physical activity	Handgrip strength	
	Diet	Mediterranean Diet Score Panagiotakos Scale 0-24	
Co-morbidities	DM, CAD, PAD, stroke, COPD		Charlson comorbidity index
Bones	Mineral bone density (DEXA)	Values from DEXA (g/cm^2)	Ostopenia ostoporosis

eGFR: Estimated glomerular filtration rate; uACR: Urinary albumin to creatinine ratio; PTH: Parathyroid hormone; Ht: Haematocrit; Hb: Haemoglobin; TSAT: Transferrin saturation; LVMI: Left ventricular mass index; DM: Diabetes mellitus; CAD: Coronary artery disease; PAD: Peripheral artery disease; COPD: Chronic obstructive pulmonary disease; CKD-EPI: Chronic kidney disease-epidemiology collaboration formula; KDIGO: Kidney Disease: Improving Global Outcomes; CF-PWV: Carotid to femoral pulse wave velocity; DEXA: Dual energy X-ray absorptiometry.

learning models for prediction of preeclampsia[44]. Burning clinical issues regarding CKD patients, especially in advanced stages, as treatment of vascular disease, heart failure with reduced or preserved ejection fraction and prevention of sudden cardiac death do not have solid answers yet[8]. Big data science from electronic health records and longitudinal follow up could be a surrogate of RCTs assisting clinical decision[6].

PRECISION MEDICINE THROUGH PATIENT PHENOTYPES

Our hypothesis is that there could be a paradigm shift in the field of nephrology regarding patient stratification and targeted management. In order to accomplish this transition the search for «biomarkers» could be helpful, as in sepsis[45]. The first step of a "prognostic enrichment", *i.e.*, select patients who are suspected to have high mortality, could be followed by "predictive enrichment", *i.e.*, patients who are likely to respond to a specific therapy (Figure 1). In this regard various biomarkers could be tested alone or in combination as: (1) Those already used in clinical practice (Table 1); and (2) the established biomarkers of cardiorenal syndrome[46] and those that could be found from multi-omics technology (blood and/or urine samples)[47].

One example of prognostic enrichment in nephrology involves the "heat map" based on GFR levels and albuminuria. It has been extensively validated and has a broad clinical application[48,49]. The CORD study in hemodialysis patients showed that vascular calcification (assessed from plain lateral abdominal X-ray), and arterial stiffness (measured by carotid-femoral pulse wave velocity) are independent prognostic markers of adverse outcome[50].

Regarding predictive enrichment one could utilize CORD study as an implementation paradigm (Figure 2). The authors showed that increased arterial stiffness -associated CV risk, is less pronounced at higher levels of calcification. Also an impressive number (19% of 993 pts "non - calcifiers" *i.e.*, with no visible calcification deposits in lateral X-ray) was identified[51]. This implies the existence of genetic predisposition. This heterogeneity of the dialysis patient population could be contributing to the inconclusive results of the EVOLVE trial. In this study, lowering parathormone levels and targeting adverse CKD-MBD parameters as serum phosphorus and vascular calcification did not produce a statistically significant benefit in preventing CV events[52]. Another example is the interaction between

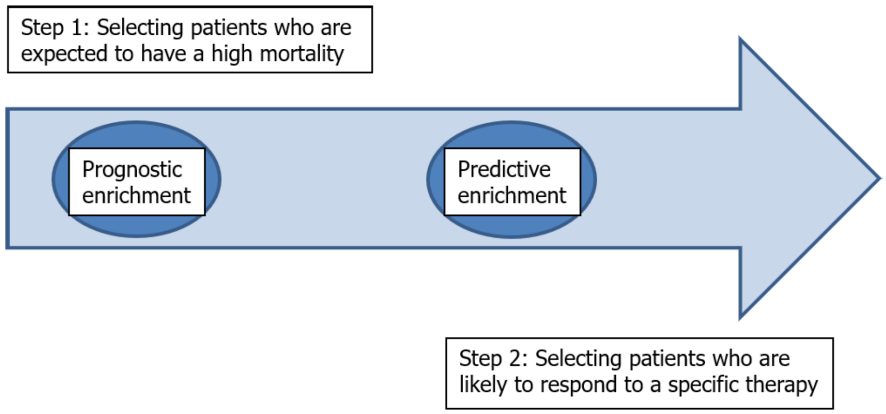

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Figure 1 The path to precision medicine through patient phenotypes.

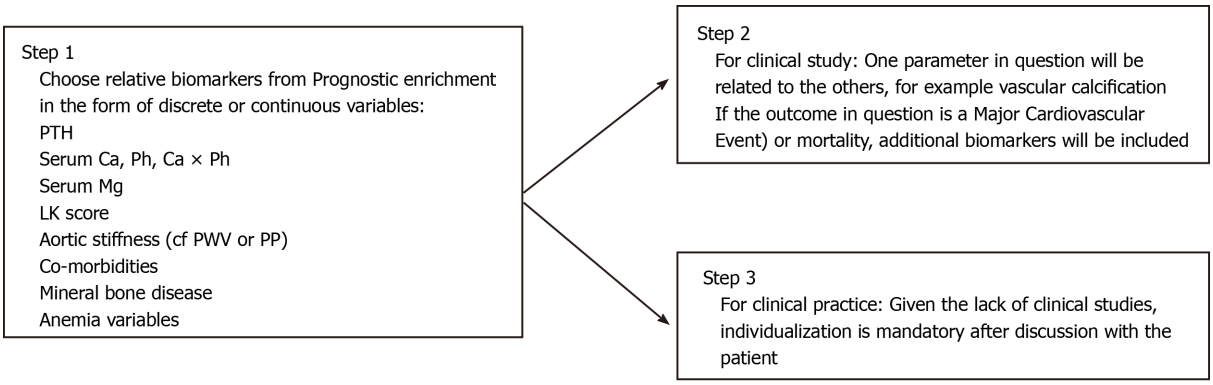

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Figure 2 Predictive enrichment. Example for clinical study and clinical practice. Clinical question: Vascular disease management in CKD-5D. Bibliography: The calcification outcome in renal disease study[50] concluded that Leena Kauppila (LK) score > 4 and carotid femoral pulse wave velocity > 12 are predictors of mortality. In non-calcifiers (LK < 4) aortic stiffness plays a major role. CKD-5D: Chronic kidney disease stage 5 dialysis; PWV: Pulse wave velocity; LK: Leena Kauppila score; PTH: Parathortmone; Ca: Calcium; Ph: Phosporus; Mg: Magnesium; PP: Pulse pressure.

two strong independent predictors of CV mortality, as serum magnesium (sMg)[53] in combination with abdominal aortic calcification (AAC). We have shown that in peritoneal dialysis patients with AAC in the higher tertile of the baseline distribution, sMg levels were not predictive of outcome[54].

Erythropoietin stimulating agents have revolutionized the treatment of CKD related anemia in the last decades. Hypoxia inducible factor polyl-hydroxylase inhibitors (HIF-PHIs) promote erythropoietin transcription and synthesis in the liver/kidney. INNO2VATE trials have proven the non-inferiority of vadadustat compared with darbopoetin - alfa concerning the cardiovascular safety[55]. However there are long-term safety concerns related to HIF pathway interactions involving tumor growth, diabetic retinopathy, and or CKD progression. Till now no HIF-PHI is licensed for the treatment of CKD-anemia within the European Union.

Considering erythropoietin use in CKD population a U-shaped effect exists[56]. The optimal erythropoietin dose to achieve the desired level of hemoglobin (10-11.5 g/dL) for the individual patient is not known and is almost always a matter of individual assessment. Furthermore, assays detecting markers of inflammation (*e.g.*, hepcidin) which would predict clinical response in anemia lack in everyday clinical use.

CONCLUSION

In the stagnant era of effective treatment in the vulnerable population of CKD for CV morbidity and mortality, a paradigm shift seems mandatory. It is time to search for specific "biomarkers" to identify those at risk and even more those that would benefit from a targeted intervention. It is time to apply precision medicine through patient phenotypes.

FOOTNOTES

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ORCID number: Dimitra Bacharaki 0000-0002-1722-2131.

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REFERENCES

1 **Go AS**, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296-1305 [PMID: 15385656 DOI: 10.1056/NEJMoa041031]
2 **Gansevoort RT**, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013; **382**: 339-352 [PMID: 23727170 DOI: 10.1016/S0140-6736(13)60595-4]
3 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527-1539 [PMID: 19007588 DOI: 10.1016/j.jacc.2008.07.051]
4 **Waziri B**, Duarte R, Naicker S. Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): Current Perspectives. *Int J Nephrol Renovasc Dis* 2019; **12**: 263-276 [PMID: 31920363 DOI: 10.2147/IJNRD.S191156]
5 **Noels H**, Jankowski J. Editorial on the Special Issue "Comorbidities in Chronic Kidney Disease". *Toxins (Basel)* 2020; **12** [PMID: 32545170 DOI: 10.3390/toxins12060384]
6 **Nadkarni GN**, Coca SG, Wyatt CM. Big data in nephrology: promises and pitfalls. *Kidney Int* 2016; **90**: 240-241 [PMID: 27418085 DOI: 10.1016/j.kint.2016.06.003]
7 **Ishida JH**, Johansen KL. Exclusion of Patients With Kidney Disease From Cardiovascular Trials. *JAMA Intern Med* 2016; **176**: 124-125 [PMID: 26618994 DOI: 10.1001/jamainternmed.2015.6403]
8 **Jankowski J**, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. *Circulation* 2021; **143**: 1157-1172 [PMID: 33720773 DOI: 10.1161/CIRCULATIONAHA.120.050686]
9 **Wald R**, Dorian P, Harel Z. Benefits and Risks of Anticoagulation in Dialysis Patients With Nonvalvular Atrial Fibrillation: Navigating Through Darkness. *J Am Coll Cardiol* 2020; **75**: 286-288 [PMID: 31976866 DOI: 10.1016/j.jacc.2019.11.033]
10 **Leifheit-Nestler M**, Vogt I, Haffner D, Richter B. Phosphate Is a Cardiovascular Toxin. *Adv Exp Med Biol* 2022; **1362**: 107-134 [PMID: 35288877 DOI: 10.1007/978-3-030-91623-7_11]
11 **Vervloet M**. Modifying Phosphate Toxicity in Chronic Kidney Disease. *Toxins (Basel)* 2019; **11** [PMID: 31505780 DOI: 10.3390/toxins11090522]
12 **Chiu YW**, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009; **4**: 1089-1096 [PMID: 19423571 DOI: 10.2215/CJN.00290109]
13 **Chaiyakittisopon K**, Pattanaprateep O, Ruenroengbun N, Sapankaew T, Ingsathit A, Mckay GJ, Attia J, Thakkinstian A. Evaluation of the cost-utility of phosphate binders as a treatment option for hyperphosphatemia in chronic kidney disease patients: a systematic review and meta-analysis of the economic evaluations. *Eur J Health Econ* 2021; **22**: 571-584 [PMID: 33677736 DOI: 10.1007/s10198-021-01275-3]
14 **Brown E**, Wilding JPH, Alam U, Barber TM, Karalliedde J, Cuthbertson DJ. The expanding role of SGLT2 inhibitors beyond glucose-lowering to cardiorenal protection. *Ann Med* 2021; **53**: 2072-2089 [PMID: 33107349 DOI: 10.1080/07853890.2020.1841281]
15 **Zinman B**, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**: 2117-2128 [PMID: 26378978 DOI: 10.1056/NEJMoa1504720]
16 **Heerspink HJL**, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; **383**: 1436-1446 [PMID: 32970396 DOI: 10.1056/NEJMoa2024816]
17 **Salvatore T**, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, Di Salvo J, Epifani R, Marfella R, Docimo G,

Lettieri M, Sardu C, Sasso FC. An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. *Int J Mol Sci* 2022; **23** [PMID: 35409011 DOI: 10.3390/ijms23073651]

18 **Chauveau P**, Aparicio M, Bellizzi V, Campbell K, Hong X, Johansson L, Kolko A, Molina P, Sezer S, Wanner C, Ter Wee PM, Teta D, Fouque D, Carrero JJ; European Renal Nutrition (ERN) Working Group of the European Renal Association-European Dialysis Transplant Association (ERA-EDTA). Mediterranean diet as the diet of choice for patients with chronic kidney disease. *Nephrol Dial Transplant* 2018; **33**: 725-735 [PMID: 29106612 DOI: 10.1093/ndt/gfx085]

19 **Ikizler TA**, Robinson-Cohen C, Ellis C, Headley SAE, Tuttle K, Wood RJ, Evans EE, Milch CM, Moody KA, Germain M, Limkunakul C, Bian A, Stewart TG, Himmelfarb J. Metabolic Effects of Diet and Exercise in Patients with Moderate to Severe CKD: A Randomized Clinical Trial. *J Am Soc Nephrol* 2018; **29**: 250-259 [PMID: 29038285 DOI: 10.1681/ASN.2017010020]

20 **Bacharaki D**, Petrakis I, Kyriazis P, Markaki A, Pleros C, Tsirpanlis G, Theodoridis M, Balafa O, Georgoulidou A, Drosataki E, Stylianou K. Adherence to the Mediterranean Diet Is Associated with a More Favorable Left Ventricular Geometry in Patients with End-Stage Kidney Disease. *J Clin Med* 2022; **11** [PMID: 36233612 DOI: 10.3390/jcm11195746]

21 **Yau K**, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 Inhibitors in Patients With CKD: Expanding Indications and Practical Considerations. *Kidney Int Rep* 2022; **7**: 1463-1476 [PMID: 35812300 DOI: 10.1016/j.ekir.2022.04.094]

22 **Cases A**, Cigarrán-Guldrís S, Mas S, Gonzalez-Parra E. Vegetable-Based Diets for Chronic Kidney Disease? *Nutrients* 2019; **11** [PMID: 31167346 DOI: 10.3390/nu11061263]

23 **Ridker PM**, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017; **377**: 1119-1131 [PMID: 28845751 DOI: 10.1056/NEJMoa1707914]

24 **Franceschi C**, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* 2018; **14**: 576-590 [PMID: 30046148 DOI: 10.1038/s41574-018-0059-4]

25 **Barreto DV**, Barreto FC, Liabeuf S, Temmar M, Lemke HD, Tribouilloy C, Choukroun G, Vanholder R, Massy ZA; European Uremic Toxin Work Group (EUTox). Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease. *Kidney Int* 2010; **77**: 550-556 [PMID: 20016471 DOI: 10.1038/ki.2009.503]

26 **Pecoits-Filho R**, Bárány P, Lindholm B, Heimbürger O, Stenvinkel P. Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. *Nephrol Dial Transplant* 2002; **17**: 1684-1688 [PMID: 12198224 DOI: 10.1093/ndt/17.9.1684]

27 **Cho Y**, Johnson DW, Vesey DA, Hawley CM, Pascoe EM, Clarke M, Topley N; balANZ Trial Investigators. Baseline serum interleukin-6 predicts cardiovascular events in incident peritoneal dialysis patients. *Perit Dial Int* 2015; **35**: 35-42 [PMID: 24711638 DOI: 10.3747/pdi.2013.00272]

28 **Carrero JJ**, Stenvinkel P. Persistent inflammation as a catalyst for other risk factors in chronic kidney disease: a hypothesis proposal. *Clin J Am Soc Nephrol* 2009; **4** Suppl 1: S49-S55 [PMID: 19996005 DOI: 10.2215/CJN.02720409]

29 **Kato S**, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3**: 1526-1533 [PMID: 18701615 DOI: 10.2215/CJN.00950208]

30 **Bacharaki D**, Diamandopoulos A. Emperor's syndrome in the COVID-19 era: Time for patient-centered nephrology? *World J Nephrol* 2021; **10**: 1-7 [PMID: 33552939 DOI: 10.5527/wjn.v10.i1.1]

31 **Hajar R**. History of medicine timeline. *Heart Views* 2015; **16**: 43-45 [PMID: 25838882 DOI: 10.4103/1995-705x.153008]

32 **Weaver RR**. Reconciling evidence-based medicine and patient-centred care: defining evidence-based inputs to patient-centred decisions. *J Eval Clin Pract* 2015; **21**: 1076-1080 [PMID: 26456314 DOI: 10.1111/jep.12465]

33 **Tay MZ**, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]

34 **Giamarellos-Bourboulis EJ**, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020; **27**: 992-1000.e3 [PMID: 32320677 DOI: 10.1016/j.chom.2020.04.009]

35 **Rovina N**, Akinosoglou K, Eugen-Olsen J, Hayek S, Reiser J, Giamarellos-Bourboulis EJ. Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia. *Crit Care* 2020; **24**: 187 [PMID: 32354367 DOI: 10.1186/s13054-020-02897-4]

36 **Kyriazopoulou E**, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, Fragkou A, Rapti A, Damoulari C, Fantoni M, Kalomenidis I, Chrysos G, Angheben A, Kainis I, Alexiou Z, Castelli F, Serino FS, Tsilika M, Bakakos P, Nicastri E, Tzavara V, Kostis E, Dagna L, Koufargyris P, Dimakou K, Savvanis S, Tzatzagou G, Chini M, Cavalli G, Bassetti M, Katrini K, Kotsis V, Tsoukalas G, Selmi C, Bliziotis I, Samarkos M, Doumas M, Ktena S, Masgala A, Papanikolaou I, Kosmidou M, Myrodia DM, Argyraki A, Cardellino CS, Koliakou K, Katsigianni EI, Rapti V, Giannitsioti E, Cingolani A, Micha S, Akinosoglou K, Liatsis-Douvitsas O, Symbardi S, Gatselis N, Mouktaroudi M, Ippolito G, Florou E, Kotsaki A, Netea MG, Eugen-Olsen J, Kyprianou M, Panagopoulos P, Dalekos GN, Giamarellos-Bourboulis EJ. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 2021; **27**: 1752-1760 [PMID: 34480127 DOI: 10.1038/s41591-021-01499-z]

37 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]

38 **Levey AS**, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global

Outcomes (KDIGO). *Kidney Int* 2005; **67**: 2089-2100 [PMID: 15882252 DOI: 10.1111/j.1523-1755.2005.00365.x]

39 **Ellam T**, Twohig H, Khwaja A. Chronic kidney disease in elderly people: disease or disease label? *BMJ* 2016; **352**: h6559 [PMID: 26780947 DOI: 10.1136/bmj.h6559]

40 **Zoccali C**, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, Kanbay M, Mallamaci F, Parati G, Rossignol P, Wiecek A, London G; European Renal and Cardiovascular Medicine (EURECA-m) Working Group of the European Renal Association - European Dialysis Transplantation Association (ERA-EDTA). The systemic nature of CKD. *Nat Rev Nephrol* 2017; **13**: 344-358 [PMID: 28435157 DOI: 10.1038/nrneph.2017.52]

