Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Greenwald M., et al., 2024. Predicting Thrombotic Events in Rheumatoid Arthritis by Using Bleeding Time: Look at the Platelet. Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5282

DOI: https://doi.org/10.18103/mra.v12i4.5282

ISSN: 2375-1924

RESEARCH ARTICLE

Predicting Thrombotic Events in Rheumatoid Arthritis by Using Bleeding Time: Look at the Platelet

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is associated with an elevated risk of thrombosis, which contributes to increased major adverse cardiovascular events and mortality in individuals with RA aged over 50, as compared to the general population. This increased thrombotic risk is thought to be due to systemic inflammation leading to platelet dysfunction. Additionally, certain RA treatments have been associated with an increased risk of clot formation. We proposed the hypothesis that a shortened bleeding time measurement could serve as an identifying marker for individuals at risk of clotting events. The bleeding time assesses platelet function. Aspirin can reverse the short bleeding time and may prevent the incidence of thrombosis.

Methods: Sequential RA patients over age 50 (n=246) at one center had bleeding time testing at the initial visit and 2 weeks after beginning a medication known to affect coagulation. These were estrogen, rofecoxib, celecoxib, naproxen, ibuprofen, aspirin, tofacitinib, baricitinib, upadacitinib, filgotinib, and anti-coagulants.

Results: The RA control group had a bleeding time of 3.7 $\pm$ 0.4 minutes. This is a shorter bleeding time than expected in the normal population, where bleeding time is 4 to 7 minutes. The RA patients who developed MACE or thrombotic events had shorter bleeding time at 2.3 $\pm$ 0.4 minutes, significantly shorter than the RA control group, $p<0.001$. A shorter bleeding time was demonstrated with COX-2 agents, rofecoxib and celecoxib at less than 2.5 minutes, and JAK agents had short bleeding time from 1.5 to 2.3 minutes, all significantly lower than the control $p<0.002$. Adding daily 81 mg low dose aspirin to JAK reversed the bleeding time to the control values. A bleeding time measured at less than 3 minutes was associated with higher incident rates of thrombotic events and MACE.

Conclusion: These findings suggest that bleeding time less than 3 minutes may serve as a clinically relevant marker for assessing thrombotic risk in RA patients. Further research with larger cohorts is warranted to validate and expand upon these observations, potentially paving the way for the incorporation of bleeding time testing into the clinical management of RA patients to optimize thrombotic risk assessment and preventive strategies.

Introduction

Rheumatoid Arthritis (RA) is associated with an elevated risk of thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and cerebral vascular accident (CVA).[1,2,3,4] This heightened incidence contributes to increased major adverse cardiovascular events (MACE) and mortality in individuals with RA aged over 50, as compared to the general population.[5] Several factors contribute to this increased thrombotic risk, such as systemic inflammation leading to platelet dysfunction, elevated platelet counts, increased fibrinogen levels, and augmented platelet receptors like glycoprotein VI (GPVI) and CLEC-2. Additionally, certain RA treatments have been associated with an increased risk of clot formation. There are multiple contributors to heightened clotting risk in RA, and we proposed the hypothesis that a shortened bleeding time measurement could serve as an identifying marker for individuals at risk of clotting events. The bleeding time (BT) assesses platelet function. Aspirin can reverse the short BT and may prevent the incidence of thrombosis.

