The use of Inari FlowTriever® aspiration thrombectomy device for the management of acute pulmonary embolism : Initial experiences at the University Hospital of Split

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THE USE OF INARI FLOWTRIEVER® ASPIRATION THROMBECTOMY DEVICE FOR THE MANAGEMENT OF ACUTE PULMONARY EMBOLISM: INITIAL EXPERIENCES AT THE UNIVERSITY HOSPITAL OF SPLIT

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LIST OF ABBREVIATIONS

BP - *Blood pressure*

CDT - *Catheter-directed thrombolysis*

CT - *Computed tomography*

CTPA - *Computed tomography pulmonary angiography*

CUS - *Lower-limb compression ultrasound*

DVT - *Deep venous thrombosis*

EVT - *endovascular therapy*

LMWH - *Low molecular weight heparin*

LV - *Left ventricle (LV)*

mPAP - *Mean pulmonary artery pressure*

PAP - *Pulmonary artery pressure*

PE - *Pulmonary embolism*

PESI- *Pulmonary Embolism Severity Index*

PVR - *Pulmonary vascular resistance*

RV - *Right ventricular (RV)*

sPESI - *Simplified Pulmonary Embolism Severity Index*

TTE - *Transthoracic echocardiography*

V/Q - *Lung scintigraphy scan*

VTE - *Venous thromboembolism*

1. INTRODUCTION

1.1. Definition of pulmonary embolism

Pulmonary embolism (PE), occurs due to an occlusion due to a blood clot, tumor, air, or fat obstructing one or more of the pulmonary arteries. Most often it is caused by a detached venous thromboembolism (VTE) originating from deep veins in the pelvis or extremities (1). Furthermore, PE can be divided according to size, anatomical location, and extent; a saddle pulmonary embolism is a large clot obstructing the main pulmonary artery and also crosses the right and left pulmonary arteries causing a bilateral obstruction. PE located in the branches of the pulmonary artery corresponding to the anatomical lung segment is called lobar, segmental, or subsegmental PE (2). A submassive (although this term is not used anymore in modern guidelines) pulmonary embolism is defined as right ventricle (RV) strain without cardiogenic shock and makes up 25% to 31% of all cases of PE (3).

Venous thromboembolism (VTE) is considered a significant health problem, it is relatively common and associated with extensive health costs and reduced overall survival (4).VTE clinically presenting as deep venous thrombosis (DVT) or pulmonary embolism(PE), is worldwide the third most frequent acute cardiovascular syndrome, ranging after myocardial infarction and stroke (1,5).

1.2. Epidemiology of pulmonary embolism

Around 100 to 140 per 100,000 persons in Europe annually suffer from venous thromboembolism (VTE), and overall VTE incidence rate is similar to that of ischemic stroke (2,4). Epidemiological studies shows that annual incidence rates for pulmonary embolism range from 39-115 per 100,000 persons and for deep venous thromboembolism (DVT) the incidence rates range between 53-162 per 100 000 persons (1,7,8). Mainly older individuals are predominantly affected by VTE, which is rare before late adolescence. Age is a common risk factor in both men and women for the incidence of both DVT and PE (2,5). Pulmonary embolism, a well-known potentially fatal complication of VTE, represents a rising proportion of the total VTE events with higher age (9). Studies show that there is an increase in the event of VTE with annual age-adjusted rate for males (130 per 100,000 persons) compared to females (110 per 100,000 persons) with a male-to-female sex ratio of 1.2:1 (4). As the population ages overall with higher life expectancy, the absolute number of venous thromboembolic events will likely increase in the future. Thus, manifestation of pulmonary embolism will also likely rise as a consequence of higher age, with associated poor survival rates in older individuals (9).

1.3. Risk factors of pulmonary embolism

Advanced age, previous VTE, cancer/malignancy, venous insufficiency, congestive heart failure, pregnancy, oral contraceptives, surgery, trauma, frailty, and for longer periods of immobility are all well-established risk factors for pulmonary embolism (1). When considering and approaching the different risk factors for VTE and development of pulmonary embolism one should consider non-modifiable risk factors such as age, gender and origin, and the modifiable risk factors that encompass "cardiovascular" risk factors such as cigarette smoking, obesity, metabolic syndrome, arterial hypertension, high red meat consumption and hypercholesterolemia. Modifiable risk factors might reduce the likelihood of DVT or PE thus they are important to take into consideration as a disease prevention (10)VTE is considered a women´s health issue; pregnancy, hormonal birth control and postmenopausal hormonal therapy each contribute as risk factors. Abe *et al.* state that pulmonary embolism accounts for 9,2 % of all pregnancy-related deaths or approximately 1.5 deaths per 100,000 live births in the United states (11).

Hospitalized patients are especially susceptible to VTE and patients with cancer, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease (especially nephrotic syndrome) and patients undergoing major surgery are all considered to have increased risk to develop VTE (10). According to Timp *et al* around 20-30 % of all first time episodes of VTE is related to cancer (12). It has been well established that active malignant disease is an important predisposing risk factor of VTE (1).

Individuals with a diagnosis of heart failure have a higher risk of developing VTE. Fanola *et al.* found out that patients with heart failure had more than a 3-fold higher risk of subsequent incident of VTE (13). It was demonstrated that patients with congestive heart failure suffers from more comorbidities and have an increased risk of extended immobilization, which might predispose them to a greater likelihood of PE event (10).

1.4. Pathophysiology of the acute pulmonary embolism

Acute pulmonary embolism is a condition that affects the circulation and gas exchange in the lungs and heart and several pathophysiological events occur in the setting of PE. The primary cause of death from PE is right ventricular (RV) failure due to acute pressure overload on the right heart. Increased pressure overload causes the right ventricle to dilate, which alters the contractions from RV myocardium by means of the Frank-Starling law. This, in turn, stimulates a neurohormonal activation cascade, resulting in inotropic and chronotropic

stimulation of RV, and a temporary compensatory rise in pulmonary arterial pressure (PAP). This mechanism helps to provide more blood flow through the obstructed pulmonary bed, thereby stabilizing systemic blood pressure (BP). However, this compensatory mechanism is temporary because the thin-walled RV is unable to maintain the acute rise in pulmonary artery pressure (1).

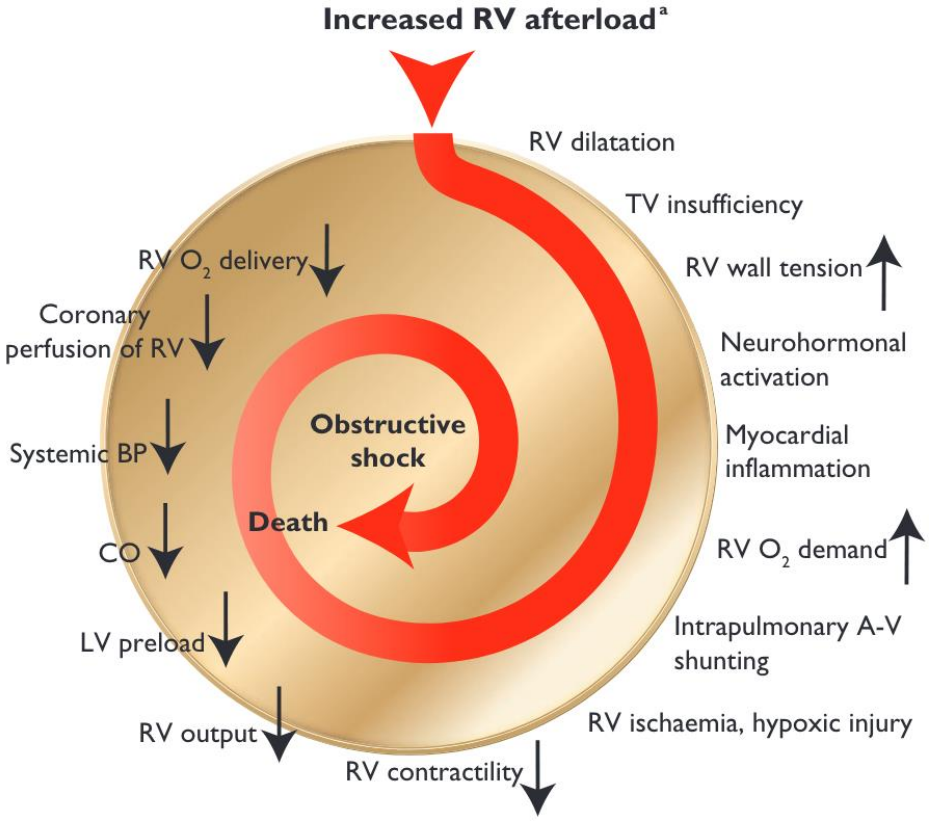

Figure 1. Key factors contributing to haemodynamic collapse in acute pulmonary embolism

Taken from 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism (1)

When the total cross-sectional area of the pulmonary arterial bed is occluded, the pulmonary artery pressure (PAP) rises. When this pressure exceeds 30-50% of the normal value of PAP (which is 20 mmHg or less), the resulting vasoconstriction leads to the release of vascular and bronchial constrictors (thromboxane A2 and serotonin), contributing to a decrease in pulmonary vascular resistance (PVR). Hypoxic vasoconstriction and anatomical obstruction in the affected lung area further decrease PVR and thereby significantly decreases arterial compliance (1).

As the right ventricle weakens due to an increased oxygen demand, the time before contraction into early diastole of the left ventricle (LV) is prolonged, resulting in a leftward

bowing of the interventricular septum. Development of a right bundle branch block may occur, and as a result, left ventricular filling becomes impeded, leading to a reduction in cardiac output, systemic hypotension, and haemodynamic instability (1).

Post-mortem investigations of patients who died within 48 hours of acute pulmonary embolism revealed a significant increase in the number of inflammatory cells like neutrophilic granulocytes, lymphocytes and macrophages damaging the structure of right ventricle. This findings indicate the negative role of inflammatory mediators contributing to the pathophysiology of PE (14).

Haemodynamic disturbance is the main cause of respiratory failure in PE. Low cardiac output leads to desaturation of the mixed venous blood. Ventilation/perfusion mismatch contributing to hypoxemia, occurs due to the zones of reduced flow in obstructed pulmonary arteries combined with the zones of overflow in the capillary bed (1). Small distal emboli in the lung vasculature might not affect haemodynamic flow, but can create areas of alveolar haemorrhage resulting in haemoptysis, pleuritis and (often mild) pleural effusion, findings also known as a *"pulmonary infarction"* (1).

In summary, pulmonary embolus might alter respiration by ventilation/perfusion mismatch and haemodynamic instability and hypoxia through increased pulmonary artery pressure as illustrated in **Figure 2** (15). As explained in the above sections, activation of excessive neurohumoral activation in PE can be the result of abnormal RV wall tension and circulatory shock (16). Pressure overload in the right ventricle leading to RV failure and haemodynamic instability indicate a high risk of early mortality. High-risk PE are life-threatening and requires emergency diagnostic and therapeutic strategy (1).

