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Progress of Nanomedicine-Integrated Treatments for Pulmonary Embolism: A Review, Challenges, and Future Possibilities

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Abstract

Introduction: Pulmonary embolism (PE) is a form of venous thromboembolism that entails the migration of a thrombus to the pulmonary vasculature, causing a blockage, and may even lead to the death of the patient. Currently, low-risk PE is treated with oral anticoagulants, with higher risk cases requiring thrombolytic or surgical interventions. Due to the time sensitive nature of severe cases, the treatments that deal with PE can improve to reduce mortality the rate. Nanomedicine provides that scope of improvement in various avenues of treatment for PE. Although no known nanomedicines have been approved for human trials associated with PE, many companies have achieved success up till animal models and provide a promising scope of discovery within this field.

Methods and Results: This study uses research articles, case reports, news articles, and statistical data to provide accurate and comprehensive information. Open-access sources, including Google Scholar and PubMed, were used to access peer-reviewed studies on nanomedicine applications in PE. The study also explored data focusing on preclinical trials with animal models and innovative therapeutic and diagnostic approaches. A review of current PE treatments and nanomedicine options was conducted, highlighting potential advancements and suggesting future directions for research to improve PE treatment strategies.

Discussion: The nanomedicines options being actively explored focus on supplementing current PE treatments available, instead of completely replacing them. The field of nanomedicines for PE is making headway within the areas of targeted drug delivery, controlled release systems (CRS), nanocarriers, magnetic nanoparticles (NPs), biosensors as well as wearables.

Conclusion: Our compiled literature presents an exhaustive summary of the strides made within nanomedical spaces to treat PE and such related diseases. Despite the lack of clinical data with human populations, the preclinical studies with animal models have unique ways to combat the challenges present with PE treatments today.

Keywords: pulmonary embolism; clot; deep vein; thrombus; nanotechnology; nanoparticles; nanomedicine; anticoagulants

Introduction

Pulmonary embolism (PE) is a life-threatening condition that has an untreated mortality rate of 30% and is the third leading cause of cardiovascular death [1]. Figure 1 shows the global age-standardized PE-related mortality in men and women per 100,000 population-years [2]. In Canada, the incidence of PE is 0.38 per 1000 person-years [3], and it is caused by the blockage of the pulmonary vasculature by blood clots, fat or a tumour, and subsequently results in symptoms such as hypoxia, tachycardia, and tachypnea [3, 4]. The stages of the disease can range from acute, where symptoms develop suddenly and dramatically, subacute, with gradual symptoms developing over days to weeks, or chronic, where symptoms may persist for months or longer. The severity of PE may be classified into high-risk PE, characterized by hypotension or shock that requires immediate treatment, intermediate-risk PE, which presents with right ventricular dysfunction or myocardial injury without hypotension, or low-risk PE, which presents with normal blood pressure and no signs of right heart strain [5]. Early detection and appropriate treatment based on the stage and severity of PE are crucial for improving patient outcomes and reducing the risk of complications [1].

According to the online statistics platform, Statista, the age group distribution of PE cases in France, 2018, show a direct correlation with PE cases [6]. Although PE can be a result of a blockage caused by any major obstruction, a majority of the cases occur due to deep venous

thrombosis, where a blood clot travels from the lower extremities up to the right side of the heart and lungs [7, 8]. Some risk factors identified for deep vein thrombosis (DVT) are age older than 60, lack of movement, obesity, genetics, surgery, and pregnancy [7].

The mortality rate from PE in Denmark over the past two decades has consistently ranged between 155 and 210 deaths per year [9]. As this death toll remains relatively stable, it is evident that no groundbreaking treatment has been able to decrease PE-related mortality [9].

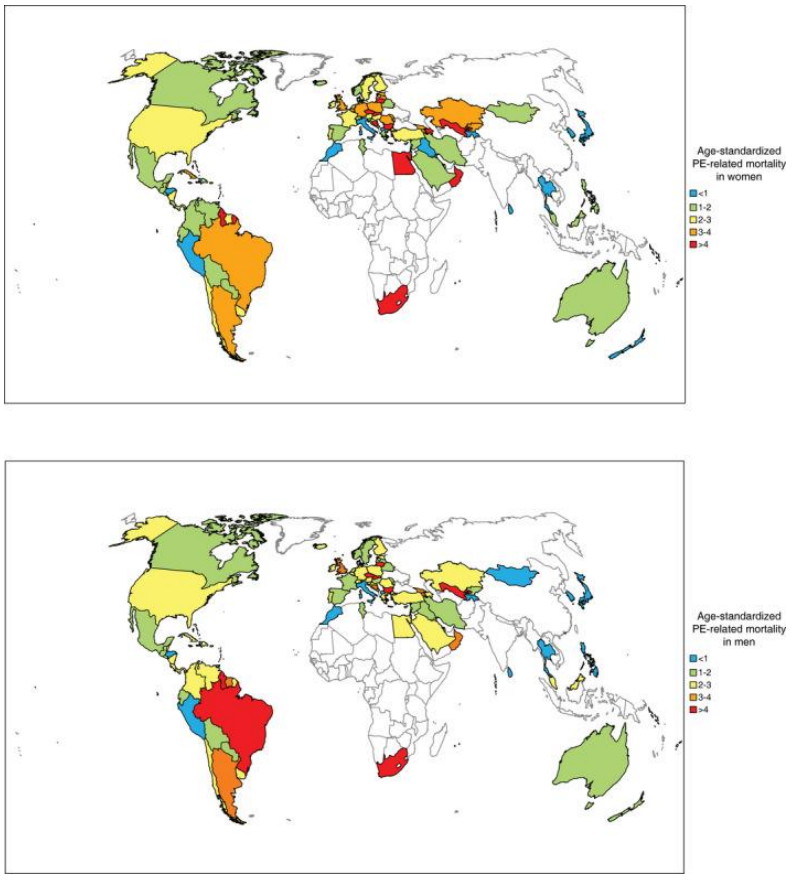

Figure 1. Overview of Global Age-Standardized PE-Related Mortality in Women and Men [per 100,000 population-years]. Adapted with permission under CC BY 4.0 from [2].