Background

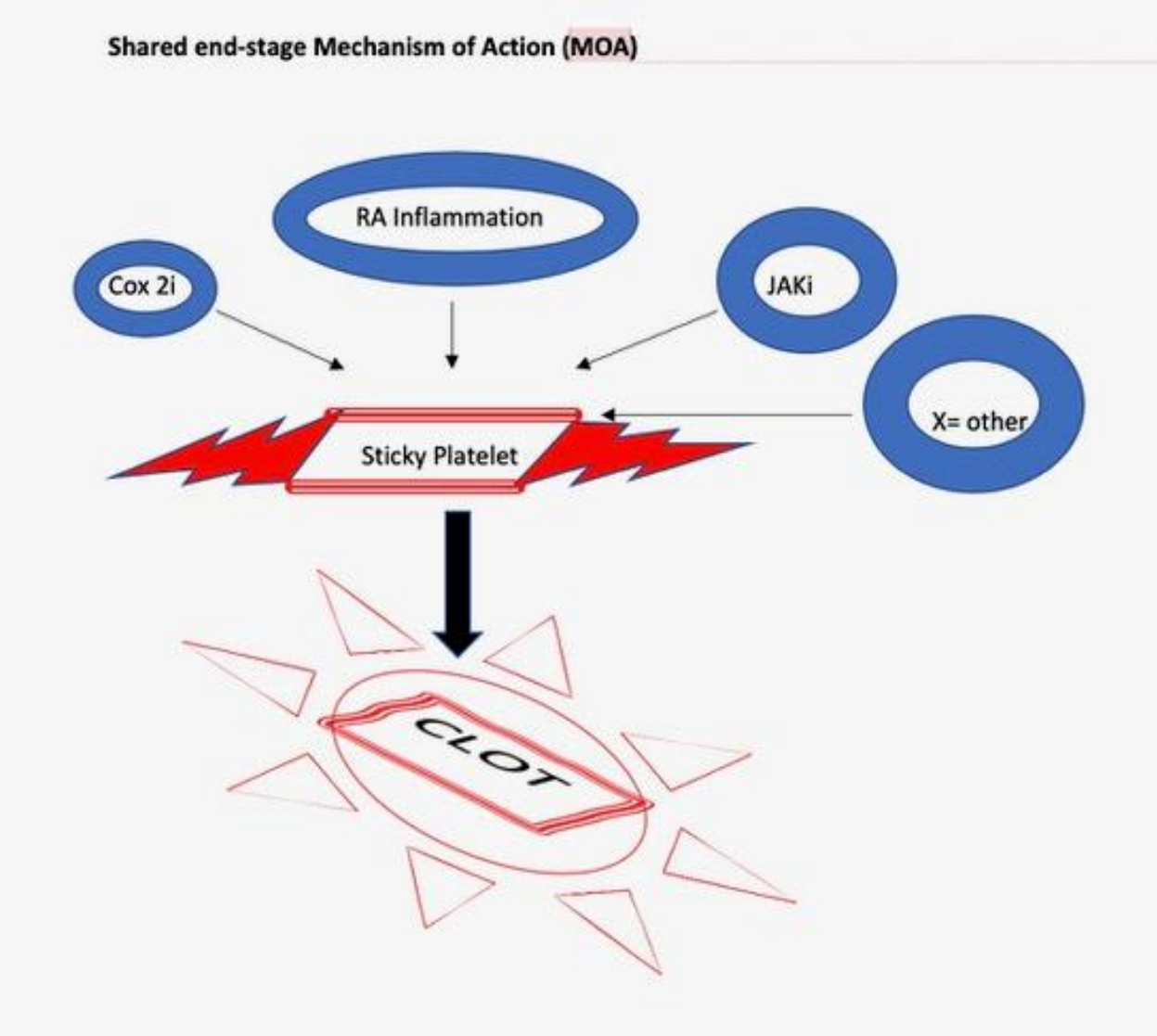
The Platelet's Role in Thrombosis:

The platelet emerges as a central player in the complex interplay leading to clot formation. Regardless of the triggering factors, platelets play a pivotal role in all clotting pathways.[6] (Figure 1) The hypothesis presented posits that by assessing platelet clot function in vivo through a bleeding time test, individuals at the highest risk of clot formation—indicated by a short bleeding time—can be identified. Early identification can facilitate the initiation of preventive measures. Specifically, aspirin, with its dual direct and indirect effects on platelet function, becomes a key player modulating thrombosis. Identifying individual RA patients, particularly those aged over 50, who are at increased risk for MACE and DVT is crucial. This exploration aims to unravel strategies for offering protection against thrombosis in this specific population.

The platelet exhibits numerous phenotypes that significantly influence both its structure and functionality.[7] These diverse phenotypes contribute to a range of physiological processes, including vascular endothelium repair, hemostasis mediation, clot formation over arterial plaque, initiation of chronic inflammation, and modulation of immune responses for host defense. In various disease states, alterations in platelet phenotype can activate specific platelet agonist receptors, triggering different functions. (Figure 2 shows RA activated sites marked by an *).

Describing platelet phenotype involves characterizing its various states, such as quiescent, thrombotic, procoagulant, primed, refractory, exhausted, angry, sticky, and inflamed. These states reflect the platelet's readiness and responsiveness to external stimuli. For instance, increased fibrinogen levels correlate with heightened clot formation, a phenomenon observed in conditions like rheumatoid arthritis (RA) inflammation. Notably, aspirin administration reduces the number of activated platelets and mitigates fibrinogen levels, demonstrating its potential in modulating platelet function.

