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MINIREVIEWS

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MINIREVIEWS

Radiation protection for the interventional cardiologist: Practical approach and innovations

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Abstract

Use of ionizing radiation during cardiac catheterization interventions adversely impacts both the patients and medical staff. In recent years, radiation dose in cardiac catheterization interventions has become a topic of increasing interest in interventional cardiology and there is a strong interest in reducing radiation exposure during the procedures. This review presents the current status of radiation protection in the cardiac catheterization laboratory and summarizes a practical approach for radiation dose management for minimizing radiation exposure. This review also presents recent innovations that have clinical potential for reducing radiation during cardiac interventions.

Key Words: Radiation; Cardiac catheterization; Quality improvement; Cathlab; Ionizing radiation

Core Tip: Radiation safety is of concern to catheterization laboratory personnel. In recent years, radioprotection has become a priority in cardiac catheterization interventions and there is keen interest in reducing radiation exposure during the procedures. This review presents the current status of radiation protection in the cardiac catheterization laboratory and summarizes traditional protection mechanism and innovations.

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INTRODUCTION

Use of ionizing radiation during cardiac catheterization interventions adversely impacts both the patients and medical staff[1]. Radiation exposure can result in long-term health effects, including skin and eye damage, and may cause certain forms of cancer by interacting with and altering cellular DNA[1]. The deleterious effect that ionizing radiation has on human tissue may result in potential stochastic and deterministic sequels[2]. Deterministic effects such as ocular lens defects are characterized by a predictable dose-related increase in severity, which can be evaluated by means of air kerma (kinetic energy released per unit mass, AK)[2]. Stochastic effects follow a linear, no-threshold risk model, in which the risk of damage to the irradiated tissue increases linearly with the amount of exposure. The exposure to low-dose radiation induces a stochastic risk in various malignancies that can be measured by dose area-product (DAP)[2].

Interventional cardiologists, given their chronic radiation exposure in cardiac catheterization laboratories, are exposed to the highest cumulative radiation among health professionals. This issue has been magnified with increased exposure in the long duration of structural or complex coronary intervention like chronic total occlusion (CTO) cases. Cataracts, thyroid cancer, and disproportionate incidence of left-sided brain tumors have been reported in interventional cardiologists[1].

In recent years, radiation dose in cardiac catheterization interventions has become a topic of increasing interest in interventional cardiology and there is a strong interest to reduce radiation exposure during the procedures[1,2].

The level of protection should be the best possible under the prevailing circumstances, maximizing the margin of benefit over harm. Physician responsibilities with regard to radiation safety should be based on the ALARA radiation principle: "as low as reasonably achievable"[1].

RADIATION REDUCTION RECOMMENDATIONS IN THE CATHETERIZATION LAB

The hazards of radiation exposure are not limited to interventional cardiologists. Radiation safety is a multi-disciplinary approach, which should involve all catheterization lab (cathlab) personnel. Traditional lead personal protective equipment (LPPE) and radiation shields are mandatory to enhance the protection of all staff members during interventional procedures. The qualities of protective measures are summarized in Table 1.

Optimizing radiation protocols and implementing a radiation safety program to improve the safety of patients and medical staff should become a priority during interventional procedures. The primary goal is to reduce radiation doses wherever and whenever reasonably achievable, thereby reducing the health risk that is assumed to be proportional to the radiation dose[3,4]. Dose Limits Recommended by International Commission on Radiological Protection are presented in Table 2.

Traditional lead personal protective equipment

All staff members working in interventional x-ray rooms are required to wear lead-equivalent radiation protection garments. Traditional LPPE consists of the following. (1) Leaded glasses. A higher incidence of cataracts (specifically posterior subcapsular) has been reported in interventional cardiologists[1]. Leaded glasses reduce eye radiation by 35%-90%[5-7]. (2) Thyroid collar. The thyroid gland is a radiosensitive organ and thyroid cancer is a known consequence of radiation exposure. Consequently, a protective thyroid shield is mandatory during interventional procedures[8]. Thyroid shields should be quality-checked annually. And (3) Protective lead aprons. Lead aprons are very effective in reducing radiation exposure to the staff members. However, many lead aprons weigh more than 7 kg causing orthopedic problems[9]. An alternative is a two-piece wraparound apron consisting of a skirt and a vest. This type of garment is lighter potentially reducing the risk for musculoskeletal injury[9]. Lead aprons should be quality checked annually for any defects to ensure that no

Table 1 Qualities of protective measures

Protective measures	Evidence[1]	Reduction	Operator protection	Patient protection
Technical issues	A[2,3,13,14]	60%	Yes	Yes
Traditional LPPE	B[5-9,51]	35-95%	Yes	No
Surgical caps	D[44]	3.3%	Yes	No
Gloves	D[9]	20-50%	Yes	No
Radiation-blocking cream	D[46]	85%	Yes	No
Shield, curtain and TRPB	B[9,10-12]	30-70%	Yes	No
CathPax®	C[16,20-22]	70- 80%	Yes	No
Zero gravity®	C[19]	78-93%	Yes	No
RadPad®	A[26,29,30]	30-35%	Yes	No
Robotic systems	B[32,34,35,42]	96%	Yes	No

[1]Clinical evidence: A ≥ 1 randomized clinical trial; B ≥ 4 conclusive non-randomized clinical studies or safety/feasibility randomized trial; C < 4 conclusive non-randomized clinical studies or safety/feasibility randomized trial; D inconclusive clinical studies.
LPPE: Lead personal protective equipment; TRPB: Transradial radiation protection board.

Table 2 Regulatory limit on occupational radiation exposure and the current status with respect to the limit

Type of dose limit	Limit on dose from occupational exposure[1]
Effective dose	20 mSv/yr averaged over 5 consecutive years and 50 mSv in a single year
Effective dose on pregnancy	The dose to embryo/fetus should not exceed 1mV during remainder of pregnancy
Equivalent dose: Lens of the eye	20 mSv/yr averaged over 5 consecutive years and 50 mSv in a single year
Equivalent dose: Skin	500 mSv/yr
Equivalent dose: Extremities (hands and feet)	500 mSv/yr

[1]Occupational Exposure: Planned exposure situations where radiological protection can be planned in advance, and exposures can be reasonably predicted.
Dose limits recommended by international commission on radiological protection (ICRP)[52].

cracks in the radioprotective layer are forming.

Equipment-mounted shielding

The main shield mounted on the equipment consists of shields suspended from the ceiling and curtains suspended from the table. Radiation shields must be discreetly placed and actively managed both before and during the procedure to be effective[4].

Ceiling-mounted shields are made of leaded clear plastic that is adjustable during the procedure and if positioned correctly can reduce the radiation dose to the operator's head and neck[4,9]. The shield should be as close as possible to the patient to stop the scatter at the source for the greatest degree of attenuation.

The lower region of the operator receives the most exposure during a procedure. Protecting the pelvic region containing the reproductive organs is essential due to their radiosensitivity. Table suspended lead drapes between the X-ray tube and the operator provide a significant lower radiation dose to operators at pelvic and thorax level[4,9,10]. Recently, a clinical trial showed that the combination of pelvic drapes and under-table shields on top of the standard protective measures of the cathlab reduced the operator radiation exposure at thorax to negligible levels[11].

Transradial radiation protection board (TRPB) is a grooved arm board with a detachable 0.5 mm lead equivalent shield designed to rest between the patient's arm and side. TRPB reduces radiation operator dose during radial approach procedures in addition to standard protection[12].

Mobile leaded shield consists of a 200 cm x 80 cm lead-equivalent mobile shield with a thickness of 2 mm positioned between the patient and the operator. A transparent 2-mm lead-equivalent window offers a permanent view of the patient. A

mobile leaded shield, combined with standard preventive measures, significantly reduces operator exposure to ionizing radiation during interventional procedures.

Technical approach

The guiding principle with regard to radiation safety should be based on the ALARA radiation principle. ALARA stands for "as low as reasonably achievable." This principle means that even if it is a small dose, if receiving that dose has no direct benefit, it should be avoided. Effective strategies to minimize patient and operator exposure during interventions are based on four principles (Figure 1)[2,3,11,13-15].

Utilize radiation only when imaging is necessary to support clinical care and limit fluoroscopy time to only when the operator is looking at the monitor.

Keep the image receptor as low as possible on the patient's chest. Optimal table positioning can reduce patient radiation dose. The patient is ideally placed as close as possible to the image receptor and further away from the X-ray source.

Minimize use of steep angles of the X-ray beam. Extreme angulations are associated with high air kerma values. Paying close attention to the angulation and placing the C-arm in 0° to 20° angulation will result in a more than 3-fold reduction in the amount of radiation scattered during fluoroscopic acquisition. The left anterior oblique view cranial angulation has the highest degree of scatter exposure to the operator (Figure 2)[3].

Minimize use of cine and shorten each cine acquisition as much as possible.

Minimize the use of magnification modes. Most modern systems have software magnification algorithms that allow for magnification without additional radiation. Nevertheless, hardware magnification should still be used when clinically indicated.

Utilize collimation to the fullest extent possible.

Monitor radiation dose in real time to assess the operator's and patient's risk/benefit ratio during the procedure. Use of real-time radiation monitoring devices that provide auditory feedback can significantly reduce radiation exposure during cardiac catheterization (Figure 3).

Adjust the fluoroscopy frame rate. Fine-tuning radiation safety protocols could reduce radiation doses without compromising the effectiveness of catheterization procedures in patients. Frame rate is typically set at 15 frames-per-second and decreasing it to 7.5 frames-per-second results in significant radiation dose reduction[2,13].

Increase the distance between the operator and radiation source. Radiation exposure is inversely proportional to the square of the distance from the X ray source. Increasing the distance between the cardiologist and the patient to 1 m can decrease a physician's occupational radiation dose by about a half.

Educate in radiation protection. Training and education in radiation protection is widely recognized as one of the basic principles of optimization programs for medical exposures. These provide practitioners of interventional cardiology adequate theoretical and practical training in radiation safety to help minimize occupational radiation dose.

INNOVATIONS

Traditional LPPE with lead aprons, thyroid shields and lead glasses are only partially effective. This protection equipment leaves body parts such as arms, hands and heads unprotected[16-18]. In recent years, new concepts in individual or semi-individual radioprotection were being marketed to reduce scatter radiation.

Suspended radiation protection system: Zero Gravity®

The Zero-Gravity suspended radiation protection system is designed to increase the level of radiation protection while at the same time eliminating the weight burden for the operator. Compared to conventional lead aprons with under-table or ceiling-mounted shields, Zero-Gravity provides superior operator protection during fluoroscopy. This system reduces fatigue and orthopedic injuries resulted from routinely wearing heavy protective apparel as well as allowing clinicians freedom of movement, especially during challenging procedures (Figure 4A and B)[19].

Mobile radiation protection cabins: CathPax®

In the last decade, radiation protection cabins (RPCs) have become used in interventional procedures. RPCs significantly reduce radiation exposure in different interventional procedures[16,17,20-23]. The cathpax® cabin (Lemer Pax, Carquefou, France) is a

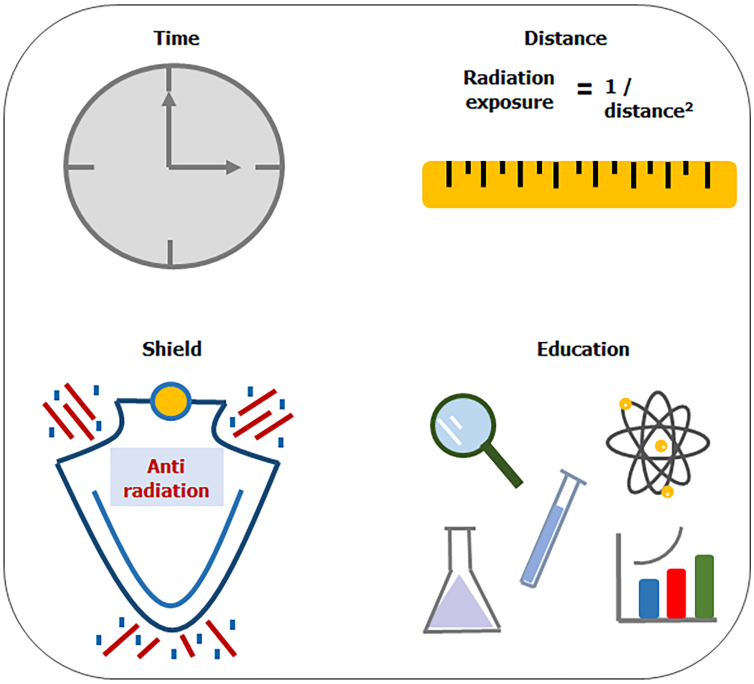

Figure 1 Radiation protection in the catheterization lab should be based on four principles. Time: radiation dose depends linearly on the exposure time. Distance: The amount of radiation exposure depends on the distance from the source proportionally to the inverse of the distance squared from the X-ray source, so staff can lower their exposure levels by a factor of four by doubling their distance from the source. Shielding: barriers of lead protection can be accomplished with different forms such as personal protective equipment or mobile shields. The greater the shielding around the source, the smaller the exposure. Education: training and education in radiation protection is one of the basic components of radiation protection programs.

mobile and height-adjustable RPC that comes in three ranges of radiation protection tailored to the specific needs of cardiac interventional operators. The CathPax® AF and the Cathpax® CRM cabins are particularly adapted for electrophysiology procedures and for cardiac devices implantations respectively. The Cathpax® AIR (Figure 4C and D) shielded with 2 mm lead-equivalent is adapted to all interventional cardiology procedures, (coronarography, complex percutaneous coronary interventions (PCIs) as well as structural ones like TAVI or left appendage closure).

One of the main concerns regarding RPCs is its comfortability and workability in a real-world setting, especially in complex scenarios such as CTOs. Recently, the Cathpax® AIR confirmed its feasibility and efficacy in a real-world setting by reducing first-operator relative radiation exposure by 78%. This effect was consistent during different types of procedures including emergent procedures, complex PCIs and structural procedures[24].

Disposable radioprotective drapes

Disposable radioprotective drapes can be particularly useful in complex interventional procedures associated with higher radiation exposure, such as CTO interventions[25,26]. They contain metallic elements (bismuth, barium, and tungsten-antimony) and are placed over the patient during fluoroscopically guided interventions. Radioprotective drapes reduce attenuate scatter radiation 12-fold for the eyes, 25-fold for the thyroid, and 29-fold for the hands[27].

The Radpad® is a disposable drape lead-free shield (Worldwide Innovations and Technologies Inc, Lenexa, KS) (Figure 5) that reduces operator radiation exposure in several studies by 20%-59% including a real-world randomized trial[16-18,26,28-30].

However, the disposable drapes shield should not be placed within the imaging field during radial angiography as such an action may trigger an automatic increase in dose rate, significantly increasing patient dose[25,26].

Robotic percutaneous systems

Robotic PCI (R-PCI) is an emerging technology with significant potential for transforming PCI[31]. In 2006, Beyar *et al*[32] developed and reported the first remote controlled robotic system to address the occupational hazards of interventional cardiology[31,32]. Five years later, Granada and colleagues reported the first in-human experience in a series of eight patients with the CorPath® 200 robotic system (Corindus,

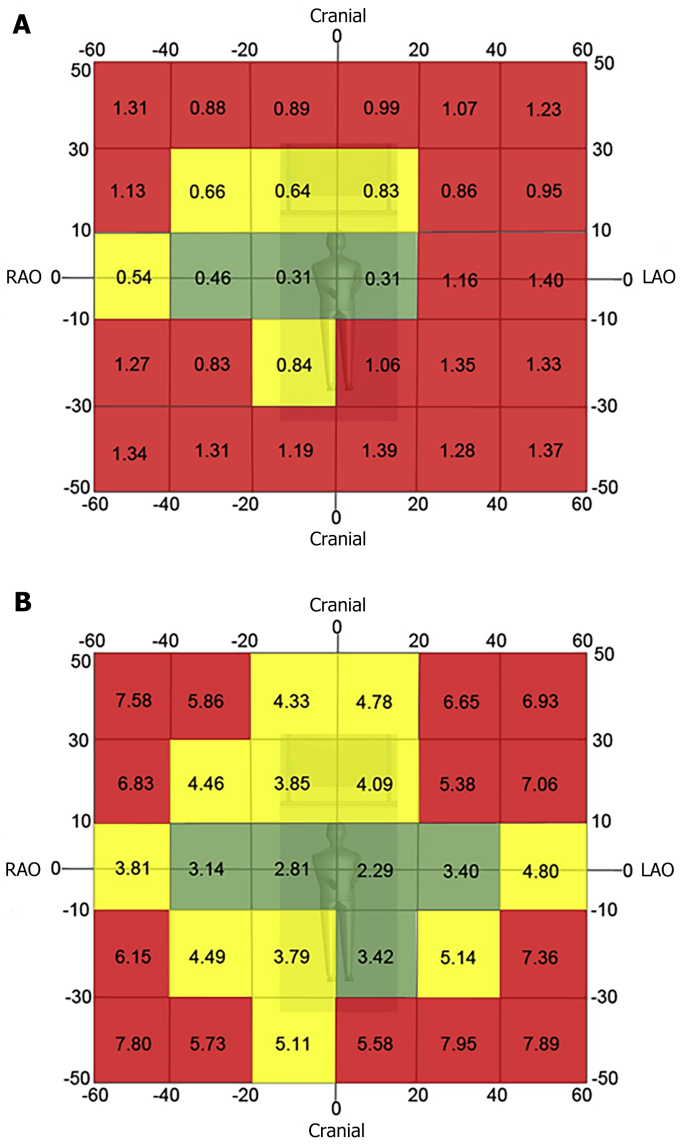

Figure 2 Two-dimensional radiation map for fluoroscopy (A) and acquisition imaging (B). The red zone denotes projections where < 26% of the image procurement occurred in the lowest tertile of Air Kerma rate. The yellow zone denotes projection where 26% to 40% of the images were procured in the lowest tertile of air kerma rate the value in each cell represents the median Air Kerma rate for the respective projection. Reproduced with permission from reference 8[3]. LAO: Left anterior oblique view; RAO: Right anterior oblique view.

Inc., Natick, Massachusetts, United States)[33]. At present, the second generation of CorPath is available. The CorPath GRX system (Figure 6) has new features that further facilitate R-PCI in complex anatomies, including remote manipulation of the guide catheter to help augment support after engagement or incorporation of wiring algorithms such as "rotate on retract and simplified device exchanges." The new system achieves tremendous reduction in radiation exposure to operators with high rates of clinical and technical success even in complex PCI scenarios such as laser atherectomy or left main stem disease[31,34,35]. The R-One (Robocath) is a new R-PCI platform that recently received regulatory approval for use in Europe. This new system has functional capabilities similar to those of the CorPath 200 system.

A key potential advancement that R-PCI could bring is in the field of tele-R-PCI. This will allow for the treatment of patients who are in geographically distant locations[36]. Performing long distance tele-R-PCI in type A coronary lesion is currently feasible with predictably successful outcomes if reliable network connectivity and local cardiac catheterization facilities are available[37].

In addition to mitigating occupational hazards for interventional cardiologists, R-PCI offers the potential advantages of more precise measurements of lesion length and more stable deployment of angioplasty balloons and stents[38].

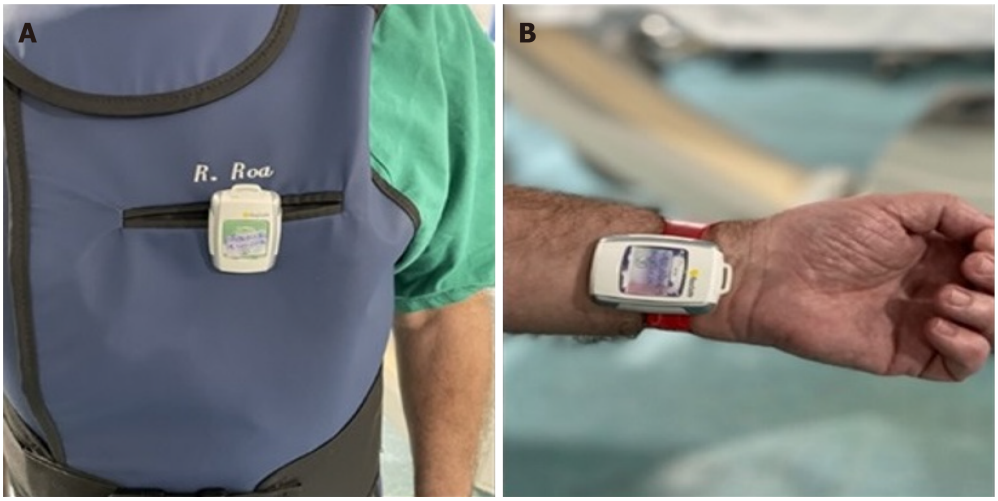

Figure 3 Real time electronic personal dosimeters placed over the apron (A) and on the left wrist of the operator (B).