41 **Jarczak D**, Kluge S, Nierhaus A. Sepsis-Pathophysiology and Therapeutic Concepts. *Front Med (Lausanne)* 2021; **8**: 628302 [PMID: 34055825 DOI: 10.3389/fmed.2021.628302]

42 **Li H**, Markal A, Balch JA, Loftus TJ, Efron PA, Ozrazgat-Baslanti T, Bihorac A. Methods for Phenotyping Adult Patients in Sepsis and Septic Shock: A Scoping Review. *Crit Care Explor* 2022; **4**: e0672 [PMID: 35372844 DOI: 10.1097/CCE.0000000000000672]

43 **Saez-Rodriguez J**, Rinschen MM, Floege J, Kramann R. Big science and big data in nephrology. *Kidney Int* 2019; **95**: 1326-1337 [PMID: 30982672 DOI: 10.1016/j.kint.2018.11.048]

44 **Marić I**, Contrepois K, Moufarrej MN, Stelzer IA, Feyaerts D, Han X, Tang A, Stanley N, Wong RJ, Traber GM, Ellenberger M, Chang AL, Fallahzadeh R, Nassar H, Becker M, Xenochristou M, Espinosa C, De Francesco D, Ghaemi MS, Costello EK, Culos A, Ling XB, Sylvester KG, Darmstadt GL, Winn VD, Shaw GM, Relman DA, Quake SR, Angst MS, Snyder MP, Stevenson DK, Gaudilliere B, Aghaeepour N. Early prediction and longitudinal modeling of preeclampsia from multiomics. *Patterns (N Y)* 2022; **3**: 100655 [PMID: 36569558 DOI: 10.1016/j.patter.2022.100655]

45 **Seymour CW**, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, Huang DT, Kellum JA, Mi Q, Opal SM, Talisa V, van der Poll T, Visweswaran S, Vodovotz Y, Weiss JC, Yealy DM, Yende S, Angus DC. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA* 2019; **321**: 2003-2017 [PMID: 31104070 DOI: 10.1001/jama.2019.5791]

46 **Goffredo G**, Barone R, Di Terlizzi V, Correale M, Brunetti ND, Iacoviello M. Biomarkers in Cardiorenal Syndrome. *J Clin Med* 2021; **10** [PMID: 34362216 DOI: 10.3390/jcm10153433]

47 **Virzì GM**, Clementi A, Battaglia GG, Ronco C. Multi-Omics Approach: New Potential Key Mechanisms Implicated in Cardiorenal Syndromes. *Cardiorenal Med* 2019; **9**: 201-211 [PMID: 30939477 DOI: 10.1159/000497748]

48 **Menon V**, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 2005; **68**: 766-772 [PMID: 16014054 DOI: 10.1111/j.1523-1755.2005.00455.x]

49 **Matsushita K**, Jassal SK, Sang Y, Ballew SH, Grams ME, Surapaneni A, Arnlov J, Bansal N, Bozic M, Brenner H, Brunskill NJ, Chang AR, Chinnadurai R, Cirillo M, Correa A, Ebert N, Eckardt KU, Gansevoort RT, Gutierrez O, Hadaegh F, He J, Hwang SJ, Jafar TH, Kayama T, Kovesdy CP, Landman GW, Levey AS, Lloyd-Jones DM, Major RW, Miura K, Muntner P, Nadkarni GN, Naimark DM, Nowak C, Ohkubo T, Pena MJ, Polkinghorne KR, Sabanayagam C, Sairenchi T, Schneider MP, Shalev V, Shlipak M, Solbu MD, Stempniewicz N, Tollitt J, Valdivielso JM, van der Leeuw J, Wang AY, Wen CP, Woodward M, Yamagishi K, Yatsuya H, Zhang L, Schaeffner E, Coresh J. Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. *EClinicalMedicine* 2020; **27**: 100552 [PMID: 33150324 DOI: 10.1016/j.eclinm.2020.100552]

50 **Verbeke F**, Van Biesen W, Honkanen E, Wikström B, Jensen PB, Krzesinski JM, Rasmussen M, Vanholder R, Rensma PL; CORD Study Investigators. Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: outcome of the calcification outcome in renal disease (CORD) study. *Clin J Am Soc Nephrol* 2011; **6**: 153-159 [PMID: 20829424 DOI: 10.2215/CJN.05120610]

51 **Honkanen E**, Kauppila L, Wikström B, Rensma PL, Krzesinski JM, Aasarod K, Verbeke F, Jensen PB, Mattelaer P, Volck B; CORD study group. Abdominal aortic calcification in dialysis patients: results of the CORD study. *Nephrol Dial Transplant* 2008; **23**: 4009-4015 [PMID: 18676346 DOI: 10.1093/ndt/gfn403]

52 **EVOLVE Trial Investigators**, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; **367**: 2482-2494 [PMID: 23121374 DOI: 10.1056/NEJMoa1205624]

53 **Xiong J**, He T, Wang M, Nie L, Zhang Y, Wang Y, Huang Y, Feng B, Zhang J, Zhao J. Serum magnesium, mortality, and cardiovascular disease in chronic kidney disease and end-stage renal disease patients: a systematic review and meta-analysis. *J Nephrol* 2019; **32**: 791-802 [PMID: 30888644 DOI: 10.1007/s40620-019-00601-6]

54 **Giannakopoulos P**, Fokas S, Drosataki E, Tsotsorou O, Duni A, Theodoridis M, Stylianou K, Ntounousi E, Passadakis P, Katsoudas S, Kyriazis P, Bacharaki D, Vlahakos D. Abdominal Aortic Calcification Score Modifies the Prognostic Value of Serum Magnesium Levels on All-Cause Mortality in Peritoneal Dialysis Patients. *Nephrol Dial Transplant* 2020; **35**: 1168 [DOI: 10.1093/ndt/gfaa142.P1168]

55 **Eckardt KU**, Agarwal R, Aswad A, Awad A, Block GA, Bacci MR, Farag YMK, Fishbane S, Hubert H, Jardine A, Khawaja Z, Koury MJ, Maroni BJ, Matsushita K, McCullough PA, Lewis EF, Luo W, Parfrey PS, Pergola P, Sarnak MJ, Spinowitz B, Tumlin J, Vargo DL, Walters KA, Winkelmayer WC, Wittes J, Zwiech R, Chertow GM. Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis. *N Engl J Med* 2021; **384**: 1601-1612 [PMID: 33913638 DOI: 10.1056/NEJMoa2025956]

56 **Regidor DL**, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 2006; **17**: 1181-1191 [PMID: 16565261 DOI: 10.1681/ASN.2005090997]

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ORIGINAL ARTICLE

Retrospective Study

Real-world five-year outcomes of FlexyRap® cobalt-chromium rapamycin-eluting stents with biodegradable polymer in patients with *de-novo* coronary artery disease

Nitish Garg, Raman Chawla, Vivek Tandon, Deepak Garg, Nilesh Parshottam, Preeti Vani, Malte Neuss

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Nitish Garg, Department of Interventional Cardiology, Cardinova Hospital, Jalandhar 144001, India

Raman Chawla, Department of Interventional Cardiology, CareMax Hospital, Jalandhar 144001, India

Vivek Tandon, Department of Interventional Cardiology, EMC Hospital, Amritsar 143001, India

Deepak Garg, Department of Interventional Cardiology, Moga Medicity Hospital, Moga 142001, India

Nilesh Parshottam, Department of Interventional Cardiology, Sunshine Global Hospital, Surat 394370, India

Preeti Vani, Malte Neuss, Medical Division, Sahajanand Laser Technology Ltd., Gandhinagar, Gujarat, 382028, India

Corresponding author: Preeti Vani, MSc, Researcher, Medical Division, Sahajanand Laser Technology Limited, A-8, G.I.D.C, Electronic Estate, Sec-25, Gandhinagar 382028, India. clinical@sltl.com

Abstract

BACKGROUND

The use of biodegradable polymer drug-eluting stents (BP-DES) has been proven to minimize restenosis and stent thrombosis. The current post-marketing monitoring was observed at the 5-year clinical outcomes of individuals who had been treated with FlexyRap® DES in the real world.

AIM

To assess the safety and effectiveness of FlexyRap® DES at the 5-year follow-up in real-world settings.

METHODS

Findings from a retrospective, multi-center, observational, post-market clinical follow-up study of patients treated with FlexyRap® DES for *de novo* coronary artery disease (CAD) were reported. During the 12-mo follow-up, the primary endpoint was target lesion failure, which was defined as the composite of

cardiovascular death, target vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization.

RESULTS

The data of 500 patients received with FlexyRap® DES was obtained at the completion of the surveillance timeline of 5-year. After the implantation of FlexyRap® DES, the device success rate was 100%. Adverse events that led to major bleeding, permanent disability, or death were not experienced in the patients. The major adverse cardiac event rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%), and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI, and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at the follow-up of 12-mo, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up.

CONCLUSION

FlexyRap® DES was proved to be safe and efficacious in real-world patients with *de novo* CAD, indicating a lowered rate of cardiac events and stent thrombosis at 5-year follow-up.

Key Words: Coronary artery disease; Drug-eluting stents; Percutaneous coronary intervention; Rapamycin; Sirolimus

Core Tip: Biodegradable polymer drug-eluting stents (BP-DES) have been proven to minimize restenosis and stent thrombosis. Our study evaluates the safety and effectiveness of FlexyRap® DES at the 5-year clinical response in real-world settings. The study proved the feasibility, safety, and efficacy of the FlexyRap® rapamycin-eluting stent for the treatment of *de novo* coronary artery disease, indicating low rates of events and stent thrombosis at 5-year follow-up.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is a frequently conducted cardiac procedure aimed at enhancing the quality of life and reducing symptoms for individuals suffering from coronary artery disease (CAD)[1]. CAD is the leading cause of mortality across the globe[2]. Drug eluting stents, commonly referred to as DES, are considered as the primary method of percutaneous coronary revascularization for patients experiencing acute coronary syndromes and stable ischemic heart disease[3]. Recent advancements in the design of newer generation DES have centered on enhancing tissue biocompatibility and facilitating arterial healing. This has been achieved by incorporating innovative stent platform materials with thinner struts, utilizing biocompatible or biodegradable polymers with improved coatings, and implementing novel antiproliferative agents by lowering the content of drug and precisely controlling the rate of elution[4]. The advent of DES has decreased the rates of restenosis and become the preferred method of choice for most of the patients undergoing the procedure of PCI [1]. These stents have become widely used across a range of anatomic and clinical aspects due to their reduced rates of restenosis and the requirement for the repetition of the revascularization procedure[2]. The utilization of a polymer that is biodegradable has the possibility of lowering the chronic inflammatory response of the wall of blood vessels, facilitating the process of re-endothelialization and reducing the likelihood of blood clots and late restenosis[5]. Biodegradable polymers are being considered and analyzed to acquire and carry drugs. Polymers like poly lactic acid, polyglycolic acid, and their copolymer, poly lactic-co-glycolic acid, are most prevalent as they sight characteristics to get completely degraded and metabolized in the body[6]. It would have improved safety and performance of DES as they deliver controlled release of anti-restenosis agent and gradual degradation of coating[7].

FlexyRap® is one such novel biodegradable rapamycin-eluting coronary stent that has been developed by using a unique patented design of radial star, semi-opened, hybrid FlexyStar® platform, with a lower 60 μm thickness of strut and flexible link made of L605 cobalt-chromium metal. This design ensures the optimal delivery of the drug, radio-opacity, radial strength, biocompatibility, and vessel

conformability. The evidence supporting the effectiveness and safety of indigenously produced drug-eluting stents in patients with newly diagnosed coronary artery disease is limited[8]. This study aimed to assess post-market clinical follow-up of real-world safety and efficacy of the rapamycin-eluting FlexyRap® coronary stent system, made of biodegradable polymer, in patients with obstructive native coronary arteries over a 5-year period.

MATERIALS AND METHODS

The FlexyRap® DES study was conducted at 5 centers with the total of 500 patients included in this study. The study was a retrospective, single-arm, multi-center, observational, post-market clinical follow-up conducted in 500 patients who were eligible for PCI and coronary artery bypass grafting (CABG). The patients in whom the target lesion located within a native coronary vessel and the target lesion diameter stenosis ≥ 50% were included in the study. Out of a total of 613 patients assessed for eligibility, 113 patients were excluded due to screen failure, and 500 patients were ultimately included in the study after meeting the predefined inclusion criteria as shown in Figure 1. The study was conducted in accordance with the declaration of Helsinki and IS0 14155:2020 GCP standards, ICH-GCP, MEDDEV 2.7.1 Appendix 1, MDR 2017/745 and applicable local regulatory requirements. The study was performed with the approval of an independent ethics committee. The PCI procedures were performed according to current standard guidelines. Clinical and angiographic data from all the patients who were treated with FlexyRap® DES were observed in this study. The clinical follow-up was performed at the time point of 12-mo, 3-year and 5-year after the discharge.

Device description

FlexyRap® cobalt chromium rapamycin-eluting coronary stent system consisting of a drug/polymer coated balloon expandable stent premounted on rapid exchange percutaneous transluminal coronary angioplasty (PTCA) balloon catheter. The stent is made from L605 cobalt chromium alloy (Co-Cr) which consists of cobalt, chromium, tungsten, iron and nickel with its strut thickness 60 μm. The stent is laser cut from the seamless tubing in hybrid design pattern and electro polished for ultra-smooth stent surface. The coating is comprised of biodegradable polymer matrix that contains an active pharmaceutical ingredient rapamycin (sirolimus). A conformal coating of a polymer carrier with approximately 1.0 μg/mm^2 of rapamycin of total stent surface area with minimal nominal drug content of 32 μg on the smallest stent (7 mm) to maximum nominal drug content of 213 μg on the largest stent (45 mm). Stent of 48 mm in length approved by the Central Drug Standard Control Organization was also implanted in the desired population. The stent delivery balloon catheter system is a semi-compliant polyamide balloon, which is nominally 0.5 mm longer than the stent. The two opaque platinum-iridium markers are nominally placed beyond the stent at each end which defines the stent location in length. Two proximal delivery system shaft markers (90 cm and 100 cm proximal to distal tip) indicate the relative position of delivery system to the end of appropriate guiding catheter. FlexyRap® DES is available in various lengths (7, 10, 13, 15, 17, 20, 24, 28, 33, 38, 42, 45 and 48 mm) and diameters (2.25, 2.5, 2.75, 3.0, 3.5, 4.0 and 4.5 mm).

Study procedure

Procedural anticoagulation was achieved using unfractionated heparin (at least 5000 IU or 70-100 IU/kg to maintain an activated clotting time of > 250s during the procedure). Aspirin (≥ 100 mg) and clopidogrel (300-600 mg) or prasugrel (60 mg) were administered before or during the procedure at the investigator's discretion. Patients continued to take aspirin (100 mg QD) indefinitely clopidogrel (75 mg QD) or prasugrel (60 mg) was administered for at least 6-mo after stent implantation in all patients and for at least 12-mo in those who did not have a high risk of bleeding. In addition, glycoprotein IIB/IIIA inhibitors were administered in certain patients at the investigator's discretion. Biomarkers and electrocardiograms were recorded at different time points to assure the safety and well-being of patients.

Definitions and study endpoints

Target lesion failure (TLF) is defined as a composite of cardiovascular death, target- vessel myocardial infarction (TV-MI), and clinically driven target lesion revascularization (CD-TLR)[9]. In the following study the primary endpoint was the TLF where the follow-up was taken at the interval of 12-mo and the secondary endpoints were cardiovascular death, TV-MI, clinically driven TLR, stent thrombosis (ST), target vessel failure, target vessel revascularization where the follow-up was taken at 12-mo, 3-year, and 5-year. The composite of cardiac death, target lesion-revascularization and myocardial infarction is defined as major adverse cardiac event (MACE). ST was also evaluated in this study which was classified according to the definitions of the academic research consortium[10]. Device success was defined as the successful delivery and deployment of the study stent at the intended target lesion, as well as the successful withdrawal of the delivery system, with final in-stent residual diameter stenosis of < 30% of all treated lesions, as determined by visual inspection or quantitative coronary angiography. Procedural success was defined as the delivery and deployment of the study stent at the intended target

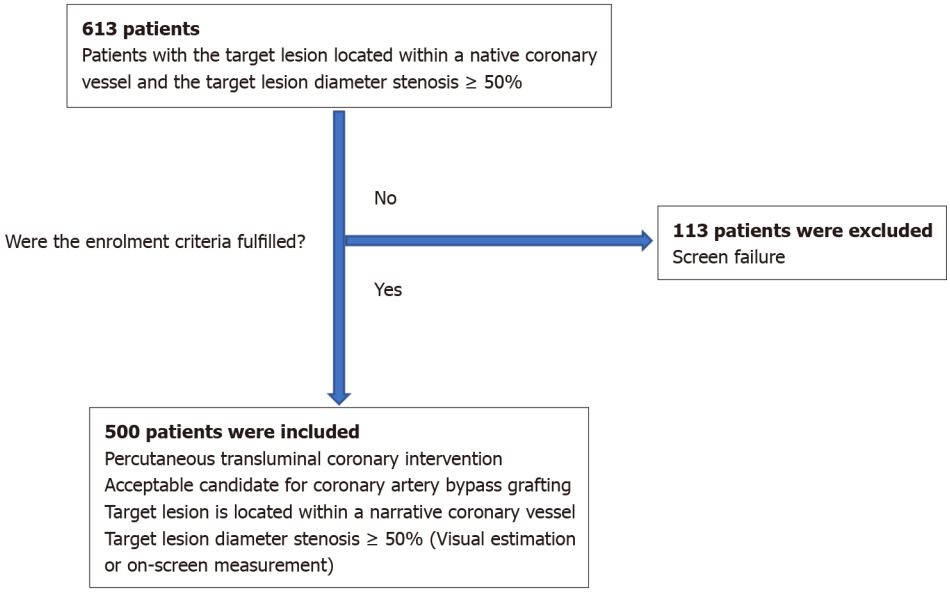

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Figure 1 Patient selection criteria flowchart.

lesion, as well as the withdrawal of the delivery system, with a residual diameter stenosis of less than 30% as determined by visual inspection or quantitative coronary angiography, and no in-hospital major adverse cardiac event (death, MI, or repeat coronary revascularization of the target lesion)[11,12].

Sample size and statistical analysis

A sample size of 500 subjects was calculated based on the primary endpoint of the study. Categorical variables were summarized by frequency distribution for each categorical component (relative frequencies and percentage). All the analysis were done by using statistical package for the social sciences (SPSS) v.20. Results were reported as mean ± standard deviation for continuous variables and as number (%) for nominal variables. For changes in pre–post differences, Wilcoxon-test was used for ordinal variables and paired t-test for continuous variables. Other variables frequency was compared using the chi-square test or fisher's exact test. Result was significant at $P < 0.05$. For time-to-event variables, survival curves were represented using Kaplan Meier estimates.