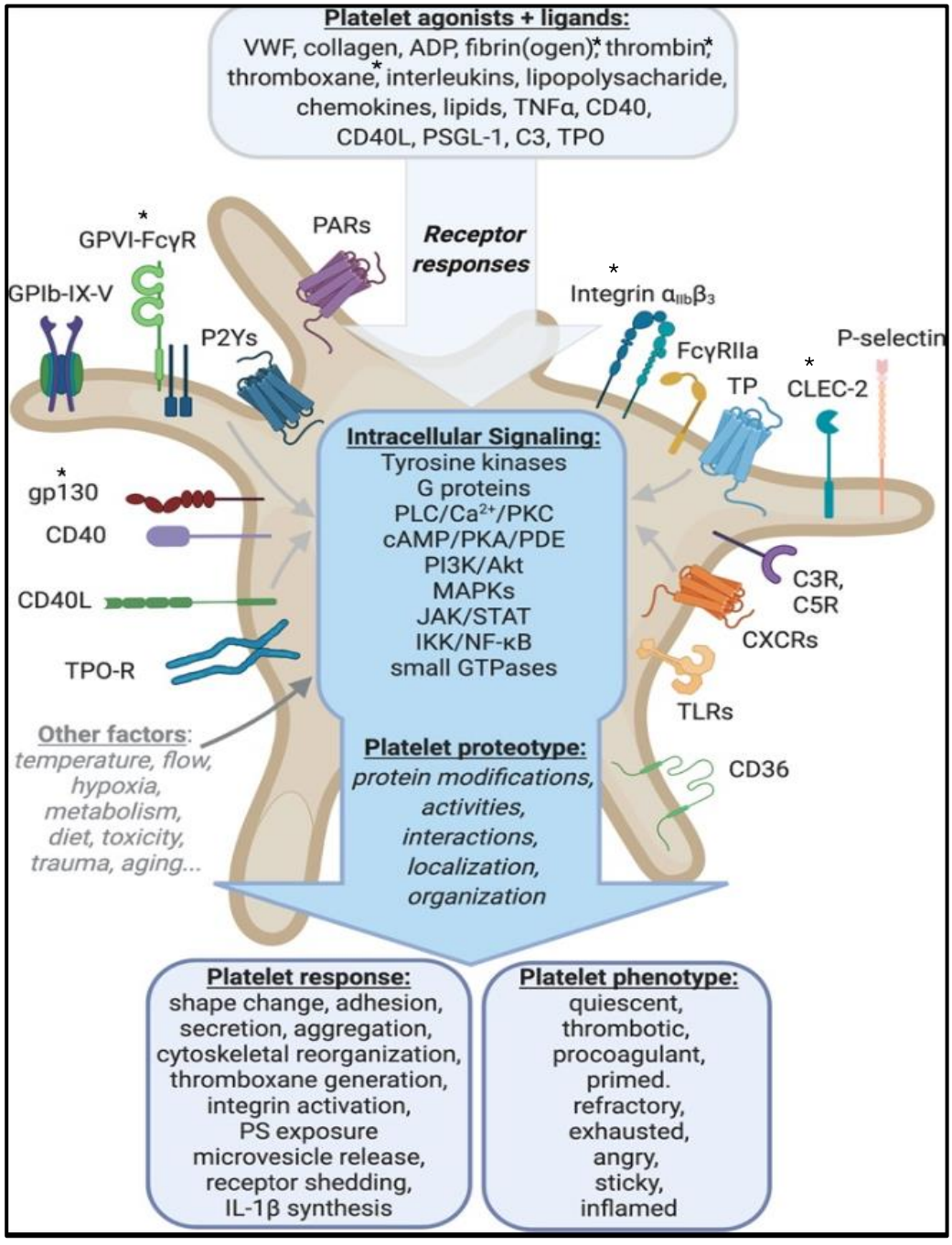
FIGURE 1: Final Common Pathway: All Roads Lead to the Platelet



X= other factors that increase clot include estrogen, Factor V Leiden, protein S deficiency, protein factor C deficiency, prothrombin mutations, anti-cardiolipin antibodies. In addition, X factors include damage to vessels from plaque, prior DVT, and cigarette smoking all known to increase thrombotic events.

FIGURE 2: Platelet Activation and Phenotypes - Reprinted with permission by Joseph Asian[7]

*Indicates RA activated sites on the platelet



Understanding Clot Formation and the Multifaceted Role of Low-Dose Aspirin

Aspirin, originally synthesized in 1898 as an anti-pyretic agent, has evolved into a crucial antithrombotic agent, and has saved countless lives in cardiovascular disease. Compelling evidence indicates that therapy with aspirin results in a 25% reduced risk of nonfatal myocardial infarction, nonfatal stroke, or vascular death in high-risk patients, regardless of sex, age, the presence of arterial hypertension, or diabetes.[8,9] While its primary function is inhibiting platelet aggregation by irreversibly

blocking cyclooxygenase-1 (COX-1), recent studies reveal additional antithrombotic effects beyond COX-1 inhibition.[10]

The Cox-1 and Cox-2 Paradigm: The potent action of aspirin on Cox-1 in platelets decreases thromboxane A2 synthesis, reducing platelet activation and clot formation. Notably, it is 170 times less effective in Cox-2 blockade. Cox-2, responsible for prostacyclin production, prevents platelet aggregation and promotes vasodilatation. Inhibiting Cox-2 increases clot risk, and has been shown to promote arterial thrombosis.[11] The synthesis of PGE_2, the main product of platelet COX-2, is also inhibited by Cox-2 selective inhibitors (Cox2i). Additionally it is important to note that acetylated COX-2 has 15-lipooxygenase activity and produces 15(R) hydroxyeicosatetraenoic acid (HETE) which also increases thrombotic events.[8] Inhibiting Cox-2 increases clot risk, emphasizing the delicate balance maintained by aspirin. In addition, combining low dose aspirin with COX-2i might prevent thrombotic events. It has been noted that in one study that rofecoxib did not prevent the anti-thrombotic activity of low dose aspirin.[12]

Other Pathways seen in RA that are influenced by Aspirin: Aspirin doesn't directly block thrombin but impairs thrombin activation by reducing factor XIII, thereby reducing thrombin generation.[13] It acetylates lysine residues in fibrinogen, enhancing fibrin clot permeability.