Finally, the ongoing worldwide coronavirus disease 2019 (COVID-19) pandemic has imposed severe restrictions on such an interventional environment. In this setting, R-PCI can provide an additional layer of protection to the healthcare personnel participating in the management of COVID patients[39].

The current robotic systems are in the early stages of development compared to standard manual PCI. Despite being a promising technology, there are still some important issues to address before its use spreads beyond a few limited centers. Most importantly, there is a need for clinical evidence from large-scale randomized clinical trials showing improved radiation safety for the operators and non-inferior angiographic and clinical results[40]. Additionally, the initial CorPath 200 system had several limitations; the subsequent version, the CorPath GRX, has overcome some of these limitations but there are still multiple technical limitations to current R-PCI technology compared to manual PCI. These include the need for operators to obtain arterial access and manually engage guide catheters prior to utilization of R-PCI systems; current R-PCI systems are limited to 0.014″ wires and rapid exchange devices; thus, rotational atherectomy or two stent deployment cannot currently be performed [41]. The absence of tactile feedback is another important issue in complex PCIs, where the interaction among the wire, lesion, and operator is key to subsequent technical success[40]. Finally, at least one team member needs to remain at the bedside for equipment exchanges and the procedure duration is significantly increased compared to traditional interventions[32,35,42].

Others

The effectiveness of other radiation safety innovations, such as radiation-blocking hats, gloves, or radiation-blocking cream, still remain uncertain[17,20,43].

A recent study showed that radiation scattering comes predominantly from under the head of the operator and surgical radio-absorbing caps do not cover this area, so the brain protection demonstrated by a surgical lead cap is minimal. It has been shown to decrease radiation dose to the brain by only 3.3%[4,44].

The hands of the fluoroscope operator should only be placed in the field of view when required by the procedure. The best way to protect the hands is to keep them away from the direct radiation beam whether protective gloves are used or not[9]. Notably, the use of protective gloves when the hands are placed in the field may trigger an automatic increase in dose rate, significantly increasing patient dose. Nevertheless, the use of radio protective gloves to reduce the exposure of the hands to scattered radiation when the hands remain outside the field is not contraindicated[45].

Radiation-blocking cream (BloXR®) is a hand lotion designed to offer radiation protection from X-rays[46]. The cream is applied prior to donning gloves, or over a glove with another glove on top. However, the commercially available cream comes with an United States Food and Drug Administration black box warning. The radiation-blocking cream could pose a radiation exposure risk to healthcare professionals due to the lack of radiation attenuation, which can occur due to inadequate or inconsistent cream formulation.

Figure 4 Zero Gravity® and Cathpax® AIR. A: Two hinged swing arm zero gravity systems installed in a hybrid room. This system consists of a single fixation point of the hinged swing arm. It can be used on both sides of the table if there is a fixation point available; B: A floor zero gravity unit. The suspended body and face shield can be repositioned for a broad range of procedures and room configurations; C, D: Photographs of the radiation protection cabin (Cathpax® AIR) in use during a coronary chronic total occlusion intervention.

PREGNANCY

Women are particularly underrepresented in cardiology procedural subspecialties, and account for < 10% of the physician workforce in interventional cardiology[47]. However, currently, the proportion of women who choose intervention cardiology as a career is increasing. The Women in the Innovations group of Cardiologists aim to provide guidance by describing the risk of radiation exposure to pregnant physicians and cardiac catheterization personnel[48].

Radiation exposure during pregnancy poses a risk to the fetus leading to two types of adverse effects: deterministic and stochastic effects. Deterministic effects consist of intrauterine growth retardation, pregnancy loss, mental retardation, small head size, reduced intelligence quotient and congenital malformations. Stochastic effects consist of risk of childhood cancer and hereditary diseases in the descendants[49]. The risk of each effect depends on the gestational age at the time of exposure with the first trimester being the period of greatest risk. Doses below 50 mGy have not been associated with an increase in fetal anomalies or pregnancy losses[50]. The fetal radiation exposure for most women who work in the cardiac catheterization laboratory is extremely low, and is much lower than the recommended limit. Protective garments specifically for pregnant women must provide at least 0.5 mm lead-equivalent protection throughout the entire pregnancy with a double thickness protective garment, specific maternity lead apron or maternity bib (for an additional lead protection layer). Additionally, an extra dosimeter at waist level under the lead apron to monitor fetal radiation exposure monthly is also recommended[48].

Although perceptions of radiation exposure risk remain widespread, with standard radiation safety measures practiced routinely, there is no statistically significant or

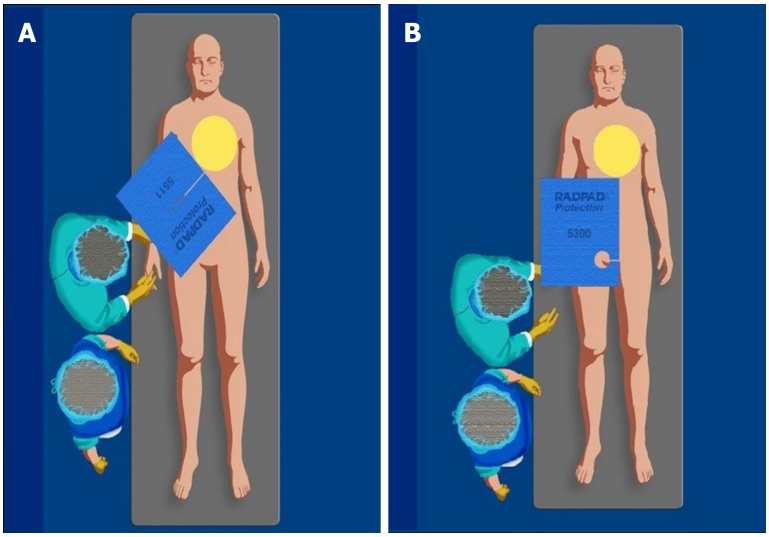

Figure 5 Correct positioning of the RadPad radioprotective drapes. A-B: The radioprotective drapes should be placed on the patient, between the image intensifier and the operator during (A) femoral and (B) radial procedures.

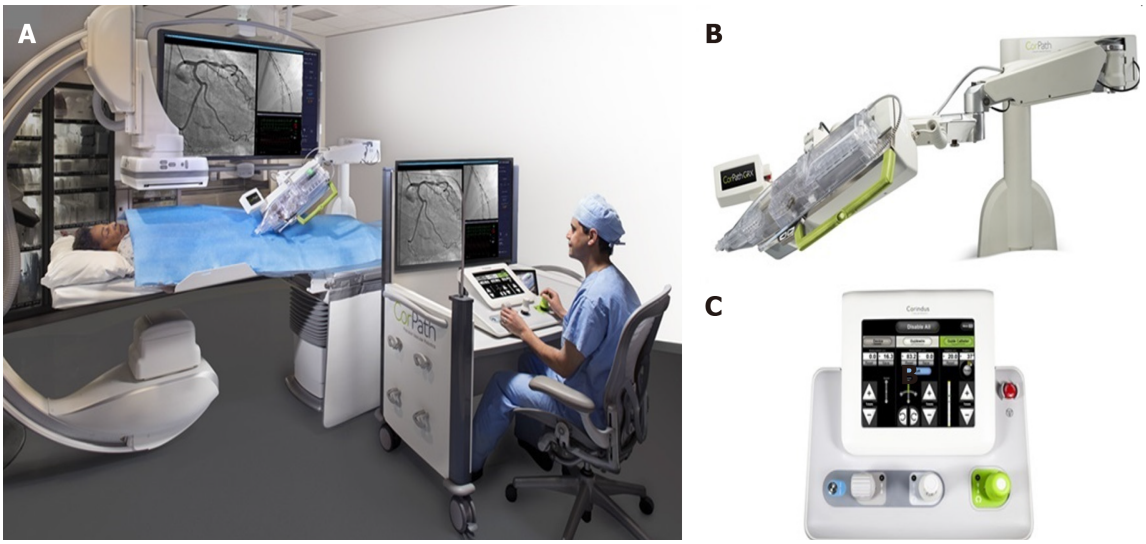

Figure 6 During robotic-assisted intervention, the interventional cardiologist sits in a radiation-shielded workstation and uses a set of joysticks and touchscreen controls that translate the physician's movements into device control. A: Control console; B: Extended-reach arm; C: CorPath cassette of the robotic system.

convincing evidence of an increased risk of pregnancy-related complications for female cardiologists exposed to radiation. This suggests that female interventionists can integrate pregnancy safely into their careers. All operators should follow common sense measures under the ALARA principle[47].

CONCLUSION

Optimal use of ionizing radiation in cardiovascular interventions is the responsibility of the healthcare professionals working in the cathlab. Efforts to reduce radiation exposure and participation in radiation safety educational programs should be encouraged by all the professionals involved in interventional procedures exposed to radiation. Professionals endeavor should be focused on the correct use of LPPE, optimal positioning and distancing to the table, the image intensifier and the operator. It is vitally important to optimize the X-ray settings, use fluoroscopy judiciously, and ensure appropriate shielding. Proper use of personnel dosimeters ensures correct radiation monitoring limiting exposure.

Based on the ALARA radiation principle, a priority should be to minimize radiation exposure in every clinical circumstance reducing radiation hazards.

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MINIREVIEWS

Chronic total occlusion revascularization: A complex piece to "complete" the puzzle

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Abstract

Treatment of coronary chronic total occlusion (CTO) with percutaneous coronary intervention (PCI) has rapidly increased during the past decades. Different strategies and approach were developed in the recent past years leading to an increase in CTO-PCI procedural success. The goal to achieve an extended revascularization with a high rate of completeness is now supported by strong scientific evidences and consequently, has led to an exponential increase in the number of CTO-PCI procedures, even if are still underutilized. It has been widely demonstrated that complete coronary revascularization, achieved by either coronary artery bypass graft or PCI, is associated with prognostic improvement, in terms of increased survival and reduction of major adverse cardiovascular events. The application of "contemporary" strategies aimed to obtain a state-of-the-art revascularization by PCI allows to achieve long-term clinical benefit, even in high-risk patients or complex coronary anatomy with CTO. The increasing success of CTO-PCI, allowing a complete or reasonable incomplete coronary revascularization, is enabling to overcome the last great challenge of interventional cardiology, adding a "complex" piece to "complete" the puzzle.

Key Words: Chronic total occlusion; Percutaneous coronary intervention; Complete revascularization; Prognosis; Coronary artery disease

Core Tip: The application of "contemporary" revascularization strategy in coronary chronic total occlusion percutaneous interventions, allowed a high procedural success rate and to achieve a complete or reasonable incomplete coronary revascularization. From a procedural and clinical management point of view, an improved accuracy in

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clinical decision making process and a state-of-the-art revascularization, led to a long-term clinical benefit, even in high-risk patients or complex coronary anatomy.

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INTRODUCTION

Treatment of coronary chronic total occlusion (CTO) with percutaneous coronary intervention (PCI) has rapidly increased during the past decade, driven by technical and technological advancements involving drug-eluting stents (DES), antithrombotic drugs management, procedural strategies and interventional cardiologists' expertise. "Contemporary" revascularization strategies include: novel and dedicated techniques, use of 2nd and 3rd generation DES and intracoronary imaging, "tailored" antithrombotic therapy management. Strategies aimed to achieve an extended revascularization with a high rate of completeness have led to an exponential increase in the number of successful CTO-PCI procedures, which translates in a long-term clinical benefit. However, CTO-PCI is still underutilized, accounting for only 5%-15% of elective PCI, despite a reported prevalence of CTO in up to one-third of patients with coronary artery disease, and 10%-18% of patients with STEMI[1,2] The presence of a CTO, compared with non-occlusive coronary lesions, greatly affects the therapeutic strategies of patients with atherosclerotic ischemic heart disease, with a more frequent referral to surgical revascularization [coronary artery bypass graft (CABG)] or medical therapy rather than percutaneous solution.

CLINICAL BENEFITS OF CTO REVASCULARIZATION: STILL AN OPEN DEBATE?

The expected benefits from the revascularization of a CTO can be summarized in: (1) Improved quality of life; (2) Improved left ventricular (LV) function; (3) Increased long-term survival; (4) Increased tolerance to potential subsequent coronary events; and (5) Reduced risk of life threatening-arrhythmias.

The available evidence in support of a favorable prognostic impact, mostly comes from observational studies (high volume single-center registries or multi-center registries), with the recognized limitations of selection and publication bias and possible residual confounders[3-6]. On the other side, such registries have the undoubted advantage to offer a view of clinical and therapeutic practice in the real world. At present, there are also extensive meta-analyses to consolidate this evidence [7-9]. Contemporary randomized clinical trials are small, and often investigate surrogate prognostic end points or non-inferiority analyses[10,11] (Table 1).

The Korean multicenter randomized DECISION-CTO trial, which was discontinued because of slow enrollment (out of 1.284 planned patients, only 834 were enrolled), showed how CTO-PCI, combined with optimal medical therapy, was not superior to medical therapy alone in reducing cardiovascular events in patients with CTO at 3-year follow-up; the primary end point, a composite of all-cause mortality, myocardial infarction, stroke, and repeat of any coronary revascularization, was 20.6% *vs* 19.6% (P = 0.008 for non-inferiority of optimal medical therapy). Five years follow-up data, published in 2019, confirmed no differences in term of primary end point (22.3% *vs* 22.4%; HR 1.03; 95%CI: 0.77 to 1.37; P = 0.86); notably, the 19.6% of the patients assigned to the no CTO-PCI strategy arm, crossed over to receive staged CTO-PCI[10]. In the Korean study, the mean age of patients was approximately 62 years, LV function 57%, and two thirds of patients had a stable coronary artery disease. It is estimated that for an adequate statistical power to detect a difference in outcome in terms of mortality between CTO-PCI and optimal medical therapy, an ideal trial would require more than 5000 patients, a figure not even remotely represented in

Table 1 Chronic total occlusion study results and clinical outcomes according to hierarchical levels of evidence-based medicine: Registries, meta-analyses, and randomized clinical trials

Studies		Patients (*n*)	CTO-PCI success	Follow-up	PCI success *vs* PCI failure	
					MACE	Death
Registries	OPEN-CTO 2020 (12) (Hybrid approach)	1000	90%	1 yr	3.4% *vs* 3.7%	0.9% *vs* 0%
	EXPERT-CTO 2019 (2) (New generation DES)	250	96.4%	1 yr	18.5% *vs* 24.4%	NR
	Valenti *et al* 2019 (3) (Elderly ≥ 75 yr)	460	72%	5 yr	9.6% *vs* 17%	84% ± 3% *vs* 72% ± 6%
	Sudhakar *et al* 2014 (4)	13443	70.6%	2.65 yr	NR	HR 0.72, 95%CI: 0.62-0.83
Metanalyses	Christakopoulos *et al* 2015 (5)	28486	71%	3.11 yr	29.1%	6.4% *vs* 9.5%
	Hoebers *et al* 2015 (6)	15459	71.7%	1-10 yr	NR	10.4% *vs* 14.9%
	Chenmin *et al* 2021 (7) (Elderly ≥ 75 yr)	4693	70.4%-78.36%	20 mo-5 yr	16.8% *vs* 28.9%	HR: 0.51, 95%CI: 0.34-0.77
RCTs	DECISION CTO 2019 (8)	834	90.6%	4 yr	22.3% *vs* 22.4%	3.6% *vs* 5.3%
	EURO CTO 2018 (9)	396	86.6%	1 yr	5.2% *vs* 6.7%	0.8% *vs* 0%

RCT: Randomised controlled trial; CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; MACE: Major adverse cardiovascular events; DES: Drug-eluting stents; NR: Not reported.

current studies.

The multicenter randomized EURO-CTO trial enrolled 450 patients, randomized to CTO-PCI *vs* medical therapy with a 2:1 ratio; procedural success in the PCI arm was 86.7%; at 12 mo follow-up, CTO-PCI group showed greater improvement in the angina frequency score (P = 0.003) and the quality-of-life score (P = 0.007) compared with optimal medical therapy; causative classification system (CCS) improved considerably more in the PCI group than in the optimal medical therapy group (P < 0.001). No differences in the primary safety end points evaluated at 36 mo were found. Major cardiovascular and cerebrovascular events (MACCE) during 12 mo follow-up were similar between the two groups (P = 0.55)[11].

The lack of positive results in terms of clinical outcomes in randomized trials may be explained, at least partially, by the exclusion of patients at higher risk of events, for whom, on the basis of a perceived or demonstrated therapeutic benefit, an interventional attitude is preferred, effectively excluding the possibilities of randomization to conservative therapy for ethical reasons. Accordingly, Galassi *et al*[12] in their study reported how, even in the absence of statistically significant differences in MACCE at a median follow-up of 16.3 ± 8.2 mo, the group of patients with severely depressed left ventricular ejection fraction (LVEF) (< 35%), showed a significantly improvement of LVEF when a successful CTO-PCI was performed.

Convincing positive results from randomized trials are still awaited to conclusively legitimize the potential benefits of CTO-PCI in patients with indication for revascularization. The lack of unequivocal answers from randomized trials, however, does not preclude the possibility of choosing a therapeutic strategy: "evidence-based medicine" is still "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"[13] and the current evidence points in favor of CTO-PCI attempts.

A meta-analysis published in 2015, conducted on more than 28000 patients, showed the association of successful CTO-PCI with improved long-term survival when compared with procedural failure (OR 0.52, 95%CI: 0.43-0.63)[7]. Another meta-analysis, conducted on 2243 patients with successful CTO-PCI, found a LVEF significant increase, with 4.4 percentage points over baseline comparison in absolute terms (P < 0.01), as well as a reduction in negative ventricular remodeling[8].

Clinical benefit of successful CTO-PCI was found also in large registries[3-6]. In the OPEN-CTO registry (1), which enrolled 1000 patients, investigators reported in the group of successful CTO revascularization a statistically significant improvement in Seattle Angina Questionnaire (SAQ) from 49.4 ± 0.9 to 75.0 ± 0.7 (P < 0.01), and, after adjusting for baseline differences, the mean group difference in SAQ between successful and unsuccessful CTO-PCI was 10.8 (95%CI: 6.3 to 15.3; P < 0.001)[3]. At 1

year, the unadjusted MACCE rate was lower in patients with successful index CTO-PCI compared to patients with unsuccessful CTO-PCI (9.4% *vs* 14.6%; $P = 0.04$)[14].

Nowadays, despite results from perspective randomized controlled trials are conflicting, and the survival benefits are still debates, the indications to drive a CTO-PCI according to guidelines of the most important scientific societies are refractory angina symptoms despite optimal medical therapy or patients with documented large ischemic area in the territory of occluded vessel[15]. Furthermore, current evidence and guidelines support the use of viability imaging to assist decision-making in patients with ischemic heart failure and coronary artery disease[15]. Distinguishing hibernating myocardium from non-viable myocardium is particularly important to select patients that are more likely to benefit from myocardial revascularization and to reduce the risk of inappropriate treatment. Despite lack of longitudinal outcome benefit in the previous clinical trials, myocardial viability assessment plays an important role on a personalized level of clinical decision making for patients with CTO and LV dysfunction. The different noninvasive modalities available to assess myocardial viability interrogate distinct pathophysiologic myocyte and myocardial processes. The single photon emission computed tomography radionuclide tracers) examine myocyte cell membrane integrity, positron emission tomography myocardial blood flow and metabolism, cardiac magnetic resonance (CMR) with late gadolinium enhancement identifies scarred myocardium, whereas dobutamine echocardiography or CMR assesses regional ventricular contractile reserve. The imaging modality of choice needs to be individualized according to each clinical scenario, technology availability and institution expertise.

CMR is a versatile imaging modality to assess multiple interrelated features of both ischemia and viability in a single test without the use of ionizing radiation. It provides accurate and reproducible assessment of global and regional ventricular function, myocardial perfusion at rest and at stress, myocardial scar and the identification of viable but dysfunctional hibernated myocardium, being able to predict its recovery after successful revascularization[16]. Previous studies showed that the use of CMR may help to select patients who could derive significant LV reverse remodeling, ischemic burden relief, and quality of life improvement after CTO recanalization[17, 18]. Nevertheless, randomized trials with larger patient numbers are warranted to explore whether CMR-guided CTO revascularization is indeed superior to other available functional imaging, and is an independent predictor of long-term improved clinical outcome. Two ongoing trials, NOBLE-CTO (the nordic-baltic randomized registry study for the evaluation of PCI in chronic total coronary occlusion; NCT03392415) and ISCHEMIA-CTO (revascularization or optimal medical therapy of CTO; NCT03564317), employing CMR and nuclear imaging are eagerly awaited. Meanwhile according to current evidences, CTO PCI should be considered in symptomatic patients despite optimal medical therapy.