RESULTS

Baseline demographics characteristics

Baseline demographics and clinical characteristics are summarized in Table 1. The data for 500 patients were collected retrospectively at 12-mo, 3-year, and 5-year. The average age of the study patients was 59.30 ± 11.27 years, with the majority being male (70.2%). The most frequently occurring comorbidities were hypertension (43.4%), smoking (40.6%), diabetes mellitus (14%), alcoholic (9.6%), and dyslipidemia (3.4%). History of myocardial infarction was found in 54.8% followed by CAD (4.8%), PCI (4.2%) and stroke (1.8%). Out of 500 patients, 299 (59.8%) were having stable angina and 201 (40.2%) patients with unstable angina.

Clinical outcomes

Lesion details are mentioned in the Table 2. Total 729 lesions were identified and 730 stents were deployed to treat the lesion. The average stent length and diameter was 26.03 ± 10.86 mm and 3.06 ± 0.41 mm. The device success rate were observed to be 100%.

The cardiac event rate associated with the use of FlexyRap® DES at the follow-up of 12-mo, 3-year, and 5-year is presented in Table 3. Total 2 (0.4%) patients experienced MACE during 5-year. The MACE rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%), and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at 12-mo follow-up, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up. The Kaplan-Meier method was used to conduct a time-to-event analysis, which showed a 98.8% result (Figure 2).

Table 1 Demographic baseline and clinical characteristics

Characteristics	FlexyRap® cobalt chromium rapamycin eluting coronary stent system; Number of patients, (*n* = 500)
Patient demographics	
Age, yr (mean ± SD)	59.30 ± 11.27
Male, *n* (%)	351 (70.2)
Female, *n* (%)	149 (29.8)
Heart rate (mean ± SD)	86.36 ± 11.34
Systolic blood pressure (mean ± SD)	133.57 ± 20.88
Diastolic blood pressure (mean ± SD)	83.36 ± 9.70
Haemoglobin (g/dL) (mean ± SD)	12.64 ± 2.45
Platelet count (mean ± SD)	205.85 ± 52.19
Baseline medical history, *n* (%)	
Hypertension	217 (43.4)
Smoking current	203 (40.6)
Diabetes mellitus	70 (14)
Alcohol current	48 (9.6)
Dyslipidemia	17 (3.4)
Previous MI	274 (54.8)
History of CAD	24 (4.8)
Previous PCI	21 (4.2)
Previous Stroke	9 (1.8)
Baseline cardiac history, *n* (%)	
Stable angina	299 (59.8)
Unstable angina	201 (40.2)
Angina class, *n* (%)	
Class I	12 (2.4)
Class II	30 (6)
Class IIA	1 (0.2)
Class IIB	12 (2.4)
Class IIC	6 (1.2)
Class III	198 (39.6)
Class IIIA	15 (3)
Class IIIB	51 (10.2)
Class IIIC	37 (7.4)
Class IV	138 (27.6)
Disease vessel, *n* (%)	
Single vessel	314 (62.8)
Double vessel	150 (30)
Triple vessel	27 (5.4)
Quadra vessel	9 (1.8)
LVEF (mean ± SD)	52.88 ± 15.46
Serum creatinine (mean ± SD)	1.47 ± 0.47

CABG: Coronary artery bypass graft; CAD: Coronary artery disease; LVEF: Left ventricular ejection fracture; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

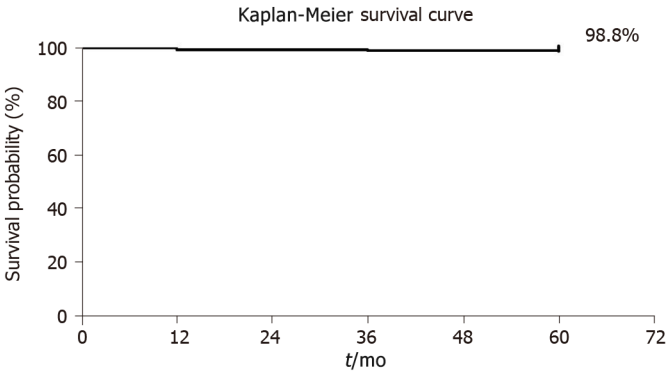

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Figure 2 Time-to-event curve at up to 5-year follow-up by Kaplan-Meier method.

DISCUSSION

In the proposed retrospective study, the FlexyRap® DES has showed exceptional positive results in the patients with *de novo* obstructive native CAD including high procedural success and clinical performance. The patient population had hypertension (43.4%), smoking (40.6%), diabetes mellitus (14%), previous myocardial infarction (54.8%), alcoholism (9.6%), and dyslipidemia (3.4%).

As per the observed study, FlexyRap® cobalt-chromium rapamycin-eluting coronary stent system consisting of drug/polymer coated balloon expandable stent is premounted on rapid exchange PTCA balloon catheter. The polymers are biodegradable, biocompatible, and bioresorbable. Degradation of these materials has been thoroughly studied and has been shown to be safely resorbed by the body after implantation. Rapamycin belongs to a class of therapeutic agents known as macrocyclic lactone or macrolide. It's a cytostatic drug and an immunosuppressant. Rapamycin inhibits T cell activation and growth in response to antigenic stimuli and cytokines such as IL-3, IL-4, and IL-15 are inhibited through a unique mechanism that differs from other immunosuppressive agents. It has been noted that a variety of elements, including the design of the stent, thickness of its struts, antiproliferative agent used, release dynamics of the drug, the duration of drug release, and the type of polymer, can have an impact on the safety and effectiveness of coronary stent system[13]. The first-generation stent were constructed with bulky stent frameworks, making their delivery quite difficult[14]. However, the newest generation boasts thin struts and has demonstrated an 8% increase in its nominal pressure to rated burst pressure. These latest-generation FlexyRap® DES offer improved ease of delivery and vessel conformability, resulting in full deployment and proper placement against the vessel wall. Its design minimizes balloon overhang, reducing the likelihood of edge dissection or injury - a typical procedural issue in PCI. The results of the study, where procedural success was accomplished in all patients, support these claims. Compared to bare metal stent, the first-generation DES featuring a long-lasting polymer have been successful in lowering the rate of re-narrowing, but they have a higher incidence of late ST[15].

Also, the FlexyRap® has the advantage of not cracking, webbing, clumping, or adhering to the balloon surface, making it a promising option for coronary applications. The finding of 100% procedural success in this study can be attributed to these favorable product features.

Iglesias *et al*[16], compared the safety and effectiveness of ultrathin strut biodegradable polymer sirolimus-eluting stents (BP-SES) with thin strut durable polymer everolimus-eluting stents in patients experiencing acute ST-segment elevation myocardial infarction (STEMI). The results showed that 25 (4%) out of 649 patients who received (BP-SES) biodegradable polymer sirolimus-eluting stents and 36 (6%) out of 651 patients who received durable polymer everolimus-eluting stents (DP-EES) experienced TLF. Shetty *et al*[17], conducted a study illustrating the late-term clinical outcomes among patients treated with ultrathin strut BP-SES and thin-strut DP-EES where significant differences in target vessel MI and target lesion revascularization was observed. Out of 884 patients with BP-SES, target lesion failure was observed in 8.2% of patients, and 13.6% of patients shown up with TLF for DP-EES out of 450 patients[17]. Dani *et al*[8], assessed the comparative performance of a BP-SES compared with a DP-EES in the treatment of calcified or narrow vessel blockages. A total of 1553 patients were implanted with BP-SES and 784 patients with DP-EES with the validation of 12-mo follow-up. TLF and TV-MI were significantly lower in BP-SES than in DP-EES in non-small vessel lesions. In the patients with TLF, calcified lesions and cardiac death were numerically higher in DP-EES than in BP-SES. Similarly, the outcomes of the proposed study are comparable with the other studies where TLR was not observed in

Table 2 Procedural characteristics

Procedural characteristics (*n* = 500)	
Lesion details	
Total number of lesions treated with FlexyRap® (*n*)	730
Total number of stents deployed (*n*)	730
Total stent per lesion (*n* = 500 patients) (Total no. stent deployed (730)/Total lesion locations (729)	1.001
Total lesion per vessel (*n* = 500 patients); Total lesion locations (729)/(Sum of total No of diseased vessel (731)	0.997
Lesion locations (729) *n* (%)	
D1	6 (0.82)
Distal LAD	17 (2.33)
Distal LCx	4 (0.54)
Distal RCA	16 (2.19)
LAD	279 (38.27)
LCx	98 (13.44)
LM	1 (0.13)
MID LAD	19 (2.6)
MID LCx	9 (1.23)
MID RCA	15 (2.05)
O Mid	7 (0.96)
OM	4 (0.54)
OM1	8 (1.09)
OM2	6 (0.82)
OM3	1 (0.13)
OMI	1 (0.13)
Osteoproximal LAD	2 (0.27)
Osteoproximal RCA	4 (0.54)
PDA	7 (0.96)
PLV	3 (0.41)
Proximal LAD	23 (3.15)
Proximal RCA	15 (2.05)
Proximal LCx	7 (0.96)
PTCA	8 (1.09)
Ramus intermedius	8 (1.09)
RCA	156 (21.40)
RCX	2 (0.27)
PLB	2 (0.27)
POM	1 (0.13)
Stent length (mean ± SD)	26.03 ± 10.86
Stent diameter (mean ± SD)	3.06 ± 0.41
Type of stenosis, *n* (%)	
de novo	500 (100)

Thrombus load (n = 731), n (%)	
None	519 (71)
Mild	90 (12.31)
Moderate	59 (8.07)
Severe	63 (8.62)
Lesion type [ACC/AHA classification] (n = 731), n (%)	
Type A	20 (2.73)
Type B1	193 (26.40)
Type B2	302 (41.31)
Type C	216 (29.55)
Stent balloon inflation pressure (atm) (mean ± SD) (n = 500)	12.52 ± 1.75
TIMI FLOW n (%)	
II	9 (1.8)
III	491 (98.2)
% of occlusion (mean ± SD) (n = 500)	88.60 ± 8.79
All values are presented in n (%) or mean ± SD	

ACC/AHA: American college of cardiology/American heart association; LAD: Left anterior descending artery; LCx-: Left circumflex; LM: Left main; OM: Obtuse marginal artery; PDA: Patent ductus arteriosus; PLV: Posterior left ventricular artery; PTCA: Percutaneous transluminal coronary angioplasty; PLB: Posterolateral branch; POM: Medial preoptic nucleus; RCAL Right coronary arterial ligation; RCX: Right Circumflex artery; SD: Standard deviation; TIMI: Thrombolysis in myocardial infarction.

Table 3 Cardiac event rate, *n* (%)

Clinical event	12-mo (n = 500)	3-yr (n = 500)	5-yr (n = 500)
TLF	0 (0)	0 (0)	0 (0)
Cardiovascular Death	0 (0)	0 (0)	0 (0)
TV-MI	1 (0.2)	0 (0)	1 (0.2)
Clinically-driven TLR	0 (0)	0 (0)	0 (0)
Late ST	2 (0.4)	0 (0)	0 (0)
TVF	0 (0)	0 (0)	0 (0)
TVR	0 (0)	0 (0)	0 (0)
Very late ST	0 (0)	2 (0.4)	0 (0)
Total MACE	1 (0.2)	0 (0)	1 (0.2)

MACE: Major adverse cardiac event; TLF: Target lesion failure; TV-MI: Target vessel myocardial infarction; TLR: Target lesion revascularization; ST: Stent thrombosis; TVF: Target vessel failure; TVR: Target vessel revascularization.

the patients and the TV-MI in 0.4% of the patients at the cumulative follow-up of 5-year demonstrating the successful clinical outcomes of the study device.

At the end of the 5-year analysis period, cumulative cardiac events presented with 0.4% of MACE where 0 (0%) cardiovascular death, 2 (0.4%) TV-MI, and 0 (0%) TLR was observed compositely, with 0.4% of late ST and 0.4% of very late ST. The unique configuration of the radial star segments and the minimal thickness of the struts ensure exceptional radial stability, facilitating the smooth navigational progress of the device through the circulatory system. Additionally, the decline in the occurrence of cardiac incidents is likely due to the biodegradable polymer's non-inflammatory properties and optimal drug release kinetics[17]. A decreased thickness of stent struts has been linked to a lower frequency of ST[8]. The main benefit of the study was that it was a 5-year follow-up thus the results were sustained in well- designed with longer follow-up duration. The positive outcomes seen in this study could be attributed to the unique design features of the product, such as the advanced stent design utilizing a

biodegradable polymer that offers strong radial strength, reduced overhang from the balloon, low recoil, and consistent support. The device and procedural success rate were 100% for the patients implanted with FlexyRap® DES. The survival probability of 98.8% was observed.

One significant drawback of this study was its observational design and examination of retrospective data. However, this approach provides a more accurate representation of a diverse patient population, unlike randomized trials with strict criteria for enrollment.

CONCLUSION

In conclusion, the present PMCF study offers evidence regarding the safety, and effectiveness of the FlexyRap® rapamycin-eluting stent for treatment of *de novo* CAD. In the present study, FlexyRap® DES was found to have clinical benefits in treating patients with CAD in a real-world setting.

ARTICLE HIGHLIGHTS

Research background

Drug-eluting stents manufactured with biodegradable polymers (BP-DES) effectively reduce restenosis and the risk of stent thrombosis.

Research motivation

The motivation of the present study is focused on the safety and effectiveness from the stent eluting rapamycin for treating the *de novo* coronary artery disease (CAD).

Research objectives

Our study evaluates the safety and effectiveness of FlexyRap® DES at the 5-year clinical response in real-world settings. The outcome of the study proved to be viable, safe, and efficacious results of the FlexyRap®, rapamycin-eluting stent for treating *de novo* CAD, indicating low rates of events and ST at 5-year follow-up.

Research methods

Findings from a retrospective, multi-center, observational, post-market clinical follow-up study of individuals treated with FlexyRap® DES for *de novo* CAD. During the 12-mo follow-up, the primary endpoint was to determine the rate of target lesion failure (TLF). TLF was established as the culmination of three events: Death caused by cardiovascular issues, a myocardial infarction in the target vessel, and the requirement for revascularization of the target lesion due to clinical findings.

Research results

The major adverse cardiac event rate at 12-mo, 3-year, and 5-year follow-up was 1 (0.2%), 0 (0%) and 1 (0.2%) respectively with 0 (0%) cardiovascular death, 2 (0.4%) TV-MI and 0 (0%) TLR compositely. Furthermore, late stent thrombosis was found in 2 (0.4%) patients at the follow-up of 12-mo, very late stent thrombosis was observed in 2 patients (0.4%) at 3-year follow-up.

Research conclusions

In conclusion, this PMCF study investigated the preliminary indications of the feasibility, safety, and effectiveness of using the FlexyRap® rapamycin-eluting stent for treating *de novo* lesion in CAD. In the present study, FlexyRap® DES was found to have clinical benefits in treating patients with CAD in a real-world setting.

Research perspectives

To improve the inner luminal diameter and decrease the likelihood of repeat blockages in the treatment of *de novo* lesions in the native coronary arteries.

FOOTNOTES

Author contributions: Vani P concept and study design, Neuss M, Garg N, Chawla R, Tandon V, Garg D, Parshottam N performed the research; All authors have reviewed and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the OM Institutional Ethics Committee.

Informed consent statement: As per ICH guidelines - E6 (R2/4.8), there is a need to obtain informed consent from subjects in the case of prospective/RCT/Observational clinical studies/investigations. However, in the case of Retrospective post-market clinical follow-up studies, where data collection is done from the hospital records, the permission for the patient (Anonymous) data collection shall be taken from the E/IRB/Head of the Institution from the medical records and not mandatorily requires Informed consent from the patient.

Conflict-of-interest statement: Ms. Preeti and Dr. Malte are employees of Sahajanand Laser Technology Ltd. (SLTL), India. All other authors have nothing to disclose.

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Country/Territory of origin: India

ORCID number: Preeti Vani 0000-0001-5665-1062.

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REFERENCES

1 **Jambunathan R**, Basavanna D, Vani P, Neuss M, Janbandhu P. One-year outcomes of a NeoHexa sirolimus-eluting coronary stent system with a biodegradable polymer in all-comers coronary artery disease patients: Results from NeoRegistry in India. *World J Cardiol* 2019; **11**: 200-208 [PMID: 31523398 DOI: 10.4330/wjc.v11.i8.200]

2 **Jain RK**, Chakravarthi P, Shetty R, Ramchandra P, Polavarapu RS, Wander GS, Mohan B, Banker DN, Dharmadhikari A, Bansal SS, Jain N, Solanki D, Dhakaan J, Sharma VP, Mohanan PP, Ashokan PK, Manjunath BV, Hiregoudar N, Patil C, Balakrishnan N. One-year outcomes of a BioMime™ Sirolimus-Eluting Coronary Stent System with a biodegradable polymer in all-comers coronary artery disease patients: The meriT-3 study. *Indian Heart J* 2016; **68**: 599-603 [PMID: 27773396 DOI: 10.1016/j.ihj.2016.09.007]

3 **Mauri L**, Doros G, Rao SV, Cohen DJ, Yakubov S, Lasala J, Wong SC, Zidar J, Kereiakes DJ. The OPTIMIZE randomized trial to assess safety and efficacy of the Svelte IDS and RX Sirolimus-eluting coronary stent Systems for the Treatment of atherosclerotic lesions: Trial design and rationale. *Am Heart J* 2019; **216**: 82-90 [PMID: 31415994 DOI: 10.1016/j.ahj.2019.07.003]

4 **Iglesias JF**, Roffi M, Degrauwe S, Secco GG, Aminian A, Windecker S, Pilgrim T. Orsiro cobalt-chromium sirolimus-eluting stent: present and future perspectives. *Expert Rev Med Devices* 2017; **14**: 773-788 [PMID: 28889769 DOI: 10.1080/17434440.2017.1378091]

5 **Hamon M**, Niculescu R, Deleanu D, Dorobantu M, Weissman NJ, Waksman R. Clinical and angiographic experience with a third-generation drug-eluting Orsiro stent in the treatment of single de novo coronary artery lesions (BIOFLOW-I): a prospective, first-in-man study. *EuroIntervention* 2013; **8**: 1006-1011 [PMID: 23339805 DOI: 10.4244/EIJV8I9A155]

6 **BaoLin G**, Ma PX. Synthetic biodegradable functional polymers for tissue engineering: a brief review. *Sci China Chem* 2014; **57**: 490-500 [PMID: 25729390 DOI: 10.1007/s11426-014-5086-y]

7 **Parsa E**, Saroukhani S, Majlessi F, Poorhosseini H, Lofti-Tokaldany M, Jalali A, Salarifar M, Nematipour E, Alidoosti M, Aghajani H, Amirzadegan A, Kassaian SE. Biodegradable-Polymer Biolimus-Eluting Stents versus Durable-Polymer Everolimus-Eluting Stents at One-Year Follow-Up: A Registry-Based Cohort Study. *Tex Heart Inst J* 2016; **43**: 126-130 [PMID: 27127426 DOI: 10.14503/THIJ-14-4997]