In RA, the platelet immune receptors GPVI and CLEC-2 are elevated and both increase thrombosis.[14] Platelets are a direct cause of thrombo-inflammation.

The platelet clot is initiated by integrins (making platelets stick to other platelets).

In resting platelets, integrins are expressed in a low-affinity state but they shift to a high-affinity state in response to cellular activation, such as seen in a RA flare.[15] Aspirin does not influence integrin B but aspirin reduces activated platelets. Therefore, aspirin can influence thrombo-inflammation without direct effect on integrins.

Anti-Phospholipid Syndrome and Immune-Mediated Thrombosis

Aspirin is a standard therapy to prevent clot for anti-phospholipid syndrome which can occur in RA. The anti-cardiolipin antibody interacts directly with the IgG receptor on the platelet.[16] Aspirin is used as primary prevention of thrombosis in many guidelines, regardless of the origin of the anti-phospholipid antibodies.[17] Aspirin both decreases the number of platelets as well as platelet activation.

JAK-STAT instigates clot and provides a potential role for aspirin

All JAK inhibitors (JAKi) interact with the platelet via glycoprotein-VI.[18] This occurs by the interaction of JAKi with STAT5 function in the platelet via the GP-VI /ITAM pathway.[19] Both ruxolitinib and baricitinib have been shown to impair glycoprotein-VI mediated platelet functions.[20] Furthermore, a JAK2 mutation[21] causes thrombocythemia with an increased number in platelets and increased platelet activity; the bleeding time is short. Clotting events are common. With baricitinib, platelet numbers increase and younger new platelets aggregate more readily. Again, shorter bleeding times result and are documented with younger platelets. The addition of aspirin might reverse part of this process.

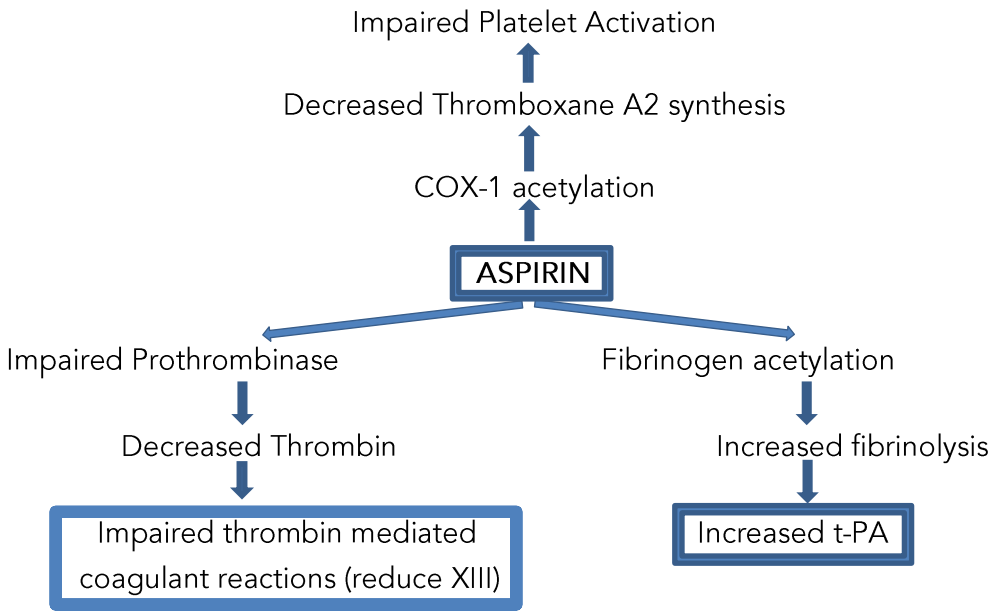
The JAKi and COX2i increased clotting activity may be linked. It has been shown that JAK3i reduced COX2, resulting in reduced prostacycline.[22,23] Then it has also been noted that COX2i reduces the phosphorylation of JAK2, Tyk 2, STAT3 and STAT4. This portrays multi-model examples of ways to increase clotting.

Aspirin Dose needed to prevent clot

Low doses of aspirin are effective in preventing thrombotic events. In multiple situations, low dose aspirin inhibits the COX-1 activity of prostaglandin permanently by acetylating a single serine residue at position 529. In contrast to anucleate platelets, nucleated cells can resynthesize their enzymes, thus prostacyclin production is recovered after a few hours in megakaryocytes.[24,25] After a single dose of aspirin, COX-1 activity is restored at the rate of 10% daily if platelet turnover is normal. Consequently, a dosage of one 30 mg to 100 mg tablet per day is sufficient to block platelet clotting even if aspirin is able to only temporarily acetylate COX-1 in megakaryocytes.

