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Assessment of Major Adverse Cardiovascular Events and Thrombotic Risk for Patients with Rheumatic Disease

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ABSTRACT

Background: Patients with rheumatic disease are at increased risk for thrombotic events and MACE due to systemic inflammation. Bleeding time is a test performed in the clinic and consistently confirms a short time to clot with known risk factors such as estrogen, cox-2 inhibitors, JAK inhibitors, and factor V Leiden. We explored whether patients with rheumatic disease have a short bleeding time.

Methods: All sequential 239 patients over age 50 with rheumatic disease had a bleeding time test (BT). Data was collected between 2022- 2024. Patients began low dose aspirin 81 mg daily in 2023 had a repeat BT. No patients had a history of cardiovascular disease. For those with MACE or a thrombotic event BT at baseline (prior to the event) and BT after the event were compared. Cohorts were analyzed by assigned treatments for rheumatic disease including methotrexate, JAK inhibitors, TNF inhibitors, abatacept, secukinumab, IL-1 inhibitors, and PD-1 agonist.

Results: Rheumatic disease patients at baseline had shorter BT results compared to historical normal controls (1.52 ± 0.77) versus 4-7 minutes found in the normal general population ($p<0.01$). There was no difference in the short BT among patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or lupus. Cohorts analyzed by treatment found BT was similarly short with each. The addition of low dose aspirin 81 mg daily dramatically raised BT nearly double. There were 15 who developed MACE or a thrombotic event prior to aspirin therapy, and death resulted for three patients. These patients all had short BT test results but did not differ from those who did not have a clotting event. The only significant findings in the MACE/thrombotic group was older age by almost a decade, predominantly male gender, and 80% were smokers.

Conclusion: All patients with rheumatic disease had short BT results. BT did not identify a specific individual who would develop MACE or a thrombotic event. BT tests did revert to normal with low dose aspirin 81 mg daily. Aspirin is now recommended prophylactically in all lupus with phospholipid syndrome. Perhaps it is time to consider low dose aspirin for patients over age 50 with rheumatic disease.

Introduction

It is clear that there is an increased risk for thrombosis for patients with rheumatic disease (RD). There is a two-fold increased risk for myocardial infarction in rheumatoid arthritis (RA), nearly a three-fold increased risk in lupus, as well as a three-fold risk for psoriatic arthritis (PsA) and ankylosing spondylitis (AS).[1,2,3] The hypothesis for this risk is the chronic presence of systemic inflammation.[4] In addition, each of these rheumatic diseases has an increased risk for systemic thrombosis including deep vein thrombosis(DVT), pulmonary embolism (PE), and cerebral vascular accident (CVA or TIA).[5] Predicting individual patients most at risk for thrombosis is important to implement mitigation where possible and encourage physicians to achieve treat-to-target goals to suppress systemic inflammation in order to save a life.

The bleeding time test (BT) can be performed in the office setting and assesses clotting function. This has been recognized for years. A simple bleeding time test can be used to diagnose factor V Leiden mutations.[6] Persons with factor V Leiden abnormalities have a 5-fold risk of thrombosis and pulmonary embolism and the bleeding time test reveals a short bleeding time. The bleeding time test in the normal general population is 4-7 minutes.[7] However, there remains a gap in understanding whether an altered bleeding time in patients with RD could serve as a predictive marker for increased thrombosis risk. Given the established link between inflammation and coagulation abnormalities, a shortened bleeding time could indicate a hypercoagulable state in these patients. Identifying a reliable and accessible test to stratify thrombosis risk in RD patients could enhance early interventions and improve patient outcomes. We tested the hypothesis that persons with rheumatic disease have a short bleeding time, explaining an increased risk for thrombosis.

Methods

The bleeding time test is a simple in office procedure that requires 5-10 minutes to perform. BT is a model for assessing platelet function by recording the time until clot forms after a standardized skin superficial incision.[7] The volar surface of the forearm in an area with little or no hair present is punctured with a bleeding time device (a surgicutt device provided by Aceriva Diagnostics, San Diego, CA). The bleeding time is measured by simple observation timing when a clot forms. There is less pain than a needle and there is no scar.

