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Review of Anticoagulation Therapy in Unprovoked Pulmonary Embolism to Prevent Recurrence.

by

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Abstract

The purpose of this research was to identify the best course of action in response to a diagnosis of unprovoked pulmonary embolism. This meta-review was compiled through a systematic query of four databases: Pubmed, Embase, CINAHL Complete, and Cochrane Review. The search was limited to peer-reviewed systematic reviews published between October 1, 2014, and October 1, 2019. 17 reviews were included in this research which evaluated relevant trials of FDA-approved anticoagulation therapies. Key search terms that were used included *anticoagulation*, *unprovoked*, and *duration*. MeSH terms applied on PubMed included *anticoagulation*, *therapy*, and *duration*. The evidence demonstrates non-inferiority status of new direct oral anticoagulants (DOAC) when indirectly compared to conventional warfarin therapy. Aspirin was also found effective in mitigating the risk of recurrence, but to a lesser extent than both DOAC agents and warfarin. Current research demonstrates all DOAC agents as potential alternatives to conventional therapy, but attention to the comorbidities of each individual patient may direct providers to find advantage with one therapy over another. The research, thus far, has not been able to identify a universally safe and an effective agent for all patients experiencing a first-time unprovoked pulmonary embolism. Additional research is needed to evaluate the duration of therapy and generate more robust data to recommend a specific therapeutic agent for all patients.

Keywords: anticoagulation, unprovoked pulmonary embolism, warfarin, direct oral anticoagulants, aspirin, anticoagulation duration

Introduction

Preventing pulmonary embolism recurrence, has generated a tremendous amount of interest and debate in recent years. The development of Direct Thrombin Inhibitors (DTI), and Factor Xa Inhibitors (FXI) collectively known as the direct oral anticoagulation drugs (DOAC), have become replacement agents for conventional therapy. Traditional anticoagulation agent, Warfarin, a vitamin K antagonist (VKA), has been the primary drug of choice for PE treatment, but due to its increased bleeding risk therapy duration was limited. The traditional VKA alternative was acetylsalicylic acid or Aspirin (ASA) which provides only a fraction of the benefit while marginally mitigating the bleeding risk. These DOACs do provide an additional choice for providers but are questionable alternatives to conventional therapy. Another concern for providers to consider is the duration of therapy, as termination of anticoagulation therapy places patients back into a high-risk category.

Statement of the Problem

First-time unprovoked pulmonary embolism presents a difficult choice for recurrence prevention. Etiology of the insult is unknown, and prevention of recurrence is of utmost importance, but with treatment comes increased risk, primarily bleeding episodes. A provider must address each unprovoked PE patient on an individual basis and evaluate risk/benefit individually. This research is designed to help providers choose the best course of action for PE recurrence prevention while mitigating risk.

Research Question

Does drug choice and treatment duration impact morbidity and mortality for first-time unprovoked pulmonary embolism?

Methods

This review was compiled through a systematic review of Pubmed, Embase, CINAHL Complete, and Cochrane Review databases. The search was limited to peer-reviewed systematic reviews published within the past five years with the cutoff date October 1, 2014. Only human trials include this review. Studies reviewed were restricted to North American and European countries, as well as Australia, and China. These countries provide similar demographics and prevalence of disease. Key search terms that were used included anticoagulation, unprovoked, and duration. MeSH terms applied to PubMed included anticoagulation, therapy, and duration. Two additional studies, a 2013 Caststelluci et al. meta-analysis and a 1997 Schulman et al. study, were cited. Both citations were published outside of the established time parameters and added to illustrate the risks and benefits of warfarin therapy. All studies that included cancer patients, antiphospholipid syndrome patients, atrial fibrillation, post-operative patients, and all heparin therapy were excluded from the included literature review.