In healthy individuals, low-dose aspirin (81 mg/d) increases clot porosity by 65%.[26] Gastrointestinal bleeding events are dose related and low when aspirin is dosed less than 100 mg/day. The risk of a serious bleed for those over age 50, such as an intracerebral hemorrhage, is very low, at about 4 per 1000 persons over a 10 year period.[27]

FIGURE 3: Direct Effects of Aspirin on Thrombosis



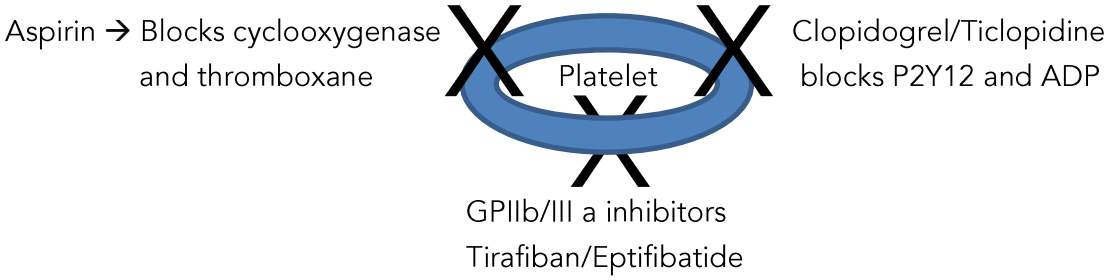
Summary of aspirin action

Certainly, a major effect of aspirin on hemostasis is its COX-1 dependent inhibition of platelet function. The inhibition of cyclo-oxygenase results in reduction of HETE (20-hydroxyeicosatetraenoic acid) and thus reduces the recruitment and migration of platelet components of clot. However, a growing body of evidence indicates that aspirin may also affect blood coagulation at several other levels, such as reducing thrombin generation and the subsequent inhibition of thrombin-mediated coagulant reactions. Then there is the effect of aspirin on endothelial cells to increase release of t-PA.[10,28] Further effects of aspirin include acetylation of fibrinogen that results in increased fibrin clot permeability and enhanced clot lysis.

Alternatives to Aspirin:

Reports of thrombosis in some individuals on aspirin have led to the identification of "aspirin resistance." This resistance may manifest as the failure of aspirin to produce expected effects, such as inhibiting platelet aggregation or suppressing thromboxane production. Documented aspirin resistance in patients with stroke or coronary artery disease occurs in over 5% of users, often associated with genetic mutations for thromboxane.[29] Non-responders to aspirin, lacking prolonged bleeding time, show increased thrombotic disease risk.[30,31] Among patients who had a history of stroke, aspirin resistance has been reported to be associated with a 10-fold increase in the risk of recurrent vascular events.[32] This prompted our current exploration of bleeding time in subjects with RA to determine why they had MACE or a thrombotic event.

FIGURE 4: Therapies directed at the platelet to inhibit clot



Alternative therapies to aspirin include anticoagulants like Factor Xa inhibitors (apixaban, betrixaban), also warfarin and heparin, which interfere with the coagulation pathway, and fibrinogen to prevent platelet aggregation.[33] Aspirin remains a key treatment for immune-mediated pathways in anti-phospholipid syndrome, to effectively prevent vascular clotting.[34]

Bleeding Time: A Test of Platelet Clotting Function In Vivo

The bleeding time test (BT) serves as a model for assessing microvascular injury and platelet function by recording the time until blood clots, after a standardized skin incision on the forearm.[35] This test allows for the quantitative evaluation of complex hemostatic events.[36]

Introduced in 1910 by Duke, the bleeding time test was the pioneering assessment of platelet function in vivo. While BT doesn't predict the safety of surgical procedures,[37] it remains a first-line clinical screening test for hemostatic defects like von Willebrand's disease, which is characterized by an extended bleeding time. Conversely, a short bleeding time can reflect multiple platelet mechanisms promoting clotting such as factor V Leiden,[38] offering an advantage for studying natural hemostasis.

The impact on hemostasis and coagulation by aspirin has been studied extensively. At a dose of 30 mg daily given for one week, aspirin was found to decrease thrombin formation in healthy volunteers.[39] This thrombin-lowering effect was manifested by prolonged bleeding time in both healthy individuals as well as those at increased risk of coronary artery disease. Further exploration of the thrombin system revealed a 25% to 40% reduction in thrombin

production after a single dose of aspirin, and depressed platelet reactivity.[40,41]

Animal studies, often utilizing tail injury to assess bleeding time, have provided insights into the effects of medications.[42,43] Aspirin and NSAIDs were found to prolong bleeding time in mice, while Cox-2i shortened it. In human studies, NSAIDs such as naproxen, ibuprofen, and diclofenac increased bleeding time (average increase of 2.4 minutes).[44,45,46] Of course, Cox-2 inhibitors did not prolong bleeding time and unfortunately shortened bleeding time was not evaluated in the human studies.[47] In animal models, after three months of Cox-2 inhibitor use, there was a shorter tail bleeding time by 50%, coupled with a 120-fold increase in HETE.[48]

Despite the wealth of information on bleeding time in response to aspirin and NSAIDs, there is currently no published data on bleeding time concerning JAK inhibitors (JAKi). A comprehensive search across PUBMED, Cochrane, and Embase databases for randomized controlled trials yielded no relevant information on the impact of JAKi on bleeding time.