PERCUTANEOUS INTERVENTION OF CHRONIC OCCLUSION AS PART OF CORONARY REVASCULARIZATION: A COMPLEX PIECE TO "COMPLETE" THE PUZZLE

Rarely, CTO presents as single vessel coronary disease. More often, the interventional cardiologist is confronted with a multivessel coronary artery disease in which CTO represents an additional element of complexity. In this scenario, it is appropriate to analyze the potential prognostic impact of percutaneous revascularization of CTO in the broader perspective of a complete or reasonable incomplete revascularization.

Pioneering studies have shown that complete coronary revascularization, achieved following PCI of at least one CTO, results in a significant reduction in long-term cardiac mortality in the setting of multivessel atherosclerotic disease[19]. Even in patients undergoing PCI for multiple CTOs, 2-year survival was significantly better in patients with a complete revascularization by PCI[20]. Further confirmation came from the publication of the subanalysis of the Synergy Between Percutaneous Coronary Intervention with Taxus And Cardiac Surgery (SYNTAX) trial, which evaluated the prognostic impact of complete revascularization achieved after PCI or CABG and its association with the presence of CTO[21]. Incomplete revascularization was found to be conditioned by the complexity of the coronary anatomy and patient comorbidities and correlated with increased mortality and MACCE at 4-year follow-up in both groups. The presence of CTO represented the strongest independent predictor of incomplete percutaneous revascularization, at a time in history still burdened by

limited procedural proficiency, as demonstrated by the lower rate of successful revascularization of CTO in the group undergoing PCI, compared with the group undergoing CABG. To emphasize the importance of these results, it is worth mentioning that they derive from analyses conducted on patients in the SYNTAX trial, with stable coronary artery disease, without previous revascularizations, in whom first-generation DES were implanted, stent associated with more frequent events of restenosis and reocclusion than current second- or third-generation DES[22]. In addition, the success rate of CTO-PCI was significantly lower (approximately 49%) than the current rate, and complete revascularization was achieved in slightly more than half of the patients undergoing PCI and in only 63% of the patients undergoing CABG. Also in the study of Jang *et al*[23] published in 2017, data showed that in patients with CTO, achieving a complete revascularization (residual SYNTAX Score = 0) or a reasonable incomplete revascularization (residual SYNTAX Score = 12) guarantees a significantly lower risk of cardiac death and all-cause death compared with incomplete revascularization (residual SYNTAX score > 12), and these results were comparable with the CABG revascularization group at a median follow-up of 42 mo.

The favorable prognostic impact of a complete coronary revascularization has also been confirmed by large meta-analyses[5,24,25]. Among nearly 90000 patients from 35 randomized clinical trials and observational studies, completeness of revascularization, most often achieved by CABG, was found to be associated with approximately 30% reduction in long-term mortality[24]. Thus, it is not the surgical or percutaneous strategy that makes the difference, but the achievement of complete coronary revascularization. Another meta-analysis published in 2016, conducted on 156240 patients undergoing PCI for multivessel coronary artery disease, confirmed the strong prognostic benefit of the association between completeness of revascularization and reduced mortality and MACCE[25]. Notably, these benefits were maintained both in the subanalysis conducted on the cohort of 5 studies with CTO (OR 0.69; 95%CI: 0.53-0.80), and in the subanalyses that took into account the different definitions of complete revascularization[25]. Also of note, complete coronary revascularization by PCI was achieved in slightly less than half of the cases. Even in the pooled-analysis of Ahn *et al*[26] published in 2017, patients with incomplete revascularization by PCI had a higher risk of all-cause mortality respect to the patients treated with CABG. Conversely, no significant differences were found between patients undergoing CABG and those undergoing PCI with complete revascularization regarding the risk of death (aHR: 1.16; 95%CI: 0.83 to 1.63; $P = 0.39$) and the composite of death, myocardial infarction, and stroke (aHR: 1.14; 95%CI: 0.87 to 1.48; $P = 0.35$).

The favorable prognostic impact of successful CTO-PCI and complete revascularization on survival was also confirmed in elderly population. Valenti *et al*[5] collected data from 460 elderly patients (> 75 years) in the Florence real world CTO registry. Patients were stratified according to success or failure of CTO-PCI. Results showed improved five-year cardiac survival in the successful CTO-PCI group ($P = 0.006$) and a further improved survival benefit if complete coronary revascularization was achieved (90% ± 3% *vs* 68% ± 5%; $P < 0.001$) (Figure 1). Moreover, multivariate analysis demonstrated that increasing age, diabetes, chronic kidney disease, LVEF < 0.40 and complete revascularization resulted independently associated with long-term cardiac survival. Even in the meta-analysis of Cui *et al*[9] published in 2020, data derived from 8 studies showed how successful CTO-PCI was associated with reduction in long-term mortality and major adverse cardiovascular events (MACE) as compared to failed PCI in elderly.

Most of the elderly patients in these studies had high prevalence of comorbidities, complex coronary anatomy and concomitant LV dysfunction and heart failure, so they are consistent to the current setting definition of "complex higher-risk and indicated patients"[27]. In this context of patients with several comorbidities and severely reduced LV function, the execution of a percutaneous CTO revascularization is considered at very high risk, both for the technical difficulty of the procedure and for the clinical characteristics of the patient. Even if data regarding use of LV assist devices for hemodynamic support during CTO-PCI procedure are still lacking, initial experiences of small retrospective studies and case reports/series seem to show encouraging results[28].

Nowadays, the application of a "contemporary" revascularization strategy, in addition to the technical and procedural aspects, involves an optimal management of antithrombotic therapy. Patients who undergo a CTO-PCI are at high risk of clinical ischemic and thrombotic events. Antiplatelet therapy could play a leading role in reducing clinical event rates. Recent data from Valenti *et al*[19] has shown that a "tailored" approach based on platelet reactivity test results and clinical aspects could

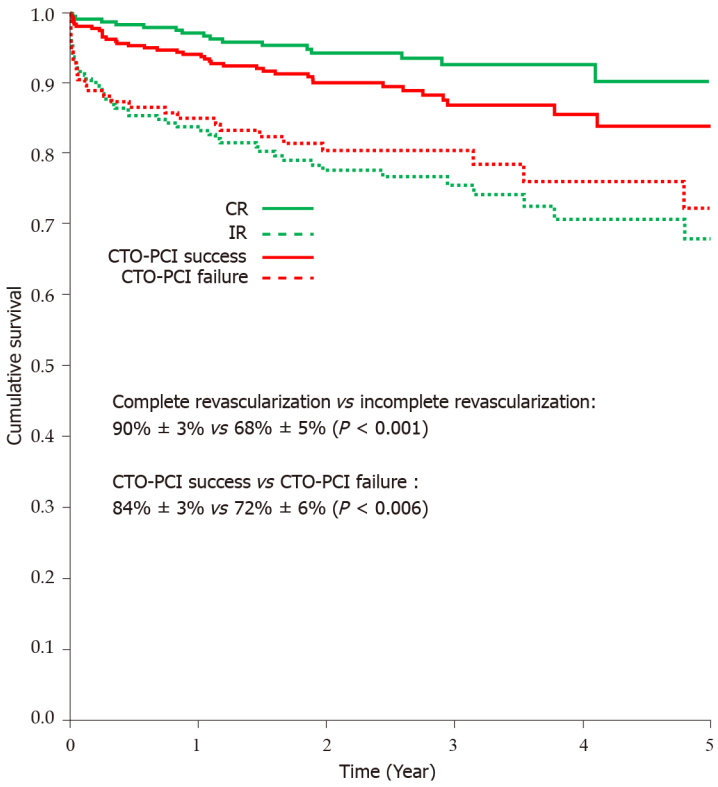

Figure 1 Long-term survival according to chronic total occlusion-percutaneous coronary intervention results and completeness of revascularization in a real-world registry investigating elderly > 75 years. Successful chronic total occlusion-percutaneous coronary intervention (CTO-PCI) group was associated with a long-term survival benefit when compared to failed CTO-PCI group at Kaplan–Meier survival analysis. Survival benefit was even greater in the complete coronary revascularization group and preserved up to 5 years. CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; CR: Complete revascularization; IR: Incomplete revascularization. Citation: Valenti R, Migliorini A, De Gregorio MG, Martone R, Berteotti M, Bernardini A, Carrabba N, Vergara R, Marchionni N, Antoniucci D. Impact of complete percutaneous revascularization in elderly patients with chronic total occlusion. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2020; 95: 145–153. Copyright ©The Author(s) 2019. Published by John Wiley & Sons, Inc[5].

lead to a survival benefit. Data showed how three-year survival was significantly higher in patients with adequate responsiveness to antiplatelet drugs: the optimal platelet reactivity group compared with high platelet reactivity patients showed a lower MACE rate (95.3% ± 0.8% *vs* 86.2% ± 2.8%; $P < 0.001$). Furthermore, in high platelet reactivity cohort of patients, escalation to a more potent antiplatelet agent allowed similar survival rates to the patients with optimal platelet responsiveness. Conversely, a prolonged clopidogrel therapy in non-responders patients (when more potent antiplatelet agents were not available) was associated with a high cardiac mortality (HR: 2.37; $P = 0.003$)[29].

Combining the evidence from randomized trials and registries, it appears clear that, although the real benefits on prognosis have yet to be fully demonstrated, it is undeniable that the revascularization of CTO leads to an improvement in patients' quality of life and more specifically to a reduction of angina. This evidence, in turn, raises further questions and in particular which strategy should be adopted in patients presenting CTO with a previous failed revascularization attempt or judged not amenable for CTO-PCI or in patient whose procedure would be at extremely high-risk to perform. Very interesting are the results of the retrospective multicenter study by Zivelonghi *et al*[30], conducted on patients with refractory angina symptoms, unsuitable for revascularization procedure or with previous revascularization failure, undergoing coronary sinus reducer (Neovasc Inc., Richmond B.C., Canada) implantation (24). In the group of patients with at least one CTO lesion, at a median follow up of 570 ± 370 d, patients experienced a statistically significant reduction in CCS class, with a significantly higher improvement respecting to the non-CTO patients' group. One of the possible explanations of these results, according to the authors, consists in the presence of collateral coronary circulation in CTO patients; this could be the key for the device mechanism of action associated with the potential clinical benefit; nevertheless, these results need to be confirmed in perspective randomized controlled trials.

ACUTE MYOCARDIAL INFARCTION WITH CONCOMITANT CHRONIC OCCLUSION

An additional complex clinical scenario is represented by acute coronary syndrome and multivessel coronary disease with the presence of a CTO.

About 50% of patients presenting with STEMI have a concomitant multivessel coronary artery disease, and about 13%-20% have a coexisting concurrent CTO; of these, only 5%-22% of cases receive an attempt percutaneous recanalization of the chronically occluded vessel, despite the current high success rate[2,31-34].

It is now recognized, from observational studies and sub-analyses of randomized trials, that the prognosis, in terms of short- and long-term survival after ST-elevation myocardial infarction (STEMI), is worse in patients with multivessel coronary artery disease and concomitant CTO. These findings have also been confirmed in a recent meta-analysis[35]. From a pathophysiological perspective, the presence of a CTO limits the possibility of providing collateral circulations to the acutely occluded vessel and, at the same time, the sudden deterioration of collaterals supplying the territory underlying the CTO may endanger a large area of myocardium.

If this intuitively explains the prognostic benefit of recanalization, which data are currently available to support this statement?

An observational study from the Florence CTO registry published in 2014[36], including patients with STEMI and concomitant CTO of the non-culprit vessel, showed a clear benefit in terms of 1- and 3-year cardiac survival in patients treated with successful CTO-PCI (performed between 7 and 30 d after primary PCI) when compared with patients with failed or non-attempted CTO-PCI; a favorable prognosis related to completeness of coronary revascularization was maintained even in very high-risk patients, such as those with cardiogenic shock, three-vessel and/or left main disease, severe LV dysfunction, and also in those patient with left anterior descending coronary artery involvement, either as culprit vessel or site of CTO (81%). In the group of patients with successful CTO-PCI, complete revascularization was achieved in 88% of cases, but even in the comparison group, extensive revascularization (non-CTO, non-infarct-related artery) was achieved in 85% of patients[36].

In 2016, the results of the randomized EXPLORE trial were published, which tested the impact of early PCI of CTO (< 7 d after the primary PCI procedure) on LV function and telediastolic ventricular volume at 4-mo follow-up[33]. Recanalization of CTO was not found to be associated with a significant improvement in LV function and telediastolic volume as assessed by magnetic resonance imaging. However, a sub-analysis of the study suggested a clinical benefit in patients undergoing PCI of the left anterior descending artery CTO[33]. Long-term follow-up (up to 5 years) showed that MACE were not significantly different in the two arms. Furthermore, no differences about the LV function were found in the two groups at 1 year[37].

The CREDO-Kyoto AMI registry analyzed 2045 patients with STEMI with or without CTO in the non-culprit vessel (18.7%). Although the presence of a CTO was independently associated with increased risk of mortality, mainly after the first 30 d after the acute event, there were no statistically significant differences in 5-year mortality between patients undergoing successful CTO-PCI and those with a failed procedure. It should be noted, however, that only 32% of cases underwent a CTO PCI, with a success rate of 64% and a low percentage of DES implantation[38].

Some evidence of MACE reduction in STEMI patients undergoing a staged CTO revascularization, compared with primary PCI and subsequent medical therapy comes from small retrospective single-center trials[39].

Although there is no clear evidence about the clinical benefit of revascularization of concurrent CTO in AMI patients, the available data are in favor of a complete coronary revascularization[40,41]. A possible explanation for the conflicting results in this setting, could be that the timing of the revascularization procedure following primary PCI must be individualized on the basis of the clinical characteristics of each patient; the application of a standardized timing in this complex clinical and procedural setting cannot be generalized.

PLANNING A TREATMENT STRATEGY: THE APPROACH TO PERCUTANEOUS REVASCULARIZATION OF CHRONIC CORONARY OCCLUSION

The first reports of CTO-PCI date back to 1985, thanks to the pioneering attempts of Japanese operators who have transferred the techniques developed in the field of

percutaneous revascularization of chronic femoro-popliteal occlusions to the coronary field. The first approach was antegrade, with procedural success in about 60% of attempts[42].

The observation that the distal cap of the occlusion is often less ambiguous and easier to penetrate than the proximal one, has soon created interest in a retrograde approach, first performed through vein grafts and then through septal collateral branches, leading to an increased procedural success, reaching 85%. Another technique borrowed again from the endovascular experience on the peripheral system is the "subintimal tracking and re-entry" (STAR), consisting in the recanalization of the occluded segment *via* a controlled subintimal dissection performed with a J-tipped wire ("knuckle"), adding a bailout strategy when failure of the "true-lumen" techniques occurs. Due to the difficulty in both navigating the guidewire and controlling the re-entry point in the true lumen, with potential loss of collateral branches, the STAR technique initially did not improve procedural success. Later, thanks to procedural refinements and devices advancements, the STAR technique has officially entered the CTO treatment option.

All these new techniques, in combination with the development of dedicated devices (among the latest the CrossBoss and Stingray system; Boston Scientific, Marlborough, MA, USA) and the use of second and third generation DES, with their improved long-term patency, have permitted a more articulated and flexible vision of CTO recanalization[22].

The indication for revascularization is conditioned by the clinical evaluation, which must take into account the patient's symptoms, LV function, comorbidities, and vitality/ischemia tests, in order to assess the expected therapeutic benefit in terms of "quality of life" and prognosis. Angiographic evaluation, on the other hand, is necessary to clarify not only the complexity of the CTO lesion, but also the probability of success and the expected risk of complications.

Indeed, only a comprehensive and integrated assessment of clinical, imaging and angiographic characteristics may define the appropriate revascularization strategy.

The goal of CTO PCI is to restore continuity between the upstream and downstream vessel segments of the occluded artery. For this purpose, two basic approaches can be used: the first one consists in penetrating the areas of loose tissue or microchannels physiologically present in part of chronic occlusions, trying to cross the thickness of the occluding plaque and proceed in the "intralesional" or "intimal" segment of the vessel; the second one aims to "bypass" the lesion, exploiting more extensively the vessel architecture and the subintimal space, proceeding within the adventitia of the vessel that, thanks to its elasticity and resistance, will constitute an operative channel.

Of note, some recently published data obtained from intracoronary imaging assessment after CTO recanalization seems to show a higher rate of all-cause mortality, post procedural myocardial infarction and target vessel revascularization in subintimal tracking techniques[43]. Subintimal recanalization was also associated with a higher prevalence of malapposed stent struts at OCT evaluation[44].

Summarizing we have two technique, intimal/intralesional and subintimal, that can be both used in antegrade and retrograde approach.

For the intimal/intralesional strategy, it's possible to adopt a wire escalation technique according to the type of guidewires used to cross the plaque, which differ in terms of stiffness, hydrophilicity, and penetrating power; mostly with two variants: (1) "Step-up" escalation (stiff-stiff-stiffest); and (2) "Step-up-step-down" escalation (stiff-soft-stiff). Conversely, it is possible to obtain recanalization through subintimal crossing with dissection and re-entry technique by surfing in the subintimal space until the patent vessel segment is reached, bypassing the occlusion.

As mentioned above, there is also the possibility of two different approaches: (1) The antegrade approach: when the lesion is tackled by advancing guidewires along the native vessel in a proximal-distal fashion, following the bloodstream; and (2) The retrograde approach: when the lesion is tackled from the distal cap, by advancing guidewires from the donor vessel through the so called "interventional" collateral.

In some cases, different approaches can coexist in the same technique, as in the controlled antegrade and retrograde subintimal tracking (CART) or reverse CART method, where a simultaneous antegrade and retrograde approach is required.

In order to select the most appropriate approach and technique, an accurate analysis of the angiogram is a key step of the procedural strategy. The angiogram for a CTO study should preferably be performed by dual, simultaneous injection of contrast medium for better definition of vessel anatomy, effective lesion length, distal segment anatomy, and characteristics of collateral circulation, combining typical and atypical projections in order to optimize the visualization of elements of interest. "Ad hoc" CTO-PCI procedures are generally discouraged in favor of careful planning. The

increased expertise in the field has allowed to identify some features of the lesions that the operator must evaluate for the choice of proper interventional strategy: morphology and localization of the proximal and distal cap, lesion length, presence of calcifications, landing zone and, finally, characteristics and quality of donor and collateral vessels.

SCORES FOR THE EVALUATION OF CHRONIC CORONARY OCCLUSIONS

Multiple scores have been developed over the years in order to stratify the procedures in various levels of difficulty. The effort was intended to provide a synthetic tool capable of predicting and expressing the procedural complexity of a CTO-PCI and to support the management of the procedural strategy. We will review below the main scores reported in the literature (Table 2)[45-48].

The Japan-CTO (J-CTO) score[45], the progenitor of the series, was developed as a model to predict the probability of success of an antegrade wiring of the lesion within the first 30 min of the procedure. It takes into account several variables, the presence of which adds one point (+ 1) to the total score. These variables are the morphology of the proximal cap, the presence of calcifications within the occluded segment, the tortuosity of the segment, the length of the lesion (cut off > 20 mm), and the failure of a previous attempt to bridge the lesion. A score of ≥ 2 identifies a lesion that is particularly difficult to overcome.

The clinical and lesion related score was then developed[46] including some angiographic parameters already used in the J-CTO score (lesion length > 20 mm, proximal cap morphology, presence of calcifications), plus the presence of a CTO in a vessel other than the left anterior descending artery and combining them with clinical variables, such as a previous myocardial infarction and/or CABG. The score obtained identifies 4 different classes, correlated with decreasing probability of successful revascularization and increasing probability of MACCE (death, myocardial infarction, need for new revascularization with PCI or CABG, tamponade, and stroke).

The ORA (ostial location, Rentrop grade < 2, age ≥ 75) includes only 3 variables, of which one clinical (age ≥ 75 years) and two angiographic (ostial location and Rentrop collateral circulation ≥ 2)[48]. In the prospective global registry for the study of chronic total occlusion score four variables are taken into account: difficult proximal cap localization, absence of collaterals, severe tortuosity, and circumflex artery CTO[47]. These last two scores, unlike the previous ones, contemplate some variables that condition the choices in the hybrid algorithm, allowing the expansion of the field of application from only antegrade crossing techniques to retrograde and combined approaches.

The RECHARGE score was a tool developed to predict technical outcomes of CTO-PCI from patients treated by "hybrid" operators with different experience levels[49]. One point is given for a long lesion length (20 mm), visible calcification on angiography, tortuosity within the CTO segment or at CTO entry, a blunt proximal cap, a diseased distal landing zone, and the presence of a bypass graft on the CTO target vessel, respectively[49].

The more recent one the Euro-CTO CASTLE score is similar to RECHARGE score but includes among the variables, the age of the patients and previous CABG (irrespective of graft location) and discard the evaluation of the distal landing zone [50]. CASTLE Score showed similar overall discriminatory capacity compared with J-CTO score, but, for more complex procedures (J-CTO > 3 or Euro-CTO CASTLE > 4), the predictive capacity of Euro-CTO CASTLE score appeared superior[51].

