Safety and Effectiveness of Catheter-directed Thrombolysis Compared to Systemic Thrombolysis in Treating Massive and Submassive Pulmonary Embolism with Hemodynamic Compromise - A literature review

Emmanuel Hernandez

PA-S, Bsc Nursing, RNBN

hernand4@myumanitoba.ca

Advisor:

Cameron Krisko, CCPA, MPAS, B.Sc.

A capstone project submitted to the Faculty of Graduate Studies of

The University of Manitoba, in partial fulfillment of the requirements for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

University of Manitoba

Max Rady College of Medicine

Winnipeg, Canada

May 15, 2023

Table of Contents

1. Abstract…… 3
2. Introduction…….. 4
3. Objectives…… 7
4. Methods……...… 7
5. Results…….. 8
6. Discussion…….. 17
7. Conclusion……. 20
8. Acknowledgement……. 22
9. Reference……... 23
10. Appendix…… 26

Abstract

Introduction: Pulmonary embolism (PE) results from a blood clot that causes a blockage to one of the pulmonary arteries in the lungs. This blockage can cause symptoms ranging from dyspnea and chest pain to more severe ones, such as signs of obstructive shock, respiratory failure, and cardiac arrest. Systemic thrombolysis (ST) has been found to effectively decrease the mortality risk of patients who are currently hemodynamically unstable due to PE but also comes with an increased risk for bleeding, such as intracranial hemorrhage. Therefore, catheter-directed thrombolysis (CDT) is used when ST fails or when contraindicated. CDT helps minimize exposure to thrombolytics because of having a localized directed infusion of the agent to lysis the clot. Due to the nature of this procedure, this could be explored if CDT is a more effective and safer choice than ST.
Methods: A systematic literature review using Scopus, PubMed, and Medline is done to search for the effectiveness and safety of catheter-directed thrombolysis in contrast to systemic thrombolysis.
Results: 49 articles were found through these three search engines. Seven articles were found to be relevant and reviewed to compare the safety and effectiveness of CDT to ST.
Conclusion: This study concludes that CDT is more effective and safer than ST in treating submassive PE with hemodynamic compromise and massive PE. This conclusion was solely based on retrospective studies. Future randomized controlled trials should be done to support this study's inference and see if guidelines regarding the standard of care can be changed.

Introduction

A literature review done by Raskob et al. has shown that venous thromboembolism (VTE) is one of the common causes of illness and death across the world (1). VTE is a general term that consists of deep vein thrombosis (DVT) and pulmonary embolism (PE). According to the Heart Disease and Stroke Statistics, a report made by the American Heart Association, there are approximately 1.22 million cases of VTE occurred in the United States in 2016 (2). In addition, 30.3% of the cases reported, or 370, 000 are cases of PE.

PE results from a blood clot that travels through the heart and blocks a pulmonary artery, compromising the blood flow to the lungs (3). The obstruction caused by the clot does cause a steady increase of the pulmonary arterial pressure, which leads to right ventricle (RV) dilation (5). The pressure the RV needs to push against is normally low compared to the left ventricle (LV), which usually has a higher systemic pressure gradient. This abnormal sustained increase in pulmonary artery pressure over time will cause RV to dilate, affecting its contractility, and if not resolved, can lead to failure. RV failure can lead to interventricular dysynchrony, which causes both the LV and RV not to contract simultaneously. This dysynchrony will cause a decrease in LV preload at the end of diastole due to the two ventricles not syncing with their systolic and diastolic phases (5). On top of that, LV preload is also affected by the structural changes in the heart due to RV dilation, which results in a lower filling space of LV (4). Combining these two factors will result in a reduced cardiac output leading to hypotension and decreased coronary perfusion. All these events can lead to symptoms ranging from dyspnea and chest pain to more severe ones, such as signs of obstructive shock, respiratory failure, and cardiac arrest. Due to the progressive deterioration that the blockage can cause, PE is linked to a substantial mortality rate, ranging from 8-30% (4).

