Effect of Aspirin Supplementation on Hemostatic Responses in Firefighters Aged 40–60 Years

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Short Title: Aspirin and hemostasis after firefighting

Abstract

Sudden cardiovascular events account for approximately 45–50% of all duty-related deaths among firefighters and a disproportionate number of these fatalities occur following strenuous fire suppression activities. The purpose of this study was to evaluate the effect of acute and chronic aspirin supplementation on hemostatic function before and after live firefighting activities in older firefighters. A double-blind, cross over design included 4 treatments: a 2-week aspirin/placebo treatment ("chronic") and a single pre-firefighting aspirin/placebo treatment ("acute"). Hemostatic function was assessed in 24 male firefighters (mean age = 48.2 ± 5.9 years) immediately before and after 18 minutes of live-fire firefighting activity. An acute bout of firefighting activity significantly decreased platelet aggregation time and decreased activated partial thromboplastin time. Compared with placebo, acute aspirin supplementation resulted in a significant increase in EPI closure time, which was further augmented by chronic supplementation. Aspirin supplementation had no effect on coagulatory or fibrinolytic factors. Our findings suggest that an acute bout of firefighting leads to increased coagulatory potential in older firefighters. In conclusion, aspirin supplementation had an antiplatelet effect that decreased platelet aggregability at rest and following an acute bout of firefighting compared with placebo.

Clinical Trial Registration: NCT01276691

Key Words: coagulation; fibrinolysis; platelet activity; firefighter health; cardiovascular event; arduous work

Introduction

Sudden cardiac events are the leading cause of line of duty death among US Firefighters, accounting for approximately 45% of line of duty deaths each year.[1] In addition to cardiac fatalities, 600–1000 firefighters suffer non-fatal cardiac events in the line of duty each year.[2] Firefighting activity increases the relative risk of sudden cardiac events 10–100 times that of non-emergency station duty.[3,4] Firefighting may serve as a trigger for sudden cardiac events due to multiple stressors, including: strenuous muscular work, emotional/psychological stress, and environmental factors.[5] Advancing age (> 45 years), increases the risk of cardiac events during firefighting.[4] Firefighting results in increased body temperature and near-maximal heart rates, and leads to a decreased stroke volume, evidence of impaired diastolic function, and increased vascular stiffness.[6-8] Recent work has also shown that acute firefighting leads to increased platelet aggregability[9,10] and increased coagulatory potential.[5,11] However, there are few published data regarding the effect of aspirin on hemostatic balance[9] and a paucity of data on coagulatory responses in older firefighters (> 40 years) and firefighters with cardiovascular disease risk factors. The purpose of this study was to determine the effects of acute and chronic aspirin (81 mg) supplementation on hemostatic responses to fighting activity in firefighters > 40 years of age. We hypothesized that both acute and chronic aspirin supplementation would have an antiplatelet effect at rest, and that aspirin supplementation would partially offset the procoagulatory changes that occur with firefighting activity.

Methods

Firefighters between the ages of 40–60 years were recruited from fire departments across the state of Illinois. Participants were excluded if they had hypertension or cardiac failure; had any contraindications to aspirin therapy; were currently taking non-steroidal anti-inflammatory

steroids, Clopidogrel, or Warfarin; or were currently taking aspirin based on physician's recommendation. All participants received a medical evaluation consistent with National Fire Protection Agency 1582 Standard on Comprehensive Occupational Medical Program for Fire Departments[12] prior to participation in the study.

This study employed a randomized, placebo controlled, double-blind cross over design to investigate the effects of aspirin administration (acute and chronic) on hemostatic balance of firefighters before and after short term firefighting activities. Subjects were initially assigned to 1 of 2 conditions: acute aspirin (81 mg enteric aspirin 60 minutes prior to firefighting), or acute placebo supplementation with a 14–60 day washout period between trials. Subjects participated in both conditions; however, the order in which they participated in each was randomized, with the washout period between trials. Subjects then completed the chronic supplementation arm (81 $mg \cdot d^{-1}$ of enteric aspirin for 14 days or placebo for 14 days) of the study, with aspirin and placebo being applied in random order. Hence, all subjects completed four trials: acute aspirin, acute placebo, chronic aspirin, and chronic placebo. Trials were separated by 17.7 ± 7.7 days for the acute protocol and 27.5 ± 3.3 days for the chronic protocol. This study was approved by the University of Illinois Institutional Review Board. All participants signed an informed consent document prior to participation. The study was registered at ClinicalTrials.gov (NCT01276691).

Subjects reported for testing following a standard meal (Ensure Original Shake (220 cal; 6 g (9%) fat, 33 g (11%) CHO, 10 g (20%) protein), Clif Bar (240 cal; 5 g (8%) fat, 43 g (14%) CHO, 9 g (18 %) protein)). This meal was ingested with the acute supplement 60 minutes before the trial. All trials were completed at approximately the same time of day to control for diurnal variations in measurements. Participants were instructed to report for testing well hydrated.