Scores can be a useful tool in several aspects of CTO-PCI performance. By providing a quantitative measure of the probability of success and complications, they offer useful information to be shared with the patient and in the evaluation context of a Heart Team. Furthermore, they can guide case selection, allowing less experienced operators to confidently tackle the simplest cases, while deferring more complex challenges to more experienced operators. Nevertheless, some studies show very good success rates among experienced operators, even in case of particularly unfavorable scores[52], confirming that the scores assessment should represent a moment of reflection, but not a reason to give up before the challenge of a percutaneous revascularization.

Table 2 Main scores for assessment of chronic total occlusions

	J-CTO score		CL score		ORA score		PROGRESS score		RECHARGE score		EURO-CTO CASTLE score	
Angiographic Features	Proximal cap blunt	1	Proximal cap blunt	1	Ostial location	1	Proximal cap ambiguity	1	Proximal cap blunt	1	Proximal cap blunt	1
	Tortuosity > 45°	1	Lesion lenght > 20 mm	1.5	Collateral filling Rentrop 0-1	2	Tortuosity	1	Tortuosity > 45°	1	Tortuosity > 45°	1
	Lenght > 20 mm	1	Calcification	2			Circumflex CTO	1	Lenght > 20 mm	1	Lenght > 20 mm	1
	Calcification	1	Non-LAD CTO	1			Absence of interventional collaterals	1	Calcification	1	Calcification	1
									Diseased distal landing zone	1		
Clinical features	Prior CTO PCI failure	1	Previous MI	1	Age > 75 yr	1			Previous CABG on CTO target vessel	1	Previous CABG	1
			Previous CABG	1.5							Age > 70 yr	1

Japan-chronic total occlusions (CTO) score (45): 1 point for the presence of each variable with classification into 4 categories of difficulty: Easy (0), intermediate (1), difficult (2), and very difficult (≥ 3). Clinical and lesion-CTO score (46): Non-anterior interventricular artery, previous MI, blunt stump (+ 1); previous coronary artery bypass graft, lesion length > 20mm (+ 1.5); severe calcification (+ 2). Four classes of probability of success are identified: High success rate (score 0-1), intermediate (score 2), low (score 3-4), and very low (score ≥ 5). PROGRESS-CTO score (47): 1 point for each variable. ORA score (48): 1 point for the variables of age and ostial location, and 2 points for the Rentrop collateral circle < 2; there are 4 degrees of difficulty: easy (0), intermediate (1), difficult (2), and very difficult (3-4). RECHARGE score (49): 1 point for each variable, grading CTO lesion complexity from 0 to 6 points. EURO-CTO CASTLE score (50): 1 point for each variable (0 to 6). At a score of 0, the mean predicted risk of failure of CTO percutaneous coronary intervention was 5.8%. At a maximum score of 6, the predicted risk of failure was 56.5%. CTO: Chronic total occlusion; CABG: Coronary artery bypass graft; LAD: Anterior interventricular artery; LCx: Circumflex artery; MI: Myocardial infarction.

DIFFERENT PHILOSOPHIES LEADING TO DIVERGING APPROACH FOR CTO REVASCULARIZATION

Taking into account and keeping in mind the characteristics listed, the operator will be able to select the best interventional strategy. Historically, it is possible to identify different philosophies, or experiences to approach CTO revascularization. Currently, there are two main strategic approaches followed by practitioners: the Japanese Eastern school and the American and European Western school, evolved in the so-called "hybrid approach".

Eastern-Japanese approach

The Japanese interventional philosophy is reflected in a dedicated and thoughtful approach to CTO: extreme importance is given to the coronary study, the analysis of the angiographic picture, the availability of dedicated hemodynamic rooms. Pre-procedural tomographic techniques (to assess the anatomy of the occlusion) and intra-procedural intravascular ultrasound (to resolve ambiguities of the proximal cap and guide the return of the guides in dissection techniques) play a paramount role. The choice of the technique, obviously based on coronary anatomy, is maintained even in spite of initial procedural difficulties, favoring a careful intra-procedural choice of instrumentation and a “great mastery” in handling the available material. The use of antegrade dissection/reentry techniques, considered suboptimal for CTO recanalization, is generally discouraged, in favor of a meticulous intraluminal advancement technique or "switch" to retrograde approach. Overall, the results of the Japanese experience are extremely valid and a "driver" for international performance, with a low prevalence of clinically relevant procedural complications[52]. A potential limitation of this approach is, however, linked to the difficulty in standardizing choices and the impossibility, in different economic contexts, to use facilities and resources with the same liberality.

In an attempt to respond to this need for efficiency and uniformity, the hybrid approach of the North American school was born.

Hybrid approach of the Western school

The philosophy of the hybrid approach[53] is to achieve recanalization of the occluded vessel by using all available techniques in the most effective, safe, and efficient way. It combines a limited number of anatomical information in a decision algorithm, which allows to establish the initial technique (the one with the highest probability of success in relation to the characteristics of the lesion) and the most effective bailout techniques in case of procedural failure. However, the peculiar aspect of this approach (that justifies its "hybrid" attribute) is the dynamic nature of the transition from one technique to another (Figure 2). It is recognized that excessive insistence on a single technique, in addition to being time-consuming, can even be detrimental in terms of success. Therefore, a quick "switch" is encouraged, with possible "re-cycling" among several techniques, whenever significant progress cannot be achieved within a reasonable time frame of 5-10 min. Practical benefits include shorter procedure duration, reduced radiation exposure, and potentially less use of contrast agents. Data from RECHARGE registry study evaluated the effectiveness of this approach in a "real-world" setting of European centers, finding a procedural success rate of 89%[49]. Similar results were confirmed in the recently published data from OPEN-CTO Registry: the application of hybrid approach led to a technical success rate of 86% in the index CTO-PCI[14].

A particular interesting finding was the actual application of the strategy predicted on the basis of the algorithm: in case of concordance, the success rate was higher[49]. Thanks to the algorithm, the hybrid approach leads to dissemination of learning and teaching of CTO revascularization, offering an easy guide for practitioners, particularly those with lower skills and experience level. It is worth noting that the algorithm does, however, some generalizations/limitations that are susceptible to interpretation and adaptation to individual needs.

In specialized centers, regardless of the approach strategy, safety outcomes have been shown to be very satisfactory. A meta-analysis of 65 studies, on a total of 18061 patients undergoing CTO-PCI, found an incidence of MACE (death, myocardial infarction, stroke, and CABG in emergency) of 3.1%, with a mortality of 0.2% and an incidence of cardiac tamponade of 0.3%[54]. Great care is also recommended in monitoring the amount of contrast medium used and fluoroscopy. All currently available strategies should be implemented to reduce the incidence of contrast-induced nephropathy.

Over the last years, new algorithms were developed with the aim of extending original "hybrid" approach: the Asia Pacific CTO Club algorithm[55] and the algorithm from the European CTO Club[56]. All these algorithms, the original one and his updates, are very similar. Indeed, all of them are focused on initial anatomy evaluation to guide the initial strategy choice, use of intravascular imaging is encouraged to avoid ambiguity, and criteria for failed procedure are listed. Tanaka *et al*[57] developed a revised algorithm, proposing a wider use of the retrograde approach, mainly in lesions with a higher J-CTO Score, highlighting how, in selected cases a primarily retrograde approach allows excellent procedural success rate with a shorter wire manipulation time.

Recently, a new revised version of "hybrid" approach was implemented, the minimalistic "hybrid" algorithm[58]. The two major points of the minimalistic "hybrid" algorithm are limiting the routine use of dual injection and encouraging the use of trans-radial access and smaller (6-7 French) guiding catheters. First results reported showed lower peri-procedural complications in the group treated according to the minimalistic approach, with similar procedural results and non-statistically significance differences in MACE[59].

Unfortunately, the multiplication of algorithms for CTO-PCI may lead to confusion rather than clarity, as also stated in a recent published editorial[60].

CTO: A CHALLENGE WITHIN A CHALLENGE

The ultimate challenge of coronary interventional cardiology, now fully shared by the scientific community, is to achieve a complete coronary revascularization. It has been widely demonstrated that complete coronary revascularization, achieved by either CABG or PCI, is associated with prognostic improvement, in terms of increased survival and reduction of MACE. In this scenario, the successful CTO revascularization plays a key role over the broad panorama of percutaneous coronary interventions. In this perspective, percutaneous revascularization can compete convincingly with the surgical revascularization that, to date, is the easiest way to achieve a

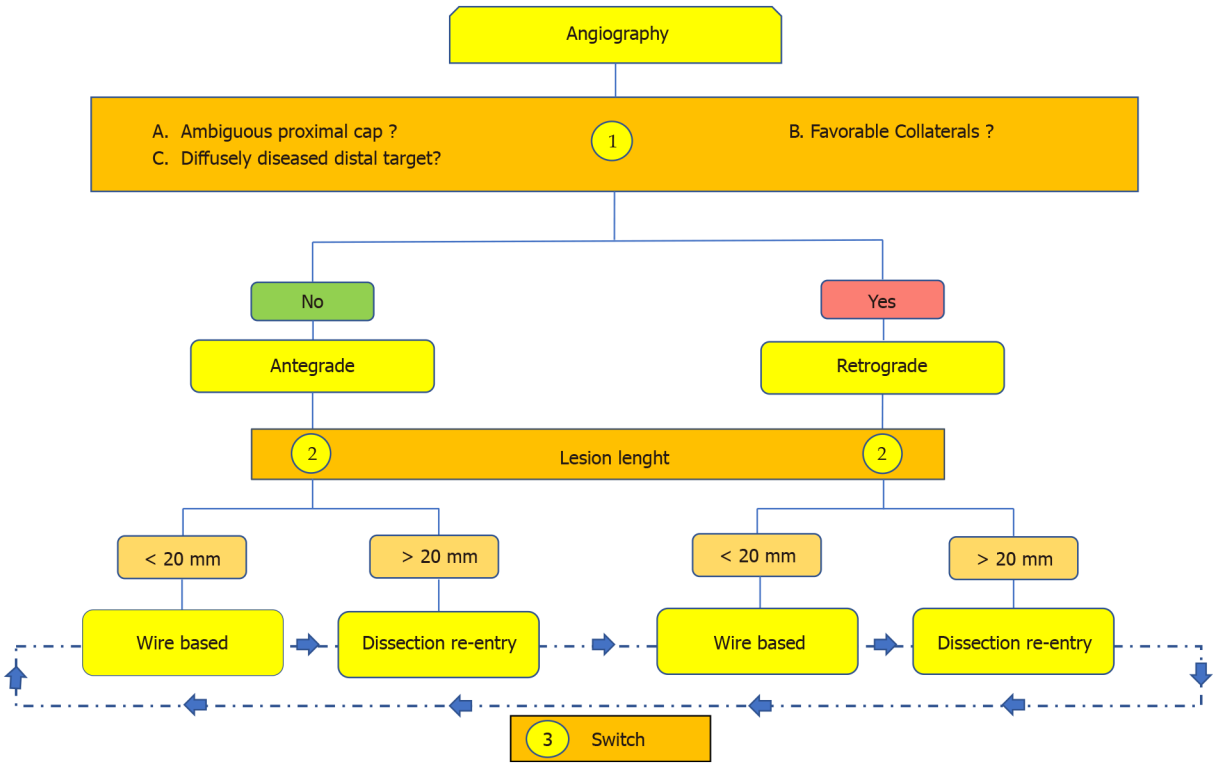

Figure 2 Hybrid algorithm for approaching strategy decision to chronic total occlusion.

high rate of complete revascularization in patients with multivessel coronary artery disease with associated CTO. When the equivalence in term of completeness between PCI and CABG will be definitively granted, we could be able to offer our patients a percutaneous revascularization associated with a long-term clinical benefit and, above all, we will be able to provide the better revascularization strategy for each patient, inspired by an "individualized medicine". Furthermore, we could finally leave behind the results of the comparison, now obsolete, between surgical and percutaneous revascularization in patients with multivessel disease of the SYNTAX trial, which still guides the revascularization modalities in the guidelines of the major cardiology scientific societies.

CONCLUSION

In conclusion, the application of "contemporary" strategies aimed to obtain a state-of-the-art revascularization by PCI allows achieving long-term clinical benefit, even in high-risk patients or complex coronary anatomy with CTO. The increasing success of CTO-PCI, allowing a complete or reasonable incomplete coronary revascularization, is enabling to overcome the last great challenge of interventional cardiology, adding a "complex" piece to "complete" the puzzle.

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MINIREVIEWS

Role of genetic testing in cardiomyopathies: A primer for cardiologists

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Abstract

Recent advances in cardiovascular genetics have transformed genetic testing into a valuable part of management of families with inherited cardiomyopathies. As novel mutations have been identified, understanding when to consider genetic testing has emerged as an important consideration in the management of these cases. Specific genetic testing has a paramount importance in the risk stratification of family members, in the prognosis of probands at higher risk of a serious phenotype expression, and finally in the identification of new mutations, all of which are discussed in this review. The indications for each type of cardiomyopathy are described, along with the limitations of genetic testing. Finally, the importance of public sharing of variants in large data sets is emphasized. The ultimate aim of this review is to present key messages about the genetic testing process in order to minimize potential harms and provide suggestions to specialized clinicians who act as a part of a multidisciplinary team in order to offer the best care to families with inherited cardiomyopathies.

Key Words: Cardiomyopathy; Genetic counselling; Genetic testing; Variant; Hereditary

Core Tip: In a considerable percentage of patients with cardiomyopathies, there is a

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genetic component. If the presence or severity of the cardiomyopathy cannot be explained by acquired causes, the genetic component should be investigated in order to reveal potential inherited forms of cardiomyopathies. The genetic testing process is also helpful to minimize potential harms and provide suggestions to specialized clinicians who act as a part of a multidisciplinary team, with the objective of offering the best care to families with inherited cardiomyopathies.

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INTRODUCTION

Cardiomyopathies represent a group of disorders of the myocardium associated with cardiac dysfunction, aggravated by arrhythmias, heart failure, and sudden cardiac death (SCD). They can be classified according to their morphological and functional phenotypes, specifically as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular (ARVC)/arrhythmogenic cardiomyopathy (ACM), and as unclassified forms[1]. In a considerable percentage of patients with cardiomyopathies, there is a genetic component, even for cases in which interaction with environmental factors cannot be excluded[2-5]. If the presence or severity of the cardiomyopathy cannot be explained by acquired causes, the genetic component should be investigated in order to reveal potential inherited forms of cardiomyopathies.

The continual rapid progress of molecular techniques over the past 2 decades and the related increased choices of different genetic testing options have led to a dramatic increase in our understanding of the genetic architecture of these diseases[6,7]. For better understanding of the terms used in the genetic testing process, relevant definitions are provided in Table 1. The aim of this review is to discuss the benefits of genetic testing in cardiomyopathies and the current indications in diagnosis and prognostication of probands and risk stratification for family members, in order to promote provision of optimal care for patients and their families.

GENETIC TESTING TECHNIQUES

The type and the available technologies for gene-based sequencing have been in constant evolution; turnaround times are shorter, while their cost has been dramatically decreasing. Whole blood, dried blood spots, or tissue specimens regarding post-mortem examination could serve as acceptable specimens for genetic testing. Conventionally, genetic testing by Sanger sequencing, for individual genes has been performed[8]. Due to the genetically heterogeneous nature of cardiomyopathies and the development and availability of next-generation sequencing (NGS) technique in the clinical setting, a multi-gene panel instead of individual gene-testing is now desirable practice for these diseases. Therefore, Sanger sequencing and targeted analysis is only preferable for cascade testing, when a pathogenic or likely variant has been identified in the proband. The composition of gene panels varies and some laboratories propose larger gene panels. However, increasing the number of genes in the panel also possibly increases the likelihood of identifying variants of uncertain significance. It is therefore evident that the ordering cardiologist should be aware of the benefits and limitations of specific test types in order to select the most appropriate technique[9]. Currently, testing a small specific panel of genes is usually recom-mended for each well-defined phenotype. Together, these techniques provide excellent precision and accuracy to detect single nucleotide substitutions that produce missense, nonsense, and splice site mutations and small insertion/deletions. A subset of cases with large insertion or deletion variants or other structural DNA changes, whereas the above analyses turn out negative, might benefit from copy number assays using microarray or multiplex ligation-dependent probe amplification[8,9].

Table 1 Terminology of commonly used genetics vocabulary

Term	Definition
Allele	One of several alternative versions of a particular gene
Heterozygote	An individual who has different alleles at a particular gene locus on homologous chromosomes (carrier of a single copy of the mutation)
Mutation	Any alteration in the inherited nucleic acid sequence of the genotype of an organism; a mutation considered in the context of a genetic disease usually refers to an alteration that causes a Mendelian disease
Penetrance	Proportion of individuals carrying a mutation who also express a cardiomyopathy phenotype
Genome sequencing	Sequencing of entire genome (coding and non-coding regions)
Exome sequencing	Sequencing of the coding regions (exons)
Proband or index case	Index case in the family, usually the one with the most severe phonotype
Variant	A change in the DNA sequence which may or may not be disease-causing
Pathogenicity	Process of determining whether a variant is causative or not

CURRENT RECOMMENDATIONS FOR EACH CARDIOMYOPATHY

The prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies are summarized in Table 2.

HCM

HCM, a disease of the sarcomere, is the most common inherited cardiomyopathy, with an autosomal-dominant type of transmission, leading to left ventricular (LV) hypertrophy and diastolic dysfunction. It is most often caused by variants in genes encoding cardiac sarcomere proteins[10]. The phenotype ranges from asymptomatic forms to SCD as the first and only manifestation, as seen especially in young athletes, all depending on the penetrance of the disease-causing mutations. Genetic testing should include not only the most common sarcomere genes [β-myosin heavy chain (MYH7); myosin-binding protein C3 (MYBPC3); troponin T2; troponin I3; tropo-myosin; actin alpha cardiac muscle 1; myosin light chain 2; myosin light protein] but also genes causing rare syndromic diseases with a HCM-phenotype [α-galactosidase (Fabry disease); protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2) (PRKAG2-glycogen storage disease); lysosomal-associated membrane protein 2 (Danon disease)][11,12]. In some of these diseases, such as Fabry or Danon disease, the positive genetic test result may change the clinical care of the proband, such as to involve enzyme replacement therapy or a more aggressive clinical management, respectively[12]. The diagnostic yield for the proband with a definite clinical diagnosis of HCM is approximately 30%-60%, and even higher in individuals who have severe LV hypertrophy, a known family history of HCM, or who were diagnosed at a younger age. MYBPC3 and MYH7 account for approximately 80% of all cases with positive genetic test.

DCM

About 30% of DCM cases appear to be familial in origin, isolated, or as a part of a syndrome[13-15]. The mode of inheritance is mostly autosomal dominant (AD). However, sporadic forms of DCM could be caused by non-genetic factors (*i.e.*, drugs, alcohol, viruses). Similar to HCM, the clinical severity of DCM is heterogeneous, so genetic testing is important for the surveillance of the asymptomatic genotype-positive carriers. Clinical screening combined with a three-generation pedigree of the proband are warranted in order to establish the need for genetic testing in DCM[5].

Over 100 genes have been implicated in DCM, all encoding sarcomeric and cytoskeleton proteins[16]. After the addition of titin (TTN) variants in genetic testing, the diagnoses of familial DCM increased by about 10%[17]. However, interpretation of the TTN mutations is challenging, due to the large size of the gene and the high frequency of benign variants in healthy populations. Mutations in the lamin A/C (LMNA) gene are also detected in approximately 4%-6% of familial DCM cases, causing a distinct phenotype characterized by systolic impairment together with progressive conduction disturbances and malignant arrhythmias[15]. DCM may also

Table 2 Prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies

Inherited CMP	Prevalence	Pattern of inheritance	Key genes	Diagnostic yield of genetic testing	Recommendation for genetic testing
HCM	1 in 500	AD	MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, MYL3, GLA, PRKAG2, LAMP2	30%-60%	For any patient with clinical diagnosis of HCM; Familial screening with a mutation after identified in the index case
DCM	1 in 2500	AD, X-linked	DES, DMD, DSP, FLNC, LMNA, MYH7, PLN, RBM20, TNNI3, TNNT2, TTN, TPM1	20%-30%	For patients with DCM and conduction disease and/or family history of SCD; Familial screening with a mutation after identified in the index case
ARVC	1 in 2000-5000	AD, AR	DSC2, DSG2, DSP, JUP, PLN, TMEM43	50%	Familial screening with a mutation after identified in the index case
RCM	Rare	AD, AR X-linked or mitochondrial	Troponin; MYBPC3, MYL3	Unknown	Familial screening with a mutation after identified in the index case

ARVC: Arrhythmogenic right ventricular cardiomyopathy; DCM: Dilative cardiomyopathy; HCM: Hypertrophic cardiomyopathy; RCM: Restrictive cardiomyopathy; AD: Autosomal dominant; AR: Autosomal recessive; MYH7: β-myosin heavy chain; MYBPC3: Myosin-binding protein C3; TNNI3: Troponin I3; TNNT2: Troponin T2; TPM1: Tropomyosin; ACTC1: Actin alpha cardiac muscle 1; MYL2: Myosin light chain 2; MYL3: Myosin light protein; GLA: Alpha-galactosidase; PRKAG2: Protein kinase AMP-activated non-catalytic subunit gamma 2; LAMP2: Lysosomal-associated membrane protein; DES: Desmin; DMD: Dystrophin; DSP: Desmoplakin; FLNC: Filamin C; LMNA: Lamin A/C; PLN: Phospholamban; DSC2: Desmocollin 2; DSG2: Desmoglein 2; JUP: Junction plakoglobin; RBM20: RNA-binding protein 20; SCD: Sudden cardiac death; TMEM43: Transmembrane protein 43; 2; TTN: Titin.

appear as a complication of neuromuscular diseases (*e.g.*, Duchenne and Becker muscular dystrophy). As the mode of inheritance is X-linked recessive, genetic testing should be provided in mothers of probands with Duchenne or Becker, because carrier females may develop later on[18]. At this point, we should also emphasize that due to phenotype overlapping among cardiomyopathies, HCM and ACM genes are included in DCM panels.