PE can be categorized based on its location, origin, cause, level of acuity, or severity. However, the grouping used most in the clinical setting and used as a basis of management recommendations for PE is by the level of its severity (6). Based on the severity level, PE can be classified as non-massive or low risk, submassive or intermediate risk, and massive or high risk PE. The American heart association (AHA) and the European Society of Cardiology (ESC) defined each type of PE based on the level of severity and their corresponding recommended treatment. Table 1, found in Appendix, summarises this information. A patient's thirty-day risk for mortality due to PE can be determined using various scoring tools, such as the pulmonary embolism severity index (PESI) and simplified PESI (sPESI) (7). An example of PESI and sPESI can be found in the Appendix section.

PE is an example of dead space, meaning there is normal ventilation but impairment in the perfusion. Restoring perfusion is the goal of treatment to re-establish proper gas exchange and can be done by dissolving the clot causing the blockage. Low risk or non-massive PE is treated through anticoagulation. Patients do not need to stay in the hospital if they can continue the anticoagulation at home and have a low risk of clinical deterioration (8). Anticoagulation is also used for low-intermediate risk or submassive PE without hemodynamic compromise. Still, patients must be admitted to the hospital in case of deterioration and worsening clinical presentation (5,8,9). On the other hand, the recommended treatment for intermediate-high risk PE/submassive PE with hemodynamic compromise and massive PE is systemic thrombolysis. Thrombolytic agents are r-tPAs (alteplase, Tenecteplase), streptokinase, and urokinase. Thrombolytic therapy has been found to effectively decrease the mortality risk of patients who are currently hemodynamically unstable due to pulmonary embolism (10). However, the trade-

off is having an increased risk for bleeding, such as intracranial hemorrhage, with risk anywhere between 2%-6% (11).

Catheter-directed thrombolysis (CDT) is the alternative to systemic thrombolysis when the bleeding risk for the patient is high or if ST fails to work (12). The skills and expertise of an interventional radiologist is needed to perform this procedure (13). This procedure is done by using a catheter entering the femoral or jugular vein and getting to the right side of the heart, specifically the right ventricle outflow tract (13). Once there, the goal is to measure the pulmonary artery pressure to determine which pulmonary artery is greatly affected by the clot, shown by increased pressure. Once this specific artery is specified, this will then be compared to the CT pulmonary angiography (CT PA) taken to see if the imaging and pressure measured are associated (13). Once the artery is confirmed, the catheter is advanced to the area of the clot and put in an optimal position to initiate infusion of the thrombolytic agent. The infusion of the thrombolytic agent usually lasts for 6 hours (14). This is longer compared to the duration of the infusion of the preferred systemic thrombolytic agent, alteplase, which is ordered at 100mg, and given over 2 hours (5). Because of the complexity of this procedure, the infusion of the thrombolytic agent happens in the intensive care unit. ICU is the optimal environment for the patient since it is a controlled and monitored environment that can ensure both the procedure's success and the patient's safety (15).

Due to the nature of the CDT, it can help minimize exposure to thrombolytics because of having a localized directed infusion of the agent to lysis the clot. However, due to the lack of studies, CDT is currently not preferred over systemic thrombolysis by the different guidelines (5, 8, 9). Thus, this study aims to see if CDT is more effective and safer than systemic thrombolysis in treating submassive PE with hemodynamic compromise and massive PE.

Objectives

This literature review addresses the primary research question: Is catheter-directed thrombolysis more effective and safer than systemic thrombolysis in treating massive and submassive PE with hemodynamic compromise? The objective of this study is to see if CDT is more effective in preventing mortality, achieving hemodynamic stability, improving RV function, and resolution of symptoms faster than ST and if CDT has less risk for bleeding events. This study will also investigate differences in cost, readmission rates, and length of stay (LOS) between the two procedures.