PE is heterogeneous in presentation, ranging from asymptomatic to fatal, which is why getting a prompt clinical diagnosis for the disease is a challenge [8]. Subsequently, the disease prognosis depends on the severity of the blockage and its impacts on the body's hemodynamics [10]. The current gold standard for PE diagnosis and detection is a pulmonary angiography, where a catheter is inserted into the femoral or brachial vein; unfortunately, it is an expensive and invasive procedure [11]. Other tests may include imaging or blood tests for detection [12]. The primary treatment for PE is anticoagulant therapy, which necessitates strict dosage monitoring as the drugs have a very narrow therapeutic index and may cause fatal bleeding events as an adverse effect [13]. Currently, there is a demand for non-invasive diagnostic tools and safe, yet effective, treatment options for pulmonary embolisms.

In order to further understand the case presentations and treatment options for the patients, we accumulated 30 PE case studies from reliable and open-access sources into Appendix A. Figure 2 displays the distribution of patient ages and sexes in the PE cases analyzed. The patients were grouped into age ranges, and sex was classified as either male or female. The majority of cases were concentrated in the 21-30 and 61-70 age ranges, with a near-equal distribution of males and females in most categories. According to the data aggregated within treatment options, it was evident that clinical symptoms of PE presented as asymptomatic to fatal at various stages of the disease. No specific symptom was indicative or reliable to pinpoint a specific stage of PE. Most common symptoms presented in patients were cough, shortness of breath, fatigue and complaints of pain in the chest.

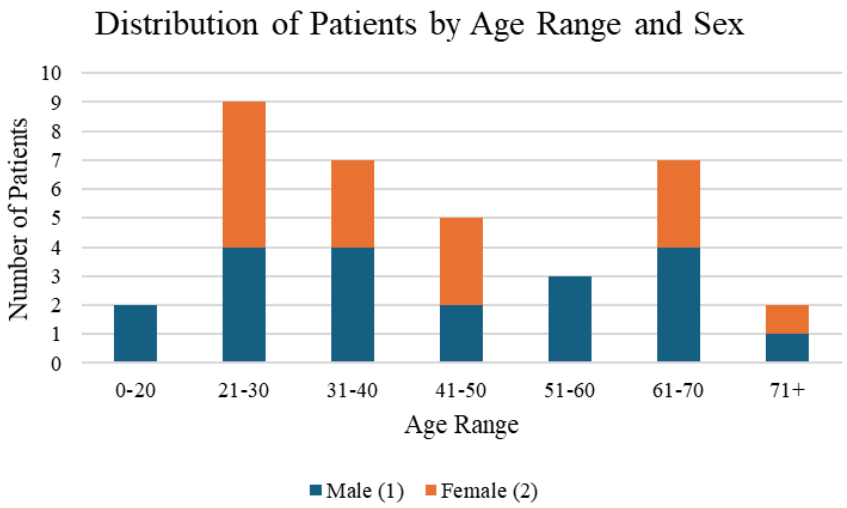

Figure 2. Age Distribution and Sex of Patients in PE Cases Exhibited in Appendix A (created using Microsoft Excel).

Figure 3 shows the distribution of treatments administered for the PE cases, 19 cases received anticoagulation therapy, 6 underwent combination therapy (anticoagulants and thrombolytics), 3 utilized other methods (IVC filter and antiplatelet therapy with anticoagulants), and 1 received thrombolytic therapy alone. Notably, there was 1 case where the patient died before treatment could be administered. Separately, the COVID-19 pandemic had an unfortunate impact on PE cases, nearly doubling the risk for survivors to develop PE [14]. This is because when sick, the body produces more coagulable substances while fighting the virus. This hypercoagulable state, along with an extended immobile period for patients with COVID-19, contributed to an increased incidence of DVT and subsequent PE [12]. As shown in Appendix A, there were certain cases where COVID-19 exacerbated PE presentation.

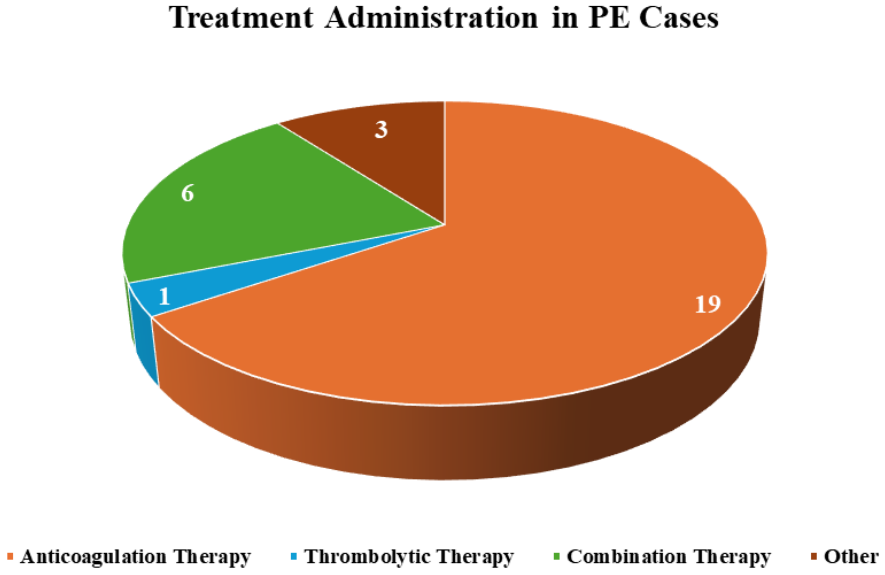

Figure 3. Distribution of Treatment Types for PE Cases Exhibited in Appendix A (created using Microsoft Excel).