Safety and Efficacy of Aspirin

Two separate trials examined the efficacy and safety of aspirin, as monotherapy in recurrence prevention of pulmonary embolism: the WARFASA and ASPIRE studies. These two studies were specifically designed to be pooled upon completion, titled INSPIRE. The independent studies were designed with strict International Normalized Ratio (INR) adherence between 2.0-3.0 through lead-in warfarin therapy. The duration of lead-in therapy varied amongst participants ranging from 6-18 months. Designated follow-up for WARFASA was at 24 months and at four years in the ASPIRE trial. The studies classified the primary outcome as reported venous thromboembolism (VTE) recurrence and the secondary outcome as safety, which was reported as bleeding episodes.

A 2016 Bauersachs review concluded the WARFASA trial demonstrated aspirin efficacy over placebo with a reported VTE recurrence of 6.6% versus 11.2% in the treatment group and placebo group respectively, p= 0.002. There was a relative risk reduction of 41% when primary and secondary outcomes were compared. The WARFASA trial reported one bleeding death and three non-fatal but qualifying bleeding episodes.

ASPIRE showed no statistically significant differences in the primary outcome between the treatment group and placebo 4.8% versus 6.5% respectively, p= 0.09. The secondary outcome was consistent between groups in the WARFASA trial results. The average follow-up in ASPIRE was 37.5 months after therapy initiation. One incidental finding of ASPIRE was the potential cardioprotective component of daily aspirin therapy. There was a 34% reduction in reported major cardiovascular events (composite VTE, myocardial infarction, stroke, or cardiovascular death), p=0.01(Bauersachs, 2016).

A retrospective cohort study (Boonyawat, 2015) of 1,919 clinical charts showed contrasting real-life effects of aspirin in preventing recurrent VTE. 256 of the reviewed charts demonstrated atherosclerosis and were subsequently placed on daily aspirin ranging from 80-160 mg. The remaining patient charts reviewed did not receive aspirin. Follow-up of these patients indicated a 17.2% recurrence risk in the treatment group versus 19.8% in the non-atherosclerotic group. There is no reported bleeding risk evaluation for this retrospective cohort study.

As of this review, only one study (Carmen 2018) has examined aspirin directly against a direct oral anticoagulant. The EINSTEIN-choice was an extension of the EINSTEIN Program examining the efficacy of rivaroxaban. In this trial, aspirin was measured against two daily doses of rivaroxaban: 20 mg and 10 mg. The study authors reported the highest primary outcome within the aspirin arm at 4.4%, whereas rivaroxaban arms reported recurrence at 1.5% and 1.2%

in 10 mg and 20 mg respectively, $p< 0.001$. All three trial arms showed non-statistically significant differences in the bleeding risk (Carmen 2018).

Safety and Efficacy of Conventional Therapy

In the Bauersachs (2016) review, he evaluated several prior studies to illustrate the safety and efficacy of warfarin therapy during treatment of recurrent VTE. He cites a 2013 Castellucci meta-review showing an 8.8% reduction per year in treatment groups over placebo. The same study showed a 1.3% increase in bleeding risk in the treatment over placebo. However, a 1997 Schulman study showed an 8.6% increase in bleeding risk at a four-year follow-up in the treatment group over control. This study also verified therapeutic benefits of warfarin were only conveyed to the treatment group, as the control group reported a higher incidence of recurrent VTE (Bauersach, 2016). In a review by Castellucci, de Witt, Garcia, Ortel, & Le Gal (2018) of the 2015 PRADIS-RE trial, the reviewers confirmed the therapeutic benefits of warfarin are only conveyed to the recipient while actively receiving the medication. The risk of recurrent VTE returns to baseline upon discontinuation of therapy (Castellucci et al., 2018).