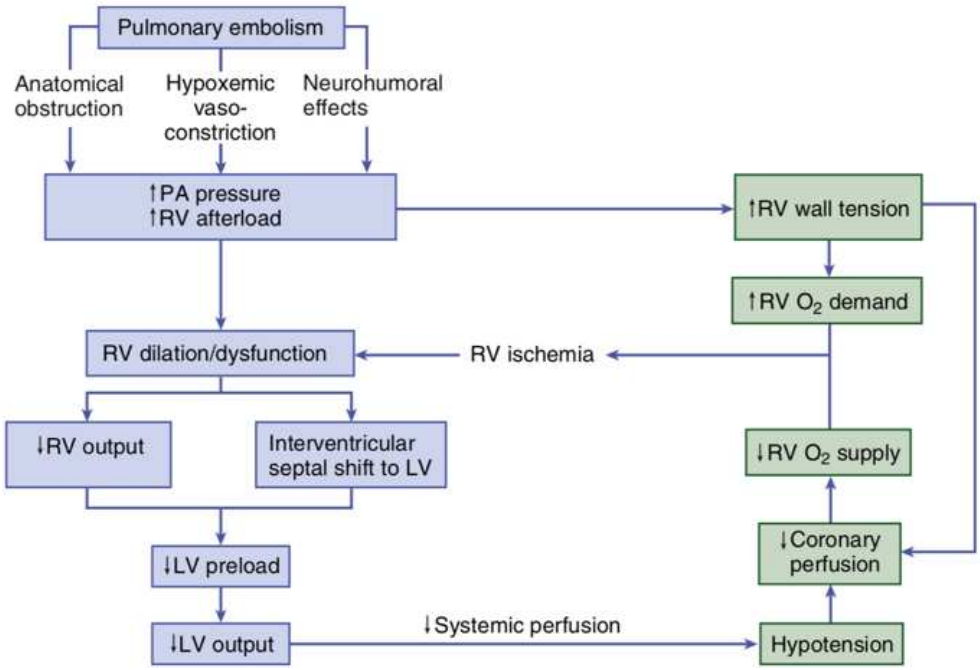

Figure 2. Pathophysiology of pulmonary embolism

Image taken and reproduced without modification from Libby P, Bonow RO, Mann, DL, Bhatt DL, Solomon DS. Braunwald´s Heart Disease. 12th ed. Elsevier; 2021 (13)

1.5. Diagnosis of pulmonary embolism

The clinical picture of pulmonary embolism can vary significantly from only coughing to acute chest pain, difficulty breathing, shock, and sudden death. PE can be suspected in a patient with dyspnea, chest pain, tachycardia, pre-syncope or syncope, or haemoptysis. PE can also be completely asymptomatic or detected incidentally while doing diagnostic workup for another disease (1). Standard diagnostic approach to patients with clinical suspicion of acute pulmonary embolism consist of sequential diagnostic tests, such as clinical probability assessment, plasma D-dimer measurement, compression ultrasonography, computed tomography pulmonary angiography (CTPA) or ventilation-perfusion lung scan (17).

1.5.1 Assessment of clinical (pre-test probability)

The degree of clinical probability of PE are measured by using Wells score and Geneva score, as illustrated in **Figure 3.** These scores indicate the graded probability of PE manifestation based on anamnesis with other clinical variables and findings such as tachycardia >100/min, recent surgery or immobilization, previous PE or DVT, hemoptysis or malignancy

(1). Previous clinical trials show the effectiveness of standardized algorithm tools for diagnosing PE and thus emphasizes the use of simplified clinical probability score, along with D-dimer testing and contrast-enhanced chest computed tomography (CT). Low clinical probability and a normal D- dimer test, can safely rule out PE (without the need for additional imaging like CT), and this will account for about 30% of patients admitted to hospital with suspected PE (18). In one study, with the use of Wells score, ruled out the need for contrast-enhanced chest CT in nearly 1 out of 4 patients (19).

Items	Clinical decision rule points	
	Original version[91]	Simplified version[87]
Previous PE or DVT	3	1
Heart rate		
75–94 b.p.m.	3	1
≥95 b.p.m.	5	2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower-limb pain	3	1
Pain on lower-limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE-unlikely	0–5	0–2
PE-likely	≥6	≥3

Figure 3. The revised Geneva clinical prediction score for pulmonary embolism

Image taken without modification from 2019 ECT guidelines for the diagnosis and management of acute pulmonary embolism (1)

1.5.2. D-dimer testing

The use of enzyme-linked immunosorbent assay (ELISA) and second generation latex agglutination test (immunoturbidimetric tests) enabled the inauguration of D-dimer testing that has been extensively evaluated in the exclusion of pulmonary embolism and provided a very high sensitivity. D-dimer testing has proven to be safe in association with clinical probability to rule of PE (17).

The D-dimer test result is positive when there is increased fibrinolysis in serum. The test is taken in case of unlikely, low or medium clinical probability of PE (1). In hospitalized patients (with a higher risk of developing PE) a negative D-dimer can be relied on to a lesser extent when deciding about doing diagnostic imaging (1). Considerations should be made using D-dimer test in older individuals because several studies did show that D-dimer levels increase with age. Usually the predetermined cutoff value are 500 μg/L for most available commercial assays (17). In one study, the ELISA D-dimer test was capable of ruling out PE in 60% of patients under 40 years but only in 5% of patients older than 80 years (20).

1.5.3. Diagnostic imaging

Multidetector computed tomographic pulmonary angiography (CTPA) are the preferred diagnostic tool used for imaging pulmonary vasculature in patients with suspected PE. When using this modality the physician can visualize the pulmonary arteries down to the subsegmental level (1). CTPA has a sensitivity of 83% and specificity of 96% in diagnosing PE (21). According the European Society of Cardiology (ESC) guidelines published in 2019, it is recommended with class I evidence to reject the diagnosis of PE (without further testing) if CTPA is normal in a patient with low or intermediate clinical probability, or when PE is highly unlikely (1).

Among the advantages of CTPA are excellent accuracy, short acquisition time, low rate of inconclusive result (3-5%), ready availability in most hospitals and short acquisition time (1). Among the disadvantages are radiation exposure, exposure to iodine contrast (iodine contrast is contraindicated in renal failure), tendency to overuse because of easy accessibility and unknown relevance of CTPA diagnosis of subsegmental PE (1).

Lung scintigraphy (V/Q) scan is another well-established diagnostic test used for the detection of PE with the purpose of increasing specificity in diagnosing acute PE. Perfusion scans and ventilation studies are combined and multiple tracers such as xenon-133 gas,

krypton-81 gas, technetium-99m-labelled aerosols among others are used. Because this method is a low-radiation and contrast medium-sparing procedure, the V/Q scan may preferentially be done in out-patients with low clinical suspicion and a normal chest X-ray, in young (especially female) patients, in pregnant women, in patients with contrast-allergy and in patients with long-standing renal failure. Lung scintigraphy (V/Q) has almost no contraindications, it is not expensive but is not readily available in all hospitals. V/Q scans cannot make alternative diagnosis if PE is excluded (1).

Pulmonary angiography was for a long time considered the "*gold standard*" method for diagnosing or excluding acute PE but is today rarely used because of the replacement of the less-invasive CTPA. With pulmonary angiography the diagnosis of acute PE is proven by direct evidence of a visualized thrombus in two projections, either as a filling defect or as amputation of a pulmonary arterial branch. Among the disadvantages are the level of invasiveness of the procedure and the high amount of radiation emitted during the procedure (1).

Transthoracic echocardiography can be used to detect the RV pressure overload and dysfunction caused by acute pulmonary embolism. Right ventricular dilation is found in >25% of patients with PE on transthoracic echocardiography (TTE) and is useful for risk stratification of the condition (22). Echocardiographic examination is not used strictly as part of routine diagnostic workup in haemodynamically stable patients with suspected PE, although it may be good to use in the differential diagnosis of acute dyspnoea. On the contrary, in high-risk PE, the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of haemodynamic instability. Echocardiographic evaluation is of importance to further help in the differential diagnosis of the cause of shock, by detecting pericardial tamponade, acute valvular dysfunction, severe global or regional LV dysfunction, aortic dissection, or hypovolaemia (1).

1.5.4. Compression ultrasonography

Embolization of the pulmonary arteries is most often due to a detached thrombus from deep veins in the pelvis or lower extremities. Venous thromboembolism appears as PE together with deep venous thrombosis (DVT) in 42% and with DVT alone in 58% of cases (23). Lower-limb compression ultrasound (CUS) has largely replaced venography for diagnosing DVT and provide a sensitivity of more than 90% and specificity of around 95% for proximal symptomatic DVT (1,24). Findings of a proximal DVT with CUS in patients with suspected PE, is considered sufficient to start with anticoagulant treatment without further testing.

Diagnostic criterion for DVT is incomplete compressibility of the vein, which indicates the presence of a clot, whereas flow measurements are unreliable (1).

1.6. Risk stratification of PE severity

To determine the appropriate therapeutic approach for acute PE, risk stratification is essential. The extent and severity of pulmonary embolism (PE) can be categorized as low-, intermediate-, and high-risk based on early mortality outcomes (25). The initial risk stratification is based on the presence of clinical symptoms and signs of haemodynamic instability. By definition, patients that are considered haemodynamically instable, have one of the following factors present; which include cardiac arrest (with the need for cardiopulmonary resuscitation), obstructive shock, and/or persistent hypotension with systolic blood pressure (SBP) <90 mmHg (1).

For haemodynamically stable patients, advanced risk stratification is also necessary and involves a set of prognostic criteria, including clinical imaging and laboratory indicators of PE severity, as well as the presence of comorbidities and any other aggravating conditions that may adversely affect early prognosis (1, 26).

Figure 4. shows the high, intermediate and low categorizations. As presented in the table, patients that categorize as high risk for early mortality are haemodynamically instable, have RV dysfunction and elevated cardiac troponin levels. Patients in the intermediate-high-risk category can either be divided into intermediate-high or intermediate low category. As the table shows, patients in this group do not present with haemodynamic instability, but they have clinical parameters consistent with PESI score of III-V. (PESI score will be explained in the section below). The intermediate-high group show evidence of both right ventricular dysfunction and elevated levels of cardiac biomarker in serum (especially a positive cardiac troponin test), in addition to deviant clinical parameters. The intermediate-low risk patients may have RV dysfunction or elevated troponin markers in serum. The patients within the intermediate category requires close monitoring to detect early haemodynamic or circulatory collapse and may require rapid rescue reperfusion therapy if deterioration occurs (1).

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/ or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

Figure 4. Classification of pulmonary embolism severity and the risk of early mortality (in-hospital or 30 days)

Taken without modification from 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism (1)

One of the most commonly utilized stratification scores in clinical practice is the Pulmonary Embolism Severity Index (PESI score). This stratification tool combines initial indicators of acute PE with any exacerbating factors and concurrent medical conditions that the patient might have (1). PESI score includes 11 variables that can easily be collected upon hospitalization, (presented in **Figure 5.**) (27). A simplified pulmonary embolism severity index (sPESI) predicts 30-day outcome of patients with PE, with lesser criteria then the PESI score (27). Considering the severity risk of PE, a PESI score of class I-II or an sPESI score of 0 is considered a reliable predictor of low risk PE (1,28). A PESI score of class IV-V constitutes an increased risk of in-hospital stay up to 24,5% and a higher mortality risk (27).

Predictors	Points assigned
Age, per year	**Age, in years**
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse ≥110/minute	+20
Systolic blood pressure < 100 mm Hg	+30
Respiratory rate ≥30/minute*	+20
Temperature < 36°C	+20
Altered mental status†	+60
Arterial oxygen saturation < 90%*	+20

A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable predictor. Points assignments correspond with the following risk classes: ≤65 class I; 66–85 class II; 86–105 class III; 106–125 class IV; and
> 125 class V. Patients in risk classes I and II are defined as low-risk. *Assessed with or without the administration of supplemental oxygen. †Defined as confusion, disorientation, or somnolence.

Figure 5. The Pulmonary Embolism Severity Index (PESI score)

Taken without modification from Donzé J, Gal G, Fine MJ, Roy PM, Sanchez O, Verschuren F, et al. Prospective validation of the Pulmonary Embolism Severity Index: A clinical prognostic model for pulmonary embolism. Thromb Haemost. 2008

1.7. Treatment of pulmonary embolism

Treatment of pulmonary embolism consist of both invasive and non-invasive approaches. Research shows that patients with a low-risk PE have a better prognosis with only anticoagulation therapy alone (1,29). High-risk patients in danger of haemodynamic collapse might need intensive circulatory and respiratory support with vasopressors, mechanical ventilation, or even extracorporeal membrane oxygenation (ECMO). Together with anti-coagulation, more advanced management options consist of systemic thrombolysis, pharmacho-mechanical catheter-assisted therapy, vena cava filter placement or surgical embolectomy (15).