Nanomedicine is a field that investigates the application of engineered nanomaterials within biomedical applications and medicine at large [15]. Nanomaterials play a significant role in drug delivery due to their small size (<100 nm) which allows them distinct physical and chemical characteristics beneficial in targeting specific areas in the body [16]. Given

the disease characteristics and mortality rate of PE, nanomedicine provides a promising scope of research development. This study incorporates research articles, review articles, case reports and statistical data to provide an exhaustive summary of nanomedicine interventions in development for PE.

Pulmonary Embolism: Evolution of Migration Strategies

Figure 4 explores a timeline following the discovery and progression of PE findings, as well as the evolution of nanomedicine integration into PE treatments. The figure is divided into 3 phases, with the first phase being a brief overview of PE discovery. The second phase details the evolution of PE treatments, which are also covered more in-depth in Section 2.3. The third and final phase, presents the introduction of nanomedicine into PE management. In this phase, some studies detailing the use of nanomedicine for enhanced thrombus imaging are noted. Further preclinical studies exploring the integration of nanomedicine in PE management are presented in Table 1.

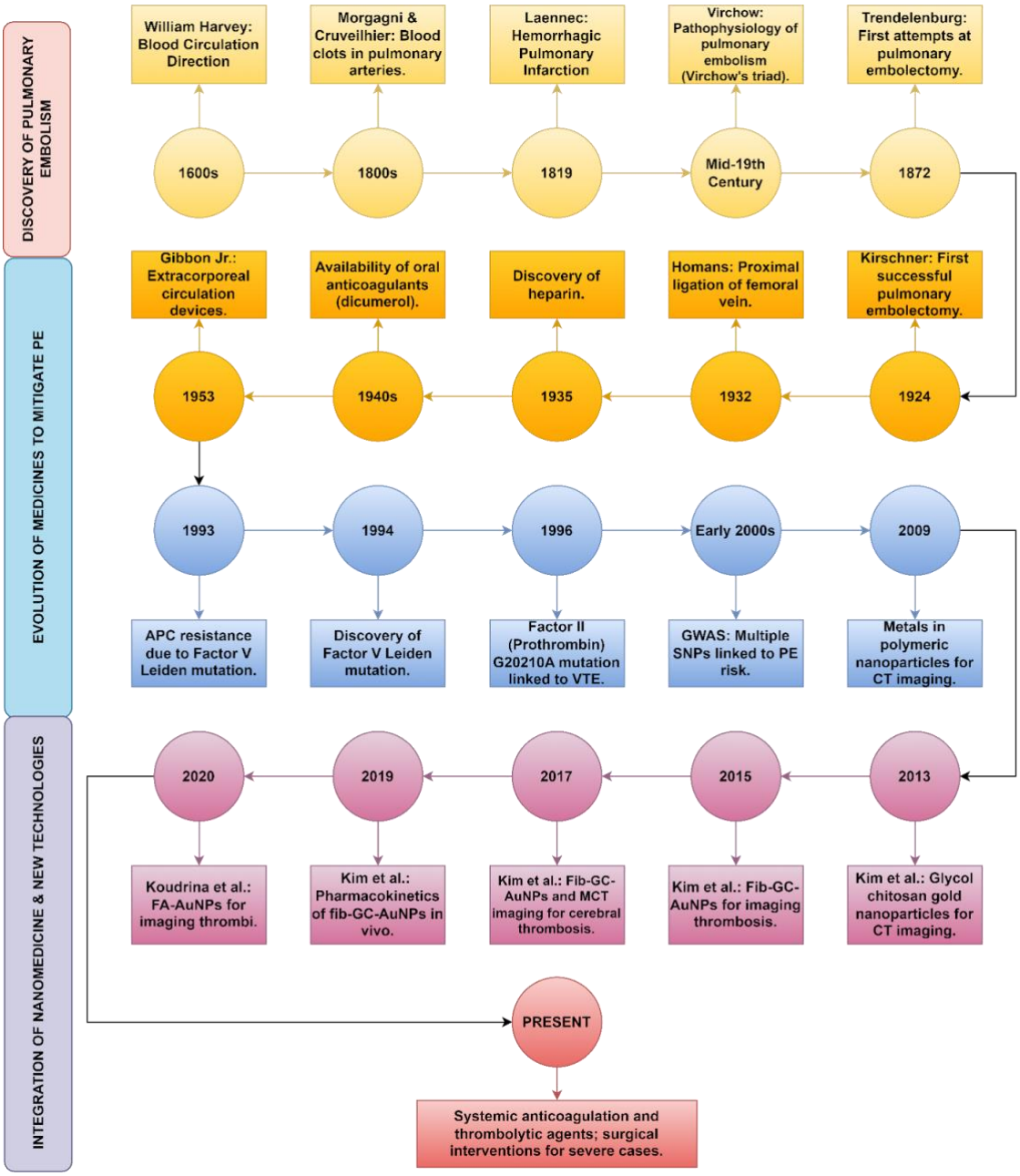

Figure 4. Evolution of Treatment for Pulmonary Embolism [17-20] (created using draw.io).

