An Aspirin a Day to Keep the Clots Away:

Can Aspirin Prevent Recurrent Thrombosis in Extended Treatment for VTE?

Running title: Wakefield et al.; Prevention of recurrent venous thromboembolism

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Patients presenting with DVT in the absence of any identifiable risk factors are said to have an unprovoked or idiopathic DVT. Recurrent events are much more common in these patients (10% vs. ≤3% at 1 year) compared to patients with a DVT provoked by a reversible risk factor, and represents a major healthcare problem.¹ Three months of anticoagulation is sufficient to decrease the risk of recurrent thrombosis related to the initial DVT. However, once therapy is discontinued, the risk for recurrence rises dramatically. It has been suggested that 30 to 50% of patients experience a recurrence at 10 years.²³ Factors associated with a higher likelihood of recurrence are male gender, elevated D dimer, incomplete resolution of DVT, body mass index ≥30, and post-thrombotic syndrome.⁴ In fact, a number of tools have been developed to determine the risk of recurrence after DVT.

In the current management paradigm, patients with unprovoked DVT are evaluated for long-term anticoagulation following initial treatment with 3-6 months of anticoagulation. The risks of major bleeding during prolonged therapy are periodically weighed against the benefits of continuing anticoagulation in high-risk patients. Data supporting this approach comes from 4 studies demonstrating a decreased in recurrent VTE by 90% with extended conventional dose VKA therapy.⁵ Major bleeding occurs in 20 per 1000 patients, and as of yet no validated prediction tool exists to predict risk-benefit ratio of extended therapy.⁶ Factors associated with an increased risk of bleeding include advanced age > 75, history of gastrointestinal bleeding, non-cardioembolic stroke, renal or hepatic disease, concomitant antiplatelet usage, and poor control of anticoagulation.⁵ In the interest of diminishing the bleeding risk while conferring protection against recurrent venous thromboembolism several approaches have been taken: subtherapeutic anticoagulation with vitamin K antagonists (VKA), new oral anticoagulant agents and aspirin.⁷
Two trials randomized patients after completing fully VKA anticoagulation (3 to 6 months) to either placebo or sub therapeutic vitamin K antagonist therapy (target INR of 1.5 - 1.9). Patients receiving indefinite sub therapeutic anticoagulation had a 62-64% relative risk reduction of recurrent VTE. While low-intensity VKA was more effective than placebo, it was less efficacious than full-dose VKA. Use of a lower INR target did not decrease the number of clinically important bleeding events, dampening overall enthusiasm for this approach.

New oral anticoagulants (NOACs) which do not require monitoring nor dosage adjustment have emerged as a convenient alternative for long term prevention of recurrent VTE. To date, 3 trials have evaluated NOACs against placebo for an additional 12 months of therapy beyond initial anticoagulation. In a pooled meta-analysis of the data, NOACs decreased the risk of recurrent VTE or VTE-related death by 84% with a number needed to treat (NNT) of 17 compared to placebo. However, bleeding remained a significant source of morbidity with a higher risk of major or clinically relevant bleeding [4.6% vs. 2.0% OR 2.69, 95% C.I. 1.25-5.77] in the NOAC group and a number needed to harm (NNH) of 39. One trial has evaluated dabigatran compared to warfarin for the extended treatment of VTE. In this trial, patients were randomized to either dabigatran 150mg twice daily or warfarin (with a goal INR of 2.0-3.0) for 12 months following completion of acute anticoagulation. The primary endpoint of symptomatic DVT, fatal PE, and all-cause mortality was similar between the two groups. A lesser risk of major bleeding (5.6% vs. 10.2%, p <0.001) was offset by the increased incidence of acute coronary syndrome in the dabigatran group (0.9% vs. 0.2%, p=0.02). The expense and lack of any commonly available reversal agents represent drawbacks to the use of NOACs.

Despite universal availability, inexpensive cost and well-established drug safety profile, the use of aspirin previously has not been extensively studied outside of the orthopedic surgery.
population for the treatment or prevention of VTE. Practically, aspirin may represent a convenient intermediate therapy between no treatment and indefinite anticoagulation, balancing the risk of bleeding with the benefit of preventing recurrent thrombosis in a moderate risk population. Two recent trials recently were completed to address this question: the Warfarin and Aspirin (WARFASA) study\textsuperscript{13} and the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study.\textsuperscript{14} In both trials, aspirin was compared against placebo following completion of a minimum of 6 weeks of anticoagulation in patients with unprovoked VTE. Patients were treated with 100mg of aspirin or placebo for 2-4 years. In both trials a decrease in recurrent VTE was demonstrated with a low risk of major bleeding. However, neither study was powered to detect moderate treatment effects amongst different subgroups of patients.

The Aspirin for the prevention of recurrent venous thromboembolism study (INSPIRE)\textsuperscript{15} was designed to more accurately delineate the treatment effects of the WARFASA and ASPIRE trials in pre-specified subgroups by combining the results at a patient level prior to unbinding of the two arms. The study, initially powered to detect with 80% confidence a 30% reduction in recurrent VTE, although due to slow enrollment, was ultimately powered to detect a 35% reduction in recurrent VTE. VTE occurred in 18.4% of patients on placebo and in 13.1% of patients assigned to aspirin (HR 0.68, CI 0.51 to 0.90, p=0.008) corresponding to a NNT of 42 to prevent one symptomatic VTE occurrence. Additional data garnered from this analysis was most valuable in identifying the populations most likely to benefit (men and individuals aged $\geq 65$) and evaluating the treatment effect over time. The absolute reduction of recurrent events was significantly greater over the first year when the risk of recurrence was highest.