1.7.1. Anticoagulation

For patients with intermediate to high clinical probability of pulmonary embolism (PE), it is recommended with class I level evidence in current guidelines (ESC guidelines 2019), to use anticoagulation therapy while awaiting diagnostic test results(1). Systemic anticoagulation

has for a time been the mainstay of treatment for PE but can take up to 24 hours to become therapeutic (30). Typically, anticoagulation is administered via subcutaneous injection using weight-adjusted low molecular weight heparin (LMWH) or fondaparinux, or via intravenous infusion using unfractionated heparin (1). However, studies performed by Buller *et al*. demonstrated that non-vitamin K antagonist oral anticoagulants (NOACs) such as factor Xa inhibitors apixaban or rivaroxaban, can also produce a rapid anticoagulant effect (31).

1.7.2. Reperfusion treatment

Thrombolytic therapy (most commonly used are recombinant tissue type plasminogen activator) can result in faster improvements of pulmonary obstruction, pulmonary arterial pressure (PAP), and pulmonary vascular resistance (PVR) in patients with pulmonary embolism (PE) compared to treatment with unfractionated heparin alone. Additionally, this therapy has been observed to reduce right ventricle (RV) dilation proved by performing post-reperfusion echocardiography (1).

The most significant improving outcome is observed when thrombolytic therapy is initiated within 48 hours of symptom onset. However, it can still be beneficial for patients who have been experiencing symptoms for 6 to 14 days (1,32). Patients suffering from high-risk PE, mainly defined as the presence of cardiogenic shock, are proven to have a significant reduction in the combined outcome of mortality and recurrent PE when given reperfusion therapy (32).

1.7.3. Vena cava filters

The purpose of vena cava interruption is to mechanically prevent blood clots from reaching the lungs. The majority of devices currently used are inserted through the skin and can be removed after a few weeks or months. Alternatively, they can remain in place for a longer period if necessary. Vena cava interruption may be recommended for patients with VTE who cannot receive anticoagulant therapy, or those who experience recurrent pulmonary embolism despite appropriate anticoagulation. It may also be used for primary prophylaxis in patients at high risk of VTE. However, the usefulness of filters for other indications, such as free-floating thrombi, has not been confirmed in patients who can receive therapeutic anticoagulation without any contraindications (1, 33).

1.7.4. Surgical embolectomy

The usual method for performing a surgical embolectomy in cases of acute pulmonary embolism involves the use of cardiopulmonary bypass, without the need for aortic cross-clamping and cardioplegic cardiac arrest. The procedure typically involves making incisions in the two main pulmonary arteries and removing or suctioning out fresh blood clots. Recent studies have shown positive surgical outcomes for high-risk pulmonary embolism, both with and without cardiac arrest, as well as in certain cases of intermediate-risk pulmonary embolism (1,34).

1.8. Percutaneous catheter-directed treatment of pulmonary embolism

Percutaneous catheter-directed treatment (CDT) of acute pulmonary embolism has a class IIa, evidence level C indication in current guidelines (ESC Guidelines from 2019), and is recommended for patients with high-risk PE, when thrombolysis is contraindicated or has failed (1,26). Catheter-directed therapy can also be considered in the treatment of stable patients in which anticoagulant treatment was not optimal, more specifically in patients suffering haemodynamic deterioration, despite precisely dosed anticoagulation (26). These methods of clot retraction have a great advantage in that they are simple to use and available at a low price (35).

Percutaneous catheter-directed treatment is done by inserting a catheter via the femoral vein into the pulmonary arteries to extract or dissolve a blood clot (29). Thereby restoring circulation and improving right ventricular function. Through a pigtail or dedicated sidehole catheter , a thrombolytic drug can be delivered directly into the pulmonary artery (1,26,29). The different catheter-directed reperfusion techniques include catheter-directed clot fragmentation, rheolytic thrombectomy, mechanical embolectomy and combined pharmaco-mechanical approaches with thrombolytic drugs. They are classified into two categories: catheter-directed thrombolysis (CDT) and catheter-based embolectomy (1,29).

Among the different types of catheter-directed thrombectomy devices available are the FlowTriever® (INARI Medical, Irvine, CA, USA) System that uses aspiration with or without mechanical fragmentation, has an outer diameter of 16, 20 and 24 Fr and is certified as a percutaneous method of treating PE (26). The Inari FlowTriever system is the main subject of this paper and will be presented later on in a separate section.

Pruszczyk *et al*. aimed to outline the currently available catheter-directed therapy (CDT) approaches in patients with pulmonary embolism and establish a standard protocol for patient selection, timing and technique of the procedure, and the anticoagulation regimens used during CDT. Today there is a lack of high-quality data from randomized controlled studies that demonstrates clinical outcomes, and primary reperfusion utilizing CDT it is not yet the initial treatment for patients with high-risk PE or for any other PE-risk categories (26).

The outcome from physically removing a thrombus in high-risk PE patients is clearly beneficial and can improve survival. Patients with increased risk of bleeding, for various reasons, poses an even higher bleeding risk when thrombolytic-based removal strategies are used. Meanwhile, the harms associated with catheter-based and surgical embolectomy may be more influenced by patient comorbidities rather than bleeding risk. As a result, the decision to utilize active thrombus removal is primarily guided by the severity of the PE, with secondary consideration given to patient-specific risk factors (29).

1.8.1. Inari FlowTriever mechanical thrombectomy device

The FlowTriever® (INARI Medical, Irvine, CA, USA) retrieval and aspiration system is the first FDA-approved mechanical thrombectomy/thromboaspiration device. This single-use mechanical thrombectomy device is designed to target peripheral vasculature and pulmonary artery embolization by removing blood clots from vessels, restoring blood flow immediately and improving the workload on the right ventricle without the need of thrombolytic drugs or for the patient to be observed in the ICU (26, 36, 37). It is recommended to use anticoagulation with heparin as a routine catheterization laboratory practice to prevent thrombosis of the catheter (36). A 16 to 24-F aspiration guide catheter is situated over a 0,035-inch wire directed up to the level of right or left pulmonary artery, proximal to the occluding thrombus. Thereafter the FlowTriever catheter is led through the aspiration guide catheter over the guidewire, and the disks are deployed into the clot. Once attached, the clot is extracted by aspiration via the AGC, illustrated in **Figure 6**.

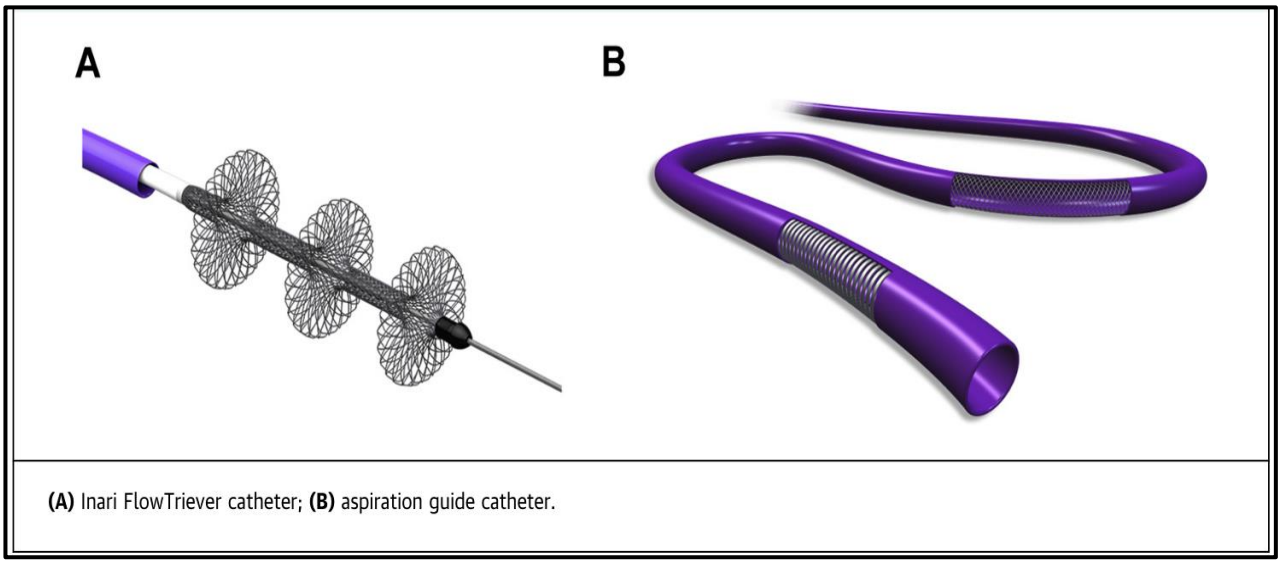

Figure 6. Inari FlowTriever® catheter and aspiration guide catheter

Taken without modification from Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, et al. A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism (36)

1.8.2. Clinical data associated with the use of Inari FlowTriever

Several studies have been performed to assess the efficacy, benefits and safety using the FlowTriever (Inari) device. The first case-report study was done by Weinberg *et al.* in 2016, and after this there has been two larger pivotal studies; the FLARE study published in JACC, and the large pivotal observational FLASH registry published by Toma *et al.* in 2021. Other studies has been performed to evaluate post-procedure device-related complications, post-procedural reduction in RV/LV ratio, device-related death, pre- and post-procedural major bleeding among others.

The FLARE study lead by Tu *et al.* during 2017 and 2018 was a single-arm, multicenter, prospective study that evaluated the safety and effectiveness of the FlowTriever Inari system in 106 patients with acute pulmonary embolism. This study concluded that the FlowTriever Inari system was effective in the removal of blood clots in patients with acute intermediate-risk PE, where the primary effective endpoint was reduction in RV/LV ratio. The average post-procedural RV/LV reduction was 25,1% and the FlowTriever System was considered to have met its performance goal (P<0,0001). The study also revealed that mean intensive care unit stay was only 1,5 days and forty-three patients (41,3%) did not require intensive care unit stay at all (36).

The FlowTriever All-comer Registry of Patient Safety and Hemodynamics (FLASH) Registry by Toma *et al*. during 2018 to 2020, was a multicenter, retrospective study that evaluated the safety and effectiveness of the FlowTriever Inari system in 250 high-and intermediate-high risk patients with PE. The endpoint of the FLASH study was to observe major adverse side-effects within 48h of the index procedure, including device-related death, major bleeding and device- or procedural related adverse events. Secondary endpoints included all- cause mortality through 30 days and device-related serious adverse events within 30 days and like the FLARE study; lengths of post-procedure hospital and intensive care unit stay (37). Some of the safety endpoints from this study was a low 30-day all-cause mortality of 0,4%. There were no device-related deaths and no intra-procedural device- or procedure-related adverse events, including no clinical deteriorations during the procedure. There was a 1,2% major bleeding rate (no events of intracerebral haemorrhages), and there were no device-related cardiac injuries (37).

Weinberg *et al.* in 2016 did the first case report with the use of FlowTriever (Inari Medical, Irvine, California) device. The study was approved by the institutional review board committee at Cedars-Sinai Medical Center. This case report included a 56-year old female with an extensive PE in a transplanted right lung, confirmed by computed tomographic angiography. The medical team working with this patient successfully used the FlowTriever® device for percutaneous endovascular clot removal (38).

Wible *et al.* during 2017 to 2019, included 46 cases of mechanical trombectomy with the FlowTriever device having a technical success rate at 100%. Results showed that the average mean pulmonary artery pressure improved significantly after the procedure for every patient and the intra-procedural reduction in mean pulmonary artery pressure was achieved in 88% of cases (N=37 of 42). Further, there were no delayed procedural complications or procedure-related deaths during 30 days, following hospital discharge. Two major procedure-related complication was registered, one was a case of self-limited haemoptysis in which the patient was extubated within 24h and released within 48h. The second complication was a single outlier maximum haematocrit drop of 15% that resulted in transfusion of 2 units of packed red blood cells (3).