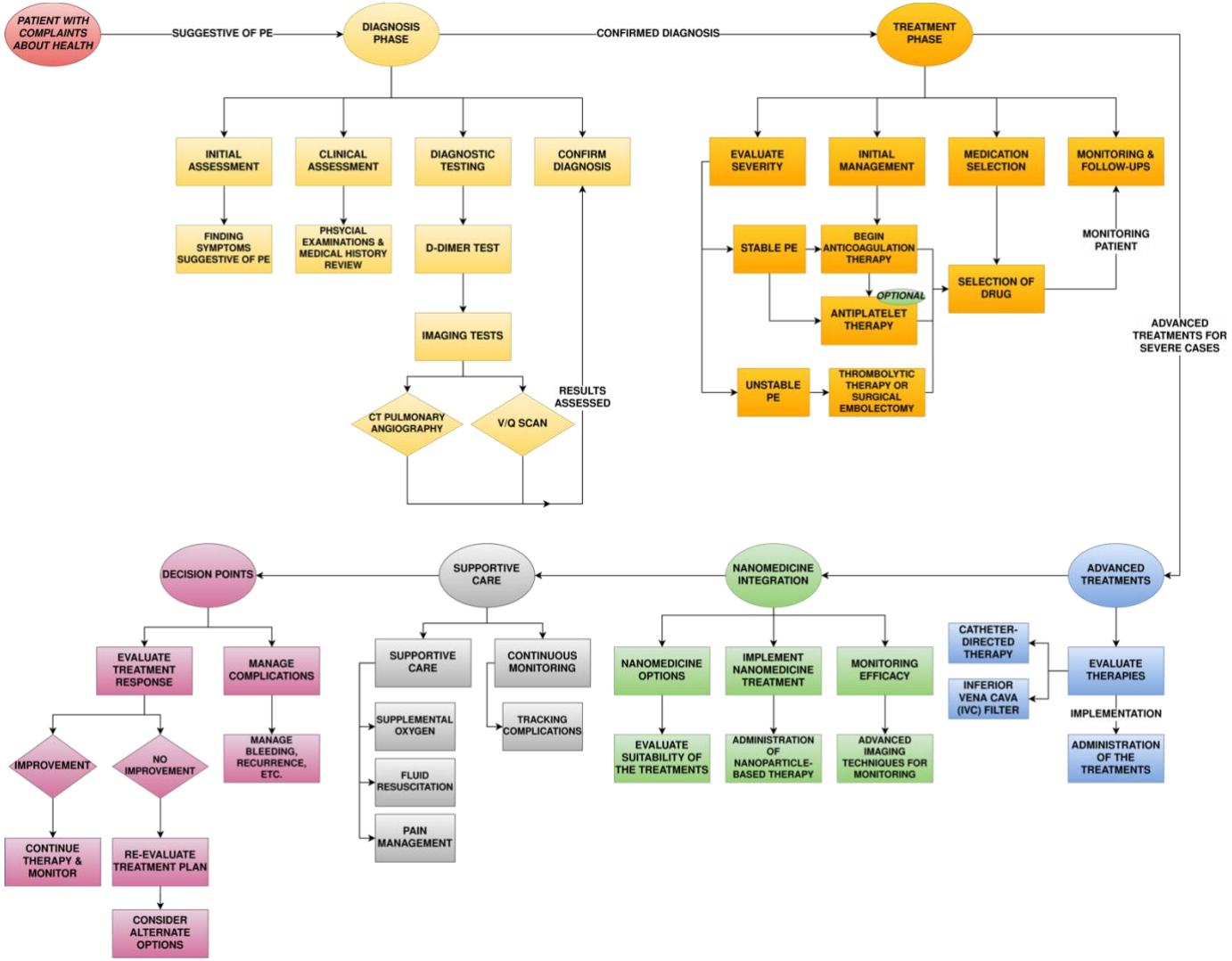

Figure 5. General Treatment Approaches for PE: An Authors' Perspective (created using draw.io).

General Diagnosis

The main objective of diagnosing PEs is to classify patients based on severity and clinical presentations in order to determine the route of treatment [20]. Patients initially suspected of having PE are often first assessed based on their haemodynamic stability [10]. A computed tomography pulmonary angiography (CTPA) is a diagnostic imaging technique used to confirm the presence of a pulmonary embolism [10,20]. A ventilation perfusion (V/Q) scintigraphy or scan is one of the oldest non-invasive imaging techniques that is used in the diagnosis of pulmonary disorders such as PE [21]. In Figure 5, a CTPA or V/Q scan is depicted as an endpoint diagnostic method to confirm the diagnosis once alternative conditions have been effectively ruled out. If the presentation of the disease is more subtle, such as a patient being hemodynamically stable, other diagnostic measures may be taken before imaging techniques to rule out other disease possibilities [10].

Although CTPAs are highly useful, possessing strong predictive negative and positive values, it is highly costly, and poses the risk of causing radiation damage to the recipient [20]. Additionally, due to the long history of V/Q scans, there are presently multiple different algorithms for result interpretation - rendering consistency an issue [21]. Thus, alternative diagnostic measures such as a probability assessment and D-Dimer test are used initially to narrow down the possibility of PE [10].

Examples of probability assessments used to determine if a patient has PE includes the Wells, modified Wells, and revised Geneva score, as well as the pulmonary embolism rule out criteria (PERC) [4]. These tests rely on patient presentation [4], which makes diagnosis difficult in nature due to the heterogeneous presentation of PE [19].

D-Dimer tests evaluate the D-Dimer levels in the body, as the component is a product of the breakdown of fibrin crosslinks [20]. Typically, a D-Dimer result of less than 500 nanograms per millilitre (ng/mL) is an indicator of pulmonary embolism [20]. Although this test is a useful tool, other physiological confounding factors may influence D-Dimer levels resulting in false positive and negative results [8]. Pregnancy, age, trauma, cancer, and multiple other physiological factors may increase D-Dimer levels, rendering the test unreliable when other comorbidities may be present [8].

Figure 5 depicts the general course of diagnosis, treatment and management of PE in a patient - as well as the points where nanomedicine may potentially be integrated into a treatment plan. As seen in Figure 5, diagnosing PE is a lengthy process that lends to significant burden on the patients [10]. Multiple diagnostic tests often need to be administered to rule out other possibilities before confirmation is possible, leading to an expensive and time-consuming treatment journey.