Data was collected at a single site in the United States between September 2022 to December 2024. We measured bleeding time on all 239 patients in our clinic with rheumatic disease over age 50 with no prior history of cardiovascular disease or thrombosis. Data were collected regarding contributing factors to thrombotic disease such as any history of smoking, use of anti-coagulant medications, aspirin, gender, estrogen, corticosteroids, NSAIDs, and current medications for hypertension, diabetes, or statins. Cohorts were analyzed by underlying rheumatic disease, and treatments including methotrexate, JAK inhibitors, TNF inhibitors, abatacept, secukinumab, IL-1 inhibitors, and PD-1 agonist therapy. Bleeding time was performed at baseline and after patients began low dose aspirin 81 mg daily in 2023. Any patient who developed a thrombotic event or a MACE event also had a second bleeding time test after the event. The study was not designed to study MACE or the incidence of thrombotic events but was an exploratory observational study of any events during this period. The requirement for informed consent was waived by Advarra Institutional Review Board due to observational data analyzed as an anonymized dataset. (#00000971)

Statistics were calculated using GraphPad Prism 10 software 2025. Continuous variables were described by mean, standard deviation (SD) minimum and maximum. Categorical variables were reported as the proportion (%) of patients. Bleeding time (BT) is reported in minutes. No multiple regression analysis was performed across cohorts for concomitant risk factors contributing to thrombotic disease due to the small numbers of concomitant factors in each cohort. Each cohort had a minimum of 30 patients for unpaired t test comparison regarding aspirin use or non-aspirin use.

Results

Patients with RD at baseline (BL) had shorter bleeding times compared to historical normal controls (1.52 $\pm$ 0.77 vs 4-7 minutes historical normal population, $p<0.01$) Once started on aspirin 81mg daily, the RD patients bleeding time

corrected to 3.28 ± 0.6, and the difference between baseline and aspirin values in RD patients were statistically different, p<0.001. There were 15 patients with a MACE event in this observation period between 2022- 2024 (incidence rate 0.06 per 100). The bleeding time for patients with a MACE or thrombotic event was 2.22 ± 0.6, with an average age of 68. This bleeding time was not statistically shorter from other age-matched RA patients without MACE or thrombotic events. None of the patients with a MACE or thrombotic event were taking aspirin or an anti-coagulant at the time of the event. All were initiated on some anti-coagulant after the event and the average bleeding time was prolonged to 5.5 minutes ± 5.6; treatment included warfarin, heparin, clopidogrel, or aspirin depending on the choices made by the primary physician. There were no statistically significant differences in the use of estrogen among the MACE patients but 80% were cigarette smokers. There were 8 females and 7 males so that males were over-represented in this RD population.

BT were collected for RD patients on treatment with methotrexate or various biologic therapies. In all cases the addition of 81 mg aspirin daily prolonged bleeding time in each individual. (Table 1)

Table 1: BT at baseline before aspirin and after low dose aspirin

RA	BT without aspirin	BT with aspirin	p (compared to asp)
Methotrexate (age 70)	1.74± 1.00	2.98± 0.69	<0.0001
JAKi (age 58)	1.38± 0.51	3.47± 1.36	<0.001
TNFi (age 59)	1.10± 0.31	3.05± 0.84	<0.001
Abatacept (age 70)	1.15± 0.50	3.47± 0.11	<0.0001
IL-1i (age 60)	1.91± 1.10	3.11± 0.59	<0.01
PD-1 agonist(age 59)	1.78± 0.93	3.76± 1.16	<0.002
PsA			
Secukinumab (age 61)	1.64± 0.98	3.31± 1.30	<0.05
SLE			
JAKi (age 58)	2.34± 0.45	6.34± 4.29	<0.05
Hydroxychloro (age 59)	1.71± 0.63	4.20± 2.24	<0.03
SLE with clot*(age 60)	1.66± 0.57	4.40± 3.40	<0.05

*Legend: *There were 3 patients with MACE or thrombotic events; 2 of 3 were anti-cardiolipin positive.*

There was no statistical difference in baseline BT among the various treatment cohorts in RA. Similarly, there was no difference in baseline BT between treatment cohorts in the Lupus subjects.