ACM, including right ventricular

ARVC is currently considered as a subtype of the broader group of ACM, with fibro-fatty replacement of the ventricular myocytes[19]. Clinical manifestations may vary with age and stage of disease, from asymptomatic but at-risk for SCD to end-stage heart failure with symptomatic arrhythmias. It is considered familial, with AD inheritance; although, there are recessive forms (*e.g.*, Naxos disease, Carvajal syndrome)[20]. Initially, it was identified as a disease caused by mutations in genes encoding desmosomal proteins. A pathogenic variant has been detected in up to 50% of cases referred for genetic testing who meet the 2010 Task Force criteria[3]. Mutations in the plakophilin-2 gene account for 20%-30% of cases, while variants in four other desmosomal genes (desmocollin 2; desmoglein 2; desmoplakin; junction plakoglobin) have also been detected. Changes in DNA sequence of the abovementioned genes should be cautiously approached, since different benign variants may present frequently in unaffected control populations[20].

Further genetic subtypes have been described recently; so, under the broad term of arrhythmogenic cardiomyopathies, additional genes should be included in the genetic testing, such as transmembrane protein 43, LMNA, filamin C, desmin, RNA-binding protein 20, phospholamban (PLN) and TTN genes. According to the revised Task Force criteria for the diagnosis of ARVC/ACM, for a definite diagnosis, two major criteria or one major and two minor criteria, or four minor criteria from different categories are needed. The presence of a disease-causing mutation is considered as a major criterion. However, in order to avoid confusing results, if the patient shows only one minor criterion from the revised Task Force Criteria, then genetic testing should not be recommended[3]. It is noteworthy that desmosome gene mutations have also been identified in patients diagnosed with DCM.

RCM

RCM is a rare form of cardiomyopathy, with a heterogeneous phenotype. Multiple causes have been identified, including infiltrative storage, non-infiltrative and endomyocardial diseases, many of which are associated with specific genes[21]. The

most frequent variants that have been found in RCM cases are in genes known to cause HCM. Therefore, genetic testing for RCM should include HCM genes[22].

IMPORTANCE OF FAMILY HISTORY IN THE PROCESS OF GENETIC TESTING

Irrespective of the type of cardiomyopathy, thorough comprehension of the proband's family history with an at least three-generation family pedigree and counselling should precede genetic testing[23]. Therefore, the family history is of paramount importance and should not be overlooked in clinical practice. Specifically, it reveals the phenotype of each member, the pattern of inheritance (AD, autosomal recessive, X-linked and maternal mitochondrial conditions) and enables the clinicians to provide preliminary recommendations for clinical surveillance[6,24]. Importantly, it also helps genetic counsellors to discuss the process of genetic testing with the proband and the family members, including providing realistic expectations of the findings and to develop a relationship of trust. Effective communication and psychological support are key points. Pre-genetic counselling constitutes an important clinical part of the medical management of such cases[4,25].

VARIANT INTERPRETATION AND RECLASSIFICATION

The most challenging aspect of the genetic testing process is the interpretation of results. According to the Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, each variant should be classified according to specific criteria in one of the following categories: Benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic (Table 3)[26]. Causality is based on various criteria, such as population frequency and type of identified variant (*i.e.*, missense, nonsense, *de novo*, truncating splice site); information of segregation in a pedigree and *in silico* tools are also used. It is important to bear in mind that in order to avoid the vast amount of uncertainty, rather than choosing a binary 'yes' or 'no' outcome, it is preferable to gather and weigh-up sufficient lines of evidence. A key step in this direction is the public sharing of important variant information among laboratories, such as through scientific repositories (*e.g.*, ClinVar) and the creation of large reference datasets[27]. Another important issue is the periodic reclassification of variants; although, guidelines on how this can be performed feasibly are lacking[28]. Certainly, the latest technologic advancements of NGS, together with bioinformatics software, allow accurate and rapid high-output sequencing of the human genome[29]. And, in the real world, the ability to efficiently sequence coding and non-coding regions has led to the production of multigene panels used in clinical practice currently.

At this point, we should also note that the complexity of cardiomyopathies and the difficulties in defining a specific phenotype according to genetic causes present new challenges for cardiologists who manage these patients singlehandedly. Therefore, a multidisciplinary team is required for genetic counselling and testing, as well as psychological support. This can be achieved through trained healthcare providers, in order to help individuals deal with the psychological, social, professional, ethical and legal implications of a genetic disease[30].

SPECIFIC BENEFITS OF GENETIC TESTING

Identification of undiagnosed family members

The principal advantage of the process of genetic testing is the detection of family members of the proband who have inherited the causal variant of the gene and are at-risk of developing the clinical phenotype of each cardiomyopathy. The importance of this procedure is huge, considering that life-threatening arrhythmias or SCD can be the first manifestation of a cardiomyopathy. Thereafter, only genotype-positive individuals need periodic monitoring instead of all first-degree relatives[5]. The importance of familial screening is better established in HCM and ARVC, where the yield of genetic testing is higher, and gives the opportunity for better planning to assess and address the need for implantable cardioverter-defibrillator (ICD) devices in genotype-

Table 3 Definitions of the variant classifications

Variant	Definition
Pathogenic	Variant is disease-causing with > 99% confidence; Cascade genetic testing should be offered to family members
Likely pathogenic	Variant is disease-causing with > 90%-95% confidence; Cascade genetic testing should be offered to family members
VUS	Variant is considered uncertain with an unknown effect on clinical phenotype, as there is insufficient or conflicting evidence for pathogenicity; Cascade genetic testing cannot be offered to family members
Likely benign	Variant is probably not disease-causing; Cascade genetic testing should not be offered to family members
Benign	Variant is not disease-causing; Cascade genetic testing should be offered to family members

VUS: Variant of uncertain significance.

positive carriers.

Regarding SCD in young people, almost 30% of cases are caused by a non-diagnosed type of cardiomyopathy[31]. Genetic testing in post-mortem samples could enhance the likelihood of finding a disease-causing variant and performing subsequent genetic screening of family members. Indeed, in a clinical screening in 198 cases of unexplained SCD in people below 35 years of age, five families suffering from inherited cardiomyopathies were detected; whereas, 27% of the cases had a definite or likely disease-causing mutation[32]. Therefore, according to European Society of Cardiology (ESC) guidelines, targeted post-mortem genetic analysis of potentially disease-causing genes should be considered for victims in whom a specific inheritable or cardiomyopathy is suspected[33].

Prognostic role

Several studies have proven that genotype status itself is associated with worse outcomes in HCM[34,35]. Sarcomere protein mutations in HCM have been found to be associated with increased rates of cardiovascular and SCD-related mortality[34]. In 628 HCM patients with a 12-year follow-up, positive genetic test result was identified as an independent prognostic factor for mortality in SCD and heart failure as well as all-cause mortality for the carrier, after adjustment for established risk factors[36]. In DCM, the approximately 5%-10% of probands with mutations in the LMNA gene are the best characterized, as LMNA variants manifest early-onset atrial arrhythmias and early development of conduction disturbances, coupled with a higher risk of SCD, often with only LV systolic impairment[37]. According to ESC guidelines, an ICD implantation should be considered in patients with DCM along with a confirmed disease-causing LMNA mutation and clinical risk factors, such as a non-sustained ventricular tachycardia, LV ejection fraction below 45% at first evaluation, male sex, and non-missense mutations[33].

Regarding ARVC, the prognostic role of genetic testing is not fully realized. Although probands with ARVC and known causal variants have been reported to develop ventricular arrhythmias approximately 4 years earlier than patients without a known mutation, no difference in mortality was detected in that study[38]. In another study of 105 probands with known ARVC-causal variants, the identification of a variant was found to be less important for predicting risk of life-threating arrhythmia or SCD than other factors, like sex and repolarization abnormalities in electrocardiogram or LV dysfunction[39]. Mutations in the PLN gene are also related to a poorer prognosis[40].

NGS analysis has allowed widespread identification of novel disease-causing genetic mutations[41]. Open availability of the ClinVar and ExAC databases in recent years has helped laboratories and clinicians to determine the possible pathogenicity of new detected variants. As a result, previously characterized genetic variants have been reclassified[42]. Genetic testing may identify predisposition for cardiomyopathies with unclear pathophysiological mechanisms; for example, risk of peripartum cardiomyopathy or anthracycline-induced cardiomyopathy may be identifiable by genetic testing. In patients with peripartum cardiomyopathy, in particular, and carrying mutations in the TTN gene, LV ejection fraction remains significantly lower compared to patients without this mutation[43]. Similarly, there is emerging evidence that a genetic predisposition may also be involved in anthracycline-induced cardiomyopathy [44,45]. Unfortunately, the current evidence is not sufficient to alter management decisions about the use of anthracycline but could lead to a personalized medicine

approach in patients carrying specific mutations[46].

Prenatal genetic counselling

Prenatal genetic counselling is helpful in couples at risk of transmitting a genetic condition to their offspring. Through this process, a certified genetic counsellor explains the risk of transmission of disease, the impact of the disease on an affected child, as well as the benefits and limitations of all the available reproductive options. These options include *in vitro* fertilization with preimplantation genetic diagnosis, prenatal genetic screening, and postnatal genetic testing. The benefits and potential harms can be discussed for each of these options, such that the individual or couple can make a fully informed decision[12].

BARRIERS IN GENETIC TESTING

Despite the novelties in genetic techniques, there are still limitations in performing genetic testing for every diagnosed cardiomyopathy. Genetic testing seems to be of little to no value in low-yield cases with unclear inheritance pattern[36-38,47]; for this reason, the guidelines discourage genetic testing in isolated cases of idiopathic DCM where no evidence of inheritance exists[4,5]. In a study of 102 patients with idiopathic DCM, a disease-causing mutation was identified in only 10, whereas the clinical management was changed for only 1 patient, who received an ICD[47]. Unfortunately, even in disease where the yield of genetic testing is high, such as in HCM, when more possible genes were added, few additional causal variants were identified[48]. Another limitation in performing genetic testing when there is no clear clinical indication is the finding of a VUS. VUS may mislead clinicians, as it can neither confirm a genetic diagnosis nor exclude the need for familial surveillance[12]. The best practice in order to avoid an uncertain result is the performance of genetic testing after a thorough evaluation of the clinical case and a multidisciplinary management in pre-genetic counselling. Hence, any result from a genetic test can be further investigated at the research level[6,12].

CONCLUSION

At present, the mainstay of genetic testing in inherited cardiomyopathies is the identification of family members who have inherited the same causal mutation with the proband, which is important in terms of clinical decision-making. On the other hand, when the mutation is not detected in family members, anxiety and unnecessary clinical screening are avoided. This procedure is more helpful in cardiomyopathies where the yield of a positive genetic result is higher, such as HCM and ARVC. However, recent studies have provided more evidence on the genetic predisposition in specific cardiomyopathies and suggested a prognostic component when pathogenic variants are found.

Despite the progress in genetic techniques, there are currently well-documented limitations of cardiac genetic testing. Therefore, the role of family history should not be downgraded when the utility of genetic testing is questioned. A specialized multidisciplinary clinic incorporating cardiologists and genetic counsellors along with a move to a more precision-based approach seems to be the ideal model of management. Last but not least, focus should be given to teamwork of worldwide research groups in order to develop large databases that may elucidate the complexity of underlying genetics in inherited cardiomyopathies.

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MINIREVIEWS

Fondaparinux: A cornerstone drug in acute coronary syndromes

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Abstract

In acute coronary syndrome (ACS), the use of anticoagulants in conjunction with antiplatelet agents in the acute phase has resulted in reduced ischemic events and is more effective than either class of drug used alone. Though parenteral anticoagulation is essential at the time of diagnosis, a balance must be made between ischemic benefit and the increased risk of bleeding when prescribing anticoagulants. Adverse events associated with anticoagulants, such as heparin-induced thrombocytopenia, bleeding problems, and the need for close monitoring of anticoagulant activity, have contributed to finding agents that reduce these limitations. Studies like the Organization to Assess Strategies in Ischemic Syndromes 5 and 6 and their meta-analysis have proven the efficacy of Fondaparinux over the entire ACS spectrum. The convenience of administration (once daily), lack of monitoring, reduction in mortality, and better safety profile make Fondaparinux a simple and effective anti-coagulant for the management of ACS.

Key Words: Acute coronary syndrome; Anti-coagulant therapy; Antiplatelet therapy; Fondaparinux; Unfractionated heparin; Enoxaparin

Core Tip: The simultaneous use of antithrombotic therapy and anti-platelet therapy in the acute coronary syndrome acute phase is associated with reduced ischemic events and is more effective than either class of drug used alone. The physicians must maintain a balance while prescribing these drugs to maintain an overall benefit-risk ratio. Fondaparinux is one of the simple and effective anti-coagulant for the management of acute coronary syndrome.

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INTRODUCTION

Acute coronary syndrome

Acute coronary syndrome (ACS) is one of the main causes of fatality worldwide. When compared to other countries, South Asians have a higher rate of myocardial infarction (MI) at a younger age (average age 53 years *vs* average age 58.8 years)[1-4]. In the Indian population as well, ACS presents a decade earlier in comparison to the West. Furthermore, India has the greatest ACS load in the world, with a burden 3 to 4 times that of White Americans, 6 times that of Chinese, and 20 times that of Japanese people. ACS is responsible for 3 million fatalities each year in India, accounting for 25% of all deaths[5]. Anti-coagulant therapies form the cornerstone in the management of ACS.

Anti-coagulant therapy in ACS

The mechanism of action of various anti-coagulant therapies is described in Figure 1. Anticoagulant medication is an important part of the treatment of ACS[6], while being only one step of the treatment pathway. In the past, unfractionated heparin was the most commonly used parenteral anticoagulant. However, as compared to other treatments, unfractionated heparin (UFH) has a variable dose-response and a small therapeutic window that necessitates frequent monitoring and is linked with a higher risk of side effects [*e.g.*, heparin-induced thrombocytopenia (HIT), hemorrhage, and osteoporosis]. Other systemic anticoagulants that do not require frequent monitoring or dose adjustment are more commonly used these days than UFH[7]. Maintaining a fine balance between reducing cardiovascular mortality and increased risk of bleeding is the main concern for the available treatments for ACS. The main objective of this review is to identify the current gaps of using anti-coagulant therapies in ACS and thus to bring in the evaluated clinical benefits of Fondaparinux in ACS patients.

CLINICAL PHARMACOLOGY OF FONDAPARINUX

Pharmacology

Fondaparinux, a synthetic anticoagulant, consists of a highly sulfated penta saccharide derived from the minimal antithrombin (AT)-binding region of heparin. It works as an indirect factor Xa inhibitor by binding to AT and producing a conformational change in AT that improves AT's ability to inactivate factor Xa (Figure 1)[8].

Anticoagulant effects

Unfractionated heparin and low molecular weight heparins (LMWHs) such as Enoxaparin act by inhibiting both factor Xa and thrombin. LMWHs have a lower effect on thrombin than the effect of unfractionated heparin. Fondaparinux specifically inhibits factor Xa coagulation factors[8].

Fondaparinux can be administered through subcutaneous (s.c.) or intravenous (i.v.) routes. The bioavailability is 100% after s.c. administration of fondaparinux in healthy volunteers and mean maximum plasma concentration is achieved at 1.7 h. The mean maximum plasma concentration with i.v. dose is achieved at an even faster rate without affecting half-life[9].

When compared to LMWHs like Enoxaparin and UFHs, fondaparinux sodium had no effect on fibrinolytic activity or bleeding time at the prescribed dose, promoting hemostasis and a favorable bleeding risk profile. Fondaparinux does not bind to or interact with other plasma proteins or cellular elements such as platelets or platelet factor 4, and thus, unlike Enoxaparin and UFH, it does not cause heparin-induced thrombocytopenia-like syndrome[10].

Metabolism

Fondaparinux is 100% bioavailable after s.c. injection. The half-life of fondaparinux is

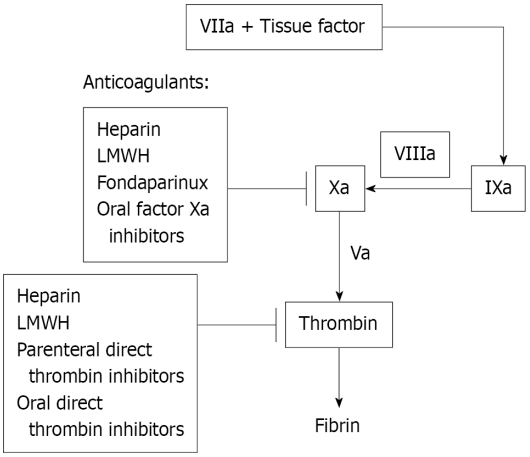

Figure 1 Mechanism of action of various anticoagulants. LMWH: Low molecular weight heparin.

17.2 h, which is quite long and allows once-daily dosing[11].

Monitoring

Fondaparinux does not require monitoring in routine clinical use. The anticoagulant effect of fondaparinux can be assessed with dedicated anti-Xa assays in high-risk patient populations (renal insufficiency, bodyweight less than 50 kg)[6].

Fondaparinux is mainly cleared through the kidney and is excreted unchanged in the urine. Clearance of this drug is reduced in individuals with reduced creatinine clearance and is therefore not recommended for use in individuals with creatinine clearance < 30 mL/min[10]. Table 1 compares pharmacokinetics, dosage frequency, and indications between UFH, LMWHs (Enoxaparin), and Fondaparinux.

FONDAPARINUX IN ACS

The effectiveness and safety profile of fondaparinux has been studied in ACS. An enormous reduction in bleeding complications in ACS has been seen in various studies where fondaparinux is utilized as an anticoagulant in ACS. Here, we present evidence on the clinical efficacy and safety of fondaparinux in patients with ACS.

OASIS 5

Organization to Assess Strategies in Ischemic Syndromes (OASIS) 5 was a randomized, double-dummy, randomized, parallel-group, controlled trial to see if Fondaparinux, when used as an anticoagulant in unstable angina and non-ST elevation ACS (NSTE-ACS), would preserve the anti-ischemic benefits of Enoxaparin while reducing bleeding. Following randomization, the study medication was administered subcutaneously. Enoxaparin 1 mg/kg twice daily s.c. for 2 to 8 d or until clinically stable, or fondaparinux 2.5 mg once daily s.c. for 8 d or until discharge, whichever came first. In patients with a creatinine clearance of 20 mL/min to 30 mL/min, Enoxaparin was given once daily at a dose of 1 mg/kg. Subjects received regular medical care, including interventions, in addition to the study medicine [percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery] [12].

Summary

Primary efficacy outcome: In terms of the primary efficacy outcome, Fondaparinux was shown to be non-inferior to Enoxaparin [Fondaparinux 5.8% *vs* Enoxaparin EX 5.7%, hazard ratio (HR), 1.01; 95% confidence interval (CI), 0.90 to 1.13] (Table 2)[12].

Primary safety outcome: When compared to Enoxaparin, Fondaparinux reduced serious bleeding rates by nearly half (2.2% *vs* 4.1%; HR, 0.52; 95%CI, 0.44 to 0.61; P = 0.001) (Table 2)[12].