8 **Dani S**, Gupta M, Pandya R, Goyal K, Vani P, Neuss M, Janbandhu P. Safety and Effectiveness of FlexyRap® Cobalt-Chromium Rapamycin- Eluting Stents with Biodegradable Polymer in Coronary Artery Disease: Results from a 2-year, Multicenter Postmarketing Study in India. *J Interv Gen Cardiol* 2019; **3**.
Available from: https://www.semanticscholar.org/paper/Safety-and-Effectiveness-of-FlexyRap%C2%AE-Stents-with-a-Dani-Gupta/dc06afa76563bbce1276ffb975421f244bb41938

9 **Garcia-Garcia HM**, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Eur Heart J* 2018; **39**: 2192-2207 [PMID: 29897428 DOI: 10.1093/eurheartj/ehy223]

10 **Cutlip DE**, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**: 2344-2351 [PMID: 17470709 DOI: 10.1161/circulationaha.106.685313]

11 **Chang CC**, Kogame N, Onuma Y, Byrne RA, Capodanno D, Windecker S, Morel MA, Cutlip DE, Krucoff MW, Stone GW, Lansky AJ, Mehran R, Spitzer E, Fraser AG, Baumbach A, Serruys PW. Defining device success for percutaneous coronary intervention trials: a position statement from the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. *EuroIntervention* 2020; **15**: 1190-1198 [PMID: 31475907 DOI: 10.4244/EIJ-D-19-00552]

12 **Hicks KA**, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL; ACC/AHA TASK FORCE ON CLINICAL DATA STANDARDS MEMBERS. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Nucl Cardiol* 2015; **22**: 1041-1144 [PMID: 26204990 DOI: 10.1007/s12350-015-0209-1]

13 **Navarese EP**, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, Kereiakes DJ, Waksman R, Mauri L, Meredith IT, Finn AV, Kim HS, Kubica J, Suryapranata H, Aprami TM, Di Pasquale G, von Birgelen C, Kedhi E. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *BMJ* 2013; **347**: f6530 [PMID: 24196498 DOI: 10.1136/bmj.f6530]

14 **Navarese EP**, Kowalewski M, Kandzari D, Lansky A, Górny B, Kołtowski L, Waksman R, Berti S, Musumeci G, Limbruno U, van der Schaaf RJ, Kelm M, Kubica J, Suryapranata H. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. *Open Heart* 2014; **1**: e000064 [PMID: 25332803 DOI: 10.1136/openhrt-2014-000064]

15 **Stefanini GG**, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J* 2012; **33**: 1214-1222 [PMID: 22447805 DOI: 10.1093/eurheartj/ehs086]

16 **Iglesias JF**, Muller O, Heg D, Roffi M, Kurz DJ, Moarof I, Weilenmann D, Kaiser C, Tapponnier M, Stortecky S, Losdat S, Eeckhout E, Valgimigli M, Odutayo A, Zwahlen M, Jüni P, Windecker S, Pilgrim T. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial. *Lancet* 2019; **394**: 1243-1253 [PMID: 31488372 DOI: 10.1016/S0140-6736(19)31877-X]

17 **Shetty R**, Prajapati J, Pai U, Shetty K. Preliminary Evaluation of Clinical and Angiographic Outcomes with Biodegradable Polymer Coated Sirolimus-Eluting Stent in De Novo Coronary Artery Disease: Results of the MANIPAL-FLEX Study. *Scientifica (Cairo)* 2016; **2016**: 9324279 [PMID: 27597929 DOI: 10.1155/2016/9324279]

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ORIGINAL ARTICLE

Retrospective Study

Prediction of permanent pacemaker implantation after transcatheter aortic valve replacement: The role of machine learning

Pradyumna Agasthi, Hasan Ashraf, Sai Harika Pujari, Marlene Girardo, Andrew Tseng, Farouk Mookadam, Nithin Venepally, Matthew R Buras, Bishoy Abraham, Banveet K Khetarpal, Mohamed Allam, Siva K Mulpuru MD, Mackram F Eleid, Kevin L Greason, Nirat Beohar, John Sweeney, David Fortuin, David R Jr Holmes, Reza Arsanjani

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Pradyumna Agasthi, Hasan Ashraf, Farouk Mookadam, Nithin Venepally, Bishoy Abraham, Banveet K Khetarpal, Mohamed Allam, John Sweeney, David Fortuin, Reza Arsanjani, Department of Cardiology, Mayo Clinic, Phoenix, AZ 85054, United States

Sai Harika Pujari, Department of Internal Medicine, The Brooklyn Hospital Center, Brooklyn, NY 11201, United States

Marlene Girardo, Department of Biostatistics, Mayo Clinic, Phoenix, AZ 85054, United States

Andrew Tseng, Siva K Mulpuru MD, Mackram F Eleid, David R Jr Holmes, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, United States

Matthew R Buras, Department of Statistics, Mayo Clinic, Phoenix, AZ 85054, United States

Kevin L Greason, Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN 55905, United States

Nirat Beohar, Mount Sinai Medical Center, Columbia University, Miami Beach, FL 33138, United States

Corresponding author: Sai Harika Pujari, MBBS, Department of Internal Medicine, The Brooklyn Hospital Center, 121 Dekalb Avenue, Brooklyn, NY 11201, United States. spujari@tbh.org

Abstract

BACKGROUND

Atrioventricular block requiring permanent pacemaker (PPM) implantation is an important complication of transcatheter aortic valve replacement (TAVR). Application of machine learning could potentially be used to predict pre-procedural risk for PPM.

AIM

To apply machine learning to be used to predict pre-procedural risk for PPM.

METHODS

A retrospective study of 1200 patients who underwent TAVR (January 2014-December 2017) was performed. 964 patients without prior PPM were included for a 30-d analysis and 657 patients without PPM requirement through 30 d were included for a 1-year analysis. After the exclusion of variables with near-zero variance or ≥ 50% missing data, 167 variables were included in the random forest gradient boosting algorithm (GBM) optimized using 5-fold cross-validations repeated 10 times. The receiver operator curve (ROC) for the GBM model and PPM risk score models were calculated to predict the risk of PPM at 30 d and 1 year.

RESULTS

Of 964 patients included in the 30-d analysis without prior PPM, 19.6% required PPM post-TAVR. The mean age of patients was 80.9 ± 8.7 years. 42.1 % were female. Of 657 patients included in the 1-year analysis, the mean age of the patients was 80.7 ± 8.2. Of those, 42.6% of patients were female and 26.7% required PPM at 1-year post-TAVR. The area under ROC to predict 30-d and 1-year risk of PPM for the GBM model (0.66 and 0.72) was superior to that of the PPM risk score (0.55 and 0.54) with a *P* value < 0.001.

CONCLUSION

The GBM model has good discrimination and calibration in identifying patients at high risk of PPM post-TAVR.

Key Words: Transcatheter aortic valve replacement; Permanent pacemaker implantation; Machine learning

Core Tip: Atrioventricular block requiring permanent pacemaker (PPM) implantation is an important complication of transcatheter aortic valve replacement. Application of machine learning could potentially be used to predict pre-procedural risk for PPM. Machine learning was used to predict patients who are at risk of developing conduction abnormalities requiring PPM at 30 d and 1 year. Our random forest machine learning model using machine learning outperforms PPM risk score model in its predictive value. Brachiocephalic to annulus distance to height ratio is the highest weighted predictor of PPM implantation at both 30-d and 1-year, which has not been previously described in the literature.

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly being used in preference to surgical aortic valve replacement (SAVR) in patients with aortic stenosis[1-3]. The most common complication of TAVR remains the development of atrioventricular conduction abnormalities, requiring permanent pacemaker (PPM) implantation, despite the use of improved implant performance and newer generation valves[4-12]. PPM is associated with increased length of hospital stay and mortality[13]. Additionally, advanced conduction defects requiring PPM implantation have been demonstrated to lead to worse functional capacity and clinical outcomes in patients with aortic stenosis[1-4]. The PPM requirement rate in TAVR is two to five-fold higher than in SAVR[15,16]. Certain baseline characteristics such as age, gender, pre-existing atrioventricular block, right bundle branch block, left bundle branch block[17,18], and size of the left ventricular outflow tract (LVOT), as well as procedure-related factors such as implantation depth have been shown to be associated with PPM requirement risk. Previous studies that evaluated risk factors associated with PPM requirement used data for older-generation valves and included only a limited number of variables, thus limiting their predictive potential[11,13,19,20]. Consequently, it is very important to risk stratify patients for potential need of PPM implantation post-procedure. Artificial intelligence (AI) refers broadly to analytical algorithms that iteratively learn from data, enabling machines to find hidden insights without the need for explicit programming where to look[21-24]. Machine learning (ML) is a computer science sector that uses computer algorithms to identify patterns with a multitude of variables in large datasets and thereby anticipates various data-

based outcomes[25]. In this study, we used supervised ML with the gradient boosting machine learning model (GBM) to predict pre-procedural risk for PPM post-TAVR at 30 d and 1 year.

MATERIALS AND METHODS

We performed a retrospective study on all patients with severe symptomatic aortic stenosis who underwent TAVR at the Mayo Clinic hospitals in Rochester, MN, Phoenix, AZ, and Jacksonville, FL between January 1, 2012, and December 30, 2017. The Mayo Clinic Institutional Review Board (IRB) approved the study protocol and research authorization to utilize medical information for clinical research was provided by the patients. A retrospective chart review of the electronic health record was used to collect baseline data, and clinical coordinators were contacted for information on follow-up visits. We identified 285 clinical variables for potential inclusion into the ML algorithm.

Out of 1200 patients, 236 individuals with prior pacemakers were excluded. The remaining 964 patients were included in the 30-d PPM risk prediction analysis. We first eliminated all variables with ≥ 50% missing and near-zero variance, where variables with near-zero variance have one unique value or the majority of the data is comprised within a single category. The GBM algorithm handles missing data internally by treating "missing" as its own category. This left 147 out of 285 variables to be included in the model. These variables were used to predict the risk of pacemakers 30 d post-TAVR using the GBM model. The model was optimized using 5-fold cross-validation repeated 10 times to get the highest prediction accuracy. Among the 964 patients without prior PPM who have undergone TAVR, 189 patients required PPM implantation by 30 d, 116 patients were deceased by 1 year, and 2 patients were lost to follow-up, leaving 657 patients who were included in the final analysis to predict the need for PPM at 1 year. There were 287 variables initially, but all variables with ≥50% missing or near-zero variance were eliminated leaving a total of 163 variables. Patient recruitment is summarized in Figure 1.

Clinical variables, comorbidities, and procedural factors were obtained from chart review. Definitions conformed to those provided by the Transcatheter Valve Therapy (TVT) Registry[26]. Echocardiographic variables were collected using standard ultrasound scanners. Comprehensive Doppler and 2-Dimensional Transthoracic Echocardiogram (TTE) were performed prior to the procedure. TTE images were acquired and interpreted according to the European Association of Echocardiography and American Society of Echocardiography guidelines. Multi-detector computed tomography (MDCT) was performed a month before the treatment. The size of the aortic annulus was determined pre-procedure.

Statistical analysis

The study population data set (n = 964 and n = 657) for 30 d and 1 year, respectively, had low event rates. Due to a small percentage of events, the entire data set was used in the modeling phase and was not broken into a test and train cohort. The *caret* R package was used to fit a GBM model from the *gbm*[3] R package using 5-fold cross-validation repeated 10 times. Model hyperparameters, specified prior to fitting the model, are tunable variables that control the chosen model's learning process. The hyperparameters tuned were the interaction depth, number of trees, and shrinkage. The minimum number of observations required at each node was fixed at 20. Figures 2 and 4 include the top 20 variables that indicate which have the highest predictive power in classifying those with events and those without events. The study population for PPM risk was limited to those that had a trans-femoral or trans-apical approach. The PPM risk score developed by Vejpongsa *et al*[20] uses 6 factors. Each factor had points associated that collapsed into a three-group score (low, moderate, or high risk). Tuning of hyperparameters optimizes the target metric, that metric being the area under the receiver operating characteristic curve (AUC). AUC is a numeric metric that measures how well the model can distinguish between patients with PPM and those without PPM.

The predicted probabilities that were generated on each fold were stacked, which was repeated 10 times for each patient. The model took the average of the predicted probabilities of all 10 repeats; the average predicted probabilities for each patient were then used to compute the final AUC. The *pROC* R package was used to produce the ROC curves along with the 95%CI for the AUC (Figures 3 and 5). Variable importance is determined by calculating the relative influence of each variable included in the model. The variable importance plot provides a ranked list of the most significant variables in descending order.

The *caret* R package was used to fit a logistic regression using 5-fold cross-validation repeated 10 times. Similar to the GBM model, this process also used 5-fold cross-validation repeated 10 times, where the predicted probabilities for each fold were stacked and then averaged over all 10 repeats for each patient. The average predicted probabilities of PPM risk for each patient were used to produce the final AUC. Categorical and ordinal variables were compared either with the chi-square or Fisher exact tests and are expressed as numbers and percentages. Continuous variables were compared with the t-test and expressed as mean ± SD. Pearson's χ^2 test and Analysis of Variance were used to assess the baseline differences. A $P < 0.05$ was considered significant. R software version 3.4.1 (Foundation of Statistical Computing, Vienna, Austria) was used to run the analysis. Baseline characteristics, echocardiographic variables, EKG variables, and MDCT variables for 30 d and 1-year analysis are shown in the Supple-

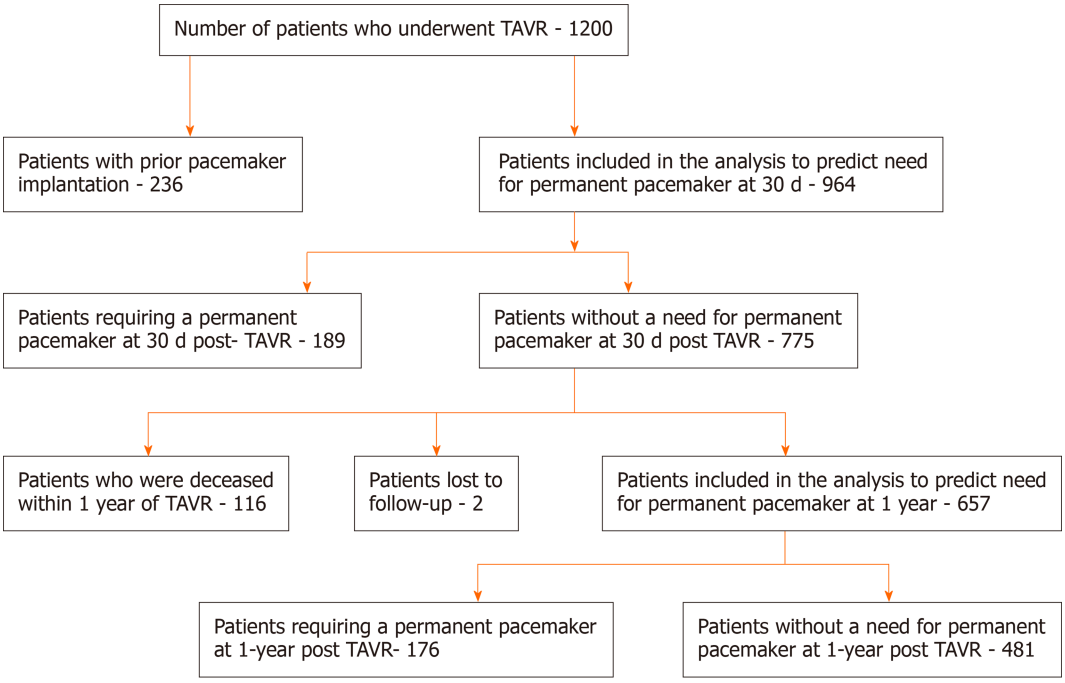

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Figure 1 Flowchart depicting patient recruitment for the analysis transcatheter aortic valve replacement-transcatheter aortic valve replacement. TAVR: Transcatheter aortic valve replacement.

mentary material. Marlene Girardo and Matthew Buras are the statisticians who ran the analysis and are also authors of the paper.

RESULTS

30-d analysis

The mean age of the patients was 80.9 ± 8.7. 42.1% of patients were female and 19.6% (n = 189) required PPM at 30 d post-TAVR. 68.8% of the entire patient cohort had a balloon-expandable valve. Patients requiring PPM post-TAVR had higher proportions of prior percutaneous coronary interventions, aspirin use, trans-femoral access, self-expandable valve use, and New York Heart Association heart failure class III/IV as compared to those who did not require PPM post-TAVR. Other baseline differences between the two groups can be seen in the Supplementary material. Using our GBM machine learning algorithm, a scoring model using the 20 highest weighted predictors of PPM requirement post-TAVR was generated. The highest weighted characteristic was a higher brachiocephalic artery to annulus distance to patient height ratio, followed by right bundle branch block (RBBB), higher brachiocephalic to aortic annulus distance, high pre-operative risk, and the use of self-expanding valves (as opposed to balloon expandable valves). Figure 2 shows the full list with the relative weights of the twenty variables. The area under ROC to predict the need for PPM at 30 d for the GBM model was 0.66 (95%CI: 0.61-0.70) *vs* 0.55 (95%CI: 0.49-0.60) for the PPM risk score model (P < 0.001). The comparison of the ROC curves of both models is shown in Figure 3.