General Treatments & Progress

Anticoagulants are a class of drugs that prevent blood from clotting too easily [22]. These drugs prevent or alter the coagulation cascade and deter the cause of any clot-related diseases. Anticoagulant therapy is the preferred first line of treatment for PE patients [8]. Anticoagulants are often prescribed as a long-term treatment plan in order to prevent recurring clots, however, they require strict dosage monitoring as the drugs have a very narrow therapeutic index and may cause fatal bleeding events as an adverse effect [8]. Anticoagulation therapy for acute venous thrombosis includes heparin-based anticoagulants, and factor Xa inhibitors like rivaroxaban and apixaban, or Vitamin K antagonists, warfarin [8].

Although the primary course of treatment for PE is anticoagulant therapy, antiplatelet therapy is a secondary prevention method that can be used. Particularly, when a patient is unable to continue the long-term use of anticoagulants, due to arising risk factors or recurrence of PE, antiplatelet therapy can prove useful [23]. Anticoagulant therapy works by inhibiting platelet function, and essentially stops them from sticking together (aggregating in the blood) [22]. A commonly known anti-platelet drug used to prevent atrial thrombosis is aspirin, which as evidence suggests can be useful in PE. However, due to multi-characterizing targeting in the body, antiplatelet drugs present a large bleeding risk, along with gastrointestinal concerns [23].

As shown in Figure 5, in the event that anticoagulation and antiplatelet therapy do not prevent recurrent pulmonary embolisms, vena cava filters may be used to prevent clots from reaching pulmonary circulation [24]. Although this treatment has been observed to decrease PE risk, it is also associated with increased risk of DVT and displays no significant effect on the risk of death or recurrent venous thromboembolism (VTE) [24].

As shown in data aggregated in Appendix A, severe cases involving pulmonary embolisms may require the administration of thrombolytics. Thrombolytics are a class of drugs that function by breaking down the clot usually by targeting intermediaries in the coagulation cascade, such as plasmin [25]. Thrombolytics have established as effective treatments and often swiftly resolve the pulmonary obstruction, especially if administered up to 48 hours after the onset of symptoms [24]. Although this treatment may offer some respite by lysing the thrombus relatively quickly, it is not without risk. The use of thrombolytics increases the probability of certain adverse effects such as severe intracranial and extracranial bleeding occurring [24].

If faced with thrombolytic therapy failure, as depicted in Figure 5, the next line of treatment is either surgical removal or percutaneous catheter-directed therapy [10]. However, like thrombolytics, the use of these interventions heightens the risk of adverse bleeding events and is therefore not recommended for all PE patients [10]. As seen in Figure 4, follow-up procedures post-PE resolution include support

care and consistent monitoring of the patient, along with treatment evaluation and management of any complications.

Methods and Results

This study reviews preclinical research to explore the use of nanomedicine in treating and detecting PE. Relevant studies were identified from open-access sources, such as google scholar and PubMed, focusing on articles that provided detailed descriptions of nanomedicine-based therapeutic and diagnostic approaches for PE. The reviewed studies encompassed various nanotechnology applications, including targeted drug delivery, cloaking mechanisms, and other innovative strategies.

Key data were extracted and organized into Table 1, which includes information on the approach, nanodevice used, its primary function, the animal model employed, observed results, and corresponding references. This study reviews diverse nanotechnology interventions, such as magnetic nanoparticles, liposomal delivery systems, transdermal nano sensors, and nanogels. Each study was analyzed for its experimental methodology, therapeutic outcomes, and the efficacy of nanomedicine approaches compared to conventional treatments. Although this review was not conducted systematically (with no predefined search terms, inclusion, or exclusion criteria), it provides a qualitative overview of the current advancements in nanomedicine for PE treatment and highlights their preclinical potential. The findings of this study are limited to available literature.

Integrating Nanomedicine: Role & Current Research

Literature explores the uses of nanomaterials in the detection of thrombosis, which may assist in early detection of pulmonary embolism cases [26]. In such applications, nanomaterials coating antibodies which commonly interact with fibrin-specific epitopes found in thrombi and can be carefully screened via CT imaging, before the structural and characteristic changes cascade in dislodging and causing pulmonary embolisms [27].

The scope of nanomedicine within the treatment of PE is vast. Specifically, the nanomedicine scope for anticoagulants is to improve the controlled release and efficiency of drugs, as systemic targeting of the medicine can lead to poor repair systems of the blood and risk of hemorrhagic bleeding or thrombocytopenia. New avenues for antiplatelet therapy in nanomedicine can be sought in making new antiplatelet drugs or finding ways to adjust the current dosage and regimen of existing drugs [23].

Nanomaterials also have shown a promising role in drug delivery mechanisms by delivering thrombolytics [26]. Although, the use of thrombolytics is limited due to their adverse effect causing excessive internal and external bleeding. Thrombolytic nanomedicine needs to meet the set criteria for thrombolytics drugs, and even surpass the systems set. Thus far, thrombolytics must show biocompatibility, bypass normal blood clots, and selectively target newly formed thrombi [23]. New nanomedicines have been shown to utilize a platelet cloaking mechanism that cloaks the thrombolytics and increases the biocompatibility of the medication [28]. Hence, nanomedicine can lead to a headway in combating PE mortality rates [27]. Appendix B.1 discusses the different drug delivery systems that are currently being explored to improve the challenges with PE treatment. Followed by Appendix B.2, which introduces nanomedicine-based devices that can be integrated to further relieve PE incidence and mortality. Figure 6 illustrates both sections in brief detail. Additionally, Table 1 illustrates different studies in which animal models were used to examine the effect of nanomedicine integrated into PE treatment and management.