Toma *et al.* in 2019 included patients in a multicenter retrospective analysis treated with FlowTriever if they met the following inclusion criteria; vasopressor dependence, PE induced respiratory failure, or decreased cardiac index (CI) measured by right heart catheterization. Over 50% of patients had >1 absolute or relative contraindication to systemic thrombolysis

(surgery recently performed, trauma patient or active bleeding). As anticipated with the use of aspiration thrombectomy, there was a notable decrease in hemoglobin levels 24 hours after the procedure (from 12,2 ± 0,5 g/dL to 10,5 ± 2,2 g/dL, *P*=0,007). On average, patients stayed in the hospital for 9,8 ± 1,6 days. There were no mortality cases during the follow-up period. Data showed that in this cohort of patients, the procedure resulted in an acute improvement of hemodynamic parameters, with a low rate of procedural failure, therapeutic escalation, and mortality (39).

Markovitz *et al.* preformed a single-center retrospective chart review that examined primary outcomes of post-procedure device-related complications within 30 days of discharge. Ten patients presented with submassiv PE and three patients presented with massive PE. Regarding the main safety outcomes, no major or minor adverse events or technical complications were detected when using either a 22 or 24 French (Fr) sheath and a large-caliber thrombectomy catheter. There were also no complications related to the procedure that appeared later or any deaths within 30 days following hospital discharge (40).

Luedemann *et al.* in 2021 included 27 patients with intermediate-to- high and high-risk PE using the Inari FlowTriever aspiration catheter system as a principal treatment of choice. Their conclusion was that the Inari FlowTriever device can be performed with an acceptable safety-profile even in high-risk PE patients (41).

Moreover, Chandra *et al.* performed a systematic review and meta-analysis of the existing literature to evaluate the safety and efficacy of mechanical aspiration thrombectomy for the treatment of pulmonary embolism. A total of 105 full-text articles were reviewed. Fourteen studies met the inclusion criteria where four were prospective case series and 10 were retrospective case series. Six studies used the FlowTriever device. Chandra *et al*. made point estimates for the proportions of in-hospital mortality, major-bleeding, clinical and technical success, that was comparable data found in previous research on other techniques of thrombectomy, thrombus fragmentation, and CDT. However, the review brings attention to the substantial diversity in the available data, that restricts the ability to make definitive conclusions from the literature. Therefore, conducting high-quality randomized controlled trials is crucial in identifying the most suitable percutaneous treatment for pulmonary embolism (25).

Feroze *et al.* from 2018 to 2021 compared large-bore thrombectomy with catheter-directed thrombolysis for the treatment of pulmonary embolism in patients with acute intermediate- or high-risk PE. The primary outcome of this study consisted of all-cause

mortality up to 1 year. Secondary outcome, among others, included all-cause readmission up to 1 year, and major bleeding defined by intracranial haemorrhage, hemoglobin loss of ≥ 3g/dL, and/or need for blood transfusion. Regarding primary outcome, this study showed that there was no significant difference in all-cause mortality at 1 year between the large-bore thrombectomy and catheter-directed thrombolysis cohorts. Among the secondary outcome, results showed that the bleeding profile amongst the two cohort groups did not show any significant difference, and all-cause rehospitalizations did not differ significantly (42).

Khandhar *et al.* reported 6-month results from the FLASH registry, looking at long-term outcomes following mechanical thrombectomy for intermediate- and high-risk PE patients. Mechanical thrombectomy can provide a rapid hemodynamic improvement after acute PE but the long-term benefits are not clear. In this study, 799 patients were included with a 75% completion rate at the end of the study. Investigations were done examining the long-term mortality, safety and chronic disease outcomes after thrombectomy. During the follow-up, mortality events had a consistent and nearly linear occurrence rate, with all deaths, except for one outlier at 291 days, occurring before 150-days following thrombectomy. After 6-months, 11 patients (1,9%) displayed evidence of chronic thromboembolic disease, while 6 patients (1%) exhibited signs of chronic thromboembolic pulmonary hypertension. Notably, all predefined echocardiographic parameters reflecting right ventricular function, demonstrated a significant improvement from baseline to 48 hours, with even further improvement six months later (43). Similar results were reported in the study by Toma *et al*. observing patients 6-months after treatment with large-bore thrombectomy, performed with the FlowTriever Inari system. Results demonstrated that the percentage of patients with normal right ventricular function on echocardiography increased from 15,1% at baseline to 95,1% after 6 months (P<0,001) (44).

Kong *et al.* compared long-term outcomes of PE managed with endovascular therapies *versus* optimal medical therapy. This single-center, retrospective cohort study included 190 patients with PE that underwent evaluation for the presence of RV dysfunction by transthoracic echocardiography, residual perfusion defects on V/Q scan, and functional capacity by a six-minute walk distance (6MWD), after a period of 3-to-6 month follow-up. During the follow-up period, results showed that 71% of patients who underwent endovascular therapy had right ventricular function returning to normal, whereas only 28% of patients treated solely with medical therapy experienced the same outcome (P<0,001). Notably, there were no significant differences between the endovascular treatment and medical therapy groups regarding

perfusion defects on V/Q scans or the distance achieved in the 6-minute walk test. However, endovascular therapy demonstrated a significant improvement with a higher normalization rate of RV dysfunction, compared to medical therapy alone (76% *vs.* 47%, *P*=0,018), and the greater distance covered during the 6-minute walk test (342 *vs.* 272 meters, *P*=0,025) (45).

All the above-mentioned results of positive long-term outcomes after the use of endovascular thrombectomy suggest that fast extraction of thrombus may prevent long-term sequelae in PE patients, although further research, especially in the form of randomized controlled trials, in this field, are urged (37, 42, 43, 45).

Because acute pulmonary embolism is a common emergency condition associated with a high risk of early mortality, it becomes clear that ensuring rapid and effective treatment options is exceptionally important. For these reasons, in this MD thesis, we wanted to examine and describe a retrospective cohort of all patients with acute pulmonary embolism who were treated with a mechanical aspiration thrombectomy by using the INARI FlowTriever® system. As this represents a novel, catheter-based, interventional modality of treatment for acute PE that was recently adopted by the University Hospital of Split, it was of special interest to examine and describe our first clinical experiences with the usage of this method and determine how this affected outcomes and pathways of care of our patients with acute PE.

2. OBJECTIVES

The main goal of the present study was to examine and describe initial clinical experiences with the use of INARI FlowTriever® device for the purpose of mechanical thromboaspiration in patients with acute pulmonary embolism.

The specific goals of the present thesis were the following:

a) To determine the baseline characteristics and comorbidities of patients with acute pulmonary embolism who were treated with aspiration mechanical thrombectomy at our Center

b) To determine characteristics and risk profile of acute pulmonary embolism among patients who were treated with aspiration mechanical thrombectomy as well as the types of indications based on which this procedure was chosen as a mode of treatment

c) To determine laboratory markers of cardiac injury and distension among patients with acute PE who were treated with thromboaspiration procedure, as well as markers of systemic inflammation and thrombosis encompassing: high-sensitivity cardiac troponin T, NT-proBNP, C-reactive protein, and D-dimers

d) To determine and describe basic echocardiographic characteristics of patients undergoing this procedure

e) To determine the efficacy of mechanical aspiration thrombectomy performed with the INARI FlowTriever® system concerning its impact on relevant hemodynamic parameters including: mean pulmonary artery pressure, heart rate, and peripheral oxygen saturation

f) To determine the safety and feasibility of mechanical thromboaspiration among these patients concerning major complications and procedure-related death

3. MATERIALS AND METHODS

3.1. Study design

This study was designed as a retrospective analysis (cross-sectional study). This research involved analysis of the procedural data and electronic medical records of patients treated for the acute pulmonary embolism at the Cardiovascular Diseases Department, University Hospital of Split during the period from April 2022 to June 2023. Only those patients that were treated with percutaneous mechanical thromboaspiration by using dedicated INARI FlowTriever® system were included in the analysis. Patients with PE were eligible and have met the clinical indication for the mechanical thromboaspiration procedure as per current ESC guidelines for the diagnosis and treatment of pulmonary embolism as well as the ESC/EAPCI clinical consensus statement on percutaneous treatment options for PE (1, 26). This study did not involve any prospective intervention and all patients were treated according to the standards of care and usual clinical judgement for their condition. All data were collected and stored and analzyed in the anonymized fashion and most were derived from the routine hospital electronic health records. This study was approved by the Ethics Committee of the University Hospital of Split (filed under No. 2181-147/01/06/LJ.Z.-23.02). The study was performed in accordance with the declaration of Helsinki.

3.2. Data collection

Patient data were almost exclusively acquired by using the hospital electronic health record system (*IBIS-Integrirani Bolnički Informacijski Sustav*) by the IN2 group d.o.o. Hospital procedural data were double-checked and compared to measurement data provided by the representative of the manufacturer (device proctor). All patients with acute pulmonary embolism diagnosis *per* International Classification of Diseases 10th Revision (ICD-10) diagnostic codes I26.X. were examined. From this pool, data of patients that received mechanical thromboaspiration procedure with INARI FlowTriever® system were extracted.

3.3. Variables of interest

Most of the data acquired were presented in a descriptive fashion. Principal variables of interest included baseline information about the patients included in the analysis and encompassed the following: age (years), sex, presence of comorbidities and other clinical conditions (history of cancer or active cancer, arterial hypertension, atrial fibrillation, diabetes mellitus, smoking, chronic pulmonary disease, thyroid disorder, chronic kidney disease, history

of venous thromboembolism, history of heart failure, and history of cerebrovascular incident). Laboratory parameters of interest were standardly processed in the Hospital central laboratory and included: hemoglobin (g/L), glucose (mmol/L), AST (IU/L), ALT (IU/L), GGT (IU/L), lactate dehydrogenase (IU/L), N-terminal pro brain natriuretic peptide (NT-proBNP, pg/mL), C-reactive protein (CRP, mg/L), high-sensitivity cardiac troponin T (hs-cTnT, ng/L), D-dimer (mg/L), and estimated glomerular filtration rate (eGFR, mL/min./1,73 m^2).

Furthermore, PE-related variables were collected with special scrutiny and included classification of PE anatomical location (unilateral, bilateral, saddle), syncope as initial presentation, dyspnea as initial presentation, underlying etiology of PE (idiopathic, surgery-related, due to immobility, due to stroke, due to active malignancy) as well as the presence of concomitant deep venous thrombosis (DVT), as assessed by the compression Color-Doppler ultrasound. Hemoydnamic and ECG parameters at admission were registered and included mean peripheral oxygen saturation (SpO_2, %), heart rate (HR, bpm), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg) and analysis of the 12-lead electrocardiogram for the presence (or absence) of sinus tachycardia, right bundle branch block (RBBB), and/or dynamic ST-T segment changes. Patients were specifically examined for the PE risk classification according to the currently valid ESC guidelines (low, intermediate, intermediate-low, intermediate-high, high-risk PE) as well as clinical indication for mechanical percutaneous thromboaspiration (deterioration of hemodynamic status despite full therapeutic anticoagulation, contraindications or failure of systemic thrombolysis, etc.). A simplified pulmonary embolism severity index (sPESI score) was calculated for each patient.

Transthoracic echocardiographic parameters were measured for each patient and included assessment of the right ventricular (RV) dysfunction (present/absent), left ventricular ejection fraction (LVEF, %), tricuspid annular plane of systolic excursion (TAPSE, mm), right ventricular dimension index (RVDI, mm), peak pressure gradient (PPG, mmHg) and pulmonary velocity acceleration time (PVAccT, msec).

Procedure-related variables that were assessed before and/or after the procedure, on the table, were SBP and DBP (only before procedure), SpO_2 (before and after the procedure), mean pulmonary artery pressure (mPAP, mmHg - measured before and after the procedure), HR (before and after the procedure). Full procedural success was considered if at least 25% of reduction in mPAP was observed, accompanied with significant visual resolution of the thrombotic mass as per image provided by the post-procedural pulmonary artery angiograms. If this was not achieved, procedure was considered as a partial success.