1-year analysis

The mean age of the patients was 80.7 ± 8.2. 42.6% of patients were female and 26.7% (n = 176) required PPM at 1-year post-TAVR. 67.6% of the entire patient cohort had a balloon-expandable valve. Patients requiring PPM at 1-year post-TAVR had higher proportions of prior aortic valve intervention, aspirin use, severe mitral stenosis, elevated filling pressures, and percutaneous transfemoral access compared to those who did not require PPM at 1 year. Other baseline differences can be seen in the Supplementary material. Based on the GBM machine learning algorithm, a scoring model using the 20 highest weighted predictors of PPM dependency at 1-year post-TAVR was generated. The five highest weighted predictors were higher brachiocephalic artery to annulus distance to height ratio, higher mitral valve diastolic mean gradient, RBBB, higher LVOT diameter, and higher distance of right coronary artery to basal ring (mm). Figure 4 shows all twenty variables with the highest weightage. The area under ROC to predict the need for PPM at 1 year for the GBM model was 0.72 (95%CI: 0.67-0.76) *vs* 0.54 (95%CI: 0.49-0.60) for the PPM risk score model (P value < 0.001). The comparison of the ROC curves of both models

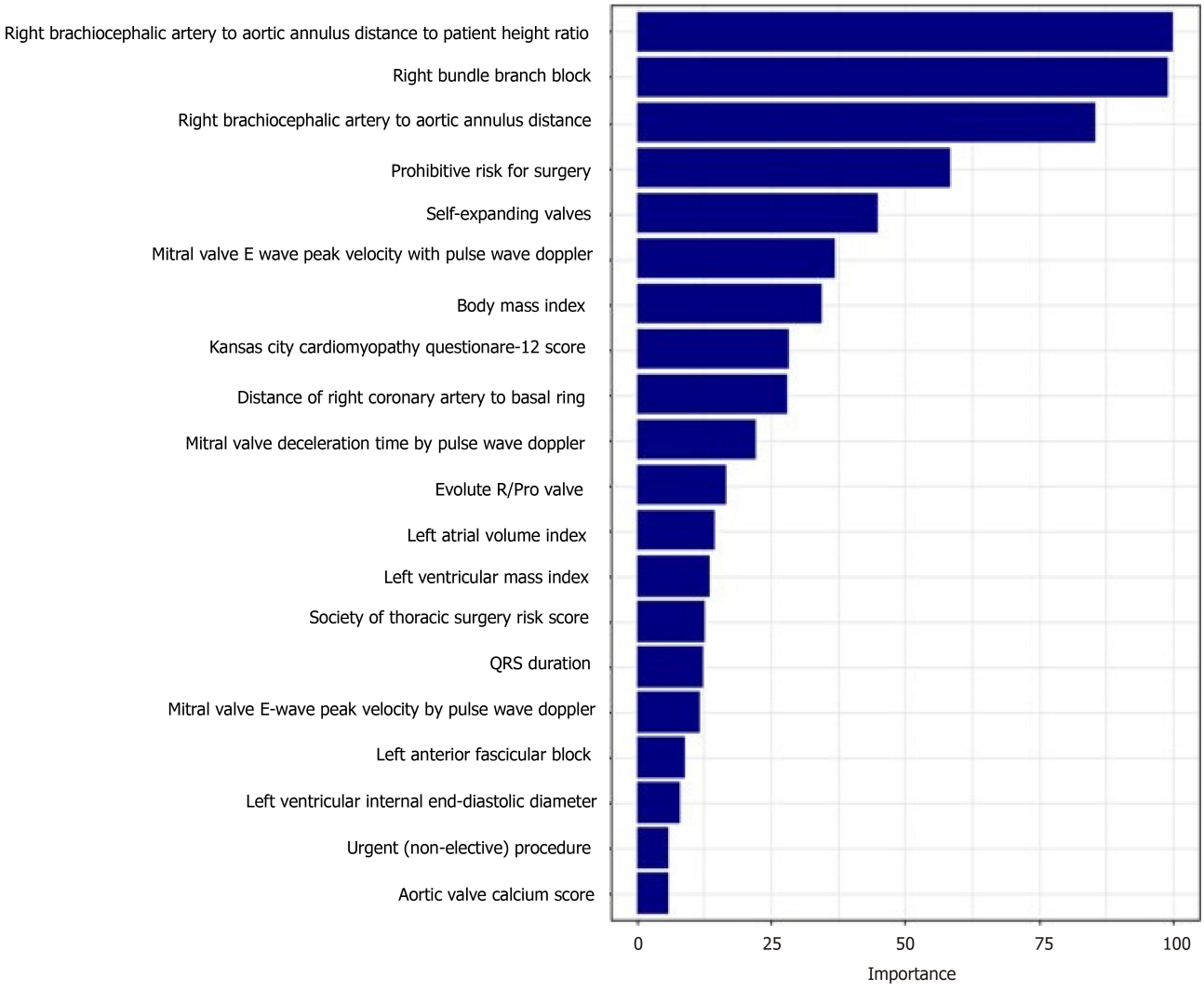

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Figure 2 Variables with the highest importance in a gradient boosting model to predict the need for a permanent pacemaker at 30 d.

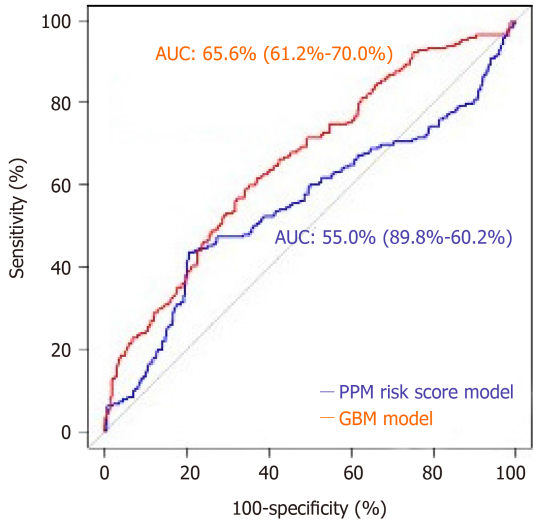

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Figure 3 Receiver operator curves of the gradient boosting model and permanent pacemaker risk score model to predict the need for a permanent pacemaker at 30 d. GBM: Gradient boosting model; PPM: Permanent pacemaker model.

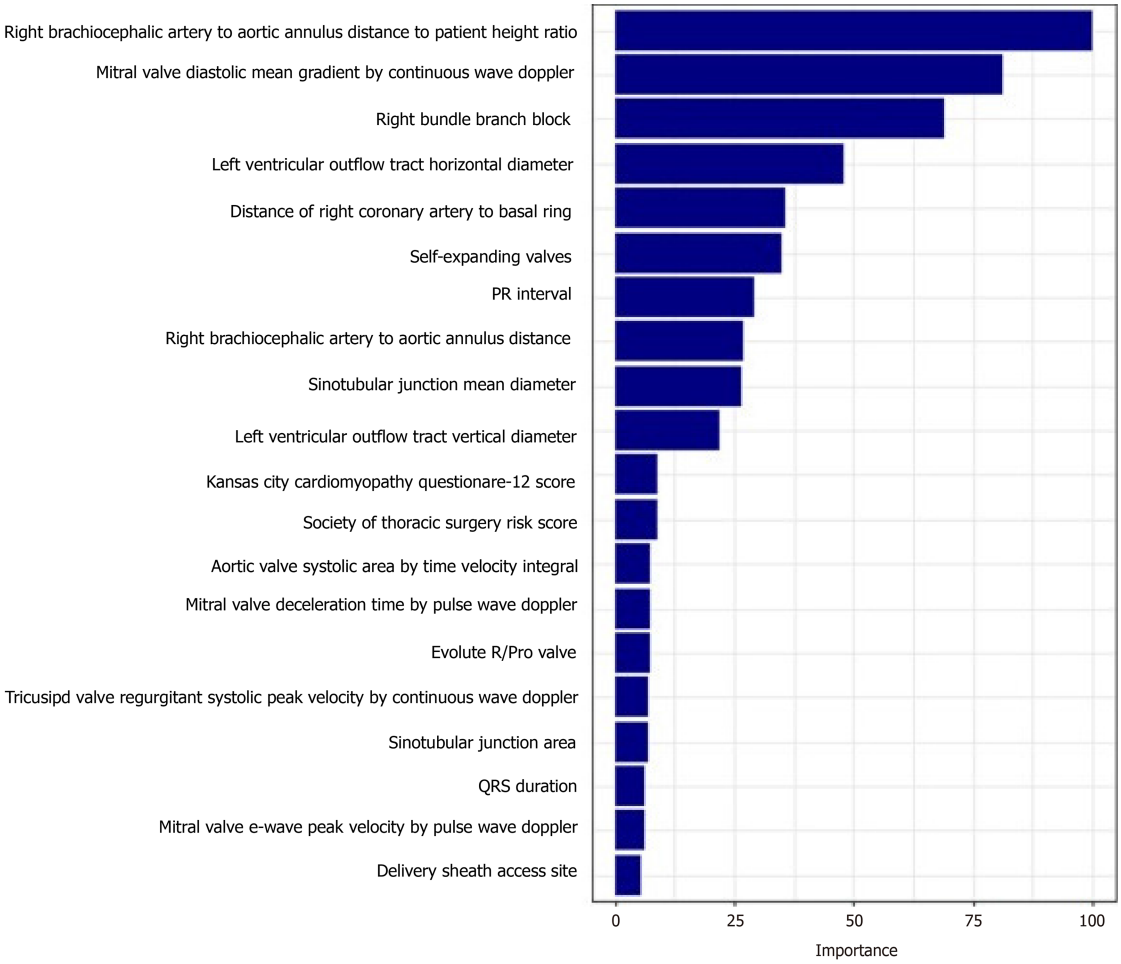

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Figure 4 Variables with the highest importance in the gradient boosting model to predict the need for a permanent pacemaker at 1 year.

is shown in Figure 5.

DISCUSSION

Given the clinical relevance of conduction abnormalities necessitating PPM, we sought to develop a risk assessment tool to predict PPM implantation in patients post-TAVR using machine learning (ML). ML seeks to mimic the thought process, learning capacity, and storage of knowledge of humans[28]. Its techniques have been in use in cardiovascular medicine, but our study is the first to predict the risk of PPM implantation in patients post-TAVR. This study demonstrates that ML could be used to accurately predict the requirement of PPM at 1-year post-TAVR with a high level of discriminatory ability. The GBM model had a modest level of discriminatory ability to predict the requirement of PPM at 30 d. Arteriovenous conduction disturbances are well-known post-TAVR. The most common conduction abnormalities post-TAVR are left bundle branch block (LBBB) and complete heart block[30,31]. Multiple mechanistic reasons for these abnormalities have been theorized, and the most popular one is that the spatial proximity of the cardiac conduction system to the calcified aortic valve[32,33], as well as the underlying conduction disease prevalence in this elderly group[34], predisposes it to damage during the TAVR procedure. Many patients require placement of PPM post-TAVR, with an incidence of 10%-15% commonly cited in the literature, with substantial variability based on the specific TAVR valve used[4]. Conduction abnormalities are clinically relevant as these patients have a higher incidence of subsequent hospitalizations, less improvement in LV function and functional status after TAVR, and possibly even higher mortality, though there is conflicting evidence regarding the latter and long-term prognosis[11,13,30,35].

The rate of PPM implantation post-TAVR in our study was 19.6% at 30 d and 26.7% at 1 year, which is similar to previous trials[8,36-39]. Pre-existing conduction abnormalities such as RBBB, LBBB, and 1st-degree AV block were significantly associated with post-TAVR PPM implantation, and these are consistent with the previous studies[12,13]. Trans-femoral access was also significantly correlated with the PPM rate, which has also been described as a risk factor in a prior registry[13]. Another variable that

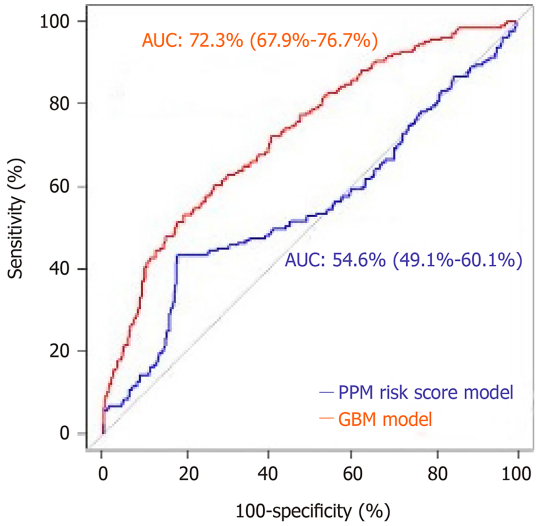

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Figure 5 Receiver operator curves curves of gradient boosting model and permanent pacemaker risk score model predicting the need for a permanent pacemaker at 1 year. GBM: Gradient boosting model; PPM: Permanent pacemaker model.

strongly associates with the PPM rate was self-expanding valves which are also known through prior studies[12,13]. High rates (13.3%-17%) of implantation with the Edwards Sapien 3 valve have previously been demonstrated which was also consistent with our study[19,36,40]. Brachiocephalic artery to aortic valve annulus distance to height ratio was the highest weighted predictor for PPM implantation post-TAVR at both one month and one year. As far as we are aware, we are the first to describe this variable as a predictor for PPM requirement, let alone as the highest weight predictor. It is not clear why it is associated with conduction abnormalities requiring PPM. We suspect that the longer distance of the ascending aorta proximal to the origin of the brachiocephalic artery allows for the TAVR valve to hug the outer curve of the aorta more, thus exerting more force on the right/non-cusp side where the conduction system lies. This needs to be confirmed in other studies.

Overall, the model used for the 30-d and 1-year predictors yielded a very similar set of variables. The main difference was the presence of mitral valve diastolic mean gradient on echo which was the second highest weighted predictor for PPM at 1 year but was not present in the 30-d predictive model. Whether it is the gradient itself that is associated with conduction abnormalities or the mitral annular calcification that is presumably associated with such gradients and would be expected in such populations with calcific aortic stenosis is unclear. The mitral valve and annular calcification were not one of our echocardiographic parameters that were included in the study, so further studies need to be completed. The subsequent evaluation of whether mitral valve or annular calcification is associated with conduction abnormalities independent of AS and TAVR is an obvious corollary. The comparison of our predictive model with the PPM risk score developed by Vejpongsa *et al*[20] which uses 6 variables for scoring, demonstrates the enhanced prognostic capability of our model (Figures 3 and 5). Other risk score models for PPM requirement post-TAVR that have been described are the Emory Risk Score developed by Kiani *et al*[19] and the risk score developed by Maeno *et al*[41]. We were unable to compare our model with these risk score models due to a lack of complete variables, including the history of syncope in the Emory risk score, and membranous septum (MS) length in the risk score. Some of the limitations of this study need to be noted. Firstly, the model is complex, and therefore its use may be limited in clinical practice. Additionally, given the large number of demographic information and clinical variables included in this model, these variables may not always be present. Nevertheless, we feel that the prognosticating ability of the model overcomes this limitation and that with the increasing use of electronic medical records, most data is available. Secondly, this was primarily a feasibility study and is retrospective in nature, which restricts our ability for defining causal associations. There is a need for prospective validation with an external cohort. Thirdly, we did not include a few variables in our model that have been included in other risk scores for PPM implantation, such as a history of syncope or distal landing zone calcium burden, as these variables were not present in enough of our cohort to include. Thus, there is a potential for change in the analysis with the inclusion of such variables. Lastly, the study included primarily referred patients in three high-volume tertiary care centers, and thus are likely higher risk and more complex than the average TAVR patient.

CONCLUSION

Machine learning was used to predict patients who are at risk of developing conduction abnormalities requiring PPM at 30 d and 1 year. Our GBM model using machine learning outperforms the PPM risk score model in its predictive value. Brachiocephalic to annulus distance to height ratio is the highest weighted predictor of PPM implantation at both 30 d and 1 year, which has not been previously described in the literature.

ARTICLE HIGHLIGHTS

Research background

For aortic stenosis, it is a fact that transcatheter aortic valve replacement use has greatly increased relative to surgical replacement with the most common complications of the procedure including atrioventricular conduction abnormalities development and permanent pacemaker requirement (PPM). Hence, it is essential to risk stratify patients for potential need of PPM implantation post-procedure. We used artificial intelligence to predict pre-procedural risk for pacemaker placement post-transcatheter aortic valve replacement at 30 d and 1 year.

Research motivation

Previous studies that evaluated risk factors associated with permanent pacemaker requirement used data for older-generation valves and also included only a limited number of variables and hence, limiting their predictive potential. Artificial intelligence does a remarkable job of predicting variables *via* machine learning and the same has been used in our study.

Research objectives

To predict pre-procedural risk for permanent pacemaker post-transcatheter aortic valve replacement (TAVR) at 30 d and 1 year.

Research methods

We performed a retrospective study on patients with severe symptomatic aortic stenosis who underwent transcatheter aortic valve replacement (TAVR). Gradient boosting machine learning model has been used for predicting probabilities.

Research results

For 30-d analysis, higher brachiocephalic artery to annulus distance to patient height ratio was the highest weighted characteristic that predicted PPM placement post- TAVR. Also for 1-year analysis, higher brachiocephalic artery to annulus distance to patient height ratio was the highest weighted characteristic that predicted PPM placement post- TAVR.

Research conclusions

Brachiocephalic to annulus distance to height ratio is the highest weighted predictor of PPM implantation in the study both at 30 d and 1 year and it was not been previously described in the literature.

Research perspectives

We sought to develop and have developed a risk assessment tool to predict PPM implantation post-TAVR using machine learning.

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FOOTNOTES

Author contributions: Agasthi P conceptualizated, did methodology, project administration, review, and editing; Ashraf H methodology and writing the manuscript; Pujari SH did the data curation, visualization, and writing; Girardo M did the formal analysis, methodology, review, and editing; Tseng A writing, review, and editing the manuscript; Mookadam F did the methodology, project administration, review, and editing; Venepally N did the writing and data curation; Buras MR did the methodology and writing; Allam M did the data curation, visualization,

and writing; Abraham B, Khetarpal BK, MD SKM, Eleid MF, Greason KL, Beohar N, Sweeney J, and Fortuin D writing, review and editing the manuscript; Holmes DRJ and Arsanjani R did the methodology, project administration, review, and editing.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available.

Country/Territory of origin: United States

ORCID number: Pradyumna Agasthi 0000-0003-3067-6979; Hasan Ashraf 0000-0002-3808-6933; Sai Harika Pujari 0000-0002-1073-7482; Andrew Tseng 0000-0002-9181-1970; Farouk Mookadam 0000-0002-9056-8956; Nithin Venepally 0000-0002-7156-1927; Reza Arsanjani 0000-0001-7081-4286.