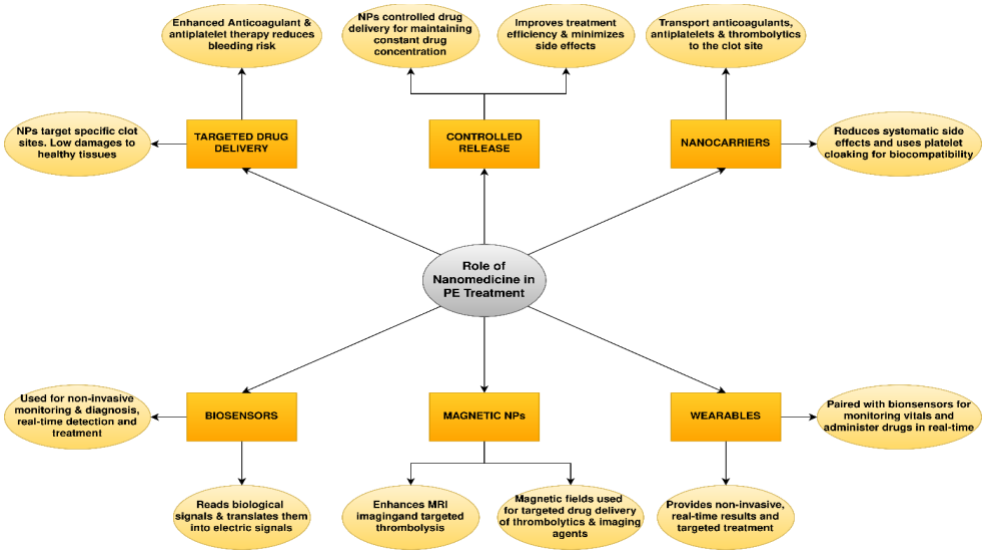

Figure 6. Overview of Nanomedicine Applications in PE Treatment [29-34] (created using draw.io).

Table 1. Pre-clinical Usage of Nanomedicine for PE

S. no.	Approach	Device	Function	Model	Results	Ref
1	Targeted drug delivery via nanocarrier	Chitosan magnetic NP (Chitosan - MNP)	tPA (tissue plasminogen activator), a thrombolytic therapeutic, is covalently bound to the NP (forming Chitosan-MNP-tPA). The complex then is delivered to its target through magnetic instruction.	Rat model	Chitosan-MNP-tPA administered at 0.2 mg/kg exerted the same thrombolytic effect in the rat embolic model as free tPA administered at 1 mg/kg. 20% of the free tPA dosage was required for Chitosan-MNP-tPA to exert the same effect.	[35]
2	Injectable NPs for CT scan imaging	Glycol Chitosan (GC) Gold NPs (AuNPs)	Injected GC-AuNPs entrap the thrombus by settling within the pores of the thrombus, allowing it to be visualized via CT scan due gold's high X-ray attenuation	Mouse model	GC-AuNPs were able to effectively detect and visualize thrombi for CT scan purposes GC-AuNPs had the ability to evaluate the performance of thrombolytic treatments, and monitor thrombus progression GC-AuNPs had an extended half-life which allowed them to stay in circulation and participate in thrombi entrapment for up to 3 weeks	[36]
3	Injectable NPs for MR imaging	Ultrasmall superparamagnetic iron oxide (USPIO) particles	Spread through the pores of thrombi to entrap them and enhance their visualization for imaging	Rabbit model	Improved T1-weighted MR imaging of thrombi was observed 24 hours after USPIO particle administration	[37]
4	Cloaked NPs with RBC membrane	Cloaked silica NPs for delivering Fols (fullerenols) NPs	Intravenous injection followed by measuring fluorescence of intended particles in major organs.	Rat model	RBC cloaking Fol enhanced thrombolysis in vivo, while reducing bleeding risk RBC cloaking adhered to fibrin 38% more.	[28]
5	Nano-delivery system	PEG-modified tPA-gelatin complex	Intravenously administered PEG-modified tPA-gelatin complex regain full thrombolytic function following ultrasound irradiation	Rabbit model	Improved recanalization observed when treatment followed by ultrasound irradiation versus without	[38]

S. no.	Approach	Device	Function	Model	Results	Ref
6	Magnetic injectable NP precision drug delivery system	Magnetic NP-shelled tPA microbubbles (MMB-SiO2-tPA)	tPA microbubbles are directed towards the thrombus site via magnetic guidance and tPA undergoes a controlled release with enhanced penetration into the clot due to ultrasound usage.	Mouse model	Thrombus size decreased by 67.5% when mice were treated with MMB-SiO2-tPA versus regular injected tPA	[39]
7	Association with a nanoconstruct/stable structure	tPA- conjugated discoidal polymeric nanoconstructs (tPA-DPNs)	tPA associates with the porous matrices of DPN to prolong its half-life and drug efficacy	Mouse models	tPA-DPNs displayed more efficiency, and protection from degradation (longer half-life) when compared with standard tPA. At 60 min, clot area was reduced by half, whereas standard tPA achieves these results by 90 min.	[40]
8	Nanocarrier liposomal target delivery system	tPA-loaded nanocarrier liposomes	tPA-loaded liposomes coated in the c-terminal end of the fibrinogen gamma chain travel to thrombus site and bind with GPIIb/IIIa on activated platelets during a thrombophilic event	Rat model	tPA half-life increased from 7 to 141 minutes when treated with tPA-loaded nanocarrier liposomes. Clot lysis increased by 35% with the tPA-loaded nanocarrier liposomes compared to conventional tPA treatment	[41]
9	Transdermal nanosensors	Thrombosis detecting nanosensors (TDNs)	Topically administered nanosensors travel transdermally through the skin, enter circulation and then release reporter molecules when the coagulation cascade is activated	Mouse model	Sustained delivery and presence of TDNs in mice for 72 hours 24 hours of diagnostic power within mice once TDNs were administered	[42]
10	Nanocarrier	Nanoscale self-titrating activatable therapeutic (nanoSTAT)	nanoSTATs use a negative feedback mechanism to circulate without releasing heparin in non-thrombotic conditions; whereas, in thrombotic conditions the nanoSTATs are activated and self-titrate heparin based on the surrounding conditions.	Mouse model	The lungs of mice administered nanoSTATs showed a 75% decrease in clotting compared to the control (mice administered no anticoagulants).	[13]