Castellucci et al. analysis of the RE-MEDY trial, which directly compared warfarin to another anticoagulant agent, dabigatran, demonstrated non-inferior status between these two medications, but a marked difference in their safety profiles. The study showed a 1.3% reported recurrence in the warfarin group and 1.8% in the dabigatran group, $p= 0.01$. This study also demonstrated the increased safety profile of dabigatran over warfarin with 13 reported major bleeds in the dabigatran group versus 25 within the warfarin group. The warfarin group reported higher rates of clinically relevant bleeding at 145 (10.2%) versus 80 (5.6%) in the dabigatran group. (Catellucci et al., 2018)

A meta-analysis performed by Jiang et al. (2018) evaluated studies comparing low dose warfarin to both placebo and conventional-dose warfarin. All patients included in this evaluation were diagnosed with first time unprovoked pulmonary embolism and all received at least three months of conventional-dose warfarin prior to beginning low-dose trial. All four studies reported reduction in the primary outcome with conventional therapy (INR 2.0-3.0) being more efficacious than low-dose therapy (INR 1.5-1.9), but both demonstrating superiority over placebo. Recurrent VTE occurred in 27 of the 706 patients (3.8%) treated with low-intensity warfarin and in 9 of the 693 patients (1.3%) treated with conventional-intensity warfarin. Another study Jiang et al. (2018) review demonstrated out of 369 patients assigned to low-intensity therapy, 16 had VTE (1.9 per 100 person-years), as compared to 6 of 369 assigned to conventional-intensity therapy (0.7 per 100 person-years); HR, 2.8.

Safety and Efficacy of Direct Oral Anticoagulants

Direct oral anticoagulant (DOAC) therapy is a broad and general term to describe multiple classes of anticoagulant agents. This group consists of direct thrombin inhibitors (DTI) like dabigatran and factor Xa inhibitors, like rivaroxaban, edoxaban, and apixaban. Both groups inhibit specific targets within the clotting cascade. Multiple studies and meta-analysis examined data which establishes the efficacy of DOACs versus placebo. The primary goal of the individual studies was to determine how well do these medications work to prevent recurrence of a pulmonary embolism as well as assessing the risk associated with anticoagulation.

A Bauersach (2016) review looked at rivaroxaban, apixaban, and dabigatran studies. These studies compared a single agent to a placebo. Lead-in therapy agent and duration varied amongst the trials. Therapy duration varied between 6-18 months. Results indicate DOAC as efficacious, or non-inferior, to warfarin with primary outcome reported as 0.4-1.2% for

recurrence in treatment arms and 5.6-8.8% in the placebo arms. Safety outcomes in this review indicate similar outcomes with reported bleeding and bleeding mortality 0.1-0.7% for the treatment arm versus 0.0-0.5% in placebo arm, $p<0.0001$. In fact, one review of the data demonstrated increased bleeding rates in the conventional therapy group over placebo when indirectly compared to all other DOAC trials, $p= 0.0012$. (Wu, Alotaibi, Alsaleh, Linkins, & McMurtry, 2015) Wu et al. (2015) go on further to advocate the threshold for net benefit in continuing DOAC may be lower than for VKA therapy and therefore provides a suitable lifetime therapy.

A meta-analysis by Becattini and Agnelli (2016) also report all DOACs were, overall, safer than conventional therapy. The primary outcome was similar between the DOAC groups and conventional therapy groups; with the risk of recurrence reported as 4.1% patient-years versus 4.4% patient-years for DOAC group and conventional therapy respectively. The review goes as far as reporting DOAC to reduce all-cause mortality over conventional therapy with an RR of 0.51. Several other incidental findings concerning primary outcome and safety outcomes in subgroup populations. Apixaban was shown to be the safest DOAC evaluated in these studies with the lowest bleeding risk showing a 69% reduction in qualifying bleeding episodes. Dabigatran was found to be safer than conventional therapy in patients over the age of 60, $p=0.0099$. Dabigatran is unique among all anticoagulation agents in that it continued to convey anticoagulation protection up to one year after discontinuing therapy.

A Berger et al. (2015) retrospective study assessed the efficacy and safety of rivaroxaban in first time unprovoked VTE. These patients received treatment beyond the initial three months of recommended conventional therapy with rivaroxaban. Recurrent VTE in the treatment group was 0.57% versus 1.19%, 1.07% versus 2.10% and 1.45% versus 2.60% at three, six, and 12-

month follow-up intervals for treatment and placebo respectively. No increased risk of bleeding was demonstrated in the treatment group versus the placebo group at three, six, and 12-month intervals.