Table 2: BT at baseline without aspirin and after anti-coagulants for patients who developed MACE or Thrombotic events

Rheumatic disease	age/gender	event	BL BT	BT with anti-coag
PsA	72 M	PE	1.06	3.60
Lupus	63 F	TIA	1.88	2.48
RA	48 F	PE	2.48	3.44
RA	78 M	TIA	1.97	4.30
Lupus	63 F	TIA	2.88	5.01
Lupus	63 F	CVA	2.48	3.01
RA	68 M	MI	3.01	4.02
RA	73 M	MI	1.06	4.12
RA	77 M	PE	2.53	4.30
RA	78 M	MI	1.55	4.22
RA	67 M	MI	3.02	4.50
Lupus	64 F	DVT	2.39	5.30
RA	54 F	DVT	2.31	2.38
RA	60 M	MI	2.87	7.21
RA	74 F	DVT/ MI	1.99	25.50

Legend: Deep vein thrombosis (DVT), myocardial infarction (MI), pulmonary embolism (PE), transient cerebral accident (TIA). Three of these events resulted in death. N=15, average age 68.

When BT at baseline was collected, no patient was on aspirin or any anti-coagulant. At baseline, among the patients with MACE or a thrombotic event, no patient was on aspirin or any anti-coagulant prior to the event. None were on estrogen but 80% were smokers. Two MACE patients had deficient protein S or protein C, and one had factor V Leiden. Average baseline BT 2.2 ± 0.6 was lower than the normal general population but not statistically different from BT in other rheumatic disease patients. The BT did not identify individuals at highest risk. The age in the MACE or thrombotic event group was about a decade older than the rest of the rheumatic disease patients and more often male in the RA population (7 male/3 female). Warfarin, clopidogrel, and dabigatran lengthened BT while anti factor Xa agents had minimal effect on BT. It was noted at the office visit that compliance was obvious when follow up BT tests were performed; patients not taking their anti-coagulants had very short BT. Twelve of these 15 patients were smokers. Smoking is well known to increase MACE and thrombotic events in the general population and in this susceptible RD patients smoking furthermore increases systemic inflammation. The use of cigarettes in the full RD group without MACE or a thrombotic event was 3%.

Discussion

The findings of this study suggest that a short BT under 3 minutes may be a common characteristic in patients with rheumatic disease. It was noted that those with MACE or a thrombotic event had a short BT under 3 minutes, were over age 65, often were smokers, and none were on aspirin at the time of the event.

However, while BT was significantly shorter in these patients compared to the general population, it did not have predictive value for identifying a specific individual at heightened risk. The uniform correction of BT with low-dose aspirin underscores the potential role of low dose aspirin to mitigate platelet function abnormalities and thrombotic risk among rheumatic disease patients. Moreover, compliance with aspirin therapy was readily confirmed by repeat BT, offering a simple, objective measure of adherence

There were 15 patients with rheumatic disease who developed a MACE or thrombotic event during the 2-year observation period (incidence rate 0.06 per 100). This study was not designed to determine the incidence of MACE or thrombotic events but to observe relevant descriptive factors. These patients were older averaging 68 years. The mortality of three out of fifteen affected patients highlights the severity of these events. The

initiation of anticoagulants by the primary physicians demonstrates the clinic response to these events and the BT corrected to an average 5.5 minutes. The primary physician chose to begin coumadin (N=5), dabigatran (N=4), clopidogrel (N=3), rivaroxaban (N=1), or apixaban (N=2). Of note as expected, the DOAC anti-coagulants had minimal effect on BT since these factor Xa inhibitors do not affect platelet aggregation.