S. no.	Approach	Device	Function	Model	Results	Ref
11	Nanogels/ sonothrombolysis	urokinase-type plasminogen activator (uPA) loaded hollow nanogels (nUK) that react to ultrasound waves	Sonothrombolysis in ischemic stroke rat models. The nanogels protected the uPAs in the blood, and increased drug time.	Rat Model	Administered through an intravenous route. Nanogels enhanced the circulation time of the nUK and enhanced the protection of the blood-brain barrier. Nanogels have the potential to increase thrombolysis upon ultrasound administration.	[43]
12	Magnetic NPs (MNP)	Magnetic NP-recombinant tissue plasminogen activator (MNP–rtPA) guided with an external magnet to the site of emboli	A permanent magnet was placed right above the emboli and on-and-off periodically movement of the magnetic flow allowed dissipation of the MNP	Rat embolic Model	Tested if MNP–rtPA composite can reach the emboli under the guidance of an external magnet, degrade the clot, and restore hemodynamics. (Can reduce blood clot lysis time when compared with no magnetism, and with free tPA, 58% and 53% respectively.)	[44]

Discussion

Integration of Nanomedicine to Complement Traditional PE Treatments and Tests

According to the research works accumulated in Table 1, these set a benchmark in nanomedicine integration for PE. While not all the research works explicitly mention PE, the medicinal composition used for these studies are similar to the compositions utilized for PE, which helps establish and correlate these for estimating possible outcomes of nanomedicine. Despite being preclinical studies, these are helpful in estimation or formulating opinions depending on the similarities available for the future of nanomedicine integration in PE.

Current roadblocks for transitioning nanomedicine research into clinical studies lies within the preclinical to clinical result variability, novel usage of nanoparticles compared to past studies, scalable production, cost reduction, as well as safety concerns [45]. So much so that only 5% of nano-therapeutics that have made it to phase 1 clinical trials are granted permission for market, due to treatment efficacy concerns or cost of production [45]. Zhang et al. summarizes nanomedicine research into 3 stages, the first stage (1964-1995) involved 30 years of research which eventually led to the approval of the first nanotherapeutic, doxorubicin, the second stage (1995-2007) encompassed the vast clinical approval and production of nanomedicines. The third stage (2008-present) involves the development of smart nanotherapeutics [46]. It is within this current stage of research, that nanotherapeutics have to break the mold of traditional drug vehicles and offer new avenues for research [45]. Thus, despite the declining tendency of clinical approval, the field of nanomedicine is awaiting its next breakthrough, that will reshape the nanomedicine market. Integration of nanomedicine in the clinical treatment of PE highlights the urgent need for continued research in this field. Although most nanotherapeutics are still in the pre-clinical, or earlier, stage of development- the use of these novel technologies for clinical use is becoming a reality day by day. Current nanomedicine research for PE focuses on enhancing existing therapies and diagnostics by addressing limitations such as half-life, resolution, and bioavailability [16].

One such combination occurs in the study done by Lin et al., which explored a nanoscale self-titrating anticoagulant [13]. As mentioned in General Treatments & Progress subheading, the limitation of anticoagulants is that they have a narrow therapeutic index and may cause excessive and fatal bleeding as an adverse effect due to their hindering of the coagulation cascade [8]. As anticoagulation is the gold standard for PE treatment, it is crucial that these drawbacks are addressed and attenuated in order to make

progress and lessen the burden upon patients [8]. The anticoagulant used by Lin et al. was unfractionated heparin, which is widely used for thrombotic conditions such as atrial fibrillation, DVT, and PE [13][47]. Unfractionated heparin shares the same limitations as all anticoagulants, as well as the ability to induce heparin-induced thrombocytopenia (HIT) as an adverse effect [47]. HIT is also known as type II thrombocytopenia and is an immunogenic version of the disease that prompts the immune system to stimulate a pro-thrombotic event within the body [47]. Thus, in turn exacerbates the initial thrombotic condition that heparin was used to treat [47]. To prevent significant adverse events, strict dosage monitoring is essential, which is addressed by the Nanoscale self-titrating activatable therapeutic (nanoSTAT) developed by Lin et al. [8][13]. The nanoSTATs utilize a negative feedback mechanism to self-titrate heparin in response to the surrounding condition being thrombotic or nonthrombotic [13]. Thrombin acts as the regulating molecule for this feedback mechanism, as it activates the release of heparin from nanoSTAT from where it will interact with circulating antithrombin to inhibit thrombin [13]. As the production of thrombin decreases, so will the release of heparin [13]. As seen in Table 1 (S no.10), when tested in a mouse model, nanoSTATs were just as effective as free heparin while not causing significant bleeding [13].

Another collaboration between nano- and conventional medicine which may reduce the burden of PE was conducted by Kim et al., who utilized glycol-chitosan (GC) gold NPs (AuNPs) to aid in CT imaging of thrombi [36]. As seen in the General Diagnosis subheading, CT scans, specifically CTPA scans, are used to confirm the presence of thrombi in patients with PE [10][20]. However, this process does not fully show the severity and dispersal of thrombi in patients with PE [36]. In order to resolve this issue, Kim et al. developed GC-AuNPs which were able to target and entrap thrombi, allowing them to be visualized via CT scans due to gold's high X-ray attenuation [36]. As seen in Table 1 (S no.2), when evaluated in a mouse model, GC-AuNPs proved to be successful in imaging thrombi, monitoring progression and evaluating therapeutics [36]. GC-AuNPs also displayed an increased half-life, staying in circulation for up to 3 weeks [36].