EINSTEIN DVT and EINSTEIN PE were open-label trials that established the dose strength of therapy when compared to enoxaparin and warfarin for extended therapy based upon risk factors warranting an extension of anticoagulation therapy (EINSTEIN Investigators, 2012 and 2010). Both studies showed rivaroxaban to be non-inferior to conventional therapy in terms of reported recurrence and an approximate 50% reduction in major bleeding events. The major bleeding used was the ISTH (International Society on Thrombosis and Haemostasis) definition of major bleeding, however, these studies did have different definitions of clinically relevant nonmajor bleeding (Cohen & Bauersachs, 2019). The XALIA-LEA was a companion study that enrolled both DVT and PE patients. The findings of this retrospective study were consistent with prior results in other studies.

A HOKUSAI-VTE review by Joseph and Bartholomew (2017) validated edoxaban's status as non-inferior with conventional therapy, with HR 0.89, and reduced bleeding risk with RR of 0.81. Edoxaban and warfarin were not directly compared in this study.

A comprehensive review of existing DOAC trials and demonstrated with pooled results, DOAC efficacy, with a 2.8% report of recurrence in therapy groups, $p<0.0001$, with an annualized event rate of 6.0% versus 1.7% in placebo and DOAC treatment groups respectively (Marik & Cavellazzi, 2015). Moodley and Goubran (2015) reiterated this finding. Their review found reported bleeding rates of rivaroxaban, apixaban, and conventional therapy as 0.49%, 0.28%, and 0.89% respectively. This review reported fewer intracranial hemorrhage or

gastrointestinal bleeding episodes in those receiving dabigatran versus first-time conventional therapy recipients.

A Cochrane Review (Robertsen & McCaslin, 2015) was conducted, and it was the first review assessing the efficacy and safety of oral anticoagulants in the prevention of recurrent pulmonary embolism. The same oral anticoagulants have been assessed in other meta-analysis but none of those directly evaluated these agents with pulmonary embolism.

The meta-analysis revealed no statistically significant differences in efficacy between oral direct thrombin inhibitors (DTI) dabigatran and conventional anticoagulation therapy, warfarin (VKA). Due to substantial heterogenicity in the two studies evaluating factor Xa inhibitors, apixaban, edoxanban, and rivaroxaban, no meaningful conclusions can be drawn regarding their efficacy.

Analysis of the data shows no differences in reported major bleeding between DOACs and conventional therapy. The studies used strict bleeding guidelines set forth by the International Society on Thrombosis and Haemostasis, ISTH.

Robertson and McCaslin were unable to comment on subgroup analysis; as some studies failed to provide necessary patient-level data. Clinical decision-making should rely on patient comorbidities and individual patient risks rather than generalities of care of certain diseases.

This Cochrane Review concluded a low risk of bias in the studies included in their meta-analysis. All the studies were, however, funded by the pharmaceutical companies in which the evaluated drug was created. Speculation as to how this could lead to bias includes an altered timeframe for reportable safety outcomes. All studies used computerized randomization but do not elaborate leading to group selection bias. The quality of evidence for DTI versus conventional therapy was graded high. The quality of evidence comparing factor Xa inhibitors to

conventional therapy was graded moderate as the level of homogeneity of the participants was not adequately explained. The quality of evidence for all-cause mortality was graded moderate as only one study included this outcome. The evidence for major bleeding remained high due to consistent and precise effect estimates. A major limiting factor in this review is the small number of included studies at five, however, the number of participants included in each trial was adequate.

The Robertson and McCaslin (2015) concluded the evidence do not adequately demonstrate the replacement of conventional therapy with DOACs. However, they feel these medications present a reasonable alternative to conventional therapy. Fixed dosing, ease of administration, lack of routine lab monitoring may provide these medications as attractive alternatives to conventional anticoagulation therapy. One point of significance at the time of publishing was the lack of adequate antidotes for DOAC and presents a serious hurdle in their use in the real world. The half-life of these medications is short but having a reversal agent will only add to the argument for their use.