Methods

A systematic literature review is done to search about the effectiveness and safety of catheter-directed lysis therapy in contrast to systemic thrombolysis. PUBMED, MEDLINE, and Scopus are the primary search engines used to find the articles used in this project. The keywords used for the search are "comparison or comparative or compared or difference," "catheter-directed therapy or intervention or thrombolysis," "massive and submassive pulmonary embolism," and "systemic thrombolysis". The inclusion criteria for the search were: studies done from 2013 to 2023; primary research; studies done in the United States, Canada, and Europe. The search using PUBMED, MEDLINE, and Scopus with inclusion criteria resulted in 49 articles. Some articles were taken out due to being duplicates between the search engines. The abstracts of the papers left were individually screened if they were relevant to the question of the study. Studies that used ultrasound-assisted thrombolysis were manually excluded during the screening, and only studies that involved standard catheter-directed thrombolysis were included. The full text of the remaining articles was then fully assessed. In the end, there were a total of six studies

that were deemed appropriate to be used in this review. An additional seventh study was added after a review of references.

Summary of results:

The following two studies used the nationwide readmission database to compare CDT and ST regarding bleeding, hospital mortality, and 30 days readmission rates.

Study 1:

Wahood and his colleagues (16) analyzed the records of 37 116 patients in their retrospective observational cohort study to determine the differences in results and thirty-day readmission rates between systemic and catheter-directed thrombolysis.

The investigators accessed the nationwide readmission database in the United States to include patients who had been admitted between 2016 and 2019 with the diagnosis of acute PE and were treated with either catheter-directed thrombolysis (18 702 patients) or systemic thrombolysis (18 814 patients). In addition, they carried out three different analyses based on other propensity-matched groups categorized by type of admission: all admissions, submassive PE-related admissions only, and massive PE admissions only. The investigators' goal is to measure the rate of complications such as intracranial hemorrhage and GI bleed after receiving respective treatments. They also measured the rate of unintended readmissions due to clinical decompensation and saw if these adverse events occurred during readmission.

Results from their study showed that ST showed higher rates of 30-day readmission rates in all admission cohorts (Average treatment effects (ATE) = 0.019, P=<0.001) and submassive cohort (ATE= 0.028, P< 0.001). ST -also was found to be associated with an increased risk for

GI bleed and intracranial hemorrhage in all admissions (GIB: ATE= 0.012, P<0.001; ICH: ATE= 0.003, P=0.017) and submassive cohort group (GIB: ATE= 0.008, P=0.003; ICH: ATE=0.002, P=0.035). However, results from massive PE-only cohorts are different. ST is still strongly associated with GIB (ATE= 0.043, P<0.001). However, that is not the same case with ST's ATE compared to CDT when it comes to readmissions rates and intracranial hemorrhage events at the massive PE-only cohort. The ATE of ST in relation to CDT is not statistically different regarding readmissions rates (ATE= -0.0007, P=0.965) and intracranial hemorrhage events (ATE=0.008, P=0.367).

The authors of this study have concluded that treating with catheter-directed interventions results in a lesser tendency to have unintended 30-day readmission and bleeding events compared to systemic thrombolysis.

Study 2:

Arora and his colleagues (17) did a retrospective observational cohort study in 2017 to distinguish hospital outcomes and readmission rates between catheter-directed and systemic thrombolysis.

A total of 4426 patients diagnosed with PE were taken from the 2013 to 2014 National Readmission Database to be included in this study. Out of 4426, 70.2% (3107 patients) did get ST, and the rest received catheter-directed interventions (CDI) (29.8% or 1319 participants). The primary outcome of this study is in-hospital mortality and 30-day readmission rates. The secondary outcome was a composite score consisting of hospital complications such as hospital mortality and bleeding such as GI bleed and ICH. 2:1Propensity scoring is done to minimize the effects of other existing variables on the outcome of the study. After propensity matching, 2256

patients were left in the systemic thrombolysis group, while 1128 patients were in the catheter-directed intervention group.

Overall, CDI did exhibit a lower percentage of in-hospital mortality (P<0.001), lower 30-day readmission rates (P=0.009), and lower composite score, which consists of in-hospital complications (P<0.001) than ST. However, CDI did lead to higher expenditure than ST (median $ 26 347 vs $ 20,549).