It is surprising, given that platelets are known to be central to thrombosis, that antiplatelet therapy was not considered sooner to be compared in a rigorous randomized control trial for
DVT prevention. However, experimental data directly supporting the role of the platelet in DVT was generally lacking. One early report with an experimental rodent model suggests platelets directly contributed to acute venous thrombosis, but most experimental venous thrombosis research over the last two decades has focused on the role of the leukocyte and vein wall. This is because of the classic dogma that the fibrin rich ‘red clot’ formation in venous thrombosis is primarily driven by the clotting pathway, while arterial thrombosis is thought to be more platelet driven. However, recent experimental data using murine models suggests that the platelet is a critical component of early DVT. First, the assembling and co-localization of the coagulation cascade occurs on the platelet surface in juxtaposition to the endothelium. Second, release of von Willebrand Factor (vWF) provides a bridge between the platelet and endothelium. Studies using vWF gene deleted mice confirmed decreased thrombus size that was not reversed with exogenous factor VIII, in a flow limited venous thrombosis model. Extrapolation of data to humans is somewhat limited with any animal model system of human disease, including partial or total stasis DVT models. Particularly relevant to the current INSPIRE study is that there are no animal models (yet) of recurrent DVT.

The pathophysiology of recurrent unprovoked DVT may be different than primary DVT. How? It is likely the vein wall is damaged with the initial thrombus insult, even in those who fully lyse their DVT. While direct tissue histopathologic examples are rare, post DVT vein wall changes are exemplified physiologically by valve reflux and thickened and noncompliant vein walls, together which culminate in post thrombotic syndrome. Thus, the endothelium that is regenerated after the thrombus has cleared may be more likely to thrombosis. Intriguingly then, the current clinical data suggests the platelet may be more central to recurrent DVT than primary DVT.
How to take this information and make current recommendations? (Figure 1) We would suggest that for patients who have unprovoked (idiopathic) VTE and are at high risk for recurrence and would normally need long-term or life-long anticoagulation, they remain on either oral vitamin K antagonists or one of the new oral anticoagulant agents and not undergo aspirin therapy. On the other hand, for patients with unprovoked VTE and moderate risk for recurrence, the use of one aspirin per day rather than nothing would be indicated. For those patients with an unprovoked VTE and low risk for recurrence, no further therapy is indicated. For patients with a provoked VTE, a total of 3 months of anticoagulation is indicated.

Many questions remain and are not answered from the current data, including:

1. Is there an optimal length of aspirin therapy in patients with unprovoked VTE and a moderate risk for recurrence?

2. Should aspirin be used in those patients with unprovoked VTE and low risk for recurrence?

3. For patients with a provoked VTE would normally would not need long-term anticoagulation (a patient with a first episode of VTE and a cause which has reversed such as VTE associated with surgery or with the use of oral contraceptives), is taking one aspirin per day at the end of a full course of anticoagulation beneficial?

4. Will other medications such as statins synergize with aspirin to reduce the incidence of recurrent VTE?

5. Will the more potent antiplatelet theinopyridines be more or less effective than aspirin?

6. As patients with cancer represented only a small proportion of patients and patients with coronary artery disease were excluded, what are the recommendations in these groups of patients?
Finally, will the current data on only a little over 1200 patients hold up in day to day clinical use?

As is the case with all good studies, more questions remain to be answered and are the seeds for future studies.

Conflict of Interest Disclosures: None.

References:


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**Table 1.** Effect of anti-thrombotic agents on recurrent VTE and major bleeding during extended therapy for treatment of unprovoked VTE

<table>
<thead>
<tr>
<th></th>
<th>Recurrent VTE*</th>
<th>Major Bleeding*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td><strong>VKA (INR 2.0-3.0)</strong></td>
<td></td>
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<tr>
<td>Apixaban</td>
<td>0.12 (0.09-0.38)</td>
<td>2.63 (1.02-6.76)</td>
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<tr>
<td>Rivaroxaban</td>
<td>0.18 (0.11-0.28)</td>
<td>0.38 (0.08-1.68)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.13 (0.06-0.30)</td>
<td>4.83 (0.23-100.83)</td>
</tr>
<tr>
<td><strong>NOAC</strong></td>
<td></td>
<td></td>
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<tr>
<td>Apixaban</td>
<td>0.18 (0.11-0.28)</td>
<td>0.38 (0.08-1.68)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.18 (0.08-0.38)</td>
<td>8.94 (0.48-166.41)</td>
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<tr>
<td>Dabigatran</td>
<td>0.13 (0.06-0.30)</td>
<td>4.83 (0.23-100.83)</td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.68 (0.51-0.90)</td>
<td>1.24 (0.46-3.33)</td>
</tr>
</tbody>
</table>

*At minimum 1 year (range 12-48 mo) of follow up; compared to placebo
†73-93% of patients with unprovoked VTE

**Figure Legend:**

**Figure 1.** Incorporation of ASA into VTE extended treatment paradigm. Low risk = patients with normal D dimer and no risk factors for venous thrombosis. Moderate risk = patients with one or more risk factors for recurrent thrombosis. High risk = patients with inherited thrombophilias, > 1 episode of venous thrombosis.
VTE

- Provoked
  - 3 mo anticoagulation
    - Low risk: No further treatment

- Unprovoked
  - 3-6 mo anticoagulation
    - Moderate risk: ASA
    - High risk: Anticoagulation
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