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REFERENCES

1 **Leon MB**, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010; **363**: 1597-1607 [PMID: 20961243 DOI: 10.1056/NEJMoa1008232]

2 **Leon MB**, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016; **374**: 1609-1620 [PMID: 27040324 DOI: 10.1056/NEJMoa1514616]

3 **Mack MJ**, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019; **380**: 1695-1705 [PMID: 30883058 DOI: 10.1056/NEJMoa1814052]

4 **Holmes DR Jr**, Nishimura RA, Grover FL, Brindis RG, Carroll JD, Edwards FH, Peterson ED, Rumsfeld JS, Shahian DM, Thourani VH, Tuzcu EM, Vemulapalli S, Hewitt K, Michaels J, Fitzgerald S, Mack MJ; STS/ACC TVT Registry. Annual Outcomes With Transcatheter Valve Therapy: From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2015; **66**: 2813-2823 [PMID: 26652232 DOI: 10.1016/j.jacc.2015.10.021]

5 **Rodés-Cabau J**. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol* 2011; **9**: 15-29 [PMID: 22083020 DOI: 10.1038/nrcardio.2011.164]

6 **Généreux P**, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, Smith C, Serruys PW, Kappetein AP, Leon MB. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012; **59**: 2317-2326 [DOI: 10.1016/j.jacc.2012.02.022]

7 **Binder RK**, Webb JG, Toggweiler S, Freeman M, Barbanti M, Willson AB, Alhassan D, Hague CJ, Wood DA, Leipsic J. Impact of post-implant SAPIEN XT geometry and position on conduction disturbances, hemodynamic performance, and paravalvular regurgitation. *JACC Cardiovasc Interv* 2013; **6**: 462-468 [PMID: 23702010 DOI: 10.1016/j.jcin.2012.12.128]

8 **De Torres-Alba F**, Kaleschke G, Diller GP, Vormbrock J, Orwat S, Radke R, Reinke F, Fischer D, Reinecke H, Baumgartner H. Changes in the Pacemaker Rate After Transition From Edwards SAPIEN XT to SAPIEN 3 Transcatheter Aortic Valve Implantation: The Critical Role of Valve Implantation Height. *JACC Cardiovasc Interv* 2016; **9**: 805-813 [PMID: 27017367 DOI: 10.1016/j.jcin.2015.12.023]

9 **Ferreira ND**, Caeiro D, Adão L, Oliveira M, Gonçalves H, Ribeiro J, Teixeira M, Albuquerque A, Primo J, Braga P, Simões L, Ribeiro VG. Incidence and predictors of permanent pacemaker requirement after transcatheter aortic valve implantation with a self-expanding bioprosthesis. *Pacing Clin Electrophysiol* 2010; **33**: 1364-1372 [PMID: 20723083 DOI: 10.1111/j.1540-8159.2010.02870.x]

10 **Husser O**, Pellegrini C, Kessler T, Burgdorf C, Thaller H, Mayr NP, Kasel AM, Kastrati A, Schunkert H, Hengstenberg C. Predictors of Permanent Pacemaker Implantations and New-Onset Conduction Abnormalities With the SAPIEN 3 Balloon-Expandable Transcatheter Heart Valve. *JACC Cardiovasc Interv* 2016; **9**: 244-254 [PMID: 26847116 DOI: 10.1016/j.jcin.2015.09.036]

11 **Nazif TM**, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, El-Chami MF, Herrmann HC, Mack M, Makkar RR,

Miller DC, Pichard A, Tuzcu EM, Szeto WY, Webb JG, Moses JW, Smith CR, Williams MR, Leon MB, Kodali SK; PARTNER Publications Office. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc Interv* 2015; **8**: 60-69 [PMID: 25616819 DOI: 10.1016/j.jcin.2014.07.022]

12 **Siontis GC**, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol* 2014; **64**: 129-140 [PMID: 25011716 DOI: 10.1016/j.jacc.2014.04.033]

13 **Fadahunsi OO**, Olowoyeye A, Ukaigwe A, Li Z, Vora AN, Vemulapalli S, Elgin E, Donato A. Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement: Analysis From the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. *JACC Cardiovasc Interv* 2016; **9**: 2189-2199 [PMID: 27832844 DOI: 10.1016/j.jcin.2016.07.026]

14 **Houthuizen P**, Van Garsse LA, Poels TT, de Jaegere P, van der Boon RM, Swinkels BM, Ten Berg JM, van der Kley F, Schalij MJ, Baan J Jr, Cocchieri R, Brueren GR, van Straten AH, den Heijer P, Bentala M, van Ommen V, Kluin J, Stella PR, Prins MH, Maessen JG, Prinzen FW. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation* 2012; **126**: 720-728 [PMID: 22791865 DOI: 10.1161/CIRCULATIONAHA.112.101055]

15 **Cao C**, Ang SC, Indraratna P, Manganas C, Bannon P, Black D, Tian D, Yan TD. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. *Ann Cardiothorac Surg* 2013; **2**: 10-23 [PMID: 23977554 DOI: 10.3978/j.issn.2225-319X.2012.11.09]

16 **Hamm CW**, Möllmann H, Holzhey D, Beckmann A, Veit C, Figulla HR, Cremer J, Kuck KH, Lange R, Zahn R, Sack S, Schuler G, Walther T, Beyersdorf F, Böhm M, Heusch G, Funkat AK, Meinertz T, Neumann T, Papoutsis K, Schneider S, Welz A, Mohr FW; GARY-Executive Board. The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J* 2014; **35**: 1588-1598 [PMID: 24022003 DOI: 10.1093/eurheartj/eht381]

17 **Nazif TM**, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodés-Cabau J, Szeto WY, Jilaihawi H, Fearon WF, Dvir D, Dewey TM, Makkar RR, Xu K, Dizon JM, Smith CR, Leon MB, Kodali SK. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J* 2014; **35**: 1599-1607 [PMID: 24179072 DOI: 10.1093/eurheartj/eht376]

18 **Schroeter T**, Linke A, Haensig M, Merk DR, Borger MA, Mohr FW, Schuler G. Predictors of permanent pacemaker implantation after Medtronic CoreValve bioprosthesis implantation. *Europace* 2012; **14**: 1759-1763 [PMID: 22733983 DOI: 10.1093/europace/eus191]

19 **Kiani S**, Kamioka N, Black GB, Lu MLR, Lisko JC, Rao B, Mengistu A, Gleason PT, Stewart JP, Caughron H, Dong A, Patel H, Grubb KJ, Greenbaum AB, Devireddy CM, Guyton RA, Leshnower B, Merchant FM, El-Chami M, Westerman SB, Lloyd MS, Babaliaros VC, Hoskins MH. Development of a Risk Score to Predict New Pacemaker Implantation After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2019; **12**: 2133-2142 [PMID: 31699374 DOI: 10.1016/j.jcin.2019.07.015]

20 **Vejpongsa P**, Zhang X, Bhise V, Kitkungvan D, Shivamurthy P, Anderson HV, Balan P, Nguyen TC, Estrera AL, Dougherty AH, Smalling RW, Dhoble A. Risk Prediction Model for Permanent Pacemaker Implantation after Transcatheter Aortic Valve Replacement. *Structural Heart* 2018; **2**: 328-335 [DOI: 10.1080/24748706.2018.1467067]

21 **Shameer K**, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart* 2018; **104**: 1156-1164 [PMID: 29352006 DOI: 10.1136/heartjnl-2017-311198]

22 **Shouval R**, Bondi O, Mishan H, Shimoni A, Unger R, Nagler A. Application of machine learning algorithms for clinical predictive modeling: a data-mining approach in SCT. *Bone Marrow Transplant* 2014; **49**: 332-337 [PMID: 24096823 DOI: 10.1038/bmt.2013.146]

23 **Deo RC**. Machine Learning in Medicine. *Circulation* 2015; **132**: 1920-1930 [PMID: 26572668 DOI: 10.1161/CIRCULATIONAHA.115.001593]

24 **Edwards FH**, Cohen DJ, O'Brien SM, Peterson ED, Mack MJ, Shahian DM, Grover FL, Tuzcu EM, Thourani VH, Carroll J, Brennan JM, Brindis RG, Rumsfeld J, Holmes DR Jr; Steering Committee of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Development and Validation of a Risk Prediction Model for In-Hospital Mortality After Transcatheter Aortic Valve Replacement. *JAMA Cardiol* 2016; **1**: 46-52 [PMID: 27437653 DOI: 10.1001/jamacardio.2015.0326]

25 **Motwani M**, Dey D, Berman DS, Germano G, Achenbach S, Al-Mallah MH, Andreini D, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJ, Cury RC, Delago A, Gomez M, Gransar H, Hadamitzky M, Hausleiter J, Hindoyan N, Feuchtner G, Kaufmann PA, Kim YJ, Leipsic J, Lin FY, Maffei E, Marques H, Pontone G, Raff G, Rubinshtein R, Shaw LJ, Stehli J, Villines TC, Dunning A, Min JK, Slomka PJ. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. *Eur Heart J* 2017; **38**: 500-507 [PMID: 27252451 DOI: 10.1093/eurheartj/ehw188]

26 **Carroll JD**, Edwards FH, Marinac-Dabic D, Brindis RG, Grover FL, Peterson ED, Tuzcu EM, Shahian DM, Rumsfeld JS, Shewan CM, Hewitt K, Holmes DR Jr, Mack MJ. The STS-ACC transcatheter valve therapy national registry: a new partnership and infrastructure for the introduction and surveillance of medical devices and therapies. *J Am Coll Cardiol* 2013; **62**: 1026-1034 [PMID: 23644082 DOI: 10.1016/j.jacc.2013.03.060]

27 Breiman L. Random Forests. *Machine Learning* 2001; 45: 5-32 [DOI: 10.1023/A:1010933404324]

28 **Krittanawong C**, Zhang H, Wang Z, Aydar M, Kitai T. Artificial Intelligence in Precision Cardiovascular Medicine. *J Am Coll Cardiol* 2017; **69**: 2657-2664 [PMID: 28545640 DOI: 10.1016/j.jacc.2017.03.571]

29 **Regueiro A**, Abdul-Jawad Altisent O, Del Trigo M, Campelo-Parada F, Puri R, Urena M, Philippon F, Rodés-Cabau J. Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Interv* 2016; **9**: e003635 [PMID: 27169577 DOI: 10.1161/CIRCINTERVENTIONS.115.003635]

30 **Weber M**, Brüggemann E, Schueler R, Momcilovic D, Sinning JM, Ghanem A, Werner N, Grube E, Schiller W, Mellert F, Welz A, Nickenig G, Hammerstingl C. Impact of left ventricular conduction defect with or without need for permanent

right ventricular pacing on functional and clinical recovery after TAVR. *Clin Res Cardiol* 2015; **104**: 964-974 [PMID: 25967154 DOI: 10.1007/s00392-015-0865-9]

31 **Bleiziffer S**, Ruge H, Hörer J, Hutter A, Geisbüsch S, Brockmann G, Mazzitelli D, Bauernschmitt R, Lange R. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010; **3**: 524-530 [PMID: 20488409 DOI: 10.1016/j.jcin.2010.01.017]

32 **Kawashima T**, Sato F. Visualizing anatomical evidences on atrioventricular conduction system for TAVI. *Int J Cardiol* 2014; **174**: 1-6 [PMID: 24750717 DOI: 10.1016/j.ijcard.2014.04.003]

33 **Moreno R**, Dobarro D, López de Sá E, Prieto M, Morales C, Calvo Orbe L, Moreno-Gomez I, Filgueiras D, Sanchez-Recalde A, Galeote G, Jiménez-Valero S, Lopez-Sendon JL. Cause of complete atrioventricular block after percutaneous aortic valve implantation: insights from a necropsy study. *Circulation* 2009; **120**: e29-e30 [PMID: 19652115 DOI: 10.1161/CIRCULATIONAHA.109.849281]

34 **Kumar P**, Kusumoto FM, Goldschlager N. Bradyarrhythmias in the elderly. *Clin Geriatr Med* 2012; **28**: 703-715 [PMID: 23101579 DOI: 10.1016/j.cger.2012.08.004]

35 **Urena M**, Webb JG, Tamburino C, Muñoz-García AJ, Cheema A, Dager AE, Serra V, Amat-Santos IJ, Barbanti M, Immè S, Briales JH, Benitez LM, Al Lawati H, Cucalon AM, García Del Blanco B, López J, Dumont E, Delarochellière R, Ribeiro HB, Nombela-Franco L, Philippon F, Rodés-Cabau J. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation* 2014; **129**: 1233-1243 [PMID: 24370552 DOI: 10.1161/CIRCULATIONAHA.113.005479]

36 **Webb J**, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, Thielmann M, Treede H, Wendler O, Walther T. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *J Am Coll Cardiol* 2014; **64**: 2235-2243 [PMID: 25456759 DOI: 10.1016/j.jacc.2014.09.026]

37 **Tarantini G**, Mojoli M, Purita P, Napodano M, D'Onofrio A, Frigo A, Covolo E, Facchin M, Isabella G, Gerosa G, Iliceto S. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. *EuroIntervention* 2015; **11**: 343-350 [PMID: 25405801 DOI: 10.4244/EIJY14M11_06]

38 **Herrmann HC**, Thourani VH, Kodali SK, Makkar RR, Szeto WY, Anwaruddin S, Desai N, Lim S, Malaisrie SC, Kereiakes DJ, Ramee S, Greason KL, Kapadia S, Babaliaros V, Hahn RT, Pibarot P, Weissman NJ, Leipsic J, Whisenant BK, Webb JG, Mack MJ, Leon MB; PARTNER Investigators. One-Year Clinical Outcomes With SAPIEN 3 Transcatheter Aortic Valve Replacement in High-Risk and Inoperable Patients With Severe Aortic Stenosis. *Circulation* 2016; **134**: 130-140 [PMID: 27400898 DOI: 10.1161/CIRCULATIONAHA.116.022797]

39 **Nijhoff F**, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. *Circ Cardiovasc Interv* 2015; **8**: e002408 [PMID: 26033967 DOI: 10.1161/CIRCINTERVENTIONS.115.002408]

40 **Binder RK**, Stortecky S, Heg D, Tueller D, Jeger R, Toggweiler S, Pedrazzini G, Amann FW, Ferrari E, Noble S, Nietlispach F, Maisano F, Räber L, Roffi M, Grünenfelder J, Jüni P, Huber C, Windecker S, Wenaweser P. Procedural Results and Clinical Outcomes of Transcatheter Aortic Valve Implantation in Switzerland: An Observational Cohort Study of Sapien 3 Versus Sapien XT Transcatheter Heart Valves. *Circ Cardiovasc Interv* 2015; **8** [PMID: 26453687 DOI: 10.1161/CIRCINTERVENTIONS.115.002653]

41 **Maeno Y**, Abramowitz Y, Kawamori H, Kazuno Y, Kubo S, Takahashi N, Mangat G, Okuyama K, Kashif M, Chakravarty T, Nakamura M, Cheng W, Friedman J, Berman D, Makkar RR, Jilaihawi H. A Highly Predictive Risk Model for Pacemaker Implantation After TAVR. *JACC Cardiovasc Imaging* 2017; **10**: 1139-1147 [PMID: 28412434 DOI: 10.1016/j.jcmg.2016.11.020]

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ORIGINAL ARTICLE

Observational Study

Effect of reperfusion strategy on QT dispersion in patients with acute myocardial infarction: Impact on in-hospital arrhythmia

Mohamed Aboel-Kassem F Abdelmegid, Mohamed M Bakr, Hamdy Shams-Eddin, Amr A Youssef, Ahmed Abdel-Galeel

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Mohamed Aboel-Kassem F Abdelmegid, Hamdy Shams-Eddin, Amr A Youssef, Ahmed Abdel-Galeel, Department of Cardiovascular Medicine, Assiut University Heart Hospital, Assiut University, Assiut 71526, Egypt

Mohamed Aboel-Kassem F Abdelmegid, Department of Cardiology, Sohag Heart and GIT Center, Sohag 85264, Egypt

Mohamed M Bakr, Department of Cardiology, Assiut Police Hospital, Assiut 71526, Egypt

Ahmed Abdel-Galeel, Department of Cardiology, Qena General Hospital, Qena 92354, Egypt

Corresponding author: Ahmed Abdel-Galeel, MD, PhD, Associate Professor, Department of Cardiovascular Medicine, Assiut University Heart Hospital, Assiut University Street, Assiut 71526, Egypt. ahmed.galeel@aun.edu.eg

Abstract

BACKGROUND

Myocardial ischemia and ST-elevation myocardial infarction (STEMI) increase QT dispersion (QTD) and corrected QT dispersion (QTcD), and are also associated with ventricular arrhythmia.

AIM

To evaluate the effects of reperfusion strategy [primary percutaneous coronary intervention (PPCI) or fibrinolytic therapy] on QTD and QTcD in STEMI patients and assess the impact of the chosen strategy on the occurrence of in-hospital arrhythmia.

METHODS

This prospective, observational, multicenter study included 240 patients admitted with STEMI who were treated with either PPCI (group I) or fibrinolytic therapy (group II). QTD and QTcD were measured on admission and 24 hr after reperfusion, and patients were observed to detect in-hospital arrhythmia.

RESULTS

There were significant reductions in QTD and QTcD from admission to 24 hr in both group I and group II patients. QTD and QTcD were found to be shorter in group I patients at 24 hr than those in group II (53 ± 19 msec *vs* 60 ± 18 msec, *P* =

0.005 and 60 ± 21 msec *vs* 69+22 msec, P = 0.003, respectively). The occurrence of in-hospital arrhythmia was significantly more frequent in group II than in group I (25 patients, 20.8% *vs* 8 patients, 6.7%, P = 0.001). Furthermore, QTD and QTcD were higher in patients with in-hospital arrhythmia than those without (P = 0.001 and P = 0.02, respectively).

CONCLUSION

In STEMI patients, PPCI and fibrinolytic therapy effectively reduced QTD and QTcD, with a higher observed reduction using PPCI. PPCI was associated with a lower incidence of in-hospital arrhythmia than fibrinolytic therapy. In addition, QTD and QTcD were shorter in patients not experiencing in-hospital arrhythmia than those with arrhythmia.

Key Words: Arrhythmia; QT dispersion; ST-segment elevation myocardial infarction; Reperfusion; Primary percutaneous coronary intervention; Fibrinolytic therapy

Core Tip: We evaluated the effect of a reperfusion strategy on QT dispersion (QTD) and corrected QT dispersion (QTcD) in patients with ST-segment elevation myocardial infarction. Primary percutaneous coronary intervention was found to be superior in the reduction of QTD and QTcD and associated with a lower incidence of in-hospital arrhythmias when compared to fibrinolytic therapy. In addition, QTD and QTcD were shorter in patients not experiencing in-hospital arrhythmia than those with arrhythmia.

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INTRODUCTION

Arrhythmia is a major cause of death in ST-elevation myocardial infarction (STEMI) patients, especially in the early in-hospital period[1]. Many studies have shown that dispersion of repolarization is the most common trigger and the main substrate for the occurrence of lethal arrhythmia in patients with STEMI [1-3]. QT dispersion (QTD), the difference between maximal and minimal QT interval calculated on a standard 12-lead electrocardiogram (ECG), measures the heterogeneity of myocardial repolarization[4]. It has previously been discovered that QT interval and QTD are increased in cases of acute ischemia and STEMI[5]. These variations may reflect the changing patterns of underlying recovery of ventricular excitability, which is profoundly disturbed at the earliest phase of acute myocardial infarction (MI)[6]. Moreover, QTD prolongation has been reported as a predictor of arrhythmia in patients with STEMI[7].

Although primary percutaneous coronary intervention (PPCI) is the treatment of choice when managing STEMI patients, fibrinolytic therapy is still an important reperfusion strategy in settings where primary PCI cannot be offered at the appropriate time[8]. Reperfusion of the infarct-related artery, either by fibrinolytic therapy or PPCI, could homogenize the duration of the ventricular action potential, thereby reducing the QTD. However, there are conflicting data about the effects of both perfusion therapy modes with respect to their abilities to reduce QTD in patients with STEMI. Moreover, there are inadequate data relating to the effects of these reperfusion strategies on incidence of in-hospital arrhythmias.

Here, we evaluate the QTD and corrected QT dispersion (QTcD) in patients presenting with STEMI by comparing those treated with PPCI with those receiving fibrinolytic therapy. In addition, the impacts of these treatment modalities on in-hospital incidence of arrhythmia are compared.