The authors have concluded that CDI displayed lower rates of in-hospital mortality, readmission within 30 days post-treatment, and treatment complications such as GI bleed and intracranial hemorrhage in comparison to systemic thrombolysis.

The following two studies used National Inpatient Sample in the United States to compare hospital mortality rates and bleeding between CDT and ST. In addition, the study by Liang also investigated differences in LOS and cost between the two procedures.

Study 3:

A retrospective comparative cohort study by Liang and his colleagues (18) examines the difference between short-term mortality and safety outcomes of systemic thrombolysis and catheter-directed intervention.

The investigators in this study used the National Inpatient Sample from 2009 to 2012 to find patients admitted to the hospital due to acute PE. This procedure yielded 263,955 patients. From this number, 5727 patients were treated with either ST or CDI, and these patients were included in this study. 4272 out of 5727 patients received systemic thrombolysis; the rest received catheter-directed intervention (1455). The primary outcome of this study is stroke,

major bleeding events, and in-hospital mortality. Secondary outcomes include other bleeding events such as GI bleed or hematoma formation, duration of hospital stay, and the total accrued cost concerning the admission.

Their study showed that treatment with ST has a higher risk for hospital death compared to CDI (ST= 17% vs. CDI= 9%; P<0.001). Major bleeding events between the two methods are statistically insignificant (P=0.5). An observation by the investigators is that CDI have a lower risk for intracranial hemorrhage but a higher risk for other bleeding events, such as the formation of hematoma and GI bleed, compared to ST. CDI also were found to lead to more extended hospital stays, contributing to higher costs. The authors did propensity matching; the only outcome that changed is that the difference in hospital mortality between ST and CDI became statistically insignificant.

The authors conclude that there is no significant difference between systemic thrombolysis and catheter-directed intervention in preventing hospital death. However, catheter-directed intervention was deemed to be a safer choice in treating acute submassive and massive pulmonary embolism due to a lower risk of developing intracranial hemorrhage than systemic thrombolysis.

Study 4:

Patel et al. (19) studied the difference in in-hospital outcomes between systemic thrombolysis and catheter-directed therapy. They also aimed to evaluate the use of CDT at that current time.

The investigators collected patients' data to be used from this study through the Nationwide Inpatient Sample between 2010 to 2012. A total of 1521 patients whose primary

diagnosis was PE and treated with either catheter-directed therapy or systemic thrombolysis were included in the study. 1169 patients were treated with systemic thrombolysis, while 352 were treated with CDT. The primary outcome of the study is death in the hospital. The secondary outcome is a combined rate of hospital death and intracranial hemorrhage. Since there is a significant difference between the number of patients in each treatment group, the investigators also did a 1:3 propensity score matching cohort in addition to an unmatched cohort group to make groups relative to each other to get a more precise evaluation of the effects of the two treatments.

The pattern of usage of CDT has been shown to have increased during the time frame used in this study by 52% (105 in 2010 to 160 in 2012; $P<0.001$). Their study showed that regardless of being unmatched or matched cohorts, CDT is associated with lower hospital deaths when compared to ST (unmatched: 10.23 vs. 20.02, $P< 0.001$; matched: 13.36 vs. 21.81, $P=0.007$). CDT was also linked to a lower combined rate of in-hospital death and intracranial hemorrhage versus the ST in both cohorts (unmatched: 10.51 vs. 21.04, $P<0.001$; matched: 13.36 vs. 22.89, $P=0.003$). In terms of economic differences, ST and CDT are shown to lead to the same amount of LOS; however, ST is shown to have a lower cost than CDT in both matched and unmatched groups (unmatched: 17, 914 vs. 24, 722; $P<0.0001$; matched: 17, 713 vs. 24, 714, $P<0.0001$).

The authors have concluded that there has been an increase in the usage of CDT. They also inferred from their study that CDT is associated with lower rates of in-hospital death and intracranial hemorrhage.

The subsequent two studies reviewed in this paper compared ST and CDT regarding improvements in RV dysfunction, resolution of symptoms, and risk for bleeding.