In-hospital outcomes of interest were in-hospital death due to any cause, procedure-related death, use of mechanical ventilation at any point during the hospitalization as well as the length of stay (LoS) in days (including post-procedural LoS and total LoS). We also examined records for the procedure-related complications (primarily vascular and bleeding complications). Similarly, pre-procedural anticoagulation regimens as well as anticoagulation therapy at discharge were examined.

3.4. Statistical analysis

All statistical analyses were carried out by using SPSS Statistics for macOS (version 23.0, Armonk, NY, USA) and GraphPad Prism for macOS (version 9, La Jolla, CA, USA). For the most part, standard descriptive statistics were used with the normality of data checked by using Shapiro-Wilk test. Data were shown as mean ± standard deviation (SD) or as median (interquartile range-IQR) based on the normality of distribution. To determine significance and magnitude of effect of percutaneous thromboaspiration on the parameters of mPAP, HR, and SpO_2 before and after procedure, a pair-wise student t-test in a *"before-after"* fashion was performed. All statistical significance values (*P*) were two-tailed and results with $P<0{,}001$ were considered statistically significant.

4. RESULTS

4.1. Description of a patient cohort with acute PE treated with thromboaspiration

As presented in **Figure 7**, the mean age and standard deviation of included patients was 61,7±14,2 years of age. A total of 14 patients were included in the analysis (intention to treat with INARI FlowTriever® device) with equal distribution with respect to sex (7 female and 7 male patients) while 13 thromboaspiration procedures were performed. All PEs were verified by the CTPA. Concerning the underlying etiology of PE, recent surgery or idiopathic etiology were equally the most common as shown in **Figure 8**. Regarding the anatomical location of PE, defined by computed tomography of pulmonary arteries, most of the embolisms were saddle thrombi (N=7, 50%), followed by bilateral PE (42,9%) while unilateral PE occured in only one case **(Figure 9)**. The presence of concomitant deep venous thrombosis, verified and confirmed by the Color-Doppler compression ultrasound of the limbs, performed during index hospitalization, occured in nearly half of the cases (42,9 %, N=6), as illustrated in **Figure 10**.

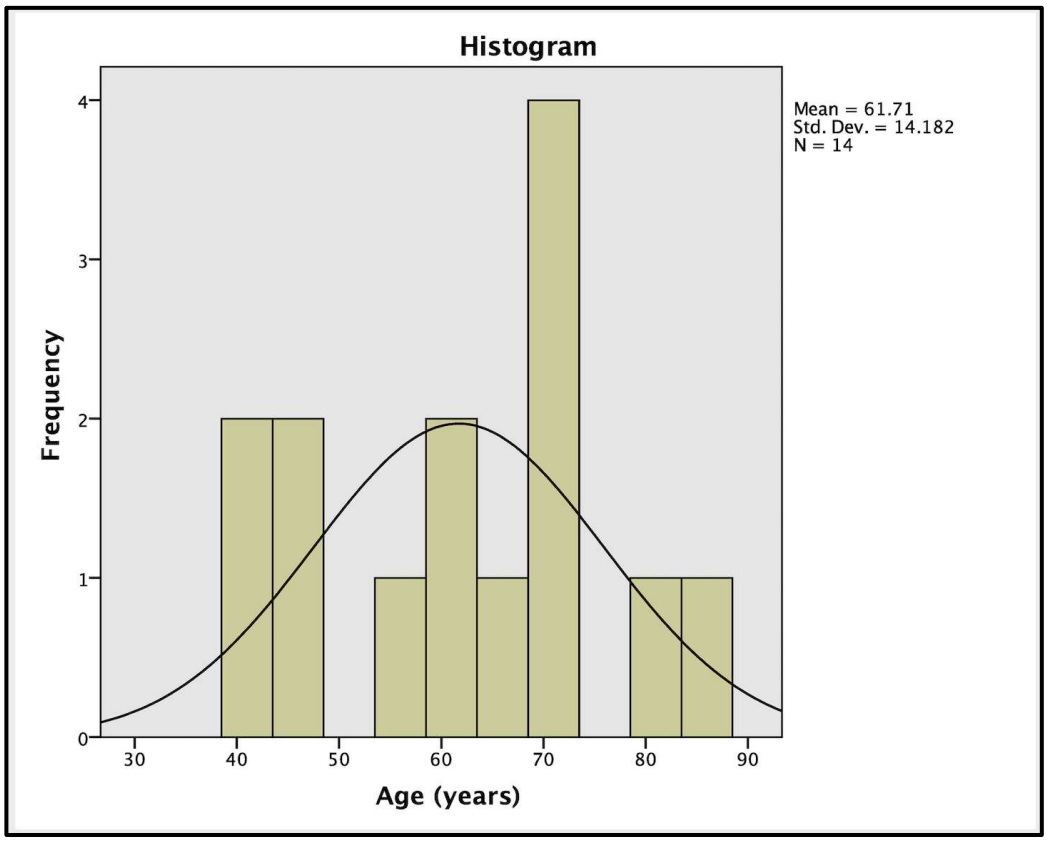

Figure 7. Frequency histogram depicting the average age of the included cohort of patients

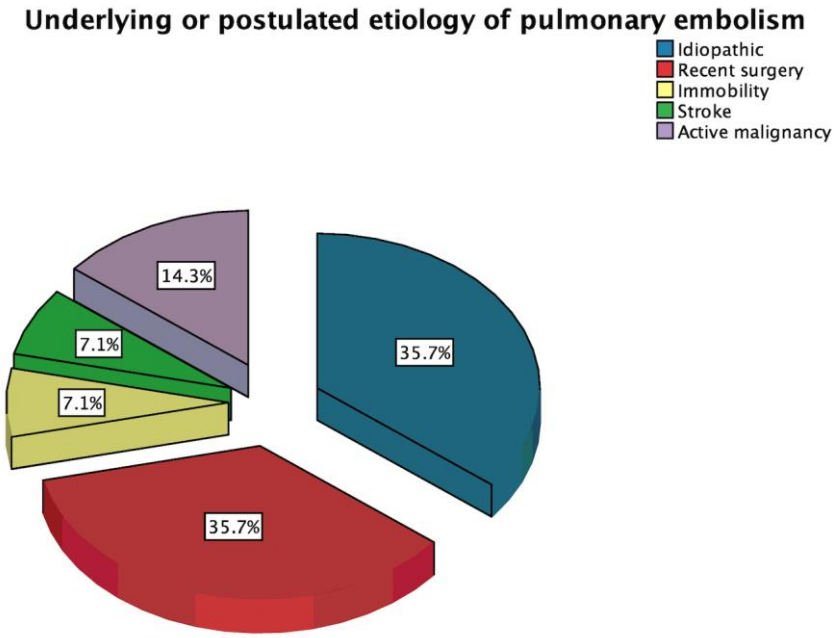

Figure 8. Underlying or postulated etiology of pulmonary embolism presentation

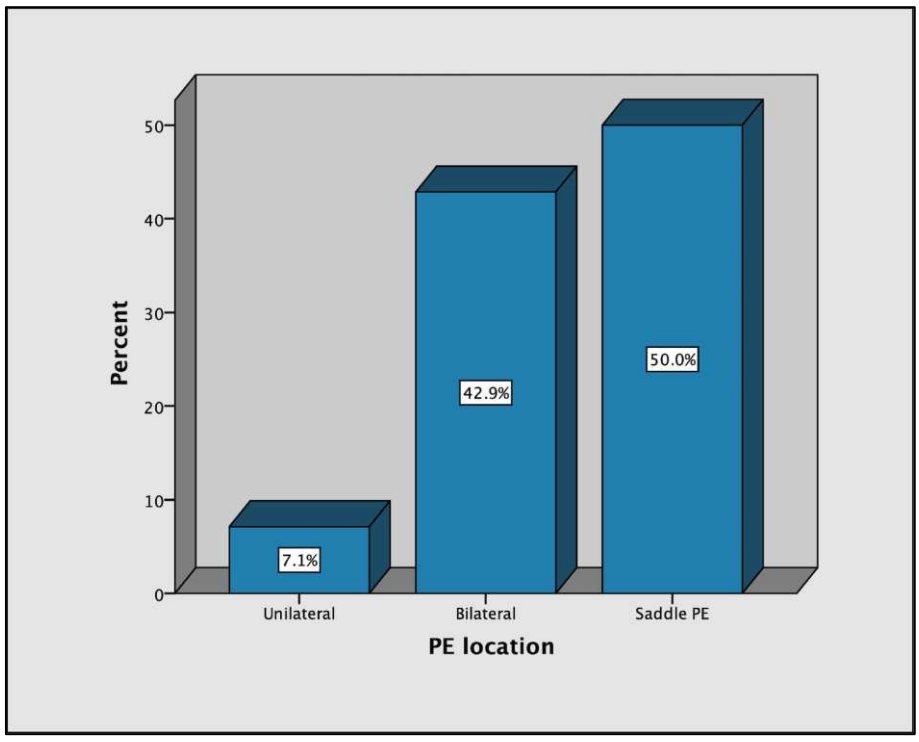

Figure 9. Anatomical location of PE as verified by the computed tomography of pulmonary arteries

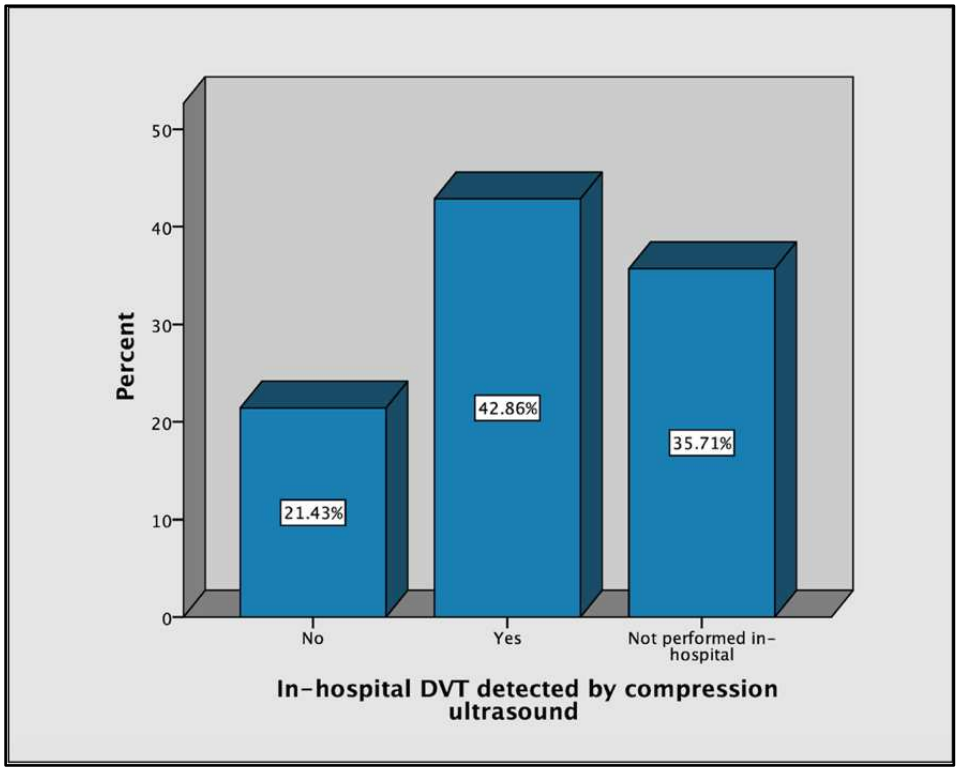

Figure 10. The prevalence of deep venous thrombosis detected and verified by the Color-Doppler compression ultrasound of the limbs, performed in hospital

4.1.2. Clinical characteristics and comorbidities of enrolled patients

Nearly two-thirds of analysed patients had sinus tachycardia at index presentation (64,3%), while 35,7% did not have sinus tachycardia. Two patients experienced syncope as their first presentation while majority of patients (85,7%) did not have a loss of consciousness. Almost all patients (N=12, 85,7%) had dyspnea at presentation. Mean peripheral SpO_2 at admission was 91,3%, with mean systolic blood pressure of 117,6 mmHg and average heart rate of 105,6 bpm. Half of patients (50%) had pathologic ST-T segment deviations on the 12-lead ECG (dominantly T-wave inversions in the anterior precordial leads) while three patients (21,4%) presented with a right bundle branch block. Patient comorbidities are presented in **Table 1**. The most common comorbidity amongst our patients was arterial hypertension (N=8, 57,1%) while a substantial proportion of patients had either history of cancer or active malignant disease. Nearly one-third of patients were active or ex-smokers (N=4, 28,6%).