MATERIALS AND METHODS

Study population

This was a prospective, observational, multicenter study that included 240 consecutive patients with first acute STEMI who were treated with either fibrinolytic therapy or PPCI. Patients with STEMI who received either fibrinolytic therapy with successful fibrinolysis or PPCI with final thrombolysis in myocardial infarction (TIMI) flow grade III were included. This study was conducted at 4 centers. PPCI-

treated patients were recruited and treated at Assiut University Heart Hospital (a center with resources to perform this procedure at any time), and the fibrinolytic therapy-treated patients were recruited and treated at Sohag Heart & GIT Center, Assiut Police Hospital, and Qena General Hospital.

The STEMI diagnosis in each case was made using the 4th universal definition of MI, which is based on typical electrocardiographic changes alongside clinical symptoms associated with elevation of cardiac biomarkers[9]. Patients were included if they had chest pain for more than 30 min, ST-segment elevation in at least 2 contiguous ECG leads, and hospital admission within 12 hr of onset of chest pain. Successful fibrinolysis was defined as the presence of at least 2 of the following criteria: (1) Disappearance of chest pain within 90 min of starting the fibrinolytic infusion; (2) resolution of ST-segment elevation (in the ECG lead with maximum ST-elevation at baseline) by more than 50% after starting fibrinolytic infusion; or (3) abrupt initial increase in cardiac enzyme levels within the first 24 hr following onset of symptoms[10].

Exclusion criteria were non-ST elevation myocardial infarction, prior history of MI or surgical revascularization, absence of sinus rhythm, presence of bundle branch block or any other inter-ventricular conduction abnormality, ventricular pacing rhythm, pre-excitation on ECG, electrolyte abnormalities, use of medications that affect the QT interval (*e.g.*, antiarrhythmic, antidepressant, and antipsychotic drugs), and cases in which the QT interval could not be measured in at least 8 ECG leads. Patients with unsuccessful reperfusion after thrombolytic therapy and those not achieving TIMI-III flow within the infarct-related artery during PPCI were also excluded.

Study design

Patients were classified into 2 groups based on the reperfusion strategy used. Group I (120 patients) were treated with PPCI and group II (120 patients) received fibrinolytic therapy (1.5 million units of streptokinase given intravenously over 30-60 min).

The 12-lead ECG was recorded at a paper speed of 25 mm/sec. and 10 mm/mV gain standardization. ECG measurements were taken on admission and 24 hr after the reperfusion with either of the two strategies using an ECG machine (EC3T 01 RD/1, MONITOR, Russia). Heart rate, QT interval, and corrected QT (QTc) interval for each ECG lead were calculated automatically using built-in software (ArMaSoft-12-Cardio software, MONITOR, Russia) using Bazett's formula[11]. QT and QTc dispersions were defined as the differences between the maximum and minimum QT and QTc intervals, respectively, in a given ECG lead. Delta (Δ) was defined as the difference in ECG measurement parameters before treatment and 24 hr after reperfusion. For example, Δ QT interval was defined as the QT interval before treatment minus the QT interval 24 hr after reperfusion. ECG data were included where there were adequate measurements using at least 8 leads total with at least 4 precordial leads. All ECGs were in sinus rhythm.

The study endpoint was designated as the occurrence of arrhythmia during admission. Examples of arrhythmias considered included frequent premature ventricular ectopic beat, non-sustained ventricular tachycardia, sustained ventricular tachycardia, ventricular fibrillation, and atrial fibrillation. The study population was further classified into 2 more groups according to the incidence of in-hospital arrhythmia. These groups comprised an in-hospital arrhythmia group whose arrhythmias were recorded and a group who did not experience arrhythmia during admission (and therefore had no recorded arrhythmia events).

Sample size calculation

Sample size calculation was carried out using G Power 3 software. The calculated minimum sample of adult patients presenting with STEMI was 238. This calculation was made based on a 2-group 1:1 design [Group I (n = 119): treated with PPCI and Group II (n = 119): treated with fibrinolytic therapy] and would have 85% power to detect an absolute difference of 35% in the mean QTD, at a 1-sided significance level of 0.05.

Ethical considerations

This study was approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University (IRB No. 17101454), and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants. The authors are accountable for all aspects of the work, including full data access, integrity of the data, and the accuracy of the data analysis. They ensure that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and those without normal distribution as median (interquartile range). Normality of the continuous variables was checked with the Kolmogorov-Smirnov test. Categorical variables were expressed as frequency and percentage (%). Continuous variables were compared using an unpaired student's t-test for normally distributed data and Mann-Whitney test for non-normally distributed data. Comparisons of ECG data before and after reperfusion therapy were conducted using paired t-tests. Chi-Square tests

or Fisher exact tests were used when appropriate to compare categorical variables. A P value of < 0.05 was considered statistically significant, with all reported P values being 2-tailed. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Table 1 shows similar baseline clinical characteristics of both groups of the study population. Moreover, there were no significant differences between the groups with respect to the location of MI and the time from chest pain onset to the start of the reperfusion (Table 1).

Regardless of the chosen perfusion strategy, there was a significant reduction in QTD and QTcD from admission to 24 hr after reperfusion. This reduction in both QTD and QTcD was due to a significant increase in the minimum QT interval (Δ = - 15.9 ± 42.4 msec) with a concomitant decrease in maximum QT interval (Δ = 8.5 ± 47.8 msec) for the QTD and an increase in the minimum QTc interval (Δ = - 22.4 ± 44.5 msec) alongside a concomitant decrease in QTc interval (Δ = 5.1 ± 47.8 msec) for the latter measurement (Table 2).

From admission to 24 hr, both QTD and QTcD decreased significantly in both groups I and II (Table 3). Following reperfusion (24 hr later), the QTD and QTcD of patients in group I were significantly shorter than those in group II (P = 0.005 and P = 0.003, respectively). Moreover, Δ changes in both QTD and QTcD were significantly higher in group I compared with group II (37.6 ± 17.1 msec *vs* 11.3 ± 7.9 msec, P < 0.001 for the former and 43.6 ± 13.6 msec *vs* 11.4 ± 8.0 msec, P < 0.001 for the latter) (Table 3).

The incidence of in-hospital arrhythmia was significantly lower in group I (8 patients, 6.7%) than in group II (25 patients, 20.8%), P = 0.001. Different types of recorded arrhythmia observed in both groups are illustrated in Figure 1. Patients who did not experience in-hospital arrhythmia had significantly reduced QTD and QTcD values compared to those who did experience in-hospital arrhythmia regardless of the perfusion strategy used (Table 4). Furthermore, the Δ changes of both QTD and QTcD were significantly higher in patients who did not experience in-hospital arrhythmia (25.9 ± 18.3 msec and 28.7 ± 20.1 msec, respectively; P = 0.003) than patients who experienced in-hospital arrhythmias (14.8 ± 18.9 msec and 19.8 ± 14.5 msec, respectively; P = 0.016) (Table 4).

DISCUSSION

It is well known that QTd has a prognostic role for stratifying MI patients who are at higher risk of arrhythmic events. In a recent large meta-analysis of 22 trials, an improved QTd after acute MI was associated with lower risk of associated serious arrhythmia. However, no prognostic role was found with respect to all-cause mortality or sudden cardiac death in such a patient population[12].

The current study provides further evidence supporting the beneficial impact of reperfusion therapy on decreasing both QTD and QTcD in the setting of STEMI. Moreover, to our knowledge, our study is the first to calculate QT and QTc intervals automatically using a software program that eliminates human bias of manual measurement. We showed that reperfusion therapy decreases QTD and QTcD in patients with STEMI regardless of reperfusion strategy. Also, our study demonstrated that PPCI had a more favorable effect on reducing QTD and QTcD (measured 24 hr after treatment) when compared to fibrinolytic therapy. Moreover, we showed that restoration of coronary reperfusion using PPCI had a greater impact in reducing the incidence of in-hospital arrhythmias than fibrinolytic therapy. In addition, QTD and QTcD were shorter in patients without in-hospital arrhythmia than in those with arrhythmia recorded during admission.

In the setting of acute coronary syndrome, evidence suggests that there are electrophysiological alterations in action potentials, causing repolarization dispersion between normal and ischemic fibers and between the epicardium and endocardium. This leads to repolarization delays in regions influenced by acute ischemia, thus causing QT and QTc prolongation[5,13-15]. The present study included STEMI patients with achievement of TIMI flow grade III in group I and successful fibrinolysis in group II. Establishing the patency of the infarct-related artery, either by fibrinolytic therapy or PPCI, could reduce regional myocardial ischemia and homogenize the ventricular action potential, thereby reducing the QTD and QTcD. This theory is supported by studies finding that TIMI flow grades II and III were associated with far lower QTD and QTcD values as compared to TIMI flow grades 0 and I[16,17]. Thus, the degree of QTD and QTcD reduction depends on the reperfusion status of the infarcted artery. The results of PPCI in STEMI patients are superior to fibrinolytic therapy with respect to reestablishing infarct-related artery patency. The present study supports this assumption, as our results revealed that PPCI more significantly reduced QTD and QTcD intervals than fibrinolytic therapy in STEMI patients.

The mechanism of QT prolongation and QTD in the setting of MI is attributed to the elevation in extracellular potassium level, acidosis, and anoxia. These conditions also cause reductions in membrane excitability, shortening of action potential duration, and prolongation of recovery of excitability

Table 1 Patient characteristics

Characteristic	Group I, *n* = 120 patients	Group II, *n* = 120 patients	*P* value
Age in yr	57.9 ± 9.6	59.1 ± 10.7	0.38
Male sex	96 (80)	93 (77.5)	0.64
Smoking	49 (40.8)	58 (48.3)	0.24
Hypertension	35 (29.2)	43 (35.8)	0.27
Diabetes mellitus	38 (31.7)	40 (33.3)	0.78
CKD	4 (3.3)	7 (5.8)	0.35
Family history of CAD	15 (12.5)	21 (17.5)	0.28
Dyslipidemia	61 (50.8)	49 (40.8)	0.12
Location of MI: Anterior MI non-anterior MI	72 (60) 48 (40)	61 (50.8) 59 (49.2)	0.15
Time from chest pain onset to reperfusion in hr	4.04 ± 1.96	4.39 ± 2.79	0.29

Data are expressed in form of mean ± SD or frequency (%). CAD: Coronary artery disease; CKD: Chronic kidney disease; MI: Myocardial infarction; SD: Standard deviation.

Table 2 Heart rate and QT interval before and after reperfusion, all patients

Parameter	Before reperfusion, *n* = 240 patients	After reperfusion, *n* = 240 patients	Δ	*P* value
Heart rate in beat/min	78.6 ± 16.2	80.5 ± 15.7	-1.8 ± 16.9	0.09
Maximum QT in msec	407.1 ± 43.0	398.7 ± 45.2	8.5 ± 47.8	0.007
Minimum QT in msec	325.4 ± 41.7	341.3 ± 43.7	-15.9 ± 42.4	< 0.001
QTD in msec	81.8 ± 21.9	57.3 ± 18.9	24.4 ± 18.7	< 0.001
Maximum QTc in msec	461.2 ± 42.5	456.1 ± 38.9	5.1 ± 47.8	0.10
Minimum QTc in msec	368.5 ± 37.6	390.0 ± 36.4	-22.4 ± 44.5	< 0.001
QTcD in msec	92.7 ± 26.1	65.2 ± 22.6	27.5 ± 19.6	< 0.001

Data are expressed in form of mean ± SD. QTc: Corrected QT; QTD: QT dispersion; QTcD: Corrected QT dispersion; Δ: Delta is change in variables before and 24 hr after the reperfusion strategy.

following an action potential[18]. The prolonged QT and QTD have been linked to the occurrence of arrhythmia in patients with congenital long QT syndrome and with drug-induced torsades des pointes [19,20]. Therefore, MI associated with increased dispersion of cardiac repolarization could lead to the occurrence of arrhythmia[7]. Opening of the infarct-related artery results in perfusion of the infarcted area and consequently washing off of the excess extracellular potassium leading to correction of tissue anoxia and acidosis. This leads to improvement in membrane excitability and recovery of excitability following an action potential, ameliorating repolarization abnormalities and decreasing QTD. Consequently, the occurrence of arrhythmia is less likely. Our results support this mechanism, as the data presented here revealed that patients without in-hospital arrhythmia had shorter QTD and QTcD intervals with higher Δ than those with arrhythmia.

Lopes *et al*[21] studied the effect of thrombolytic therapy on QTD in patients with STEMI, and showed that QTD was significantly shorter in patients with STEMI who underwent successful thrombolysis (Table 5). On the other hand, they found that QTD did not correlate with ventricular arrhythmia; however, QTD was higher in patients with ventricular arrhythmia than those without. This conclusion is undermined by the study design (retrospective) and the inclusion of patients with unsuccessful thrombolysis who had high post-procedure QTD. Furthermore, this study measured QT values manually, which introduces the possibility of measurement bias. In line with the present study, Ornek *et al*[22] and Mulay *et al*[23] not only found that thrombolytic therapy reduces QTD significantly in STEMI patients in the 1st wk of admission, but also that patients with ventricular arrhythmia had higher QTcD values than patients without arrhythmia (Table 5).

In concurrence with our study, Pan *et al*[24] demonstrated that QTcD measured before PPCI was significantly longer than 24 hr after PPCI administration. Furthermore, they showed that the absolute QTcD change after PPCI was an independent predictor of the development of major cardiovascular

Table 3 Heart rate and QT interval before and after reperfusion, group I *vs* group II

Parameter	Group I, *n* = 120 patients			Group II, *n* = 120 patients			*P* value				
	Before	After	Δ	Before	After	Δ	*P*1	*P*2	*P*3	*P*4	*P*5
Heart rate in beat/min	81.0 ± 15.7	82.7 ± 16.4	-1.7 ± 18.9	76.2 ± 16.3	78.2 ± 14.8	-2.0 ± 14.9	0.34	0.14	0.02	0.02	0.87
Maximum QT in msec	411.7 ± 38.4	392.0 ± 44.1	19.7 ± 48.8	402.6 ± 46.9	405.3 ± 45.6	-2.8 ± 44.3	< 0.001	0.49	0.10	0.02	< 0.001
Minimum QT in msec	320.2 ± 34.6	338.1 ± 39.0	- 17.9 ± 34.4	330.6 ± 47.4	344.6 ± 48.0	-14.0 ± 41.3	< 0.001	0.001	0.06	0.25	0.48
QTD in msec	91.5 ± 20.6	53.9 ± 19.1	37.6 ± 17.1	72.0 ± 18.5	60.7 ± 18.1	11.3 ± 7.9	< 0.001	< 0.001	< 0.001	0.005	< 0.001
Maximum QTc in msec	474.3 ± 45.9	453.8 ± 38.1	20.6 ± 53.1	448.1 ± 34.1	458.4 ± 39.7	-10.4 ± 35.8	< 0.001	0.002	< 0.001	0.35	< 0.001
Minimum QTc in msec	369.9 ± 43.2	393.0 ± 32.1	- 23.1 ± 51.7	367.1 ± 31.1	388.9 ± 40.3	-21.8 ± 36.2	< 0.001	< 0.001	0.56	0.38	0.82
QTcD in msec	104.4 ± 22.1	60.8 ± 21.6	43.6 ± 13.6	80.9 ± 24.4	69.6 ± 22.8	11.4 ± 8.0	< 0.001	< 0.001	< 0.001	0.003	< 0.001

Data are expressed in form of mean ± SD. *P*1: *P* value comparing before and after PPCI in group I. *P*2: *P* value comparing before and after thrombolytic therapy in group II. *P*3: *P* value comparing group I and group II before reperfusion strategy. *P*4: *P* value comparing group I and group II after reperfusion strategy. *P*5: *P* value comparing group I and group II regarding delta change. QTc: Corrected QT; QTD: QT dispersion; QTcD: Corrected QT dispersion; Δ: Change in variables before and 24 hr after reperfusion; SD: Standard deviation.

Table 4 QT and corrected QT dispersion before and after reperfusion in patients with or without in-hospital arrhythmia

Parameter	In-hospital arrhythmia group, *n* = 33 patients			No in-hospital arrhythmia group, *n* = 207 patients			*P* value				
	Before	After	Δ	Before	After	Δ	*P*1	*P*2	*P*3	*P*4	*P*5
QTD in msec	82.1 ± 19.3	67.3 ± 22.7	14.8 ± 18.9	81.7 ± 22.3	55.8 ± 17.7	25.9 ± 18.3	< 0.001	< 0.001	0.91	0.001	0.003
QTcD in msec	94.0 ± 25.3	74.2 ± 24.9	19.8 ± 14.5	92.5 ± 26.2	63.7 ± 21.9	28.7 ± 20.1	< 0.001	< 0.001	0.75	0.03	0.02

Data are expressed in form of mean ± SD. *P*1: *P* value comparing before and after reperfusion strategy in in-hospital arrhythmia group. *P*2: *P* value comparing before and after reperfusion strategy in no in-hospital arrhythmia group. *P*3: *P* value comparing in-hospital arrhythmia group and no in-hospital arrhythmia group before reperfusion strategy. *P*4: *P* value comparing in-hospital arrhythmia group and no in-hospital arrhythmia group after reperfusion strategy. *P*5: *P* value comparing in-hospital arrhythmia group and no in-hospital arrhythmia group regarding delta change. QTD: QT dispersion; QTcD: Corrected QT dispersion; Δ: Change in variables before and 24 hr after reperfusion; SD: Standard deviation.

events at 1 year (Table 5). Hamza *et al*[25] reported that PPCI was effective in reducing QTc and QTD after 24 h, although the study showed no effect on these arrhythmogenic indices 90 min after successful revascularization with PPCI (Table 5). However, it should be emphasized that they did not monitor patients for the occurrence of arrhythmia.

In contrast to our results, other studies have shown that thrombolytic therapy decreased QTD over time, but without statistical significance. Studies have also shown a decrease in QTD 24 hr after PPCI treatment; however, this decline was also not significant[26,27] (Table 5). Oni Heris *et al*[26]'s study included patients with successful or unsuccessful thrombolysis who had high QTD following treatment, which would have affected the results of the QTD measured. Additionally, this study compared time points at 1 hr before thrombolytic therapy and 4 d later. Babapour *et al*[27]'s study was retrospective in design and included all patients with PPCI, irrespective of the final TIMI results. In this study, TIMI 0 and I had a higher value of QTD and QTcD than TIMI II and III, affecting the final results. Our prospective study included patients with successful fibrinolysis or PPCI with final TIMI flow grade III [17]. Moreover, our ECG parameters were computed automatically, thus reducing potential bias and variability.