A subsequent Cochrane Review (Roberston, Yeoh, & Ramli, 2017) was conducted to evaluate the efficacy of extended duration pulmonary embolic prophylaxis. Five studies and a total of 5000 participants were included in this meta-analysis. No evidence was found which showed favorability for extended prophylaxis over placebo in terms of prevention of recurrent VTE, death, bleeding, or serious side effects such as myocardial infarction or stroke. Subgroup analysis demonstrated placebo may be favorable over aspirin in the prevention of recurrent VTE. In one study, rivaroxaban was shown to be more effective than aspirin in the prevention of recurrent VTE while demonstrating no major differences in bleeding. Only one study compared prophylactic agents against one another.

Robertson et al. (2017) determined, at present, insufficient data is available to conclude the efficacy and safety of VTE prophylaxis treatment in first time unprovoked VTE with any agent. All studies included used strict bleeding guidelines set forth by the International Society on Thrombosis and Haemostasis. All studies included used similar drug concentrations in the treatment groups. Patient homogeneity was achieved across all trials due to strict inclusionary criteria and statistical heterogeneity was low in all outcomes measured except recurrent VTE. The timeframe for measuring outcomes varied greatly in the trials, varying from nine months to 37 months. Studies also varied in the timing of measured outcomes. Some measured outcomes at the end of the treatment period, whereas others measured the outcome near the end of treatment. This difference could potentially alter the efficacy reported upon discontinuation of the treatment during follow-up. The total number of participants across the six studies examined was relatively small and analysis was based upon 3,436 participants. The authors were unable to comment on any subgroup analysis as some studies failed to provide necessary patient-level data.

Regarding extended prophylaxis versus placebo and for recurrent VTE and all-cause mortality the evidence was graded moderate accounting for concerns arising from increased risk of bias in individual studies. All other outcomes form the review; VTE-related mortality, bleeding, stroke, and other serious adverse effects, the quality of evidence was low due to substantial risk of selection bias and concerns over imprecision with wide confidence intervals pertaining to the estimated effect and the small number outcome events. Data that compared different prophylactic agents to one another was graded moderate due to imprecision, a low number of outcome events, and wide confidence intervals reported. There was only one study in which agents were compared to one another, and it did not demonstrate selection bias. Two

studies included participants under the age of 18, but the mean age of the participant was 67; the influence of those non-adult participants was negligible.

Robertson et al. (2017) were unable to offer a definitive opinion regarding extended VTE prophylaxis with any agent due to the inadequately low numbers of the eligible studies. There is a need for larger studies that use a stricter methodology in the assessment of the question of prophylaxis. Any future studies should include groups of patients at the highest risk of recurrence and a high risk of bleeding, which would reflect real-world demographics.

Discussion

The results of these studies demonstrate aspirin's potential as an anticoagulation agent. Moodley and Goubran (2015) argue, with a relative risk reduction of 42% in pooled data, aspirin looks to be a quality agent in the prevention of VTE recurrence. Several key issues were noted, however, for example demographic discrepancy between the WARFASA and ASPIRE groups. The WARFASA group tended to be older (average age 62), male (63%), and a smoker. Whereas the ASPIRE group the average age was 54 and 54% were male and non-smokers. Male sex, increasing age, and smoking status are all known risk factors for coagulopathies. With a deeper analysis of the participants, it can be speculated that the increased efficacy of the WARFASA group is due to an increase in risk factors requiring anticoagulation, thus possibly inflating reported success rate. This discrepancy can also explain the statistically insignificant difference in the primary outcome found in the ASPIRE group, these folks were already less likely to require anticoagulation due to fewer risk factors. Group bias may explain potential cardioprotective properties demonstrated in the ASPIRE trial; as the atherosclerosis risk factors are similar in those for pulmonary embolism. The retrospective chart review failed to show a

reduction in primary outcomes for those receiving aspirin therapy, but since withholding aspirin for those with atherosclerosis is morally dubious, no definitive conclusion can be made about the protective element of aspirin therapy.