Secondary outcomes: At the end of 30 d, the Fondaparinux group showed 17% lower mortality (P < 0.02) and 23% lower stroke rate *vs* the Enoxaparin group. Bleeding rates were significantly reduced too. The effect on death, stroke, and major bleeding was

Table 1 Comparison of unfractionated heparin, low molecular weight heparins (Enoxaparin), and Fondaparinux

	UFH	Enoxaparin	Fondaparinux
Source	**Biological**	**Biological**	**Synthetic**
Bioavailability	30%	90%	100%
Mechanism	Augments AT effects on Factor Xa and thrombin. Binds to plasma proteins not specifically → unpredictable dose-response	Augments AT effects more on Factor Xa than on thrombin. Low binding to plasma proteins → more predictable dose-response, low inter-patient variability	Augments anti-Xa activity of AT, no direct effect on thrombin. Specific for AT → no binding to other plasma proteins, predictable dose-response
Plasma half-life	1-2 h	4.5-7 h	17-21 h
Reversal agents	Protamine sulfate	Protamine sulfate	Irreversible by protamine factor VII- limited data
Routine monitoring	Yes	No	No
Dosing frequency in ACS	Treatment - Continuous i.v. infusion	BID	Once daily
Clearance	Hepatic & Reticuloendothelial clearance. No renal adjustments	Renal	Renal
		Adjustment needed for CrCl < 30 mL/min	Contraindication: CrCl < 30 mL/min
Ability to cause HIT	Yes	Yes	No cases in major trials
Bleeding risk	Increased	Increased	Lesser

UFH: Unfractionated heparin; HIT: Heparin-induced thrombocytopenia; AT: Antithrombin; ACS: Acute coronary syndrome; LMWH: Low molecular weight heparin.

Table 2 Organization to Assess Strategies in Ischemic Syndromes 5: Primary efficacy and safety outcomes at 9 d

Outcomes	Fondaparinux	Enoxaparin	HR (95%CI)	*P* value
Primary efficacy outcome: Cumulative event rate-Death, MI, refractory ischemia at 9 d				
Cumulative event rate	5.80%	5.70%	1.01 (0.90-1.13)	0.007
Primary safety outcome: Major bleeding at 9 d				
Major bleeding	2.20%	4.10%	0.52 (0.44-0.61)	$P < 0.001$

CI: Confidence interval; HR: Hazard ratio.

maintained till the end of the study (Figure 2). Fondaparinux also resulted in significant reductions in the combined endpoints of death/MI/stroke at 30 d (-11%) and 180 d (-11%). There was also a significant reduction in fatal and severe bleeding rates for Fondaparinux as compared to Enoxaparin both at 30 d and 180 d. The difference in mortality favoring Fondaparinux in this study was almost completely attributed to the reduced bleeding rates[12].

Subgroup analysis

Balance of benefit and risk: The major effectiveness and safety outcomes were combined to determine the balance of benefit and risk. At 9 d, patients in the Fondaparinux group had a considerably reduced rate of death, MI, refractory ischemia, and severe bleeding than those in the Enoxaparin group. This disparity continued until the study's conclusion. The benefits and risk were consistent across subgroups, including age and gender, renal function spectrum, whether unfractionated heparin was provided before randomization, and whether revascularization was conducted within 9 d[12].

The safety of Fondaparinux over Enoxaparin was also validated in three key subgroups: Those with a wide range of renal impairment in the OASIS 5 trial, those who underwent PCI within 24 h, and those who took glycoprotein (GP) IIb/IIIa inhibitors.

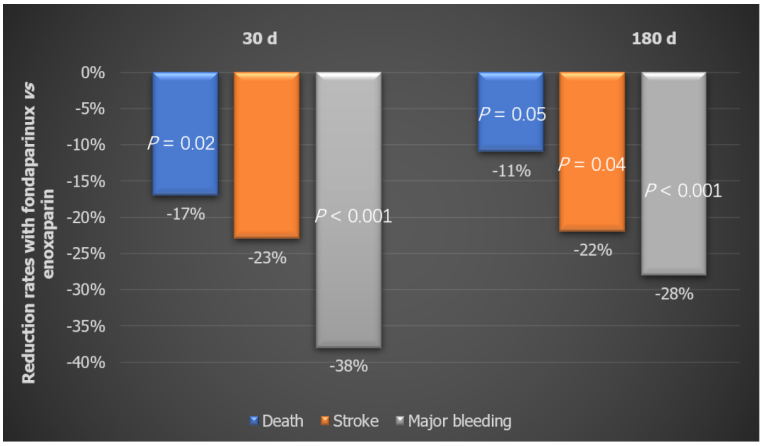

Figure 2 Secondary efficacy and safety outcomes. Outcomes-based at 30 d and 180 d.

Renal function and efficacy and safety of Fondaparinux vs Enoxaparin in NSTE-ACS

This subgroup analysis assessed if the enhanced bleeding risk with Enoxaparin was related to the level of kidney function in study participants. Efficacy and safety data have been grouped into quartiles according to estimated glomerular filtration rate [(eGFR): < 58 (n = 5141); 58 to 71 (n = 4845); 71 to 86 (n = 5012); and ≥ 86 mL/min/1.73 m^2 (n = 4996), respectively][13].

When compared to Enoxaparin, Fondaparinux was associated with significantly fewer bleeding episodes. Across all eGFR quartiles, Fondaparinux treatment was linked with decreased severe bleeding on day 9 (Figure 3). This pattern maintained for the next 30 d and 180 d. Those with an eGFR of less than 58 mL/min/1.73 m^2 had the most noticeable bleeding disparities[13].

Only individuals with an eGFR of less than 58 mL/min/1.73 m^2 saw a substantial reduction in the composite outcome of mortality, MI, and refractory ischemia at day 30. In comparison to Enoxaparin, the other eGFR groups had similar endpoint rates [13]. Therefore, the benefits of Fondaparinux over Enoxaparin in NSTE- ACS are most marked among patients with renal dysfunction and are largely due to a better safety profile of Fondaparinux due to lower rates of major bleeding with Fondaparinux.

Comparative efficacy and safety of Fondaparinux and Enoxaparin in ACS patients who went through PCI in the OASIS 5 trial

More than 60% of patients had catheterization and more than 30% had PCI In OASIS 5. When the last dose of Enoxaparin was more than 6 h before the procedure, patients were given weight adjusted UFH during PCI. An additional dosage of i.v. Fondaparinux was given to individuals who had received a s.c. dose of Fondaparinux before undergoing PCI. Following sporadic reports of catheter thrombosis, an adjustment to the protocol was made to allow investigators to use open-label UFH in patients receiving Fondaparinux[14].

When Fondaparinux was used instead of Enoxaparin on day 9, serious bleeding was considerably reduced (2.4% *vs* 5.1%, HR 0.46; P < 0.00001). When compared to Enoxaparin, Fondaparinux was associated with a slight increase in the rate of catheter-related thrombi (in patients having PCI) (0.9% *vs* 0.4%) (Table 3). The findings show that upstream Fondaparinux therapy in NSTE-ACS patients undergoing early PCI was superior to Enoxaparin in lowering severe bleeding by 50% while maintaining the same effectiveness, resulting in a superior net therapeutic benefit[14]. Patients who received open-label UFH before the treatment had a considerably lower rate of catheter-related thrombi in both groups. The Fondaparinux with Unfractionated Heparin (FUTURA) trial, which is addressed later in this article, looked at this evidence further.

In patients with ACS treated with GP IIb/IIIa inhibitors or thienopyridines, the efficacy and safety of Fondaparinux were compared to Enoxaparin. Patients with ACS (n = 20078) were randomized to either Fondaparinux or Enoxaparin as part of the OASIS 5 study. The treating physician selected whether or not to utilize GP IIb/IIIa inhibitors or thienopyridines. Fondaparinux reduced significant bleeding and improved net clinical outcome in individuals using GP IIb/IIIa inhibitors or thienopyridines when compared to Enoxaparin.

Table 3 Organization to Assess Strategies in Ischemic Syndromes 5: Fondaparinux *vs* Enoxaparin in non-ST elevation acute coronary syndrome patients undergoing percutaneous coronary intervention

Outcome day 9	Enoxaparin (*n* = 3072)	Fondaparinux (*n* = 3106)	Hazard ratio	*P* value
Death, MI, or stroke	6.2	6.3	1.03	0.79
Major bleeding	5.1	2.4	0.46	< 0.00001
Catheter thrombosis	0.4	0.9	3.59	0.001

MI: Myocardial infarction.

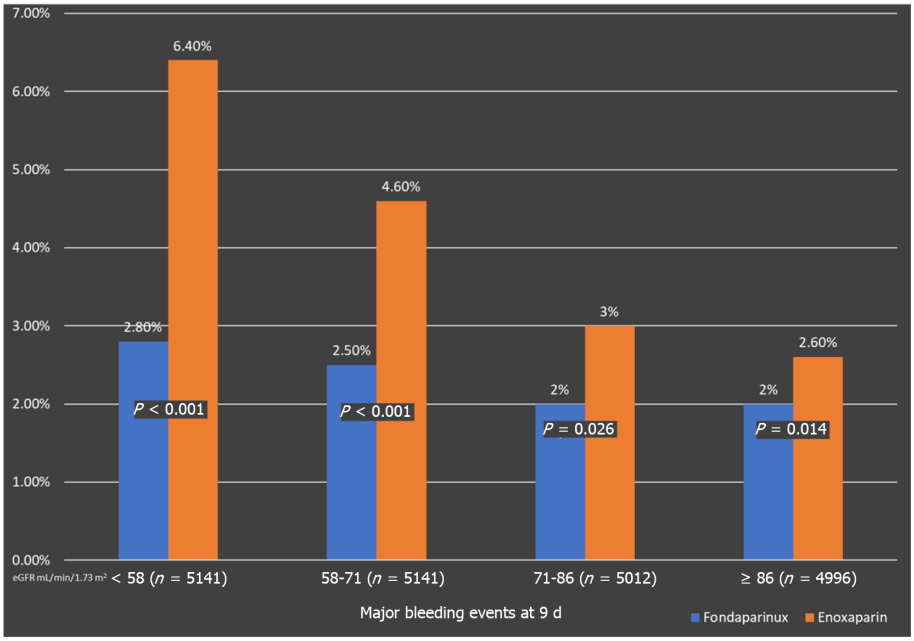

Figure 3 The figure shows comparative major bleeding events with Fondaparinux and Enoxaparin. The major bleeding events were noticed significantly lower as compared to Enoxaparin and thus its use was kindred with less major bleeding across all estimated glomerular filtration rate quartiles. eGFR: Estimated glomerular filtration rate.

Overall results from the OASIS 5 trial and subgroup analyses

While Fondaparinux and Enoxaparin both reduce the risk of ischemic events, the rate of serious bleeding with Fondaparinux was much lower than with Enoxaparin. In addition, Fondaparinux has a lower rate of combined mortality, MI, refractory ischemia, and severe bleeding than Enoxaparin. As a result, Fondaparinux at a daily dose of 2.5 mg is an appealing option for preventing ischemic events in patients with acute coronary syndromes without ST-segment elevation in the short term, and because it is associated with significantly less bleeding–this effect translates to lower long-term mortality and morbidity compared to Enoxaparin[12-14].

FUTURA/OASIS 8

FUTURA during revascularization in ACS (FUTURA/OASIS 8): The trial compared the safety of two UFH treatment regimens during PCI in high-risk patients with NSTE initially treated with Fondaparinux in a double-blind, randomized, parallel-group, multicenter trial with 2026 NSTE-ACS patients undergoing PCI within 72 h treated with Fondaparinux[15].

UFH regimens: The regimens were divided into low dose group and standard-dose group. All patients received 50 IU/kg UFH irrespective of the use of GP IIb IIIa in the low dose group. In the standard UFH group, the mean dose was 85 IU/kg to maintain activated clotting time (ACT) between 300-350 s and was reduced to 60 IU/g in those receiving GP IIb IIIa. The primary goal of the FUTURA trial was to see if low fixed-

dose unfractionated heparin *vs* standard ACT guided unfractionated heparin during PCI reduces the composite of peri-PCI major, minor bleeding, and vascular access site complications in ACS patients treated with Fondaparinux. The secondary goal was to see if major bleeding rates in FUTURA were higher than in OASIS 5 PCI (with Fondaparinux used alone)[15].

Summary

Primary outcome: There were no significant differences between low fixed-dose and standard-dose unfractionated heparin in the primary outcomes of peri-PCI major bleeding or major vascular access site problems (P = 0.27) (See Table 4).

Key secondary outcome: The primary secondary outcomes of Peri-PCI major bleeding, mortality, MI, and target vessel revascularization had a nominally significant difference. The low-dose UFH group had a rate of 5.8% at 30 d compared to 3.9% in the standard-dose UFH group (odds ratio, 1.51; 95%CI, 1.00-2.28; P = 0.05). There were very little catheter thrombus rates (0.5% in the low-dose UFH group and 0.1% in the standard-dose UFH group, P = 0.15). The low-dose regimen was linked to a numerically higher rate of definite stent thrombosis (n = 12 *vs* 5) but no reduction in severe bleeding (Table 5)[15].

Comparison with OASIS 5 PCI

The risk of major bleeding within 48 h was 1.1% in the standard-dose unfractionated heparin arm and 1.2% with low-dose heparin in FUTURA/OASIS 8, compared with 3.6% with Enoxaparin in OASIS 5. As a result, UFH + Fondaparinux has no effect on peri-PCI severe bleeding, and rates appear to be lower than when Enoxaparin is administered (Table 6)[15].

Overall Summary of FUTURA trial

When UFH was used for PCI on a Fondaparinux background, severe bleeding was not increased when compared to Fondaparinux alone, and it was lower than when Enoxaparin was used for PCI prior. Adding UFH to Fondaparinux during PCI preserves Fondaparinux's advantages and safety (*e.g.*, reduced bleeding) while reducing catheter thrombus. The finding that augmenting ACT-guided conventional UFH to Fondaparinux during PCI does not increase severe bleeding in patients with non-ST segment elevation MI (NSTEMI) is significant for interventional cardiologists. As a result, NSTE-ACS patients who have been treated with Fondaparinux can safely undergo PCI with UFH. There is no need to deviate from the UFH regular dose regimen advised by the guidelines[15].

OASIS 6

Overall Summary of FUTURA trial

Fondaparinux *vs* control in patients with ST-elevated MI (STEMI) was randomized within 24 h after the start of symptoms in a randomized, double-blind, controlled, parallel-group, multi-center, global trial. For the use of UFH, patients with confirmed STEMI were randomized to one of two strata based on the indication[16].

Summary

Primary efficacy outcomes: At 30 d, the Fondaparinux group had a significantly reduced risk of death or reinfarction than the control group (9.7% *vs* 11.2%, HR, 0.86; P = 0.008), and the results were similar at 9 d (HR, 0.83, P = 0.003) and at the end of the study (HR, 0.88; P = 0.008) (Figure 4). At 9 d, the relative risk reduction was 17%, 14% at 30 d, and 12% at the end of the study. This difference remained throughout the study, showing that treatment benefits accrue quickly and are sustained over time (Table 7).

Primary safety outcomes: At 9 d, the risk of significant bleeding in patients receiving Fondaparinux was 1.8% (107/6036), compared to 2.1% (130/6056) in patients given placebo or UFH. At 9 d, Fondaparinux was associated with significantly fewer serious bleeds (79 for placebo/UFH *vs* 61 for Fondaparinux) as well as significantly fewer cardiac tamponade episodes (48 *vs* 28; P = 0.02)[16].

Table 4 Fondaparinux with unfractionated heparin during revascularization in acute coronary syndromes 8: Primary outcomes at 48 h

Primary outcomes at 48 h	Standard dose UFH (*n* = 1002)	Low dose UFH (*n* = 1024)	Odds ratio	95%CI	*P* value
Peri-PCI major, minor, bleeds and vascular access complications	5.80%	4.70%	0.80	0.54-1.19	0.27
Components					
Major bleeds	1.20%	1.40%	1.14	0.53-2.49	0.73
Minor bleeds	1.70%	0.70%	0.40	0.16-0.97	0.04
Major vascular access site complications	4.30%	3.20%	0.74	0.47-1.18	0.21

UFH: Unfractionated heparin; CI: Confidence interval; PCI: Percutaneous coronary intervention.

Table 5 Fondaparinux with unfractionated heparin during revascularization in acute coronary syndromes 8: Secondary outcomes at 30 d

Secondary outcomes at 30 d	Standard dose UFH (*n* = 1002)	Low dose UFH (*n* = 1024)	Odds ratio	95%CI	*P* value
Peri-PCI major bleeding, Death, MI, TVR	3.90%	5.80%	1.51	1.00-2.28	0.05
Death, MI, TVR	2.90%	4.50%	1.58	0.98-2.53	0.06
Death	0.60%	0.80%	1.31	0.45-3.78	
MI	2.50%	3.00%	1.22	0.72-2.08	
TVR	0.30%	0.90%	2.95	0.80-10.9	
Stent thrombosis	0.50%	1.20%	2.36	0.83-6.73	0.11
Catheter thrombosis	0.10%	0.5%	4.91	0.57-42.1	0.15

UFH: Unfractionated heparin; CI: Confidence interval; PCI: Percutaneous coronary intervention; TVR: Target vessel revascularization.

Table 6 Fondaparinux with unfractionated heparin during revascularization in acute coronary syndromes 8: Comparison to Organization to Assess Strategies in Ischemic Syndromes 5 major bleeding (< 48 h of percutaneous coronary intervention)

Adjusted major bleeding rate	OASIS 5 PCI	OASIS 5 PCI
	Fondaparinux	Enoxaparin
	Major bleeding	Major bleeding
FUTURA	1.5%	3.6%
Standard dose UFH 1.1% (0.6-2.1)		
FUTURA		
Low dose UFH 1.2% (0.6-2.2)		

PCI: Percutaneous coronary intervention; FUTURA: Fondaparinux with unfractionated heparin; OASIS: Organization to Assess Strategies in Ischemic Syndromes; UFH: Unfractionated heparin.

SUBGROUP ANALYSIS

In subgroups defined by the time from symptom onset to randomization in men and women, in those older or younger than the median age (61 years), with the use of various concurrent therapies or various types of thrombolytic medicines, the outcomes on death or MI were not statistically diverse.

A subgroup analysis of the OASIS 6 trial looked at the role of Fondaparinux as an addition to thrombolytic treatment in acute MI. The major goal of this subgroup

Table 7 Primary efficacy outcome of Fondaparinux *vs* unfractionated heparin (control) in preventing death or reinfarction at 30 d and 3 or 6 mo and relative risk reduction of fondaparinux *vs* control through study end

Measures	Fondaparinux	Control (UFH)
Primary composite outcome: Death or reinfarction		
Frequency at 30 d	9.70%	11.20%
P value	*P* = 0.008	
Relative risk reduction	14%	
Frequency at 9 d	7.40%	8.90%
P value	*P* = 0.003	
Relative risk reduction	17%	
Frequency at 3-6 mo	13.40%	14.80%
P value	*P* = 0.008	
Relative risk reduction	12%	

UFH: Unfractionated heparin.

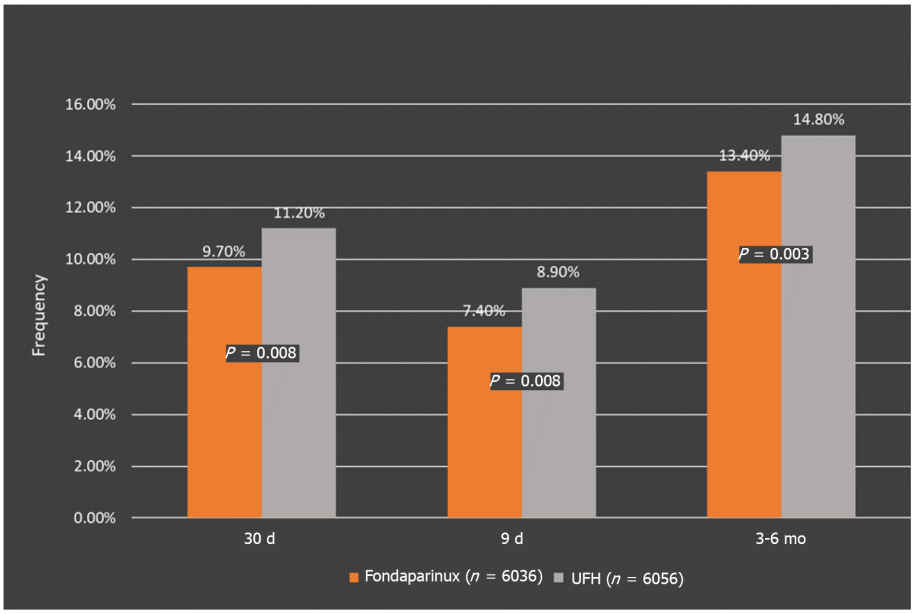

Figure 4 Primary composite outcome. Death or reinfarction was significantly lower in the Fondaparinux group compared with the control group at 30 d and at 3 or 6 mo.

analysis was to compare the efficacy and safety of Fondaparinux to a control (placebo or UFH) in thrombolytic treatment patients. Streptokinase was the most used thrombolytic agent (73%). Streptokinase and urokinase were non-fibrin specific thrombolytic medicines. Tissue plasminogen activator, reteplase, and tenecteplase were fibrin-specific thrombolytic drugs (See Table 8). In this study, stratum 1 included 4415 patients who did not have an indication for unfractionated heparin, and stratum 2 included 1021 patients who did have such an indication.