For each trial, participants performed prescribed live firefighting drills wearing full personal protective equipment and self-contained breathing apparatus (weight ~20 kg), in a training structure that contained live fires. The firefighting drills lasted 18 minutes and consisted of 9 two-minute periods of alternating rest and work. The work cycles included stair climbing, simulated forcible entry, a simulated search, and simulated hose advance. Throughout the firefighting drills, trained personnel controlled the temperature in the training structure by adding small fuel packages to the fire sets sequentially and controlling the ventilation conditions in the room. The temperatures at 1.2 m above the floor were maintained at roughly 70–82^{o}C and the floor temperatures were maintained at approximately 35–41^{o}C.

All participants received a medical evaluation prior to participation. During this evaluation cardiovascular risk factors were evaluated and maximal oxygen consumption was estimated using a treadmill protocol that required participants to achieve 85% of age-predicted maximal heart rate.[13] Descriptive characteristics were obtained prior to participating in firefighting drills. Height was measured (to the nearest 0.01 m) using a stadiometer and body mass was measured (to the nearest 0.5 kg) using a digital beam balance platform. Body mass index was calculated as the body mass in kilograms divided by the height in meters squared. Body temperature was measured continuously throughout the protocol using a monitor and a silicone-coated gastrointestinal core temperature capsule (Mini Mitter, VitalSense; Philips Respironics, Bend, OR). Participants swallowed a small disposable core temperature sensor capsule 6–12 hours before the study was conducted. Heart rate was measured using a heart rate monitor (Vantage XL; Polar Electro, Inc., Lake Success, NY).

Venous samples were drawn pre- and post-firefighting activity from the antecubital vein using a 21 gauge needle by a trained phlebotomist. Platelet count was assessed at a local clinic

from venous whole blood as part of a complete blood count analysis, using the electrical impedance method (with an instrument such as the COULTER® LH 700 Series; Beckman Coulter, Inc., Fullerton, CA). Platelet function was assessed by epinephrine (EPI)-induced and adenosine 5´-diphosphate (ADP)-induced platelet aggregability using a platelet function analyzer (PFA-100; Dade Behring, Deerfield, IL). Blood samples were collected in a Vacutainer containing 3.2% sodium citrate, maintained at room temperature and analyzed within 2 hours of collection. Blood was pipetted (800 μL) into the disposable cartridges and then aspirated under high shear rates (5,000–6,000 s^{-1}) through an aperture cut into the membrane coated with collagen and ADP and a membrane coated with collagen and EPI. Time to occlusion was reported.

Blood samples were collected in tubes containing 3.2% sodium citrate for measurements of all coagulation and fibrinolytic factors, except for the assessment of tissue plasminogen activator (t-PA) activity, for which samples were drawn into Stabilyte tubes (Biopool, Wicklow, Ireland). All samples were centrifuged at 2,300 rpm for 25 minutes at 4°C with the plasma removed and placed into aliquots, and stored at -70°C for later analysis. All coagulatory and fibrinolytic variables from all subjects were batch-processed at a contracted clinical laboratory (LabCorp). Fibrinogen was analyzed via the Clauss method within 14 days of blood collection and preparation. Plasminogen activator inhibitor (PAI-1) activity and antigen and t-PA antigen were analyzed using an enzyme-linked immunosorbent (ELISA) methodology. Tissue plasminogen activator (t-PA antigen) activity was analyzed in duplicate using a chromogenic technique. Activated partial thromboplastin time (aPTT) was analyzed using clotting time comparisons with similarly treated plasma controls.

Statistical analyses were performed using STATA statistical software (Release 13; StataCorp LP, College Station, TX). All tests of significance employed 2-tailed alpha = 0.05. Tests of statistical assumptions preceded hypotheses testing, and appropriate statistical adjustments were made to correct for violations. Given the completely within-subjects experimental design, with all subjects participating in all conditions, and repeated observations pre- and post-firefighting, we analyzed our study outcomes using mixed-effects linear regression methods (commonly referred to as hierarchical linear models or multi-level model methods). These are recent extensions to repeated-measures ANOVA and have the added advantage of the ability to incorporate missing data and/or heterogeneous effects among subjects. We did experience occasional missing observations in this experiment, though heterogeneous effect terms (i.e., random slopes) were not necessary for any of our outcomes. Therefore, we evaluated the effects of a Drug intervention (Aspirin vs. Placebo), Supplementation timeframe (Acute vs. Chronic), and Firefighting activities (pre- vs. post-firefighting) in fully factorialized mixed-effects models with fixed beta coefficients evaluating the main effects and interactions among these terms, and random intercepts to incorporate the within-subjects experimental design. Data are presented as mean ± standard error in figures and mean ± standard deviation or frequency in text and tables.