Aspirin does have a place within the anticoagulation decision algorithm. It is a suitable alternative to DOAC and warfarin in patients with one or fewer risk factors. It may also present a safer option for fragile patients requiring indefinite therapy, where warfarin or DOAC are contraindicated or inappropriate based upon extrinsic factors. Patients with significant comorbidities consideration are those with liver or kidney failure and other fragile patients. Additional studies will be needed to evaluate long-term therapy to compare to DOAC to specific subgroup populations which require anticoagulation. Future studies will need to adequately power their research to examine bleeding risks with a comprehensive and well-defined bleeding outcome. Discrepancies in data can be attributed to differences in group demographics and future studies could equalize these differences for more robust results.

The efficacy of conventional warfarin therapy is well established within the literature. The question is not, if this agent is effective, but rather, is the patient equipped to handle this medication, and if so, how long should anticoagulation take place? The data suggests the longer a patient is on warfarin the greater the risk for bleeding. One important factor in selecting conventional therapy is warfarin has an antidote in vitamin k. It is readily available and cheap to administer. Warfarin, itself, is cheap, accessible, and has a long half-life. Some of the issues with warfarin are compliance concerns. A Moodley and Goubran (2015) review found a 79.9% non-compliance rate for target INR: 2.0-3.0. The same study reports a 51.5% discontinuation rate against medical advice. Also, frequent monitoring with multiple dosage adjustments can complicate administration for many patients. Warfarin also has many drug-drug interactions and

requires patients to avoid certain foods. All these issues presents a major challenge for providers in maintaining patient compliance. One possible alternative is low-dose warfarin with reduced INR 1.5-1.9 (Jiang et al., 2017) The reduction in dose does convey some protection, albeit significantly lower than conventional dosing, but allows for alternating monthly monitoring with reduced dose adjustments. Data overwhelmingly has shown warfarin compliance will reduce recurrent VTE, but it appears the risks must be weighed on a patient-to-patient basis when considering indefinite therapy.

The conclusion of current data indicates newer anticoagulant agents like rivaroxaban, edoxaban, apixaban, and dabigatran are just as effective as conventional warfarin therapy with statistically similar rates of PE recurrence. In his review, Bauersachs (2016) noted the DOAC studies showed a 0.4-1.2% for VTE recurrence in the treatment arms and 5.6-8.8% recurrence rate in the placebo arms. Safety outcomes in this review indicate similar outcomes with reported bleeding and bleeding mortality of 0.1-0.7% in the treatment arm versus 0.0-0.5% in the placebo arms, $p<0.0001$. The Berger et al. retrospective review of rivaroxaban showed statistically significant improvements at incremental follow-up periods in extended duration anticoagulation therapy over placebo, all without demonstrating any increased risk for bleeding in the treatment group.

Despite conclusions of DOAC studies, two separate Cochrane Reviews directly examined the efficacy of these newer medications and their safety profile. Both Cochrane reviews found the evidence moderately convincing with some concern over population selection and trial size. Both the 2015 and 2017 Cochrane Reviews indicated several areas of future needs to upgrade recommendations. Both Cochrane Reviews also indicate additional studies are needed to

evaluate the long-term effects, as well as direct head-to-head comparisons of these newer agents with conventional therapy.

Many fragile patients were not included in the DOAC studies; fragile is defined as over 75 years old, reduced CrCl (creatinine clearance) <50, or bodyweight below 50 kg. Patients less than 50 kg and those over 100 kg were also not adequately represented across trials. Apixaban is to be avoided in patients with CrCl <25, as all other DOACs are not recommended for renal patients with CrCl<30. These exclusions could have contributed to favorable results in primary efficacy outcomes as well as improved safety profile results, as the study participants tended to be younger and have fewer co-morbidities. The strict inclusionary criteria for these studies were not indicative of real-world patients and the resulting data may not translate to real-world fragile patients.