The main trial's major outcomes were employed, namely the 30-d rates of mortality, MI, and serious bleeding. Fondaparinux dramatically reduced the risk of death, re-MI, and serious bleeding in STEMI patients treated with thrombolytic drugs (mostly streptokinase). The results were consistent in both strata, over varied time periods from symptom start to treatment, and across different types of thrombolytics[16].

Table 8 Subgroup analysis Organization to Assess Strategies in Ischemic Syndromes 6, *n*

OASIS 6	Stratum I		Stratum II		Total
	Placebo	Fondaparinux	UFH	Fondaparinux	
	2835	2823	3221	3213	12092
Non-fibrin specific thrombolytic	2216	2179	83	83	4561
Fibrin specific thrombolytic	9	11	436	419	875
Any thrombolytic	2225	2190	519	502	5436

The number of patients who received thrombolytic therapy. OASIS: Organization to Assess Strategies for Ischemic Syndromes; UFH: Unfractionated heparin.

Fondaparinux's effects in individuals with ST-segment elevation acute myocardial infarction who aren't getting reperfusion therapy.

In the OASIS 6 trial, this sub-study assessed the efficacy and safety of Fondaparinux to placebo or UF heparin in a pre-specified subset of 2867 patients who were not undergoing any sort of reperfusion therapy. When compared to conventional care (UF heparin infusion or placebo), a treatment plan with Fondaparinux 2.5 mg s.c. once daily reduced the composite of mortality or cardiac re-infarction without increasing severe bleeding or strokes in STEMI patients who were not getting reperfusion therapy[16].

Overall results from the OASIS 6 trial and subgroup analyses.

In patients with STEMI, Fondaparinux significantly reduced death and reinfarction *vs* UFH/placebo at 30 d. There is a trend to a lower rate of severe bleeding with Fondaparinux use in STEMI. Fondaparinux *vs* UFH/placebo resulted in a significant reduction in death and MI, with benefits appearing early (9 d) and being constant throughout the study. Fondaparinux had a considerably reduced rate of mortality, MI, and serious hemorrhage compared to UFH/placebo.

Fondaparinux lowers mortality and reinfarction in STEMI patients, particularly those who are not undergoing primary percutaneous coronary intervention, without increasing bleeding or strokes. Fondaparinux, on the other hand, showed no benefit in patients receiving PCI[16].

SWEDEHEART registry

The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) was a prospective, multicenter cohort study of NSTEMI patients treated with Fondaparinux or LMWH (n = 40616). The outcome measures were severe bleeding events and mortality (in-hospital), 30- and 180-d major bleeding, stroke, death, and recurrent MI. In-hospital bleeding rates and death were lowered by 46% and 25% with Fondaparinux as compared to LMWH. The positive impact on bleeding was maintained over the 30-d and 180-d periods. Similarly, the composite outcome of MI, death and bleeding, also showed a reduction over the longer time intervals (Figure 5). The decrease in mortality was significant for both the 30-d and 180-d periods.

However, treatment with Fondaparinux was associated with lower severe in-hospital bleeding rates within each renal function strata, an effect that was maintained over the long term (30 and 180 d). Similarly, in-hospital mortality rates were also reduced with Fondaparinux *vs* LMWH in almost all categories of renal function. Since the SWEDEHEART analysis was conducted in a routine clinical care setting across patient subgroups, the short and long-term benefits of Fondaparinux in NSTEMI were reinforced by this analysis[17].

BRAZILIAN REGISTRY

A retrospective analysis of Brazilian NSTE-ACS patients (n = 2282) treated with Fondaparinux or Enoxaparin with in-hospital all-cause mortality as the primary outcome and secondary outcome being combined events (cardiogenic shock, reinfarction, death, stroke, and bleeding) showed a significant impact of Fondaprinux

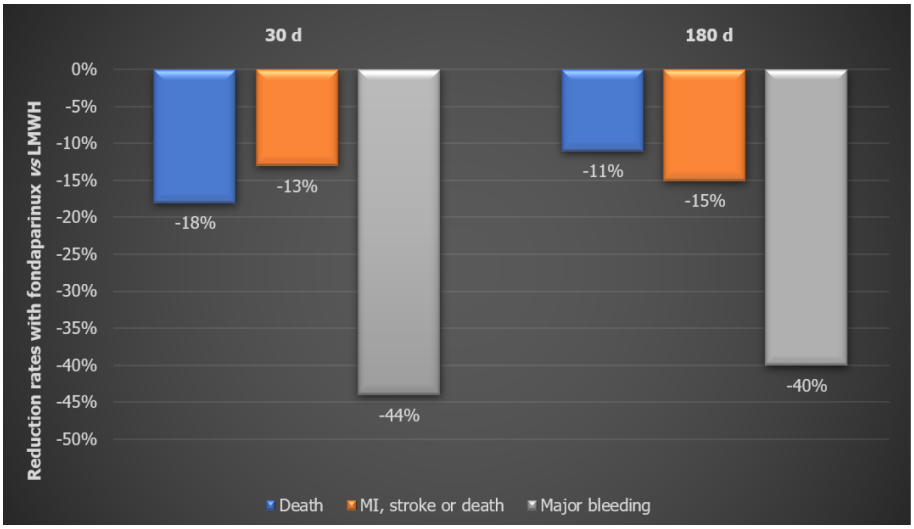

Figure 5 The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Analysis. Outcomes at 30 d and 180 d. LMWH: Low molecular weight heparin.

therapy on bleeding as well as combined events (Figure 6). This study further established the superiority of Fondaparinux over Enoxaparin in NSTE-ACS patients. Several additional studies provide clinical evidence favoring the use of Fondaparinux in ACS patients (Table 9)[17].

Position of Fondaparinux in recent guidelines and some studies

Fondaparinux is recommended by several guidelines for use in ACS. Its use is recommended in case of both invasive and conservative management strategies. The latest ESC guidelines[18] recommend Fondaparinux in NSTE-ACS as having the most favorable efficacy–safety profile with respect to anticoagulation. ACC/AHA 2014[19] and National Institute for Health and Care Excellence 2010 guidelines also recommend its use in NSTE-ACS management (Table 10). Various Studies like the OASIS 5 and 6 also showed the efficacy of Fondaparinux in ACS. The convenience of once-daily administration, lack of monitoring, reduction in mortality, and better safety profile make Fondaparinux a simple and effective anti-coagulant agent. Fondaparinux is a reasonable choice in NSTE-ACS where patients are managed with invasive approaches like angiography and possible revascularization and thus are at increased risk of the bleeding[6].

Cost-effectiveness of Fondaparinux

Compared to Fondaparinux, Enoxaparin is a twice-daily formulation with the dose tailored to the bodyweight of the patient. This increases the cost of the medication and the time invested by the clinician in calculating and administering the appropriate dose. The cost-effectiveness of Fondaparinux has been proven in economic analyses carried out in several countries such as Brazil, Thailand, United States of America (US), and Canada.

In Thailand, when compared to Enoxaparin, Fondaparinux was 99% more cost-effective [threshold of 160000 Thai Baht (THB), *i.e.* 4857.3 USD/ quality-adjusted life-year (QALY)], especially in NSTEMI patients. The benefit was 2-fold, from both the provider and societal perspectives. In another analysis, the economic benefit of Fondaparinux was observed across all the subgroups studied, with maximum impact seen in younger patients, in those at high cardiac risk, and those with the greatest risk of bleeding. Avoidance of the costs associated with managing major bleeding also makes Fondaparinux an attractive option.

Fondaparinux was also more cost-effective than Enoxaparin in the Brazilian registry for NSTE-ACS patients. In a Canadian study, data from the OASIS 5 trial were used to evaluate short-term (180 d) and life-term costs with Fondaparinux *vs* Enoxaparin. Fondaparinux was found to be more cost-effective with a saving of $439 for 180 d and a lifetime incremental cost-effectiveness ratio of $4293/QALY. This was determined by not only its lower acquisition cost but also due to the decrease in clinical event rates over 6 mo post-treatment. In a US study evaluating the OASIS 5 data, the 180-d cost saving with Fondaparinux was found to be $547 per patient. This resulted in long-term

Table 9 Comparative studies between low molecular weight heparin/enoxaparin and fondaparinux

Name of study	Type of study	No of patients	Endpoints	Results	Conclusions
Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes	Network metanalysis of 42 randomized controlled trials	117353	Death, MI, revascularization, bleeding	Death and MI rates with Fondaparinux were lower than that with 5 other anticoagulant regimens. [UFH + glycoprotein IIb/IIIa inhibitor (GPI), UFH ± GPI, Bivalirudin, LMWH, and Otamixaban (a direct Factor Xa inhibitor)].	Fondaparinux had the most balanced profile compared to other evaluated strategies, ranking high for both efficacy and safety.
Comparison between Fondaparinux and low molecular-weight heparin in patients with acute coronary syndrome	Meta-analysis	62900	MACE, mortality, major bleeding events	Fondaparinux had significantly lower rates of MACE and major bleeding events. Lower all-cause mortality (-16%) *vs* LMWH.	In this meta-analysis of head-to-head comparisons, fondaparinux-based regimens presented advantages in MACE and major bleeding, as well as a net clinical benefit, compared with LMWH.
Choosing between Enoxaparin and Fondaparinux for the management of patients with acute coronary syndrome: A systematic review and meta-analysis	Meta-analysis	9618	Mortality, MI, Stroke, Minor/Major and all bleeding	Fondaparinux resulted in significantly lower bleeding rates during short-term (10 d) and long-term (30 d or 6 mo to 1 yr) intervals.	Fondaparinux could be a better option *vs* Enoxaparin, especially in NSTEMI patients, in terms of short to mid-term bleeding risk.
Comparison of Efficacy, Safety and Hemostatic Parameters of Enoxaparin and Fondaparinux in unstable coronary artery disease	Prospective, comparative study	180	Recovery, recurrence, major and minor bleeding	Recurrent MI or angina numerically more in the Enoxaparin group. At 30 d, enoxaparin showed a higher incidence of hemorrhage than fondaparinux ($P < 0.05$).	Fondaparinux appears to be better than enoxaparin in efficacy. Fondaparinux also has a better safety profile. Therefore, Fondaparinux is an attractive option compared to Enoxaparin in NSTE-ACS patients.

MACE: Major adverse cardiac–events; NSTE-ACS: Non-ST elevation acute coronary syndrome; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; GP: Glycoprotein; GPI: GP inhibitor; NSTEMI: Non-ST segment elevation myocardial infarction.

Table 10 Guideline recommendations for fondaparinux in acute coronary syndrome patients

AHA/ACC 2014	SC Fondaparinux for the duration of hospitalization or until PCI is performed.	2.5 mg s.c. daily	IB
ESC 2015	Fondaparinux is recommended as having the most favorable efficacy – safety profile regardless of the management strategy. In patients on Fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70-85 IU/kg, or 50-60 IU/kg in the case of concomitant use of glycoprotein IIb/IIIa inhibitors) is recommended during the procedure.	2.5 mg s.c. once daily	IB
NICE 2010	Fondaparinux is offered to patients who do not have a high bleeding risk (unless coronary angiography is planned within 24 h of admission). It should not be used in patients with significant renal dysfunction (those with a serum creatinine > 265 μmol/L were excluded from the trial).	2.5 mg s.c. once daily	NA
SIGN 2016	When there are ischemic electrocardiograph changes or elevation of cardiac markers, treat immediately with Fondaparinux. Continue for 8 d, or until hospital discharge or coronary revascularization.	2.5 mg s.c. once daily	1++
CPG Malaysian guidelines 2011	Fondaparinux for 8 d or duration of hospitalization.	2.5 mg s.c. daily	IA
SBC Brazilian guidelines 2015	Fondaparinux once a day for 8 d or until hospital discharge.	2.5 mg s.c. daily	IB

PCI: Percutaneous coronary intervention; UFH: Unfractionated heparin; NICE: National Institute for Health and Care Excellence; i.v.: Intravenous; s.c.: Subcutaneous.

cost-effectiveness both in terms of cost as well as QALYs across the range of event risks observed. These analyses add yet another positive aspect to the treatment of ACS with Fondaparinux, making it one of the best options available to clinicians today.

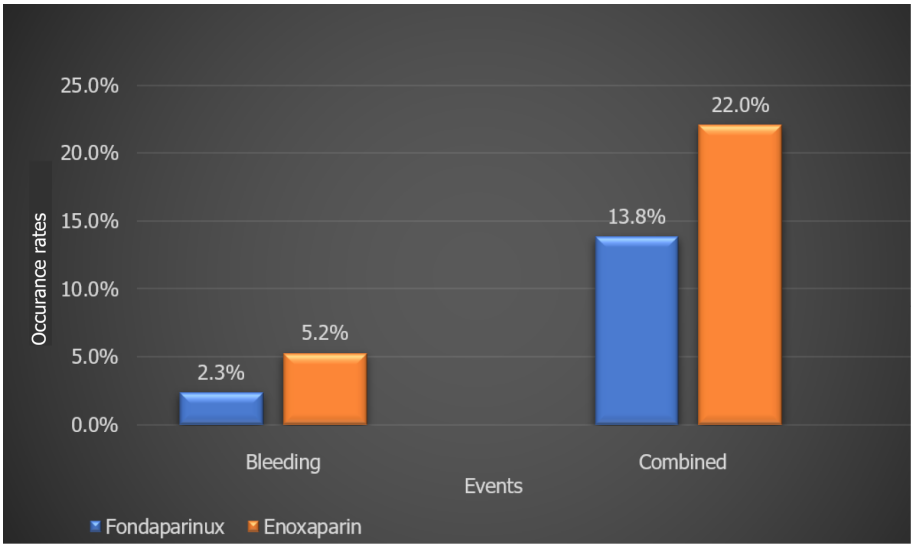

Figure 6 Brazilian registry data. Outcomes for bleeding and combined events.

CONCLUSION

In India, registry data have shown that the prevalence of ACS is quite varied, and the time taken to reach the hospital after symptom onset is more than in the western world and it is an area of concern. Hence, a patient who is presented later than 6 h (*i.e.* has been suffering for an extended period) especially needs prompt and effective treatment. Effective antithrombotic treatment in the form of antiplatelet agents and anticoagulants has been accepted as the cornerstone of therapy for ACS. However, reducing ischemic events without increasing bleeding risk with matchless anticoagulant therapy is the need of the hour. This requirement is remarkably fulfilled by the novel anticoagulant Fondaparinux, with its unique mode of action, once-daily administration, efficacy across patient groups, and consistent effectiveness in reducing bleeding risk. Moreover, several studies conducted in ACS patients have compared Fondaparinux to Enoxaparin and found it to be a safer and equally effective option. Its proven clinical efficacy has resulted in several reputed organizations recommending its use in ACS patients. Fondaparinux also scores over Enoxaparin in terms of cost-effectiveness, both by way of actual costs and QALYs. All these aspects reaffirm that Fondaparinux is one of the best choices in the treatment of ACS.

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CASE REPORT

Anesthetic management of a child with Cornelia de Lange Syndrome undergoing open heart surgery: A case report

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Abstract

BACKGROUND

Cornelia de Lange syndrome (CdLS) is a congenital multisystemic genetic disorder. The expected lifespan of children with this disorder has been prolonged in parallel with the advances in medicine in recent years. However, they still more frequently undergo cardiac surgery. There are some challenges for clinicians when faced with CdLS patients. We present the perioperative management of a child with CdLS undergoing open-heart surgery.

CASE SUMMARY

Severe pulmonic and subpulmonic valvular stenosis, enlargement of the right side of the heart, mild tricuspid regurgitation, atrial septal defect, and patent ductus arteriosus were diagnosed in a 14-month-old boy with manifested cyanosis, developmental delay, and malnutrition. Attempted balloon valvuloplasty was unsuccessful due to a severe stenotic pulmonary valve, therefore it was decided to perform an open surgical repair. Following a successful and uncomplicated intraoperative course, the patient was extubated on postoperative day 5, and adrenalin and dopamine infusions were gradually decreased and stopped on postoperative days 6 and 10, respectively. Moderate laryngomalacia and suboptimal vocal cord movements were diagnosed, and tracheotomy and percutaneous endoscopic gastrostomy were performed under general anesthesia in the same session at postoperative day 32. The patient was discharged on postoperative day 85 after a challenging postoperative period with additional

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airway and nutritional problems.

CONCLUSION
This is the first report of the perioperative anesthetic and clinical management of a CdLS patient undergoing open-heart surgery.

Key Words: Cornelia de Lange Syndrome; Brachmann de Lange Syndrome; Pulmonary valve stenosis; Valvular heart disease; Cardiac surgery; Anesthesia; Case report

Core tip: Cornelia de Lange Syndrome (CdLS) is a congenital multisystemic genetic disorder with multiple congenital abnormalities. The expected lifespan of children with CdLS has been prolonged in parallel with the advances in medicine in recent years. Patients with CdLS undergo cardiac surgery more frequently. In any patients with multiple medical challenges, anesthesiologists, cardiovascular surgeons and pediatricians may face unexpectedly unusual perioperative courses with additional difficulties when undergoing congenital open-heart surgery. The case presented here demonstrates an example of a challenging perioperative management period of a child with multisystemic congenital disease undergoing multiple high-risk surgeries.

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INTRODUCTION

Cornelia de Lange Syndrome (CdLS), also known as Brachmann–de Lange Syndrome, is a genetic developmental disorder with a prevalence of 1.24 per 100 000 births[1]. It is characterized by congenital craniofacial, gastrointestinal, cardiac, musculoskeletal, genitourinary, behavioral and neurodevelopmental anomalies[2]. Although CdLS patients are expected to have growth retardation, intellectual disabilities and a shorter lifespan due to these multiple severe malformations, there have been no previous population-based studies on survival, and some of the patients (particularly with the milder forms) have been reported to reach adulthood[3,4]. Most patients need diagnostic and/or interventional procedures and surgical operations under general anesthesia (GA) to survive. Previous research has described anesthetic implementations in non-cardiac surgery. We present the perioperative management of a child with CdLS undergoing open-heart surgery.

CASE PRESENTATION

Chief complaints

A 14-month-old male patient presented with severe cardiac manifestations including pulmonic and subpulmonic valvular stenosis with 91 mmHg gradient, enlargement of the right side of the heart, mild tricuspid regurgitation, atrial septal defect (ASD), and patent ductus arteriosus (PDA).

History of present illness

After genetic evaluation, CdLS diagnosis was approved, and the *SMC3* gene was reported to be implicated. When the patient was aged 14 mo, the decision to undertake pulmonary valvuloplasty was taken.

History of past illness

The patient was born at 37 wk gestation after a standard spontaneous vaginal delivery,

weighing 2009 g due to intrauterine growth retardation because of ABO maternal–fetal incompatibility. The baby was admitted to the neonatal intensive care unit for 15 d (intubated in the first 2 d) due to respiratory distress and a cleft lip and palate. In the first month after delivery, severe pulmonic stenosis (PS) was diagnosed, and the patient was admitted to a cardiology follow-up program. Lip adhesion surgery was conducted for the cleft lip at age 5 mo.

Personal and family history

The patient was born in Syria, and no information was available regarding his family history.

Physical examination

The patient was a 14-month-old boy weighing 4700 g, 60 cm in height (< 3rd percentile) and 39 cm head circumference (< 3rd percentile). Mild exertional dyspnea, cyanosis, developmental delay, and malnutrition were manifest. Synophrys, brachycephaly, long and thick eyelashes, depressed nasal bridge, repaired cleft lip, micrognathia, short neck, and thickened helices in both ears were distinguishing craniofacial features (Figure 1). There was no apparent renal, musculoskeletal, gastrointestinal and neurological involvement. There was a systolic thrill at the left upper sternal border. The auscultation of the patient revealed a grade 2–3/6 midsystolic (ejection systolic) murmur, systolic ejection click, and a widely split, fixed S2 at the upper left sternal border. Also, there was widened S2 and delayed pulmonic component of S2 due to the increased duration of systole and late closing of the pulmonary valve.

Laboratory examinations

In the preoperative laboratory examination all parameters were normal except: white blood cell count 13.1 10^3/μL, hemoglobin 11.0 g/dL, hematocrit 32.7%, platelet count 504 K/μL, aspartate aminotransferase 71 U/L, and urea 58 mg/dL.

Imaging examinations

Echocardiographic evaluation revealed severe cardiac manifestations including severe PS and sub-PS with 91 mmHg gradient, enlargement on the right side of the heart, mild tricuspid regurgitation, atrial septal ASD, and PDA (Figure 2).