As depicted in Figure 5 and Appendix A, thrombolytic therapy usually acts as a second line of treatment if anticoagulants fail to alleviate the PE or if the case is severe. Thrombolytics are effective but pose the risk of causing severe intracranial and extracranial bleeding as a side effect [20]. Recombinant tissue plasminogen activator (tPA) is the only clinically approved thrombolytic, and it aids in the conversion of plasminogen to plasmin - which in turn breaks down the fibrin networks holding thrombi together [10]. tPA also may cause brain haemorrhages as it retains the ability to cause excessive bleeding and regulate the permeability of the blood-brain barrier [10]. In order to reduce this problem, specific targeting of thrombi by tPA is needed to avoid unintended interactions [10]. Chen et al. ventured to address this issue by developing Chitosan magnetic NP (Chitosan - MNP) [35]. This technology uses magnetic direction to guide the Chitosan-MNPs, which are bound to tPA, to the thrombi [35]. As seen in Table 1 (S no.1), when this intervention was evaluated in a rat model it was observed that the rats that were administered Chitosan-MNP-tPA only required 20% of the dose amount that rats administered free tPA did [35]. This may also relieve some adverse effects of the drug, as tPA is dose-dependent and its effects are heightened as the dosage increases [48].

As seen in Table 1, the current integration of nanomedicine in PE mitigation is still primarily at the preclinical stage. Various animal models have and continue to explore the ways that nanomedicine may alleviate the burden of PE diagnosis, treatment and monitoring, however there is still a distinct lack of clinical research in this field.

Replacement of Traditional PE Treatment and Diagnostic Methods with Nanomedicine

As discussed in the Integration of Nanomedicine to Complement Traditional Treatments and Tests subheading within the Discussion section and Table 1 the supplementation of traditional methods to treat, diagnose and monitor PE with nanomedicine is currently being explored in a pre-clinical context. Presently, there is a distinct lack of clinical research regarding this topic, especially research exploring the replacement of traditional methods with nanomedicine. Most current literature delves into the use of nanotechnology as targeted drug delivery systems in order to assuage persistent issues such as narrow therapeutic ranges, short half-lives, adverse drug reactions and interactions as well as other pharmacokinetic complexities [49]. As seen in the Discussion section, nanocarriers act as conduit in these cases to not only resolve these issues but also to enhance overall performance and quality of treatment [49].

Exploring new avenues such as the use of nanomedicine alone to combat PE rather than an accessory to traditional methods may be beneficial for the future development of novel treatments. However, most current studies focus on the use of nanotechnology for drug and targeted delivery services [49].

An example of a way NPs themselves can be used for the treatment of PE is by employing ones that contain materials which alleviate the pathogenicity of PE. One instance of this was in a study conducted by Zhao et al. in which they used a NP with antioxidant properties that was loaded with an anticoagulant [50]. In this case, the NP itself exhibited therapeutic effects as it utilized H_2O_2 as a substrate, therefore reducing the oxidative stress of the environment [50]. Addressing oxidative stress may be beneficial in the treatment and management of PE as the literature suggests that it may be indicated in the pathogenesis of PE [51]. The usage of loaded NPs that exhibit a synergistic effect with the drug they carry in the management of PE is highly favourable as it targets multiple dilemmas with one treatment.

Conclusions

As mentioned in the Replacement of Traditional PE Treatment and Diagnostic Methods with Nanomedicine subheading within the Discussion section, there is a shortage of literature depicting nanomedicines as the primary and sole therapeutic in treating PE. At the moment, a vast majority of studies depict nanomedicine as a supplemental tool to enhance the efficacies and pharmacokinetics of existing and traditional PE management methods. The exploration of nanomedicine as an independent treatment method may be beneficial in reducing cost of treatments, developing new therapeutics and discovering other potential functions of nanomedicines. Current limitations in the literature include the lack of clinical research depicting the use of nanomedicine in PE treatment and management. Table 1 and the Discussion section both review studies in which an animal model was used to conduct pre-clinical tests of these novel technologies, however in present times there is still a gap in clinical research. Clinical trials and research on the implementation of nanomedicine into PE management is crucial to formulate treatments that are effective and safe for public use. The promise shown by nanomedicine in the treatment, diagnosis and management of PE is immense, even at the preclinical stage. More research into the utilisation of nanomedicine as an individual entity along with ample clinical research will most likely increase the quality and quantity of significant developments made in this field. This information would allow the scientific community to understand nanomedicine better and develop new ways to implement it into the treatment plans of other complicated diseases, such as Alzheimer's and Parkinson's disease.

List of Abbreviations Used

AuNPs: gold nanoparticles
CRS: controlled release systems
CTPA: computed tomography pulmonary angiography
DVT: deep vein thrombosis
GC: glycol-chitosan
HIT: heparin-induced thrombocytopenia
MNP: magnetic nanoparticle
nanoSTAT: nanoscale self-titrating activatable therapeutic
NPs: nanoparticles
PE: pulmonary embolism
PERC: pulmonary embolism rule out criteria
tPA: tissue plasminogen activator
V/Q scan: ventilation (V) and perfusion (Q) scan
VTE: venous thromboembolism

Conflicts of Interest

The author(s) declare that they have no conflict of interests

Ethics Approval and/or Participant Consent

This literature review did not require ethics approval and/or participant consent as it is a literature review.

Authors' Contributions

ZA: contributed to the literature search, drafting and revising process, abstract, introduction, discussion, and gave final approval of the version to be published.
AB: contributed to the literature search, drafting and revising process, abstract, discussion, conclusion, and gave final approval of the version to be published.

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