Methods

This study was carried out in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. All investigation sites received approval from the institutional review board or ethics committee, Advarra IRB#00000971.

Sequential RA patients over age 50 at one center had BT testing at the initial visit and 2 weeks after beginning a medication known to affect coagulation. These were estrogen, rofecoxib, celecoxib, naproxen, ibuprofen, aspirin, tofacitinib, baricitinib, upadacitinib, filgotinib, and anti-coagulants. Bleeding time has been routinely measured in the clinic as part of hemostasis evaluation and several patients were identified with Factor V Leiden and others with protein S and protein C deficiencies. The hypothesis that bleeding time might predict thrombosis in RA was proposed when rofecoxib was suspected of increasing thrombotic events. Data analyzed for this manuscript was collected between 1995-2022, when medications known to affect coagulation were initiated. BT was performed with a surgicutt device (Accriva Diagnostics, San Diego, CA) by using a tourniquet at the upper arm inflated to 40 mm Hg and using the BT device at the volar surface of the forearm.

Statistics

Observed data analyses are presented for each group. Unpaired T-test results are reported with a two-tailed p value. RA patients before beginning therapy other than methotrexate (MTX) serve as the control group. BT is reported with SD. Sample size is too small for comparison between individual groups. Sample size for the control group was determined with a significance level of 0.05, statistical power of 0.8, and an effect size of 0.8 (cohens d). This yielded a sample size of 20 for the control. Some groups had less than 20 subjects because there were only a few on that treatment (e.g. estrogen).

Results

Bleeding time results are listed here. Test results compared each group to control.

Population	N	Gender	age	BT (min)	Δmin	p
RA control	20	85% F	55yr	3.7+ 0.4	--	--
RA clopidogrel	3	33% F	65yr	7.0+ 3.6	+3.3	<0.02
RA warfarin	6	66% F	66yr	11.7+ 12	+8.0	<0.01
RA aspirin 81mg/d	20	85% F	57yr	5.7 + 0.6	+2.0	<0.01
RA MACE or thromb	15	53% F	68yr	**2.3 + 0.4**	**-1.4**	**<0.001**
RA estrogen	6	100%F	56yr	2.1 +0.5	-1.6	<0.01
RA rofecoxib 25 mg	20	87% F	72yr	2.5 + 0.7	-1.2	<0.005
RA rofecoxib 50 mg	16	75% F	68yr	2.2 + 0.6	-1.5	<0.002
RA celecoxib 400 mg	20	85% F	64yr	2.5 + 0.4	-1.2	<0.002
RA tofacitinib 5mg bid	20	80% F	72yr	2.1 + 1.4	-1.6	<0.002
RA baricitinib 4 mg	20	80% F	78yr	1.5 + 0.8	-2.2	<0.001
RA upadacitinib 15 mg	20	85% F	58yr	2.3 + 1.1	-1.4	<0.001
RA filgotinib mg	20	75% F	56yr	3.1 + 0.7	-0.6	<0.03
RA tofacitinib 10 mg+asp	20	80% F	73yr	3.4 + 0.7	---	ns
RA baricitinib 4 mg+asp	20	85% F	76yr	4.1 + 0.5	---	ns

The ethnicities of tested subjects were 55% Hispanic, 40% Caucasian, and 5% Asian. All subjects in the control group were on stable methotrexate (MTX) but on no aspirin, no estrogen, non-smokers, no anti-coagulants, and no other RA therapy. The control group had a bleeding time (BT) of 3.7 ± 0.4 minutes. This is a shorter BT than expected in the normal population, where BT is 4 to 7 minutes in most series.[49,50] To assess reproducibility of the BT test, duplicate measurement was performed in 10 control subjects and results were very similar, within 25 seconds. Small differences in the duplicate BT tests were not significant. BT was reproducible and reliable without leaving scar. [51,52] The RA patients who developed MACE or thrombotic events were generally older by about a decade, much more often male, 80% were current or former smokers, and had shorter BT at 2.3 ± 0.4 minutes, which was highly significant ($p<0.0001$). Two MACE subjects had deficient protein S and protein C, and one MACE subject had factor V Leiden, as additional concomitant risk factors for thrombotic events; of these with genetic risks, two were female and one was male.