Study 5:

Avreginos et al. (20) performed a retrospective comparative cohort study at the University of Pittsburgh Medical Center (United States) to see the difference between outcomes of patients who underwent systemic thrombolysis as opposed to patients who went through catheter-directed intervention.

The primary outcome of this study is to have a complete resolution or prevention of decompensation due to submassive pulmonary embolism without complications of treatment such as bleeding, stroke, or death. Participants included in the study were patients seen in the facility between 2006 to 2016 that went through either catheter-directed intervention or systemic thrombolysis to treat submassive or massive pulmonary embolism. A total of 317 patients were included in the study, of which 213 received the catheter-directed intervention, and 104 received systemic thrombolysis.

Results from this study showed that 87.8% of the patients in the CDI group (187 / 213) and 66.3% in the ST group (69 / 104) were treated successfully. It is also shown in the data they gathered that complications with these treatments most minors occurred with CDI compared to ST (Bleeding: CDI 8.0% vs. ST 19.2%, P=0.003; Stroke: CDI: 1.4% vs. ST 4.8%, P=0.120; and death CDI 1.4% vs. ST 13.5%, P< 0.001). Changes in patients' echocardiographic measurements such as RV/LV, pulmonary artery pressures, and tricuspid regurgitant jet velocity) were measured within 30 days post-treatment. It was found that patients who received CDI had shown

better improvement in their RV function than those who received ST (0.27 +/- 0.20 vs. 0.18 +/- 0.15; P= 0.037).

The authors concluded that treating with CDI had shown to result in more improvement in RV function compared to being treated with ST and shown to have a lesser occurrence of adverse effects such as bleeding, stroke, and death. The authors, however, emphasized the importance of thoroughly assessing each patient since CDI and ST are complementary to each other. Choosing between the two treatments should be based on the patient's current condition, risk for adverse events, and facility resources regarding equipment and staff proficiency to perform the skills involved with each treatment.

Study # 6:

Macovei and his group (21) investigated the efficacy and safety of pulmonary intra-arterial thrombolysis in comparison to systemic thrombolysis.

The study included 52 patients who were found to have acute high-risk pulmonary embolism. The patients were admitted to the intensive care unit to be closely monitored when receiving treatment. Patients were then randomly assigned to either the intraarterial thrombolysis group (28 patients) or the systemic thrombolysis group (24 patients). Each patient was screened to record their echocardiogenic and hemodynamic measurements, clinical features, and angiographic measurements pre-treatment. During this assessment, it was found that 18 patients in each group had cardiogenic shock. These patients are still included in the study, and the resolution of their shock became a part of evaluating the efficacy of the two treatments. The safety and effectiveness of each method were measured after receiving the treatment, and it was

determined based on bleeding incidents and improvements on the baseline measurements, respectively.

In terms of efficacy, the study reported that pulmonary intra-arterial thrombolysis resolved symptoms related to pulmonary embolisms, such as dyspnea, chest pain, and syncope in 96.4% of the patients (27/28) in the pulmonary intra-arterial group. In contrast, systemic thrombolysis could only resolve these symptoms in 70.8% of the patients (17/24) in that group. Pulmonary intra-arterial thrombolysis was also shown to fully stabilize cardiogenic shock in the affected patients in that pulmonary intra-arterial group. Whereas systemic thrombolysis could not wholly address cardiogenic shock, leaving 29.2% of the patient in the group (7/24) with unresolved cardiogenic shock. Intra-arterial thrombolysis was also shown to have produced more significant reductions in pressures such as pulmonary arterial pressure and pressure gradient between the right atrium and right ventricle. This method also produced better reduction of the diameter of the chambers of the heart than systemic thrombolysis.

Regarding safety, the correlation of bleeding events between the two methods was shown not to be statistically significant. Systemic thrombolysis was also the only procedure that caused death in this study for seven patients.

The authors concluded that patients who underwent pulmonary intra-arterial thrombolysis are superior to systemic thrombolysis in resolving clinical symptoms of PE, hemodynamic instability, and right ventricular dysfunction, which results in better clinical outcomes.