Few studies have compared the effects of PPCI and fibrinolytic therapy on ventricular repolarization ECG parameters. However, previous attempts to explore the impact of these treatments on the incidence of in-hospital arrhythmia have been deficient. In agreement with our findings, Cavusoglu *et al*[28] showed that PPCI was associated with more significant decreases in QTD and QTcD as compared to

Table 5 Studies addressing repolarization changes following reperfusion in ST-segment elevation myocardial infarction

Ref.	Study type	Study population	Time to evaluation	Reduction of QTD and QTcD	In-hospital arrhythmia	Remarks
Lopes *et al* [21], 2006	Retrospective	Thrombolytic (*n* = 154)	4 d	Sig. after 4 d	QTD not correlated with arrhythmia	CA after 48 h; Reduction in QTD is a predictor of coronary reperfusion
Ornek *et al* [22], 2014	Prospective	Thrombolytic (*n* = 20)	7 d	Sig. after 7 d	QTD correlated with arrhythmia	Use 24-h Holter monitor
Mulay *et al* [23], 2004	Prospective	STEMI (*n* = 100) *Normal* (*n* = 100)	24 hr On discharge	NA	Sig. high QTD in patients with ventricular arrhythmias compared to those without	Sig. higher QTD on admission, at 24 h, and at discharge than normal subjects
Pan *et al*[24], 2011	Prospective	PPCI (*n* = 81)	24 h	Sig. after 24 h	NA	QTcD change was an independent predictor of MACE at 1 yr
Hamza *et al* [25], 2014	Retrospective	PPCI (*n* = 54)	90 min 24 hr	Not sig after 90 min Sig. after 24 h	NA	
Oni Heris *et al*[26], 2014	Prospective	Thrombolytic (*n* = 160)	1 hr 4 d	Not sig. after 1 hr Not sig. after 4 d	NA	
Babapour *et al*[27], 2018	Retrospective	PPCI (*n* = 77)	24 h	Not sig. after 24 hr	NA	
Cavusoglu *et al*[28], 2001	Prospective	PPCI (*n* = 21) Thrombolytic (*n* = 21)	24 h	Sig. in PPCI group Sig. in thrombolytic group Sig. in PPCI compared with thrombolytic	NA	
George *et al* [29], 2015	Prospective	PPCI (*n* = 25) Thrombolytic (*n* = 25)	24 h	Sig. in PPCI group Not sig. in thrombolytic group Sig. in PPCI compared with thrombolytic	NA	
Valizadeh *et al*[30], 2020	Prospective	PPCI (*n* = 70) Thrombolytic (*n* = 115)	24 h	Sig. in PPCI group Not sig. in thrombolytic group Not sig. in PPCI compared with thrombolytic	QTD mean in patients with arrhythmia was reduced before and after treatment with a significant reduction after PPCI as compared to thrombolysis	

CA: Coronary angiogram; MACE: Major adverse cardiovascular event; NA: Not applicable; PPCI: Primary percutaneous coronary intervention; Ref.: Reference; Sig.: Significant; STEMI: ST-elevation myocardial infarction.

thrombolytic therapy (Table 5). Similarly, George *et al*[29] found that PPCI was superior in reducing QTD and QTcD in patients with STEMI as compared to thrombolytic therapy. However, these reports included only a small number of patients, were single-center studies, measured ECG parameters manually, and did not observe patients for arrhythmia. On the other hand, Valizadeh *et al*[30] observed that no significant decreases were seen in QTD and QTcD values in the PPCI group compared to the thrombolytic group, but QTD values in the PPCI group showed a greater reduction after treatment (Table 5). Unlike ours, this was a single-center study and used PPCI or fibrinolytic drugs based on the patient's clinical status. This also raises the possibility of bias in patient assignment to either group, and obviously, PPCI improves survival and decreases complications whatever the patient clinical status. Moreover, this study included all patients who received thrombolysis whether successful or not, and who underwent PPCI regardless of the final TIMI flow. Furthermore, QT values were manually measured, again raising the possibility of bias and error, which the authors themselves stated as a limitation. Nonetheless, they found that mean QTD values in patients with arrhythmia were lower before and after treatment, with a significant reduction after PPCI group as compared to the thrombolytic group, similar to our results.

The present study indeed also has some limitations. Our sample size was relatively small, even though it was powered sufficiently to identify the pre-specified endpoints. Still, the findings need to be endorsed by further studies in larger cohorts. Additionally, various medications can affect the QT interval; however, these could not be standardized at the time of patient enrolment. Finally, long-term observation for arrhythmia development in these patients was not performed, and therefore our findings are only applicable to the acute phase of STEMI.

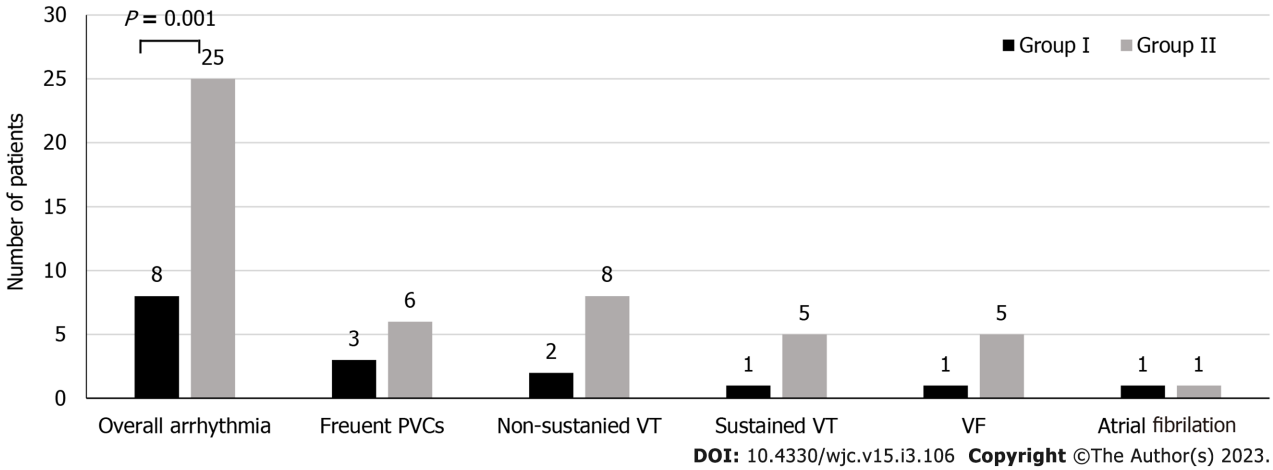

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Figure 1 Types of arrhythmia in group I and group II. Overall incidence of in-hospital arrhythmia was significantly lower in group I than in group II. PVC: PolyVinyl chloride; VT: Ventriculartachycardia; VF: Ventricularfibrillation.

CONCLUSION

We demonstrated that reperfusion with PPCI or fibrinolytic therapy was effective in reducing QTD and QTcD in STEMI patients. Reperfusion with PPCI was associated with shorter QTD and QTcD than thrombolytic therapy 24 hr after reperfusion. Moreover, PPCI was associated with a lower incidence of in-hospital arrhythmia than fibrinolytic therapy. Additionally, patients with in-hospital arrhythmia had a higher QTD and QTcD than patients without arrhythmia. Therefore, QTD and QTcD measurements in STEMI patients are important arrhythmogenic parameters that respond to reperfusion therapy.

ARTICLE HIGHLIGHTS

Research background

ST-elevation myocardial infarction (STEMI) increases QT dispersion (QTD) and corrected QT dispersion (QTcD), and is also associated with ventricular arrhythmia. Fibrinolytic therapy or primary percutaneous coronary intervention (PPCI) was used as the reperfusion strategy in acute STEMI patients.

Research motivation

Cardiac arrhythmia in the setting of acute myocardial infarction (MI) has serious impact on patient morbidity and mortality. Every effort should be made to prevent post-MI arrhythmia and to predict its occurrence as early as possible.

Research objectives

To compare the impact of revascularization with fibrinolysis or PPCI in STEMI patients on cardiac electrical stability, as indicated by QTD and QTcD measurements.

Research methods

Two groups of patients were treated for acute STEMI; 1 group of patients were treated with fibrinolysis, and the other group of patients were treated with PPCI. QTD and QTcD were measured at baseline and at 24 hr following successful reperfusion. We compared these measures between the two groups and observed all patients for incidence of arrhythmia during hospital admission.

Research results

There were significant reductions in QTD and QTcD at 24 hr in both study groups. QTD and QTcD were found to be shorter in group I at 24 hr than in group II. Moreover, the incidence of in-hospital arrhythmia was significantly higher in group II as compared to group I.

Research conclusions

In STEMI patients, both PPCI and fibrinolytic therapy effectively reduced QTD and QTcD, with a more significant reduction observed after PPCI. Furthermore, PPCI was associated with a lower incidence of in-hospital arrhythmia.

Research perspectives

PPCI was superior to fibrinolytic therapy with respect to the electrical stability of the heart.

FOOTNOTES

Author contributions: Abdelmegid MAF conceived and designed the study; Bakr M collected and analyzed the data; Shams-eddin H drafted the manuscript and performed statistical analysis; Youssef A critically revised and assisted in writing the manuscript; Abdel-Galeel A critically revised and coordinated the submission of the manuscript.

Institutional review board statement: This study was approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University (IRB No: 17101454), and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare having no conflicts of interest.

Data sharing statement: All supplementary data related to the current research work are available and ready to be shared upon request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Egypt

ORCID number: Mohamed Aboel-Kassem F Abdelmegid 0000-0003-4130-0619; Mohamed M Bakr 0000-0002-3739-4037; Hamdy Shams-Eddin 0000-0002-8410-0943; Amr A Youssef 0000-0002-9343-3475; Ahmed Abdel-Galeel 0000-0003-3712-5424.

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REFERENCES

1 **Gheeraert PJ**, De Buyzere ML, Taeymans YM, Gillebert TC, Henriques JP, De Backer G, De Bacquer D. Risk factors for primary ventricular fibrillation during acute myocardial infarction: a systematic review and meta-analysis. *Eur Heart J* 2006; **27**: 2499-2510 [PMID: 16952926 DOI: 10.1093/eurheartj/ehl218]

2 **Shenthar J**, Deora S, Rai M, Nanjappa Manjunath C. Prolonged Tpeak-end and Tpeak-end/QT ratio as predictors of malignant ventricular arrhythmias in the acute phase of ST-segment elevation myocardial infarction: a prospective case-control study. *Heart Rhythm* 2015; **12**: 484-489 [PMID: 25557980 DOI: 10.1016/j.hrthm.2014.11.034]

3 **Yu Z**, Chen Z, Wu Y, Chen R, Li M, Chen X, Qin S, Liang Y, Su Y, Ge J. Electrocardiographic parameters effectively predict ventricular tachycardia/fibrillation in acute phase and abnormal cardiac function in chronic phase of ST-segment elevation myocardial infarction. *J Cardiovasc Electrophysiol* 2018; **29**: 756-766 [PMID: 29399929 DOI: 10.1111/jce.13453]

4 **Malik M**, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000; **36**: 1749-1766 [PMID: 11092641 DOI: 10.1016/s0735-1097(00)00962-1]

5 **Parale GP**, Adnaik AR, Kulkarni PM. Dynamics of QT dispersion in acute myocardial infarction. *Indian Heart J* 2003; **55**: 628-631 [PMID: 14989514]

6 **Higham PD**, Furniss SS, Campbell RW. QT dispersion and components of the QT interval in ischaemia and infarction. *Br Heart J* 1995; **73**: 32-36 [PMID: 7888257 DOI: 10.1136/hrt.73.1.32]

7 **Aziz F**, Doddi S, Alok A, Penupolu S, Singh V, Benz M, Abed M. QT dispersion as a predictor for arrhythmias in patients with acute ST elevation myocardial infarction. *J Thorac Dis* 2010; **2**: 86-88 [PMID: 22263025]

8 **Ibanez B**, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský

P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39**: 119-177 [PMID: 28886621 DOI: 10.1093/eurheartj/ehx393]

9 **Thygesen K**, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018; **72**: 2231-2264 [PMID: 30153967 DOI: 10.1016/j.jacc.2018.08.1038]

10 **Pomés Iparraguirre H**, Conti C, Grancelli H, Ohman EM, Calandrelli M, Volman S, Garber V. Prognostic value of clinical markers of reperfusion in patients with acute myocardial infarction treated by thrombolytic therapy. *Am Heart J* 1997; **134**: 631-638 [PMID: 9351729 DOI: 10.1016/s0002-8703(97)70045-0]

11 **Ahnve S**. Correction of the QT interval for heart rate: review of different formulas and the use of Bazett's formula in myocardial infarction. *Am Heart J* 1985; **109**: 568-574 [PMID: 3883731 DOI: 10.1016/0002-8703(85)90564-2]

12 **Bazoukis G**, Yeung C, Wui Hang Ho R, Varrias D, Papadatos S, Lee S, Ho Christien Li K, Sakellaropoulou A, Saplaouras A, Kitsoulis P, Vlachos K, Lampropoulos K, Thomopoulos C, Letsas KP, Liu T, Tse G. Association of QT dispersion with mortality and arrhythmic events-A meta-analysis of observational studies. *J Arrhythm* 2020; **36**: 105-115 [PMID: 32071628 DOI: 10.1002/joa3.12253]

13 **Perkiömäki JS**, Koistinen MJ, Yli-Mäyry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol* 1995; **26**: 174-179 [PMID: 7797747 DOI: 10.1016/0735-1097(95)00122-g]

14 **Nash MP**, Bradley CP, Paterson DJ. Imaging electrocardiographic dispersion of depolarization and repolarization during ischemia: simultaneous body surface and epicardial mapping. *Circulation* 2003; **107**: 2257-2263 [PMID: 12707245 DOI: 10.1161/01.CIR.0000065602.78328.B5]

15 **Rautaharju PM**, Gregg RE, Zhou SH, Startt-Selvester RH. Electrocardiographic estimates of regional action potential durations and repolarization time subintervals reveal ischemia-induced abnormalities in acute coronary syndrome not evident from global QT. *J Electrocardiol* 2011; **44**: 718-724 [PMID: 22018486 DOI: 10.1016/j.jelectrocard.2011.08.007]

16 **Moreno FL**, Villanueva T, Karagounis LA, Anderson JL. Reduction in QT interval dispersion by successful thrombolytic therapy in acute myocardial infarction. TEAM-2 Study Investigators. *Circulation* 1994; **90**: 94-100 [PMID: 8026057 DOI: 10.1161/01.cir.90.1.94]

17 **Nikiforos S**, Hatzisavvas J, Pavlides G, Voudris V, Vassilikos VP, Manginas A, Hatzeioakim G, Foussas S, Iliodromitis EK, Hatseras D, Kremastinos DT, Cokkinos DV. QT-interval dispersion in acute myocardial infarction is only shortened by thrombolysis in myocardial infarction grade 2/3 reperfusion. *Clin Cardiol* 2003; **26**: 291-295 [PMID: 12839049 DOI: 10.1002/clc.4950260611]

18 **Shaw RM**, Rudy Y. Electrophysiologic effects of acute myocardial ischemia: a theoretical study of altered cell excitability and action potential duration. *Cardiovasc Res* 1997; **35**: 256-272 [PMID: 9349389 DOI: 10.1016/s0008-6363(97)00093-x]

19 **Day CP**, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990; **63**: 342-344 [PMID: 2375895 DOI: 10.1136/hrt.63.6.342]

20 **Shah RR**. Drug-induced QT dispersion: does it predict the risk of torsade de pointes? *J Electrocardiol* 2005; **38**: 10-18 [PMID: 15660342 DOI: 10.1016/j.jelectrocard.2004.09.001]

21 **Lopes NH**, Grupi C, Dina CH, de Gois AF, Hajjar LA, Ayub B, Rochitte CE, Ramires JA, Hueb WA, Kalil R. [QT interval dispersion analysis in acute myocardial infarction patients: coronary reperfusion effect]. *Arq Bras Cardiol* 2006; **87**: 91-98 [PMID: 16951825 DOI: 10.1590/s0066-782x2006001500005]

22 **Ornek E**, Duran M, Ornek D, Demirçelik BM, Murat S, Kurtul A, Çiçekçioğlu H, Çetin M, Kahveci K, Doger C, Çetin Z. The effect of thrombolytic therapy on QT dispersion in acute myocardial infarction and its role in the prediction of reperfusion arrhythmias. *Niger J Clin Pract* 2014; **17**: 183-187 [PMID: 24553029 DOI: 10.4103/1119-3077.127545]

23 **Mulay DV**, Quadri SM. QT dispersion and early arrhythmic risk in acute myocardial infarction. *Indian Heart J* 2004; **56**: 636-641 [PMID: 15751519]

24 **Pan KL**, Hsu JT, Chang ST, Chung CM, Chen MC. Prognostic value of QT dispersion change following primary percutaneous coronary intervention in acute ST elevation myocardial infarction. *Int Heart J* 2011; **52**: 207-211 [PMID: 21828945 DOI: 10.1536/ihj.52.207]

25 **Hamza O**, Bouzid A, Mouffok M, Azzouz A, Mokhtar OA, Bendaoud N, Saidane M, Latrèche S, Benkhedda S, Merad K. Evaluation of corrected QT and QT dispersion changes in acute ST elevation myocardial infarction after primary percutaneous coronary intervention. *Arch Cardiovasc Dis* 2014; Suppl 6: 26-27 [DOI: 10.1016/S1878-6480(14)71337-0]

26 **Oni Heris S**, Rahimi B, Faridaalaee G, Hajahmadi M, Sayyadi H, Naghipour B. QT Dispersion after Thrombolytic Therapy. *Int Cardiovasc Res J* 2014; **8**: 161-165 [PMID: 25614860]

27 **Babapour B**, Shahbazzadegan B, Khademi B. Effect of primary percutaneous coronary intervention on ventricular repolarization through evaluation of QT dispersion in patient with acute myocardial infarction. *Int J of Community Med Public Health* 2018; **5**: 506-510 [DOI: 10.18203/2394-6040.ijcmph20180226]

28 **Cavusoglu Y**, Gorenek B, Timuralp B, Unalir A, Ata N, Melek M. Comparison of QT dispersion between primary coronary angioplasty and thrombolytic therapy for acute myocardial infarction. *Isr Med Assoc J* 2001; **3**: 333-337 [PMID: 11411196]

29 **George KS**, Waly HMF, Abdul Moteleb MT. Assessment of QT Dispersion in Patients with Acute STEMI Receiving Thrombolytic Versus those Performing Primary Percutaneous Coronary Intervention (PCI) Therapy. *Med J of Cairo Univ* 2015; **83**: 1023-1030

30 **Valizadeh A**, Soltanabadi S, Koushafar S, Rezaee M, Jahankhah R. Comparison of QT dispersion in patients with ST elevation acute myocardial infarction (STEMI) before and after treatment by streptokinase versus primary percutaneous coronary intervention (PCI). *BMC Cardiovasc Disord* 2020; **20**: 493 [PMID: 33228554 DOI: 10.1186/s12872-020-01767-9]

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