As expected, for patients taking anti-coagulants clopidogrel or warfarin, BT was much longer. RA patients taking aspirin also had slightly longer BT by about 2 minutes. None were aspirin resistant. As expected, RA patients on estrogen had shorter BT by about 1.6 minutes consistent with the usual effect of estrogen on BT.

Many RA therapies are associated with increased thrombotic events and MACE. Consistent with the increased risk of thrombosis seen with cox-2 inhibitors, our data showed a significantly

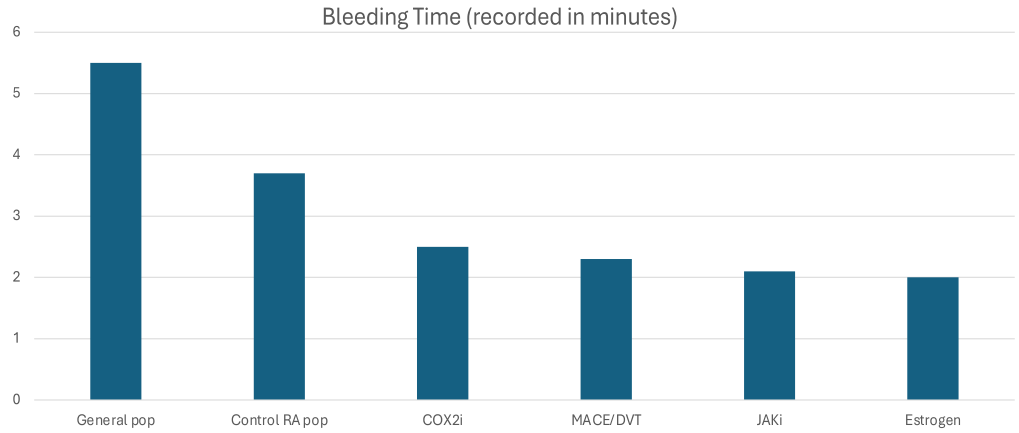
shorter BT with rofecoxib or celecoxib. In rofecoxib this shortened BT was dose related. Another therapy that increases thrombotic events in RA is JAKi. Four different JAK inhibitors were evaluated and all caused significant shortened BT; baricitinib, tofacitinib, upadacitinib, and filgotinib, listed here in order of the measured time to clot by BT. The JAKi groups differ only by a numerical difference; the sample sizes are too small to show significance difference between the JAKi groups.

If aspirin 81 mg daily is added to the JAKi baricitinib or tofacitinib, the BT normalized to the RA control group. In our small group of MACE or thrombotic events (n=15), none were taking anti-coagulants or any aspirin at the time of the event.

Discussion

Rheumatoid arthritis (RA) has been associated with an elevated risk of thrombotic events, encompassing deep vein thrombosis, pulmonary embolism, and major adverse cardiovascular events (MACE), when contrasted with the general population.[53,54] In our study, the RA control group displayed a shorter bleeding time compared to the general population. This intriguing finding raises the possibility that a short BT could serve as a predictive risk factor for thrombotic events in RA patients. The correlation between BT results and known increased thrombosis risks associated with factors such as estrogen, cox-2 inhibitors (cox-2i), and Janus kinase inhibitors (JAKi) further strengthens the hypothesis that a short BT may be indicative of in vivo clot risk.

FIGURE 3: Risk of Thrombosis escalates with shorter BT



BT	5.5	3.7	2.2	2.3	2.1	2.1
Incidence rate /1000 pt yrs for thrombosis	0.17	0.2	0.8	N/A	1.5	2.0

Thrombotic risk is estimated from an unrelated set of research articles.[5,55,68,69,70] All subjects are over age 50 and those on COX2i or JAKi have RA. The thrombosis with estrogen at age 60 is from the Women's Health Initiative. The BT results are from table 1. The estimates for an incident rate (IR) for thrombosis goes up as the BT becomes shorter.

The shortened BT in the RA control group may reflect an underlying prothrombotic state, potentially contributing to the increased incidence of thrombotic events observed in RA patients. This aligns with previous research establishing a link between RA and a heightened risk of clot-related complications.[56,57,3] The increased risk of clot in RA is multifactorial. Inflammation, immune complexes, COX-2i, JAKi, and estrogen can all play a role. Since the Surveillance report on tofacitinib[5], the report for increased thrombotic events for JAKi vs TNFi was confirmed in the WHO database.[58] The increased risk of thrombotic events associated with JAKi in RA patients, particularly those over the age of 50, has raised concerns. Despite post hoc evaluations and extensive analysis of biomarkers in surveillance subjects, no specific biomarkers associated with the increased thrombotic risk with JAKi have been identified.[59]

All data reported in our series demonstrated a short BT, less than 3 minutes, in groups with increased risk of MACE and thrombotic events. Providing care to patients at increased thrombotic risk, such as RA subjects over age 50 with a BT less than 3 minutes, may warrant caution in choice of RA therapy and possibly the addition of an anti-thrombotic agent like aspirin and adequate control of RA inflammation. Notably, systemic inflammation, a well-known factor in conditions like rheumatoid arthritis, is associated with higher thrombotic events. Inflammation controlled by canakalimab (an IL-1 inhibitor) reduced the incidence of MACE in a large clinical trial.[60] The platelet plays a pivotal role in thrombotic events and MACE, and it highlights possible use of bleeding time (BT) as a valuable parameter to identify individuals at risk for such events.