The impact of COX-2 inhibitors and JAK inhibitors on BT further strengthens the association between a short BT and increased thrombotic risk. We have previously shown that rofecoxib and celecoxib shorten BT in rheumatic disease patients.[8] The effect on BT on rofecoxib was dose related 2.5± 0.7 at 25 mg daily and 2.2± 0.6 at 50 mg daily. The BT on celecoxib 400mg daily was 2.5± 0.4. Both of these agents corrected to normal BT similar to the general population with low dose aspirin. It is notable that BT under 3 minutes has been correlated to increased risk of clotting with these COX-2 inhibitors.[9,10,11] We have also previously published that use of JAK inhibitors causes shortening of BT tests.[8] Subsequently, the use of JAK inhibitors in patients over age 65 has been clearly shown to increase risk of MACE and thrombotic events.[12,13] The correlation between short BT and clotting risk suggest that BT could serve as a pharmacodynamic marker for prothrombotic tendencies in patients and help direct best therapy.

There are several limitations to this study of bleeding time. We made the hypothesis that a short bleeding time would be a risk factor for thrombotic events. But a hypothesis may not be proven true. Historical observational evidence strongly supported our concept; look at the short BT results and increased risk for thrombosis seen with cox-2 inhibitors, JAK inhibitors, estrogen, and now in this study patients with rheumatic disease as well as lupus patients.[14,15,16] The clinical guidelines recommend adding low dose aspirin to all lupus patients with anti-cardiolipin antibodies.[17,18] Future study regarding the universal use of low dose aspirin in RD patients would require a randomized prospective trial using low dose aspirin to mediate thrombotic risk. Assuming an incidence of 0.06 per 100 in RD patients for MACE and a reduction in risk by 20-25% by aspirin, the sample size would necessitate about 200 patients. Our cohorts had 30 or more patients, each treated with different conventional or biologic therapies, and could not be combined to assess reduction in risk using aspirin.

It is known that different therapies for RA raise or lower thrombotic risk.[19,20] It is possible that the improved BT achieved with aspirin would result in reduced risk, but it is by no means certain. Additionally, while this study examined different RD therapies, BT did not differentiate between treatment modalities, despite known variations in thrombotic risk. Other factors such as endothelial function and inflammatory burden contribute to thrombosis risk beyond platelet function alone. It is now known that JAK inhibitors raise the risk of MACE and thrombotic events in RA patients over age 50 and TNF inhibitors do not raise those risks.[12,13] Our BT results did not discriminate between the two therapies. However, aspirin use did revert BT to above 3 minutes in each cohort. As of this date, prophylactic use of aspirin is recommended only for lupus with anti-cardiolipin activity.[21] Whether prophylactic use of low dose aspirin would improve outcomes in most RD requires a larger sample size and a prospective program.

Another major limitation due to the small sample size is that it precluded a detailed multivariate analysis of contributing thrombotic risk factors.[22,23] Genetic predispositions, such as deficiencies in protein S, protein C, or factor V Leiden, as well as comorbidities like diabetes, hypertension, and smoking, may significantly influence thrombosis risk but could not be thoroughly evaluated in this study. Future research with a larger cohort is needed to delineate the relative contributions of these factors. Furthermore, while aspirin consistently prolonged BT beyond 3 minutes, its clinical impact on cardiovascular outcomes in RD patients remains speculative. Given the established role of aspirin in lupus patients with antiphospholipid antibodies, further investigation into its prophylactic use of low dose aspirin in broader RD populations is warranted.

Conclusion

There are several conclusions and possible recommendations that may be considered given the real-world experience of MACE and thrombotic events in the RD population.

- BT is shorter in rheumatic disease patients than the general population

- BT can be corrected by adding 81 mg daily aspirin
- BT cannot identify a specific individual with rheumatic disease who will develop MACE or a thrombotic event
- BT at a follow up visit can be used to confirm compliance with aspirin or the use of most anti-coagulants (not DOAC)
- The highest risk for MACE or a thrombotic event in the rheumatic disease population is age over 68, male gender, smoking, and no concomitant use of aspirin.

Mitigation includes adding 81 mg aspirin to patients over age 50, instituting smoking cessation programs, and avoiding Cox-2 inhibitors and JAK inhibitors in patients over 50.

Conflict of Interest:

None

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