The last study reviewed in this paper did talk about the efficacy and safety of CDT in resolving RV dysfunction.

Study # 7:

Dilektasli and his colleagues (22) examined the efficacy and safety of CDT in addressing RV dysfunction in acute PE through a retrospective study.

The study was performed at Uludag University Faculty of Medicine in Bursa, Turkey. The study included 15 patients diagnosed with acute massive or submassive PE with RV dysfunction and treated by CDT. Dilektasli and his colleagues (22) described RVD dysfunction as the "presence of one or both of the following criteria: "1. RV dilation or RV systolic dysfunction on echocardiography 2. RV dilation on CT". The primary outcomes were mortality, resolution of symptoms, and any complications such as bleeding. The secondary outcome is the changes in hemodynamic status which are compromised by changes in measurements of systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation, and shock index. These values were taken pre-treatment and then measured at 2 hours, 8 hours, and 24 hours post-treatment. In addition, RV measurements, as well as pulmonary artery pressure changes, were also monitored.

Their study showed that hospital mortality and 30-day mortality after receiving CDT are 13.3% and 20%, respectively. In terms of bleeding complications, hematoma and ecchymosis happened in 1/3 of the participants in the study. Return of hemodynamic stability was also shown to be achieved by CDT as early as 2 hours and to improve 24 hours post-treatment continuously. 93.3% (14/15) of patients in the study achieved complete resolution of hemodynamic instability in the 24 hours post-treatment artery pressure was also to decreased by an average of 35% post-treatment.

The authors of this study have concluded that CDT has shown efficacy and safety in helping achieve the resolution of symptoms and RVD in patients with massive PE and submassive PE with RVD.

Discussion

The study aims to investigate if CDT is more effective and safer than ST in treating submassive PE with hemodynamic instability and massive PE. The current recommended standard of care for massive and submassive PE with hemodynamic instability is ST (5, 8, 9). However, numerous studies have supported that systemic thrombolysis is associated with an increased risk for significant bleeding incidents such as intracranial hemorrhage (8, 10). Therefore, CDT can be a possible solution due to lesser exposure to systemic thrombolysis. Nevertheless, CDT is currently only recommended as an alternative if ST fails or if contraindicated (5, 8, 9). This is because there have been minimal prospective and randomized controlled trials done to thoroughly examine the effectiveness and safety of CDT in contrast to ST. Seven studies included in this paper were retrospective studies that explored the effectiveness and safety of CDT compared to ST.

Bleeding correlates with ST and CDT based on the studies reviewed in this paper. However, six studies have shown that the risk for bleeding events, such as intracranial hemorrhage and GI bleeding, is higher in the ST group than in the CDT group. This could be related to the localized area of thrombolytic infusion, as well as the lesser amount needed to resolve symptoms related to PE (6). CDT was also associated with decreased in-hospital mortality risk in the five studies included in this paper compared to ST. This could be due to

having lesser risk for complications that increase mortality risk, such as bleeding. This could also be because CDT can resolve symptoms and achieve hemodynamic stability faster than ST.

Regarding effectiveness, two studies in this review have discussed the resolution of symptoms and RV dysfunction with CDT and ST. The echocardiographic signs that signify RV overload or failure are an increase in RV/LV ratio, RV, inferior vena cava and pulmonary artery dilation, regurgitation flow to tricuspid valve, deformation of interventricular septum, paradoxical ventricular septal motion, and contractile synergy, hypokinesia or akinesia of RV wall (4). The two studies have shown that CDT was shown to be able to produce better recovery and improvement in RV function compared to ST, as evidenced by improvements in these echocardiographic signs post-treatment. The two studies have also shown that CDT is associated with a higher rate of success, higher by approximately 20% than ST in both studies (20, 21). RV dysfunction is one of the risk markers used by the ESC guidelines in determining the mortality risk of a patient with PE (5). This is important since RV dysfunction can lead to RV failure if not addressed promptly. RV failure combined with obstructive shock presentation is the leading cause of mortality in patients with high-risk PE, with documented rates surpassing 20% (4, 5). The other advantage of CDT is that it can it is shown to be able to quickly produce hemodynamic stability and symptom resolution as early as 2 hours, with almost all participants having full resolution at 24 hours based on the study done by Dilektasli et al. (22). This earlier resolution of symptoms and hemodynamic stability is related to the earlier initiation of dissolution of clot, causing relief of the burden of RV. This quicker response might have been linked to the more targeted nature of CDT. This earlier dissolution of the clot can help decrease prolonged strain in the heart that can lead to more insidious events such as cardiac arrest and death.