For prevention of thrombotic events,[61] aspirin has been the gold standard for secondary prevention of MI, cerebral vascular events, anti-phospholipid syndrome, thromboprophylaxis after extremity fracture,[62] genetic variants,[63] and key to anti-coagulant combinations of stents, angiography, and fibrinolysis. The cause of the thrombosis may be trauma, tissue damage, immune clotting antibodies, plaque, or inflammation but the treatment includes aspirin regardless of the underlying cause. The widespread use and overall safety of low-dose aspirin, particularly at 81mg, is an attractive option for primary and secondary prevention of thrombotic events. Adding low-dose aspirin to JAK inhibitors resulted in an increase in bleeding time above 3 minutes, potentially mitigating the increased clotting risk associated with JAKi. Overall safety of low dose aspirin is considered acceptable for large swaths of the general population in the development of the polypill today. Aspirin is consistently one of the three ingredients in the polypill.[64]

In this study, we found short BT for the control patients with RA compared to age-matched people without systemic inflammation. Certain medications, including estrogen, COX-2i, and JAKi, shorten BT further and have been proven to increase the risk of clotting. The dose-dependent manner in which these medications shorten BT suggests a potential mechanistic link between their phamacodynamic activity and clinical outcomes related to clotting. The reliable increase in clotting with estrogen has been clinically useful therapeutically to improve hemostasis with uremia.[65,66] Uremia is associated with a long BT and hemolysis, which has been treated by adding estrogen to partially reverse the risk of hemolysis.

Given the short BT noted, caution must be exercised when use of estrogen, COX-2i, or JAKi is considered for RA patients, especially those over 50 years old, given the additional risk of clot associated with systemic inflammation. Additionally, due to the genetic factors that contribute to clotting risk, testing for genetic risk factors before prescribing JAKi to subjects over 50 with a short BT may be prudent. Our MACE series noted 20% had genetic reasons to clot. (Table 2) Given the higher risk for clot in the RA population, perhaps testing for Factor V Leiden, prothrombin mutations, protein C and protein S is reasonable before prescribing JAKi to a subject over age 50 with a BT shorter than 3 minutes.

Table 2: Prevalence of genetic causes for high risk in VTE: reprinted with permission from UpToDate[67]

Genetic inheritance	% general population	% in patients with DVT	Relative risk
Factor V Leiden	2-5%	12-18%	5-fold
Prothrombin mutat'n	2%	5-8%	4-fold
Protein C deficiency	0.2-0.5%	2-5%	7-fold
Protein S deficiency	unknown	1%	5-fold
AT deficiency	up to 0.2%	1-7%	16-fold

Limitations of this study include the small sample size of the groups. Certainly larger studies of RA subjects over age 50 will be necessary to evaluate whether BT can identify individuals at high risk for thrombotic events and MACE. Because the sample size is small, further study with larger numbers of RA subjects would permit comparison between groups. It is too early to say if BT will consistently act as an alert for patients at risk for thrombotic events or MACE, but our small series suggests that a short BT measurements below 3 minutes did concur with those with known real outcomes of MACE and thrombotic events. This BT evaluation included only RA, but evaluating BT in other populations with systemic inflammation such as psoriatic disease, ankylosing spondylitis, and even gout would be of interest. If BT did identify individuals at risk, the clinical utility to the addition of low dose aspirin to JAKi or COX2-I should be evaluated. Further study can also assess overall safety for GI toxicity versus the outcomes of MACE and thrombotic events in order to assess the balance of benefit to risk. Most studies assessing 81 mg aspirin daily have found extremely low serious GI toxicity but these were not performed in an RA population. In the future, it would also be of interest to test BT with other common RA therapies, such as TNFi, CTLA4, IL-6, rituximab; all with and without a daily low dose aspirin. Until further data is available, patients over age 50, with a BT under 3 minutes, might warrant careful consideration of RA choice for therapy, adequate control of systemic inflammation, and the possible addition of primary prevention with 81mg daily aspirin.

Conclusion

In conclusion, our findings suggest that BT less than 3 minutes may serve as a clinically relevant marker for assessing thrombotic risk in RA patients. Further research with larger cohorts is warranted to validate and expand upon these

observations, potentially paving the way for the incorporation of BT testing into the clinical management of RA patients to optimize thrombotic risk assessment and preventive strategies.

Conflict of Interest Statement:

None

Acknowledgement Statement:

None

Funding Statement:

There are no financial disclosures to this research for any of the authors. There was no government funding; no funding from NIH, CDC, or FDA.

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