FINAL DIAGNOSIS

The ASA Class III patient was scheduled for percutaneous pulmonary valvuloplasty under general anesthesia.

TREATMENT

Percutaneous pulmonary valvuloplasty

The patient was transferred to the catheter laboratory with an O_2 supply without premedication. After standard monitoring with ECG, oxygen saturation (SpO_2) and noninvasive blood pressure, anesthesia was induced with 2 mg/kg intravenous (iv) 1% propofol followed by 1.5 mg/kg iv fentanyl and maintained with 2% sevoflurane in 50:50% O_2 in air. I-Gel No. 2 was used in airway management without any problems. Due to the severe stenotic pulmonary valve (Figure 3), the attempted balloon valvuloplasty was unsuccessful. Therefore, the decision to perform an open surgical repair was taken.

Correction of PS and closure of PDA and ASD

Nine days after valvuloplasty, the patient was transferred to the cardiac theater with supplemental nasal O_2 without premedication. After standard monitoring with ECG, SpO_2 and NIBP, anesthesia induction was begun with 8% sevoflurane in 100% O_2 followed by 3 mg/kg iv fentanyl, 0.75 mg/kg iv midazolam, 1 mg/kg iv rocuronium, and 1.2 mg/kg iv dexamethasone after insertion of a 20 G cannula. Intubation was easily achieved with a 4.5-mm uncuffed endotracheal tube (grade 1 Cormack–Lehane). Anesthesia was maintained with 2% sevoflurane in 50:50% O_2 in air and 0.5–1.0 mg/kg iv rocuronium, 0.5 mg/kg iv midazolam, and 2–5 mg/kg iv fentanyl intermittently as

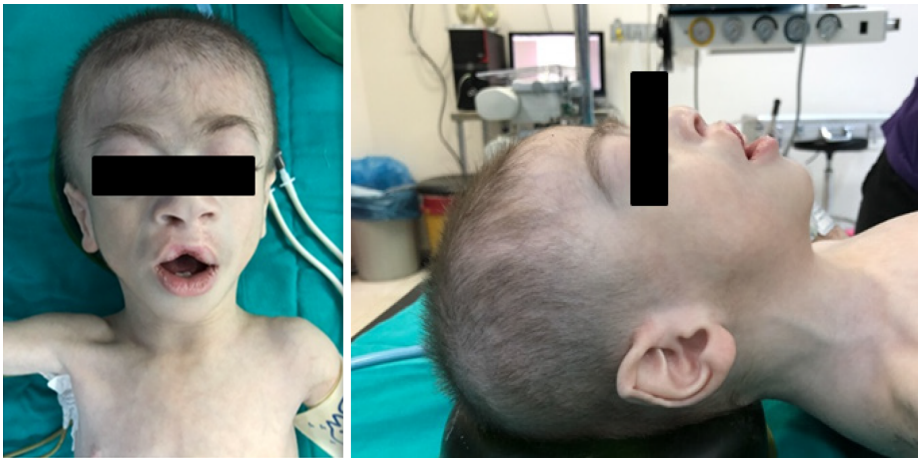

Figure 1 Distinguishing craniofacial features of the patient.

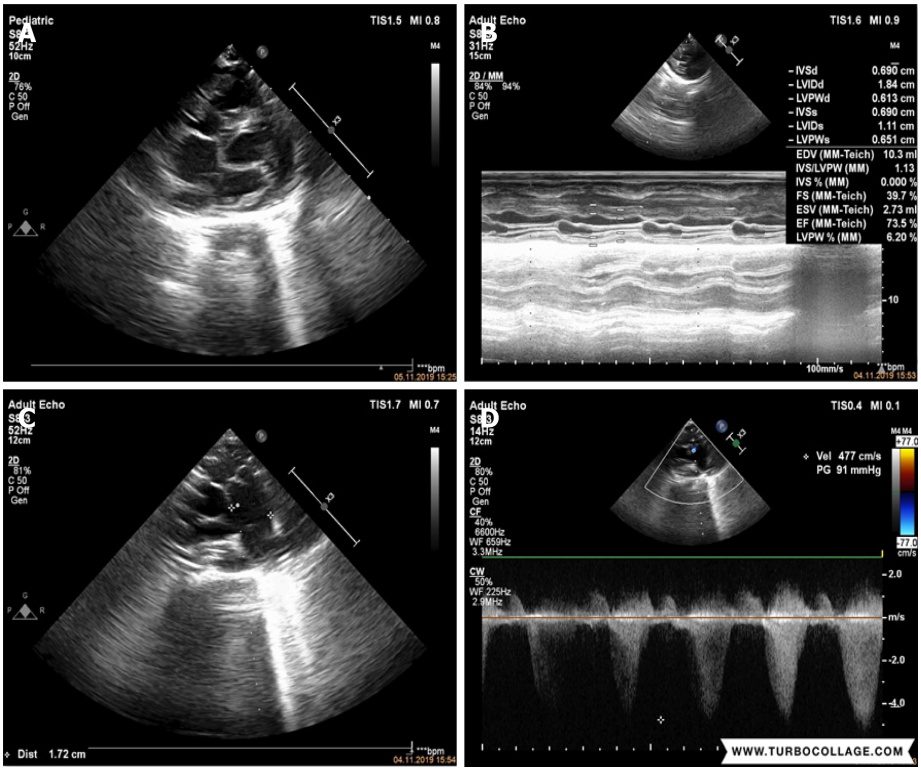

Figure 2 Echocardiographic images. A: The heart of the patient; B: Mild to moderate regurgitation in the tricuspid valve; C: Left ventricular systolic function was observed, functions were maintained (EF: 73.5 %, FS: 39.7 %); D: 91 mmHg gradient was obtained at pulmonary valve level in parasternal short axis imaging.

needed. Canulations were completed with the placement of a 20 G 5-cm arterial cannula with floswitch (BD Arterial Cannula; Becton Dickinson Infusion Therapy Systems Inc, Sandy, UT, USA) placed in the left femoral vein; a 4 F 8-cm double lumen central venous catheter (Royal Fornia Medical Equipment Co. Ltd., Guangdong, China) placed in the right femoral vein; and a 20 G 5-cm single lumen catheter (FMTO; Royal Fornia Medical Equipment Co. Ltd.) placed in the left femoral artery.

After standard anticoagulation with heparin (3 mg/kg) and ensuring activated clotting time of > 400 s, cardiopulmonary bypass (CPB) was established by aortic and bicaval cannulations. Under hypothermic (28 °C) CPB and cold crystalloid cardioplegic arrest, transatrial and transpulmonary incisions were performed. A 15 mm 25 mm ASD, subpulmonic infundibular stenosis and pulmonic valvular stenosis were present. Intracardiac repair with excision of the infundibular membrane and pulmonary valvular commissurotomy were achieved. At the pulmonic level, the outlet admitted a size 12 Hegar's dilator (normal size 11). The ASD closure was done through the right atrium using an autologous pericardial patch. After rewarming to 35 °C and

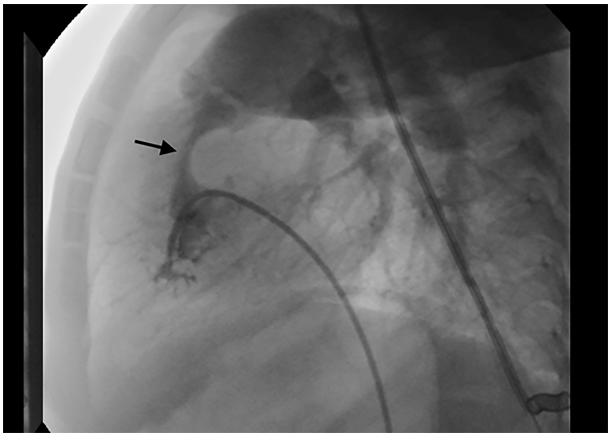

Figure 3 Appearance of the stenotic pulmonary valve in the angiography image.

ensuring normal serum electrolytes, the patient was removed from CPB. The child had a stable sinus rhythm after discontinuing heart–lung machine support. For heparin neutralization, 3 mg/kg protamine was applied. CPB was terminated with 52 min aorta cross-clamp time and 81 min of CPB. During anesthesia, iv infusions of 5 g/kg/min dopamine, 0.1 g/kg/min adrenaline, and 0.5 g/kg/min milrinone (after 50 g/kg loading for 1 h) were begun. Intravenous methylprednisolone (5 g/kg/min) and 10 mg/kg iv tranexamic acid were given in the off-pump period. Arterial blood gas analysis was conducted intermittently during surgery (Table 1). The total amount of saline and gelatin fluid (Gelofusine; B. Braun Medical AG, Crissier, Switzerland) and erythrocyte suspension given were 60 mL, 20 mL and 70 mL, respectively. Fresh frozen plasma was not used. The total urinary output was recorded as 350 mL. The hemodynamically stable patient was transported intubated to the pediatric cardiac intensive care unit (CICU).

OUTCOME AND FOLLOW-UP

The patient was extubated on postoperative day 5; adrenalin and dopamine infusions were gradually decreased and stopped on postoperative days 6 and 10, respectively. On postoperative day 14, the patient was transferred to the pediatric ICU (PICU). On the first day in the PICU, continuous positive airway pressure (CPAP) support (due to respiratory distress) and total parenteral nutrition (TPN) were started. Endoscopic evaluation by the ear, nose and throat (ENT) consultant revealed moderate laryngomalacia and suboptimal vocal cord movements. Intermittent CPAP therapy was terminated upon recovery of respiratory functions after 4 d. Enteral nutritional (EN) was begun. With the improvement of the general medical condition, a tracheotomy (based on the ENT consultant's recommendation) and a percutaneous endoscopic gastrostomy (PEG) to provide a convenient way of feeding were performed under GA in the same session on postoperative day 32.

The patient was discharged on postoperative day 85 after the parental educational discharge program. The general medical condition of the patient was good at the time of discharge. The patient was breathing spontaneously *via* tracheotomy cannula without requiring additional oxygen therapy with SpO_2 95–96%. The hemodynamics were within the normal range without inotropic support. The nutritional support was achieved with enteral nutritional products. The parental educational discharge program included content for feeding and general care of the patient at home. The patient's medical care was planned to be implemented within the home health service program of the Ministry of Health.

DISCUSSION

The present case is the first report of perioperative management of a CdLS patient undergoing open-heart surgery. CdLS is a multiple congenital anomaly and mental retardation syndrome accompanied by multiple disorders in different clinical forms, including classical and mild forms. Although the estimated prevalence of CdLS has

Table 1 Results of arterial blood gases conducted at different timings

Parameters	Beginning of surgery	Beginning of bypass	End of surgery	End of bypass
pH	7.43	7.46	7.52	7.38
PCO_2 (mmHg)	30.8	29.1	27.6	38.1
PO_2 (mmHg)	200	172	186	68.3
Hb ($g.dL^{-1}$)	9.7	11.4	12.2	13.3
Htc (%)	30	35.1	37.4	40.9
SaO_2 (%)	99.6	98.9	99.3	92.8
K^+ (mmol/L)	3.4	3.3	3.1	2.7
Na^+ (mmol/L)	149	143	146	150
Ca^{2+} (mmol/L)	1.25	1.16	1.14	0.87
Glucose (mg/dL)	77	191	196	177
Lactate (mmol/L)	1.0	1.9	1.8	1.1
Base (mmol/L)	-3.1	-2.6	0.3	-2.2
HCO_3^- (mmol/L)	22.2	22.9	25.6	22.6

been reported as 0.5–1.0 per 100 000 Live births, when the mild forms are also taken into account, the prevalence has been reported to be as high as 1 per 10 000 live births. Due to problems in the diagnosis of the syndrome, particularly for the mild forms because of the lack of objective diagnostic criteria for this subgroup, the exact prevalence is still unknown. Barisic *et al*[1] have given the overall prevalence including mild and classical forms of CdLS as 1.6–2.2 per 100 000 births.

Prior to the definitive molecular studies, CdLS was thought to be caused by defective expression of a multifunctional protein involved in chromosomal function, gene regulation, and DNA repair[5]. More recently, CdLS has been genetically found to be a cohesinopathy disorder caused by autosomal heterozygous or X-linked mutations in the cohesion core subunits of the genes of SMCA1, SMC3, RAD21, or in the cohesion-associated factors NIPBL and HDAC8[6]. The phenotype of this syndrome is a spectrum that is formed by classical forms as well as nonclassical variants that are caused by pathogenic alternatives in genes involved in cohesion functioning[7].

The characteristic phenotype of patients with CdLS includes thick eyebrows that meet in the midline, a short nose with a depressed or wide nasal ridge, anteverted nares with upturned nasal tip, a long and smooth philtrum, a thin upper lip and downturned corners of the mouth[6]. These phenotypic features may overlap with the appearance of patients with other chromatin disorders such as Wiedemann–Steiner syndrome, Rubinstein–Taybi syndrome, and Coffin–Siris syndrome[8]. Also, patients with this syndrome may present different phenotypic features that are completely dissimilar to each other. This phenotypic diversity poses a major challenge in diagnosing patients with this syndrome in clinical practice.

CdLS is characterized by multisystem involvement. Common craniofacial features of classic form are synophrys, micro-brachycephaly, long and thick eyelashes, a high and arched palate with clefts, micrognathia, short neck, and hairy ears with thickened helices[9]. The most prominent and existing comorbidity that can be seen in almost every patient, particularly in the neonatal period, is gastroesophageal reflux and related complications. Congenital cardiac abnormalities such as ventricular septal defects, ASD, PS, tetralogy of Fallot, hypoplastic left heart syndrome, and bicuspid aortic valve can be diagnosed in approximately 25% of patients[10]. Syndactyly, clinodactyly, bradydactyly, oligodactyly, clubbed feet, poikilothermia, pectus excavatum, scoliosis, and hip dislocation or dyplasia are common and diagnostic musculoskeletal findings[3,11]. Renal functions may be adversely affected by structural kidney and/or urinary tract anomalies such as vesiculoureteral reflux, pelvic dilation and renal dysplasia[12]. Peripheral neuropathy, autonomic dysfunction, and seizures are reported as possible neurodevelopmental manifestations.

Patients with CdLS with all genetic variants may have global developmental delays, intellectual disabilities, and prenatal and postnatal growth retardation. When evaluated from this point of view, prenatal diagnosis becomes even more important.

The major indications for prenatal diagnosis are a history of having an earlier child with CdLS, a recent pregnancy in a family with a known genetic problem in a *CdLS* gene, and suggestive features of CdLS on fetal ultrasonography[7]. Since our patient and his family were Syrian immigrants and only his delivery was performed in a state hospital in Turkey, there was no prenatal care according to the information we received from the parents. The diagnosis of CdLS was made after the genetic examination performed in our university hospital when our patient was aged 5 mo. The absence of prenatal care and the presence of other pathologies that may cause growth retardation can cause delays in diagnosis, as in our patient.

There are some challenges for clinicians when facing CdLS patients, and our patient underwent four different surgical operations under general anesthesia in 85 d. Airway management is of particular interest. Different authors have referred to difficult airway probabilities, and various reports have mentioned some device suggestions instead of a conventional laryngoscope such as a laryngeal mask airway, fiberoptic endoscopes, and a Pentax Airway Scope GlideScope video laryngoscope[13-15]. Uncomplicated airway management, particularly in the intraoperative period has also been reported[16,17]. In our case, micro-brachycephaly, short neck, macroglossia, micrognathia, and a cleft lip and palate were some craniofacial features that could increase the probability of difficulties in airway management. Although no airway difficulties were encountered during the intraoperative period, our patient suffered postoperative respiratory problems, failed to reach adequate extubating criterion during the weaning period, and could not be extubated until postoperative day 5. Despite intermittent CPAP treatments, the patient underwent a tracheotomy in line with ENT consultant's recommendations after diagnosing moderate tracheomalacia and suboptimal vocal cord movement.

Gastroesophageal reflux and related complications such as esophagitis, aspiration, chemical pneumonitis, and irritability can be seen in almost every CdLS patient, particularly in the neonatal period[18]. Gastroesophageal reflux and intestinal malformations may lead to regurgitation and aspiration of gastric contents, particularly in the anesthesia induction period. Although rapid sequence induction and intubation should be considered as a precaution to avoid regurgitation and aspiration of gastric contents, we did not have a chance to apply these until a secure intravenous line had been achieved.

Another possible severe risk is the presence of perioperative nutritional problems and underfeeding in the postoperative course. Malnutrition is an accepted problem in children with congenital heart disease because of unmatched energy requirements with poor feeding, and inadequate caloric intake[19]. Major surgery (mainly upper gastrointestinal surgery and cardiac surgery) and existing gastrointestinal abnormalities are additional risk factors. Although early oral feeding is the recommended mode of nutrition for surgical patients in the early postoperative period, EN is considered admissible for any surgical patient at nutritional risk[20]. We started TPN on postoperative day 1 and EN *via* a nasogastric tube on postoperative day 5 after extubation. Early extubation is particularly critical for patients with a cleft palate as prolonged intubated may impair sucking and swallowing reflexes. EN is problematic in the pediatric CICU, and satisfactory EN support is provided after performing the PEG procedure.

PS occurs in 0.6–0.8 per 1000 live births, and its prevalence is 8%–12% of all congenital heart defects[21]. It can be an isolated lesion or associated with other congenital heart defects such as ASD, ventricular septal defect, PDA, and tetralogy of Fallot[22]. There are three different morphological types of valvular PS. In the classic or dome-shaped pulmonary valve, there is a narrowed central orifice with a preserved mobile valve mechanism. In the dysplastic pulmonary valve that represents approximately 20% of all cases, there are poorly mobile and marked myxomatoses-thickened leaflets without commissural fusion. In the third type, the pulmonary valve is unicuspid or bicuspid and mostly seen in the context of tetralogy of Fallot[23]. Obstruction of the right ventricular outflow tract leads to a rise in right ventricular afterload, which also induces ventricular muscle hypertrophy producing thicker chamber walls, decreased compliance, increased ventricular stiffness, and higher right atrial filling pressures[24]. As the obstruction increases, cardiac output and the patient's physical activity is increasingly limited due to impaired compliance and worsening diastolic dysfunction. When obstruction becomes critically severe, right ventricular systolic and diastolic dysfunction and ischemia can occur. At this point, chest pain, dyspnea, arrhythmia, syncope, and even sudden cardiac death can be seen. For patients with severe PS (peak-to-peak transcatheter gradient > 50 mmHg), who have not undergone surgical correction, poor long-term outcomes have been reported. In contrast, excellent survival rates have been achieved in patients with > 80 mmHg

gradient after surgical valvotomy[25]. In our patient, the cardiac pathology was severe due to the severe PS with 91 mmHg gradient, which was combined with PDA and ASD, and the main purpose of the surgical operation was to prolong the lifespan of the patient.

The severity and characteristics of stenosis determine the clinical consequences and optimal treatment modality. An obstruction in the right ventricular outflow tract with a gradient of > 64 mmHg (peak velocity > 4 m/s) on Doppler imaging indicates repair [22]. Although balloon valvuloplasty is the first-choice treatment option, in some circumstances, such as hypoplastic and severely dysplastic valves, infundibular stenosis, and associations of other congenital lesions, surgical repair may be required. Due to the various risks associated with the surgical intervention such as procedural complications, prolonged hospitalization and recovery times, and a higher cost than nonsurgical interventions, surgical intervention is reserved only for more complex diagnoses or in cases in which intervention is not possible[26]. In our case, the guidewire could not be passed through the severe stenotic pulmonary valve, and the decision to undertake a surgical repair was made due to procedural failure.

Severe PS and pulmonary hypertension increase right ventricular work while decreasing left ventricular output, and are significant independent risk factors for mortality and morbidity in both cardiac and noncardiac surgery[27]. The essential targets of anesthetic management are the maintenance of adequate right ventricular preload and contractility and left ventricular afterload with decreasing systemic and pulmonary vascular resistance. In the intraoperative period, right ventricular filling pressure is significant in optimizing myocardial contractility and maintaining hemodynamic stability[28]. Intravascular volume status is also crucial as acute right heart failure and cardiac arrhythmias can easily be precipitated by excessive intravenous fluid. The total amount of intravenous fluids and erythrocyte suspension is limited during surgery. Although all volatile anesthetics may worsen right ventricular dysfunction by reducing preload, afterload, and contractility, desflurane and nitrous oxide, unlike others, are reported to increase pulmonary vascular resistance and should be avoided[29].

CONCLUSION

CdLS is a complex disease in which many organs and systems are affected. The existence of milder forms of CdLS has been demonstrated by advanced molecular and genetic diagnostic methods. In addition, with the medical developments in recent years, the expected lifespan of children with CdLS has been prolonged, with these patients undergoing cardiac surgery more frequently. In CdLS patients who present various anesthetic challenges, anesthesiologists, cardiovascular surgeons, and pediatricians may face unexpectedly unusual perioperative courses with additional difficulties in congenital open-heart surgeries.

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