Cost, LOS, and readmission rates are also discussed in some of the articles reviewed in this study. Patients who received CDT have been found to have a lower likelihood of having readmitted in the first 30 days after hospital discharge (16, 17). The study done by Arora (17) has found that most common etiologies that cause readmission are hypercoagulability, cardiac causes, respiratory causes, bleeding complications, infections, and gastrointestinal causes. ST has been located to have more instances of etiology causing readmissions; however, an observation made is that CDT does cause a higher risk for DVT compared to ST. This could be related to prolonged stay in bed that happens during the duration of treatment. The studies reviewed in this paper also commented on the cost and LOS between the two procedures. CDT has been consistently found to accumulate a higher price than ST. Regarding LOS, the study by Liang et al. (18) showed a different result from that of Patel et al. (19). In the study done by Liang et al. (18), CDT was found to result in a longer LOS while the study done by Patel et al. (19) showed no significant statistical difference between CDT and ST in terms of LOS. The higher cost of the CDT results from the cumulative cost of materials used and professionals involved to do the procedure, as well as prolonged LOS. As mentioned earlier in this paper, CDT involves extra materials such as the catheter and the expertise of interventional radiologists and the ICU team. The patient also stays longer in the ICU due to the need for continuous monitoring during CDT, which also adds to the cost. However, even if the studies have shown that CDT accrues a higher price during the hospital stay, the cumulative cost of readmission that happens with ST could also add to the charge that might be comparable, if not more, than the total cost used by CDT. This can be a study done in the future to see a healthcare lifetime cost of a patient that goes through a CDT compared to ST.

There are limitations to this literature review. The first limitation is that this review only included articles about standard CDT that involves direct infusion of the thrombolytic agent to the location of the clot. Standard CDT is only one of the procedures under catheter-directed interventions that all access the patient's vascular system the same way but do things differently to address the clot present (12). The other procedures under these interventions are fragmentation and embolectomy, which are not talked about in this paper. A recommendation would be doing a study comparing the CDT with these other interventions to determine if one is safer and more effective. This study's second limitation is that it excluded studies that used ultrasound-assisted thrombolysis (USAT) to compare effectiveness and safety with ST. The ultrasound aspect of this procedure is a topic that needs to be explored to see if this feature plays an advantage in resolving PE compared to just a standard CDT. Lastly, most of the studies used in the study are retrospective. Due to this, the studies did depend on databases only and missed much detailed information that could be explored as well, such as dosing and type of thrombolytics used, and timing and duration of administration. A randomized controlled trial to compare the two procedures could help solidify the interpretation of these studies. Also, a prospective study exploring the long-term effects of both methods on patients' quality of life and overall health is recommended.

Conclusion

Massive PE and submassive PE with RV dysfunction are associated with high morbidity and mortality when not treated in a timely manner. Based on this review, CDT is shown to be more effective by achieving a higher success rate in hemodynamic stability and resolution of symptoms in a shorter amount of time than ST. CDT has also been found to be less associated

with bleeding risk in contrast to ST. This review concludes that CDT is more effective and safer than ST in treating submassive PE with hemodynamic compromise and massive PE. Based on this conclusion, CDT could be considered a first-line treatment for submassive PE with hemodynamic compromise and massive PE. This conclusion was solely based on retrospective studies reviewed in this paper. Future randomized controlled trials should be done to support this study's inference and see if guidelines regarding the standard of care can be changed.