Most studies did not exclusively evaluate first-time pulmonary embolism patient. Patients with deep vein thrombosis (DVT) and cancer patients were included as well. With similar pathophysiology, authors reasoned the inclusion of DVT patients within these studies. The severity of disease status is much higher in first-time unprovoked PE than DVT. Only one review parsed out the pulmonary embolism data away from general group data. The risk of recurrence between DOAC and VKA was statistically similar 2.4% versus 2.6% OR 0.89%; CI 95%. This analysis also showed a 50% reduction in major bleeding with the DOAC group over the VKA group. However clinically significant rates of bleeding between DOACs and VKA were similar, 10.2% versus 11.3%; OR 0.89 95% (Becattini & Agnelli, 2016)

Lead-in therapy for these studies was not homogenous across the studies. Agents used as lead-in therapy and their duration varied from study to study. Therapy duration was not uniform in any of the DOAC studies and follow-up periods also varied across studies which may provide

a potential in reporting bias in both efficacy and safety categories. Varying approaches to lead-in therapy included; a single drug approach or multidrug approach. The multidrug approach used conventional therapy during the initial three months following the insult then switching to second medication during the extended therapy.

The role of warfarin in anticoagulation therapy is well-established and effective. The issue resides in the side effect profile, risk of major bleeding, and patient compliance. The risks and compliance challenges increase with aging patients. Providers and patients must reassess risk/benefit regularly. Aspirin's role has been evaluated and is considered inferior to both DOAC and conventional therapy but does convey some protection. The declaration of DOAC as a wholesale replacement to conventional anticoagulation therapy is grossly overstated. Indirect drug comparison studies have used to establish non-inferiority of DOACs. There are many questions concerning the strict exclusionary criteria employed in these studies which may not reflect accurate results when applied to real-world patients.

Additional trials are needed to evaluate the efficacy and safety profile of DOAC directly against conventional therapy. The RE-MEDY trial was the only included trial to evaluate dabigatran against conventional therapy. Elmi, Di Pasquale, & Pesavento (2017) review of the RE-MEDY trial did show improved safety profile of dabigatran over warfarin when directly compared; 5.6% reported major bleed or clinically relevant bleeding in the dabigatran group versus 10.2% report in warfarin group, $p = 0.06$, with similar rates of recurrence 1.8% versus 1.3% in dabigatran and warfarin respectively. A yet to be published clinical trial has been submitted for approval and is titled COVET (Comparison of Oral Anticoagulants for Extended Venous Thromboembolism) which will directly warfarin to apixaban and rivaroxaban to compare safety outcomes and reduction of recurrent VTE. Additional trials are also needed to

evaluate the long-term efficacy and more importantly risks associated with indefinite anticoagulation therapy. Current issues regarding data inconsistency across study groups which prevents a direct comparison. Varied trial length and inconsistent follow-up schedules varied from one trial to the next. Heterogenous lead-in therapy is another valid concern of these studies used to prove the safety and efficacy of DOACs. Future studies would benefit to normalize lead-in duration and agent employed. Standardized follow-up periods could also help eliminate potential bias in safety and efficacy reporting. More accurate representative trial populations with looser exclusionary criteria would allow for stronger recommendations for the use of DOAC therapy instead of conventional therapy. As of this review, DTI and Factor Xa inhibitor classes provide an alternative to conventional therapy with moderate recommendations at most.

Applicability to Clinical Practice

The purpose of this research was to assist in simplifying the decision-making process when considering anticoagulation therapy specifically after unprovoked pulmonary embolism. The risks associated with anticoagulation continue throughout the duration of therapy, which is typically indefinitely in the case of unprovoked pulmonary embolism. Whether on therapy or if the patient forgoes treatment risk is expected. Currently, patients and providers perform a risk/benefit analysis to weigh the risks of therapy versus the risk of recurrence. There are many factors that must be examined. The hope was to find evidence in the literature to ease the burden shared decision-making. Unfortunately, the data does not bear out a definitive answer; in respect to either agent or duration. On the other hand, the data does suggest some protection with newer DOAC or aspirin therapy in certain population subgroups where conventional therapy is deemed unsatisfactory. Unfortunately, additional studies are warranted and until more concrete

information becomes available an individual approach to anticoagulation is the best-practices approach.

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