Table 1. Baseline characteristics of included patients with respect to medical conditions

Condition	N of patients	Percentage
History of cancer	6	42,9%
Active malignant disease	2	14,3%
Arterial hypertension	8	57,1%
Atrial fibrillation	1	7,1%
Diabetes mellitus	1	7,1%
Smoking	4	28,6%
Chronic pulmonary disease	3	21,4%
Thyroid disorder	3	21,4%
Chronic kidney disease	2	14,3%
History of venous thromboembolism	1	7,1%
History of heart failure	1	7,1%
History of cerebrovascular incident	1	7,1%

Laboratory diagnostic parameters measured at the hospital admission are presented in the **Table 2**.

Of special interests were values of cardioselective biomarkers that are important for the prognosis in PE. Therefore, the median value of high-sensitivity cardiac troponin T at admission was 56,9 ng/L (IQR 46,9-84,8 ng/L) while median circulating level of NT-proBNP was 2033 pg/mL (IQR 387-4670 pg/mL). The median C-reactive protein level was 13,5 mg/L (IQR 8,1-97,6 mg/L) while median D-dimer level at admission was 11,9 mg/L (IQR 6,0-22,7 mg/L).

Table 2. Values of laboratory parameters from peripheral blood at admission. Results are presented as mean±standard deviation or median (interquartile range), based on the statistical normality of distribution

Condition	Value
Hemoglobin (g/L)	136±18,8
Glucose (mmol/L)	8,7±3,1
AST (IU/L)	35 (24-71)
ALT (IU/L)	41 (19-107)
GGT (IU/L)	33 (19-81)
Lactate dehydrogenase (IU/L)	255 (206-389)
NT-proBNP (pg/mL)	2033 (387-4670)
hs-cTnT (ng/L)	56,9 (46,9-84,8)
C-reactive protein (mg/L)	13,5 (8,1-97,6)
D-dimer (mg/L)	11,9 (6,0-22,7)
eGFR (mL/min./1.73m^2)	66,7±34,2

Abbreviations: eGFR-estimated glomerular filtration rate

4.1.3. Echocardiographic findings

Signs of right ventricular dysfunction as evidenced by transthoracic echocardiography during hospitalization were seen in nearly all patients (92,3%, **Figure 11**). On transthoracic echocardiography the mean left ventricular ejection fraction (LVEF) was 58,4±10,1%, mean tricuspid annular plane of systolic excursion (TAPSE) was 17,3±4,3 mm, mean right ventricular dimension index (RVDI) was 41,7±6,0 mm, peak pressure gradient (PPG) was 46,4±7,7 mmHg while mean pulmonary velocity acceleration time (PVAccT) was 74,4±28,4 msec.

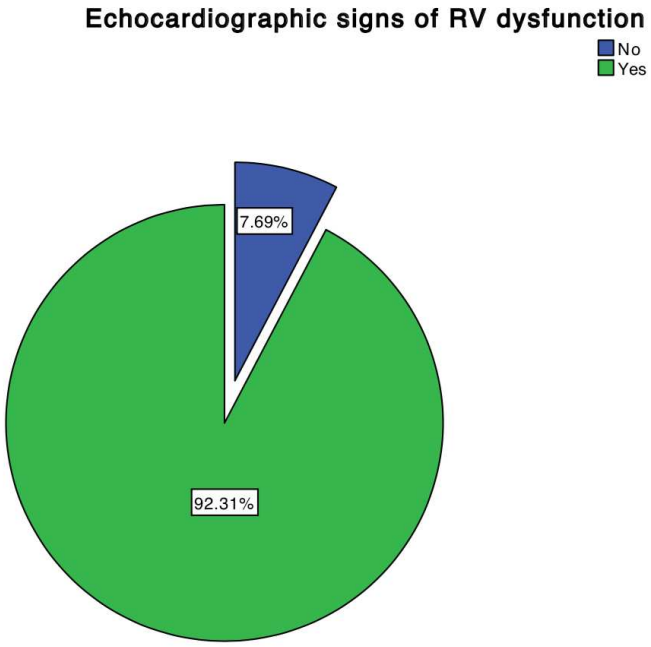

Figure 11. Prevalence of right ventricular dysfunction as assessed by transthoracic echocardiography

4.1.4. In- hospital outcomes

The median length of hospital stay (days post-procedure) was 6 days (IQR 4,5-11,5 days). The median of total length of stay (whole hospitalization) was 7 days (IQR 5-13,8 days). One patient required mechanical ventilation at any point during hospitalization (7,1%) while three deaths during the whole period of hospitalization were recorded (21,4%). None of the deaths were adjudicated as related to thromboaspiration procedure and did not occur during or shortly after the procedure. One death event occurred in a patient who had an end-stage malignant disease with systemic dissemination (metastatic melanoma) and in whom palliative goals of care were set. One patient that died had an active brain malignancy (primitive neuroectodermal tumor of the brain) that was only partially oncologically treated while one death occurred in a frail patient with advanced age and multiple comorbidities who suffered concomitant ischemic stroke at presentation and was also mechanically ventilated. After the thromboaspiration procedure, that was performed in 13 patients, post-procedural anticoagulation was administered in all patients. More specifically, eleven patients received

full therapeutic dose of low-molecular weight heparin (85%) while two patients received prophylactic dose of LMWH (15%).

All patients that survived hospitalization were prescribed with full therapeutic anticoagulation regimen at hospital discharge and direct oral anticoagulants (DOACs) were most commonly prescribed (72,7% of cases) while 27,3% of patients received parenteral anticoagulation, as shown in **Figure 12**. Most commonly prescribed DOAC was apixaban that was prescribed in 36,4% of cases, followed by rivaroxaban (18,2%), edoxaban (9,1%) and dabigatran (9,1%).

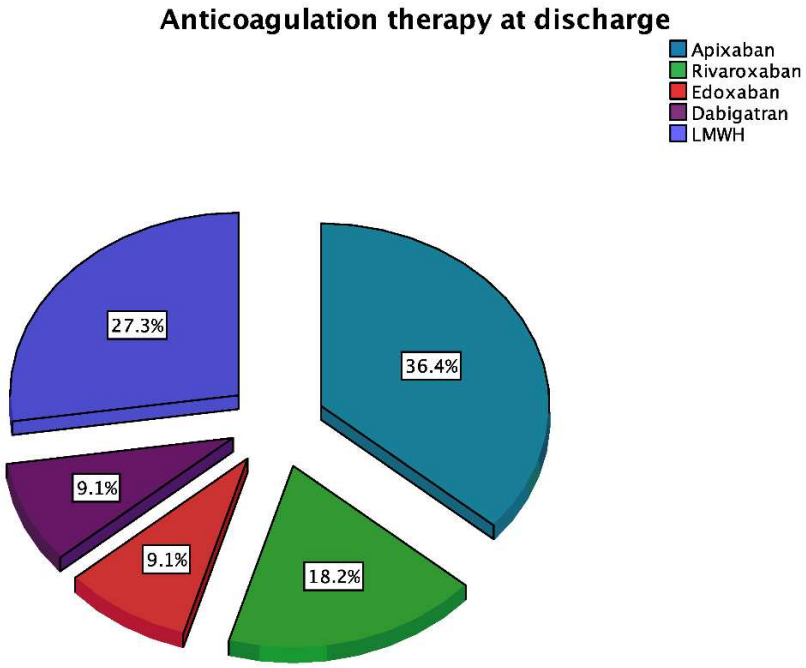

Figure 12. Distribution of anticoagulation therapies prescribed at discharge

4.2. Indications for percutaneous mechanical thromboaspiration and risk stratification among included patients

In our study, most of the patients indicated for the thromboaspiration treatment were due to persistent deterioration of hemodynamic and/or respiratory status despite full therapeutic anticoagulation and other supportive measures (N=11, 78,6% of patients), one patient had a

contraindication to systemic thrombolysis while two had contraindication to full therapeutic dose of anticoagulant or anticoagulation was deemed risky (N=2, 14,3%).

With respect to PE risk stratification, nearly all of our patients belonged to intermediate-to-high risk category per ESC guidelines (N=13, 92,9%) while there was only one case of high-risk PE (7,1%). According to calculated sPESI score, all enrolled patients were classified as high-risk (N=14, 100%) with mean sPESI score of 2,0±1,1 points.

4.2.1. Procedural results

There were a total of 13 mechanical thromboaspiration procedures performed with Inari FlowTriever® system, with intention to treat 14 patients who met the clinical indication. In case of one patient, thromboaspiration procedure was not initiated at all due to the right ventricular perforation caused by hydrophilic guidewire during the initial diagnostic catheter positioning. This complication caused a non-dynamic pericardial effusion (3 mm at the RV border and 5 mm at the inferoapical region) that did not cause any hemodynamic compromise of a patient and did not progress to cardiac tamponade. Patient was intensely monitored with respect to vital signs while possible pericardial effusion expansion was evaluated several times in the next 48 hours by using the standard transthoracic echocardiographic protocols. This patient was treated conservatively and was successfully discharged from the hospital.

The mean arterial pressures, on the table and before intervention were following: systolic blood pressure of 109,5±30 mmHg and diastolic blood pressure of 72,9±18 mmHg.

Out of 13 performed procedures, full procedural success with excellent angiographic result and marked reduction in mean pulmonary artery pressure (mPAP) was achieved in 85% of cases (11/13 procedures) while in 15% of cases (2/13 procedures) there was a partial procedural success with only slight-to-moderate improvement of the final angiographic result and or mPAP reduction. In these 2 cases, one patient had a chronic thromboembolic pulmonary hypertension (CTEPH) and other had superior vena cava syndrome with concomitant pulmonary embolism and a large mass of organized, white, old thrombus that did not respond adequately to thromboaspiration.

In general, a significant reduction (P<0,001) in mean pulmonary artery pressures was observed - from the mean of 33,6±7,3 mmHg before thromboaspiration to mean of 16,6±5,6 mmHg immediately after thromboaspiration (**Figure 13**).

The average reduction in mPAP was -17,0±6,7 mmHg (95% confidence interval of pressure reduction ranging from -13,0 to -21,0 mmHg).