Acknowledgments

I would like to thank my capstone adviser, Cameron Krisko, and my faculty advisor, Steven Piotrowski, for their guidance and support during this project. I would also like to thank the Master of Physician Assistant Studies faculty and staff for their support over the past two years of my studies.

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Appendix:

Table 1: Different definitions of PE types based on the severity level per different guidelines.

Type of PE	Definition by AHA (23)	Definition by ESC (5)
Massive/ High risk	"Acute PE with sustained hypotension (systolic BP<90 for at least 15 mins or requiring inotropic support. This sustained hypotension is caused only by PE and not by other causes such as arrhythmias, sepsis, or LV dysfunction), pulselessness or persistent bradycardia (heart rate < 40 bpm with the presence of signs of shock)." (23)	"Acute PE with signs and symptoms of hemodynamic instability such as cardiac arrest, obstructive shock (systolic BP <90 or vasopressors needed to achieve systolic BP≥ 90 despite adequate volume status) or persistent hypotension (systolic BP < 90 or systolic drop ≥ 40 for > 15mins and not caused by other conditions other than the PE)." (5)
Submassive/ Intermediate risk (High and Low)	"Acute PE with the presence of either RV dysfunction or evidence of myocardial necrosis but without the presence of hypotension (systolic BP ≥ 90)." (23) * RV dysfunction is defined as having one of the following: evidence of RV dilation (RV/LV > 0.9) in either ECHO or CT, RV systolic dysfunction, the elevation of BNP (> 90 pg/mL), and pro-BNP (> 500 pg/mL) and ECG changes	**Intermediate - High** "Acute PE with the absence of hemodynamic instability but has a moderate to high PESI score and both evidence of increased cardiac biomarkers and RV dysfunction in ECHO or CT PA." (5)
		Intermediate- Low "Acute PE with the absence of hemodynamic instability but has

	such as right bundle branch block, anteroseptal ST elevation or depression or T wave inversion. (23) □ Evidence of myocardial necrosis is either an increase in troponin I (> 0.4 ng/mL) or troponin T (>0.1 ng/mL) (23)	moderate to high PESI score and either one or no evidence of increased cardiac biomarkers or RV dysfunction in ECHO or CT PA." (5)
Low Risk	"Acute PE with no hemodynamic instability and no signs of RV dysfunction on CT PA or ECHO and no elevation of cardiac biomarkers" (23)	"Acute PE with no hemodynamic instability, low PESI score, and absence of evidence of increased cardiac biomarkers and RV dysfunction in ECHO or CT PA" (5)

Table 2: Pulmonary Embolism Severity Index (PESI) (24)

Predictors	**Score assigned**
Age	Age in years
Male sex	+ 10 points
Cancer	+ 30 points
Heart Failure	+ 10 points
Chronic lung disease	+ 10 points
Pulse ≥110 beats/min	+ 20 points
Systolic blood pressure < 100mm Hg	+ 30 points

Respiratory rate ≥ 30/min	+ 20 points
Temperature < 36 C	+ 20 points
Altered mental status	+ 60 points
Arterial oxygen saturation < 90 %	+ 20 points

Risk Stratification for PESI (24)

Class	Score	30-day mortality risk
1	≤ 65 points	Very low mortality risk (0-1.6%)
2	66 – 85 points	Low mortality risk (1.7 % - 3.5%)
3	86-105 points	Moderate mortality risk (3.2% - 7.1%)
4	106-125 points	High mortality risk (4.0 % – 11.4%)
5	> 125 points	Very high mortality risk (10.0 % - 24.5%)

Table 3: Simplified PESI (sPESI) (25)

Predictors	Score assigned
Age > 80 years old	1 point
Cancer	1 point
History of heart failure and chronic pulmonary	1 point

disease	
Pulse ≥110 beats/min	1 point
Systolic blood pressure < 100mm Hg	1 point
Arterial oxygen saturation < 90 %	1 point

Risk Stratification for sPESI (25)

Class	Points	30-day mortality risk
Low	0	1.0 % (95% CI 0.0-2.1%)
High	≥ 1	10.9% (95% CI 8.5-13.2%)