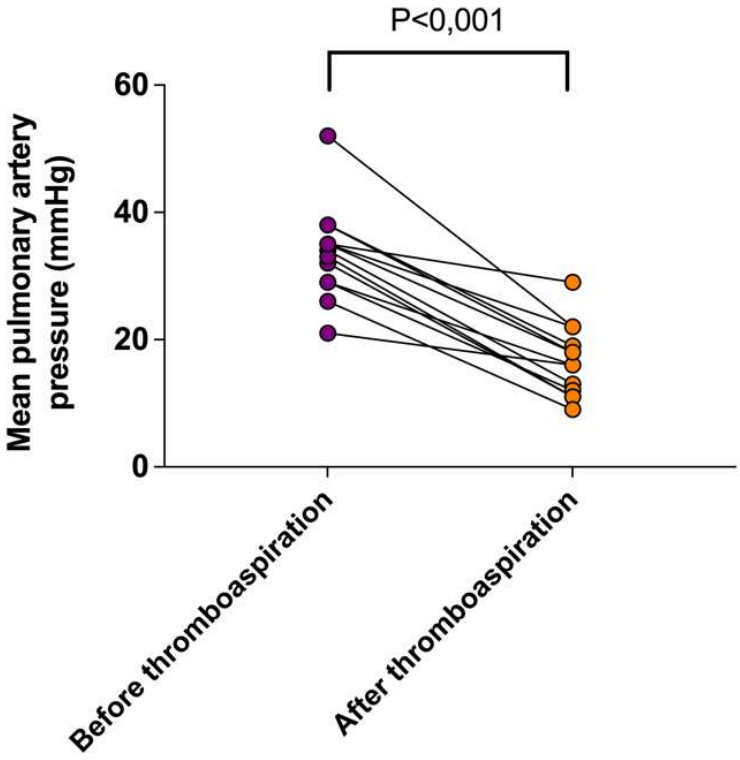

Figure 13. Mean pulmonary artery pressures before and after thromboaspiration

Similarly, a significant reduction in heart rate was observed (P<0,001) as mean heart rate measured before intervention was 115±21 bpm while it decreased to 92±11 bpm following the intervention (**Figure 14**). The mean reduction of HR observed was -23±14 bpm (95% confidence interval of HR reduction ranging from -15 to -32 bpm).

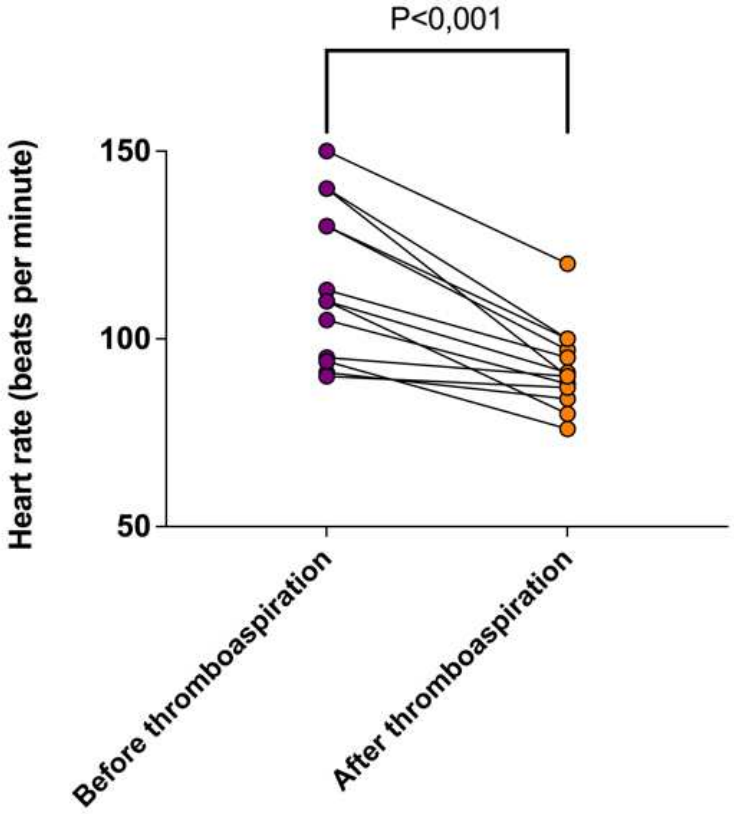

Figure 14. Mean heart rate before and after thromboaspiration

Finally, we observed a significant improvement in peripheral oxygen saturation, as SpO_2 increased from the mean of 88,8±6,5 % before procedure to 97,3±3,2 % after the procedure (P<0,001), as shown in **Figure 15**.

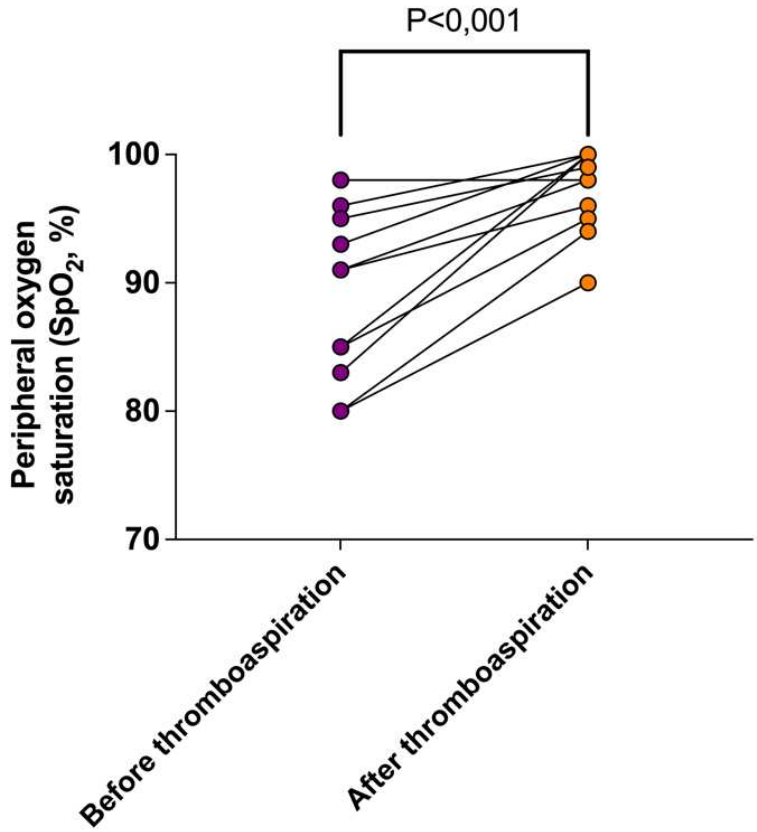

Figure 15. Peripheral oxygen saturation before and after thromboaspiration

5. DISCUSSION

The aim of this work was to describe our initial experiences with the use of INARI FlowTriever® mechanical thromboaspiration system for treating patients with intermediate-to-high and high-risk acute pulmonary embolism. Herein, we will comment on our experiences at University Hospital of Split and compare them to similar studies available in the existing literature (including registries, studies or case-series), emphasizing the efficacy, feasibility, and safety of this procedure.

In short, we report that the use of INARI FlowTriever® device was effective, feasible and safe treatment option, without procedural complications and procedure-related deaths among patients with intermediate-to-high and high-risk PE. This device was able to confer positive effects on relevant hemodynamic parameters as evident in significant and immediate reduction of mean pulmonary artery pressures, abrogation of tachycardia and improvement in peripheral oxygen saturation. We report a procedural success rate with excellent angiographic result and marked reduction of pressures in pulmonary circulation in 85% (N=11) of cases.

So far, in regards to technical success, a high level of procedural success rate with this system was also reported in similar studies. For example, Wible *et al.* reported a 100% technical success rate with the use of INARI FlowTriever® system (3). A study by Markoviz *et al.* revealed no adverse events or technical complications associated with the use of this system when using even largest diameter sizes of catheter such as 22 or 24 French (40). Further on, Salinas *et al*. had a high success rate of catheter-based thrombectomy (defined as technical procedure completed without procedural complications or 48-hour deaths) at 90,9% (46). In the FLASH registry there were no procedural recorded deaths and no intra-procedural device- or procedure-related adverse events (37). The above-mentioned results strongly suggest that Inari FlowTriever® thromboaspiration is a safe device that can be used for percutaneous thrombus retrieval in patients with PE and has very low rate of procedural complications.

In several studies mentioned in the introduction segment of this paper, mean post-procedural mPAP was significantly reduced. In the FLASH registry, mPAP reduced significantly by 22.2% (P<0,001). Wible *et al*. reported significantly improved mPAP in 88% of their patients, and this result is comparable to our cohort where we achieved significant and immediate reduction of mPAP in 85% of patients. In two of our patients we observed a partial improvement in mPAP as mPAP was reduced, but only marginally. One of these two patients had CTEPH with huge territory of old and chronic pulmonary tree thrombi while another patient had *superior vena cava syndrome* with great amount of old white thrombus.

In the FLARE study, average post-procedural mPAP decreased significantly from pre-procedure (29,8 mm Hg vs. 27,8 mm Hg), similar to our result from the mean of 33,6±7,3 mmHg vs. mean of 16,6±5,6 mmHg post- thromboaspiration.

A significant improvement in tachycardia (P<0,001) was seen in our patient cohort, and this finding was similar to the finding of Luedemann *et al.* that also confirmed post-procedural reduction of tachycardia (P<0,001) (41). In addition, the researchers in this study also reported a significant post-procedural decrease in mPAP (P=0,002).

In our cohort, we report a marked respiratory status improvement as reflected in increased peripheral oxygen saturation (88,8±6,5% before procedure *vs.* 97,3±3,2% after procedure). Taken together, these important clinical and cardiorespiratory parameters that were improved post-procedurally provide unequivocal evidence that this method was efficient and provided rapid hemodynamic relief for the patients.

In a retrospective study conducted by Markovitz *et al.*, no post-procedural complications and no deaths were recorded within 30-days following hospital discharge and they also used Flowtriever® device as the catheter-directed treatment for PE (40). In our cohort, we registered three in-hospital deaths, however, these events were not associated with the procedure itself and should be interpreted in the context of severe comorbidities, advanced age and active long-standing malignant disease that were present in these patients. Toma et al. reported, in the long-term outcomes analysis that included 800 patients from the US cohort of FLASH Registry treated with FlowTriever®, that all-cause mortality was 0,3% at the 48-hour visit, 0,8% at the 30-day visit, and 4,6% at the end of the enrolment of the study (median was 199 days following thromboaspiration) (44).

It is also important to note that mechanical thromboaspiration with INARI FlowTriever® also exerts positive and sustained hemodynamic effects on important echocardiographic parameters that reflect RV function in patients with PE. An extended analysis from the FLASH Registry revealed that, at the 6-month follow-up after the use of FlowTriever®, right ventricular function was normalized in 95,1% of patients, right ventricular size was normalized in 88,2% of patients, mean RV-to-LV ratio was 0,80 while mean RV systolic pressure was 27,3 mmHg (43). Toma *et al.* reported similar results on the full sample of 800 patients from the US cohort - they reported that a percentage of patients with normal RV function on echocardiography increased to 95,1% from the baseline of 15,1% (44). These positive long-term outcomes highlighted above, following the use of thromboaspiration technique with FlowTriever®, are encouraging and indicate that mechanical extraction of thrombotic mass in acute PE not only provides acute relief

and abolishes short-term mortality in PE but also provides sustained and long-term benefits for PE patients.

However, these studies were observational and designed in a single-arm fashion while in the future we need randomized controlled trials that are required to confirm these results and validate them against other modalities of treatment such as catheter-directed thrombolysis and medical antithrombotic therapy. As of this moment, such efforts are ongoing - PEERLESS study is an active randomized controlled trial that is designed to execute *head-to-head* comparison between aspirational thrombectomy with FlowTriever® system against catheter-directed thrombolysis in patients with PE (ClinicalTrials.gov Identifier: NCT05111613). As of this moment, the only prospective study that was stopped prematurely was the FlowTriever for Acute Massive Pulmonary Embolism (FLAME) study (ClinicalTrials.gov Identifier: NCT04795167) that evaluated the effects of FlowTriever® *vs.* other therapies on the composite outcome of all-cause mortality, clinical deterioration, bailout and major bleeding from the time of the primary treatment for high-risk pulmonary embolism through hospital discharge or 45 days. This study was stopped prematurely because mortality rate in the FlowTriever® arm was only 1,9% compared to the context arm that exhibited mortality of 29,5%. Similarly, composite outcome occured in 17% of cases in the FlowTriever arm while it occurred up to staggering 63,9% in the context arm.

The treatment of intermediate-to-high and high-risk PE imposes a serious clinical challenge, particularly in patients that are experiencing acute clinical deterioration despite full anticoagulation regimen or those who have contraindications to thrombolytic therapy or in whom thrombolytic therapy failed. Several studies have demonstrated the clear usefulness of mechanical thromboaspiration in such cases, as it can be performed in a short time frame of less than 2 hours, without the need for thrombolytic drugs. In a study conducted by Wible *et al.* it was found that as much as 26% of patients had contraindication to tissue plasminogen activator (tPA) (3). Treatment with endovascular interventional approach made it possible for these patients to be treated without the need to utilize thrombolytic therapy and they were able to receive likely a life-saving procedure. In our cohort, one patient had a contraindication for thrombolysis while two patients had contraindication to full therapeutic dose of anticoagulant and were clinically deteriorating, thus making the percutaneous thrombectomy with Inari FlowTriever® device an effective and safe treatment modality for these patients.

One of the limitations of this work is that this was not a randomized study neither we made any comparison of thromboaspiration *versus* any other treatment modality such as heparin or catheter-directed thrombolysis in the intermediate-to-high risk group or systemic thrombolysis in

the high-risk group. However, there has been an active current research in this field. Of note, catheter-based treatments for PE were found to be associated with a reduction of mortality compared with medical therapy. Kong *et al*. in a retrospective study of long-term follow-up in patients presenting with acute PE, showed that those patients receiving endovascular therapy (EVT) together with medical therapy, had a significantly greater improvement in RV dysfunction compared to patients treated with medical therapy alone, at 3 to 6-month follow-up (45). Results revealed that 71% of patients who received EVT had normalization of their RV function compared to 28% of patients that were treated with medical therapy alone (P<0,001).

Very recently, Iannaccone *et al.* conducted a meta-analysis of 77 studies involving nearly 1,2 million patients, reported that a 30-day mortality rate for patients with intermediate-to-high risk pulmonary embolism who received medical therapy was 9,1%, and 9,5% rate in patients with PESI score >3. Even longer-term mortality in medical therapy group was rather high, with a mean mortality rate of 21,5% at follow-up over 2,1 years. In contrast to the 30-day mortality rate observed in cohorts receiving medical management, findings revealed a low - 2,1% 30-day mortality rate in the interventional catheter-directed therapy (CDT) cohort. Interestingly, the CDT group also exhibited a remarkably low overall (predominantly minor) bleeding rate of 4,9% (varying from 2,4% to 8,9%). These findings emphasize the safety and efficiency of percutaneous directed therapy in relation to bleeding risk and long-term mortality outcomes among patients with intermediate-to-high risk acute PE (47).

Based on the results of this thesis and discussion elaborated above, we hold that percutaneous mechanical thromboaspiration and catheter-directed modalities should be regarded as legitimate methods for the treatment of patients with intermediate-to-high risk PE and selected patients with high-risk PE. However, future randomized trials and carefully designed prospective studies are required to confirm these clear signals of benefit obtained from dominantly observational studies and meta-analyses. This is very important from the practical standpoint since these findings are surely to change current practical guidelines for the acute PE treatment.

In our study, it was demonstrated that percutaneous mechanical thromboaspiration with INARI FlowTriever® device was feasible, safe, and effective in treating patients with acute PE.

6. CONCLUSIONS

This thesis aimed to examine the feasibility, safety, and efficacy of percutaneous mechanical thromboaspiration with the INARI FlowTriever® device.

Based on the results from our retrospective analysis of hospitalized patients with acute PE, treated with percutaneous mechanical thromboaspiration, we observed the following:

- Percutaneous mechanical thromboaspiration with INARI FlowTriever® device is a viable and effective treatment of acute pulmonary embolism in selected patients with intermediate-to-high and high-risk PE.
- The procedural success rate was high, with a full success achieved in 11/13 patients (85%) while partial success was achieved in 2/13 patients (15%).
- Excellent angiographic results and significant reduction in mean pulmonary artery pressures (mPAP decreased from 33,6±7,3 mmHg before the procedure to 16,6±5,6 mmHg after the procedure, $P<0,001$).
- Significant reduction in heart rate was observed ($P<0,001$), as mean heart rate measured before intervention was 115±21 bpm while it decreased to 92±11 bpm following the intervention, providing evidence of rapid hemodynamic improvement.
- Significant improvement of peripheral oxygen saturation with an increase in mean SpO_2 from 88,8±6,5 % before to 97,3±3,2 % after the procedure ($P<0,001$).
- No procedure-related deaths or procedure-related complications (including vascular and bleeding complications) were observed.

In summary, we can conclude that percutaneous mechanical thromboaspiration with the INARI FlowTriever® device is a safe and effective treatment option for treating acute intermediate-to-high and high-risk PE. However, future research is needed and should focus on conducting randomized controlled trials to confirm and validate these results up-against other treatment modalities, such as catheter-directed thrombolysis or other contextual therapies.

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8. SUMMARY

Objectives: Acute pulmonary embolism is a common medical emergency associated with a high risk of early mortality. The present thesis aimed to examine and describe the cohort of patients with acute pulmonary embolism (PE) who underwent catheter-directed percutaneous mechanical thromboaspiration with INARI FlowTriever® device and to assess safety and feasibility of this interventional method in this group of patients.

Patients and methods: We retrospectively analyzed hospital records of all patients that underwent percutaneous mechanical thromboaspiration with INARI FlowTriever® device for acute PE since the adoption of this treatment method at the Cardiovascular Diseases Department, University Hospital of Split in April 2022 until June of 2023. Standard descriptive statistics were used to describe the cohort of PE patients and disease characteristics while for the assessment of the effectiveness of this treatment, we used a *"before-after"* pairwise student t-test for comparison concerning relevant procedural hemodynamic variables such as mean pulmonary artery pressure (mPAP) measured invasively, heart rate (HR) and peripheral oxygen saturation (SpO_2).

Results: A total of 14 patients who met clinical indications for mechanical thromboaspiration were analyzed while 13 procedures were performed. The mean age of the population was 61,7±14,2 years while 7 patients were women and 7 were men. Most of the PEs were saddle PEs affecting main branch bifurcation (50%), followed by bilateral (42,9%) and unilateral PE (7,1%). The vast majority of patients belonged to the intermediate-to-high risk category as per ESC guidelines (92,9%) while one patient was high-risk. The most common identifiable etiology of PE was recent major surgery (35,7%) while non-identifiable, idiopathic etiology was equally represented (35,7% of all cases). The mean length of hospital stay after procedure was 6 days (IQR 4,5-11,5). The median NT-proBNP levels and high-sensitivity cardiac troponin T values were 2033 pg/mL (IQR 387-4670) and 56,9 ng/L (IQR 46,9-84,8), respectively. Procedure-wise, mechanical thromboaspiration with INARI FlowTriever® device was associated with a significant reduction of mPAP (from 33,6±7,3 mmHg before the procedure to 16,6±5,6 mmHg after the procedure, P<0,001), reduction in HR (from 115±21 bpm before the procedure to 92±11 bpm after the procedure, P<0,001), and improvement in SpO_2 (from 88,8±6,5 % before the procedure to 97,3±3,2 % after the procedure, P<0,001). Full procedural success was achieved in 11/13 patients (85%) while partial success was achieved in 2/13 patients (15%). No procedure-related complications or procedure-related deaths were observed. All patients were anticoagulated with parenteral low-molecular weight heparin regimen after the procedure. During the whole hospitalization, 11 out of 14 patients were

discharged while 3 out of 14 patients died (21,4%), all of them due to the severity of underlying comorbidities and/or advanced age while none of these deaths were associated with the procedure.

Conclusion: Percutaneous mechanical thromboaspiration with the INARI FlowTriever® device was a safe and effective treatment option among patients with intermediate-to-high or high-risk PE.

9. CROATIAN SUMMARY

NASLOV RADA: Uporaba INARI FlowTriever® aspiracijskog trombektomijskog sustava u liječenju akutne plućne embolije: inicijalna iskustva u Kliničkom bolničkom centru Split

Ciljevi: Akutna plućna embolija je učestalo medicinsko hitno stanje koje je povezano sa visokim rizikom rane smrtnosti. U ovom radu, cilj je bio opisati kohortu pacijenata sa akutnom plućnom embolijom (PE), a koji su liječeni kateterom posredovanom mehaničkom tromboaspiracijom koristeći INARI FlowTriever® sustav. Nadalje, cilj rada je bio procijeniti sigurnost i izvedivost korištenja navedene metode u toj skupini pacijenata.

Pacijenti i metode: Retrospektivno su analizirani bolnički podatci svih pacijenata sa akutnom plućnom embolijom koji su liječeni metodom perkutane mehaničke tromboaspiracije sa INARI FlowTriever® sustavom od trenutka prve uporabe metode u travnju 2022. godine, zaključno sa lipnjom 2023. godine, na Klinici za bolesti srca i krvnih žila Kliničkog bolničkog centra Split. Standardna deskriptivna statistika je korištena za opis navedene kohorte pacijenata sa plućnom embolijom dok je za procjenu učinkovitosti navedene metode liječenja korišten *"prije-poslije"* upareni student t-test za usporedbu i analizu relevantnih proceduralnih hemodinamskih varijabli kao što su srednji tlak u plućnoj arteriji (mPAP) koji je mjeren invazivno, srčana frekvencija (HR) i periferna saturacija kisikom (SpO_2).

Rezultati: Ukupno je analizirano 14 pacijenata koji su imali kliničku indikaciju za mehaničku tromboaspiraciju dok je učinjeno 13 procedura. Prosječna starost populacije bila je 61,7±14,2 godina, 7 pacijenata bile žene, a 7 muškarci. Većina plućnih embolija su bile one sa jašućim trombom na bifurkaciji (50%), 42,9% su bile bilateralne i jedna unilateralna (7,1%). Većina pacijenata je pripadala skupini srednjeg-visokog rizika prema ESC-ovim smjernicama (92,9%) dok je jedan pacijent bio visokog rizika. Najčešća identificirana etiologija plućnog embolizma bila je nedavni kirurški zahvat (35,7%) dok je idiopatska etiologija plućne embolije bila zastupljena u jednakom broju slučajeva (35,7%). Medijan tranja hospitalizacije bio je 6 dana (interkvartilni raspon-IQR 4,5-11,5). Medijan vrijednosti NT-proBNP-a i visoko-senzitivnog srčanog troponina T iznosii su 2033 pg/mL (IQR 387-4670) odnosno 56,9 ng/L (IQR 46,9-84,8). Proceduralno, mehanička tromboaspiracija sa INARI FlowTriever® sustavom je bila povezana sa značajnom redukcijom mPAP-a (33,6±7,3 mmHg prije procedure na 16,6±5,6 mmHg nakon procedure, P<0,001), redukcijom srčanom frekvencije (od 115±21 otkucaja/min. prije procedure na 92±11 otkucaja/min. nakon procedure, P<0,001) te poboljšanjem SpO_2 (od 88,8±6,5 % prije procedure na 97,3±3,2 % nakon procedure, P<0,001). Potpuni proceduralni uspjeh je postignut u 11/13 pacijenata (85%) dok je djelomično uspješan rezultat postignut u

2/13 pacijenata (15%). Nije zabilježeno komplikacija ili smrtnih ishoda vezanih za samu proceduru. Svi pacijenti su nakon procedure bili antikoagulirani sa parenteralnim aplikacijama niskomolekularnog heparina. Od svih pacijenata, 11 je otpušteno iz bolnice, a 3 pacijenta su umrla za vrijeme hospitalizacije radi razloga u čijoj su pozadini bili brojni komorbiditeti i/ili uznapredovala životna dob. Nijedna unutarbolnička smrt nije bila dovedena u vezu sa samom procedurom.

ZAKLJUČCI: Perkutana mehanička tromboaspiracija sa INARI FlowTriever sustavom se pokazala kao sigurna i učinkovita metoda liječenja pacijenata sa akutnom plućnom embolijom srednjeg do visokog ili visokog rizika.