Results

The average participant age was 48.2 ± 5.9 years. Total mean cholesterol was in the borderline high range; mean low-density lipoprotein cholesterol was in the borderline high range; and mean high-density lipoprotein cholesterol was in the average range.[14] Table 1 presents descriptive characteristics of study participants, while Table 2 provides cardiovascular disease risk factor distributions of participants. Nine of the firefighters were obese based on BMI standards.[15]

Firefighting activity resulted in a significant increase in heart rate, reaching a mean peak heart rate of 172 ± 12 beats·min^{-1} during the firefighting evolution ($P < 0.001$). Firefighting activity also resulted in a significant increase (1.08 ± 0.38°C) in core body temperature ($P < 0.001$). Additionally, we observed a small (0.21 ± 0.37°C) but significantly higher core body temperature during the acute supplementation phase of the study compared to the chronic supplementation ($P < 0.01$). While not reaching traditional levels of statistical significance ($P < 0.06$), we detected a slightly greater increase in core temperature following firefighting with chronic aspirin supplementation (+1.12 ± 0.29°C) compared to acute aspirin supplementation (+0.89 ± 0.25°C).

Platelet closure time post-firefighting was significantly faster for blood stimulated with ADP ($P < 0.001$) and EPI ($P < 0.001$). ADP closure time decreased post-firefighting but was not affected by Drug intervention or Supplementation timeframe, nor were there any significant interactions (Figure 1). However, in addition to the Firefighting main effect, EPI closure time was also significantly affected by Drug intervention ($P < 0.001$) and Supplementation timeframe ($P < 0.001$) with an increased closure time for the Aspirin intervention (vs Placebo) and for the Chronic timeframe (vs Acute) (Figure 2). Additionally, we observed a significant Supplementation by Drug interaction on EPI closure time ($P < 0.001$), whereby the mean EPI closure time was much higher with Aspirin relative to Placebo in Chronic supplementation conditions, relative to virtually no difference between aspirin and placebo in the Acute supplement conditions.

As seen in Table 3, neither fibrinogen nor prothrombin time were affected by firefighting or by aspirin treatment. Activated partial thromboplastin time decreased significantly post-firefighting ($P < 0.001$); however, aspirin treatment had no effects on aPTT. The fibrinolytic

variables t-PA activity and PAI-1 antigen were both significantly increased post-firefighting ($P < 0.001$ and $P < 0.03$, respectively). Aspirin treatment had no effect on t-PA antigen or PAI-1 activity.

Discussion

To our knowledge this is the first study to investigate the effect of acute and chronic aspirin supplementation on hemostatic responses to live firefighting activity in firefighters > 40 years of age. This group of firefighters is of particular concern as sudden cardiac events are more likely to occur in this group than in younger firefighters.[4] We extend previous research by documenting significant changes in platelet function, coagulation and endogenous fibrinolysis immediately following live firefighting in a group of occupationally active, apparently healthy, older firefighters. Additionally, we demonstrated that aspirin had an antiplatelet affect that was evident at rest and persisted with firefighting, and that chronic aspirin supplementation had a greater effect than acute aspirin supplementation. However, aspirin supplementation had no effect on coagulatory or fibrinolytic factors and also did not affect functional coagulatory potential (as reflected by aPTT).

There is strong epidemiological evidence that strenuous physical exertion increases the risk of thrombotic events in individuals with underlying cardiovascular disease.[16,17] Experimental evidence has shown that strenuous physical activity increases platelet number and platelet function, and activates both coagulation and fibrinolysis.[17,18] A procoagulatory state may explain the increased incidence in cardiovascular events during and immediately following strenuous physical activity.

Firefighting is a unique case of physical exertion that involves heavy muscular work often performed in high ambient temperatures. Firefighting requires high levels of oxygen

consumption (often > 12 METs) and results in substantial activation of the sympathetic nervous system, elevated core temperature, dehydration, near maximal heart rates, and a decrease in plasma volume and stroke volume.[7,8,19,20] Sudden cardiac death is the leading cause of line of duty death among firefighters. A potential mechanism is an increase in coagulatory potential, either independent of or in conjunction with a disruption in vascular endothelium, that leads to a thrombus.

As we previously reported with young firefighters,[5,21] we found that firefighting resulted in increased platelet aggregability (decreased platelet closure time for EPI and ADP) and functional coagulation. Consistent with previous research, we found that aspirin supplementation prolonged platelet closure time when whole blood was stimulated with collagen and EPI. This effect was more pronounced when low dose aspirin was administered for 14 days versus a single dose. As expected, there was little effect of aspirin supplementation on ADP closure time.

Firefighting activity resulted in increased platelet aggregation, as evidenced by a shorter EPI closure time, but the post-exercise closure times remained significantly longer than non-supplemented resting values. Some previous studies have found that aspirin did not affect the exercise-induced platelet activation or aggregation following incremental exercise to maximum.[22,23] Hurlen et al.[22] reported similar findings in patients with previous myocardial infarction who had been prescribed a daily aspirin regime (160 $mg \cdot day^{-1}$). Our results are consistent with these findings, indicating that strenuous firefighting results in increased platelet aggregability (evidenced by a reduced platelet closure time, for both ADP and EPI stimulated blood). However, EPI-induced platelet closure time was much longer in the chronic supplementation case. Although firefighting resulted in a decrease in EPI closure time, the post-firefighting EPI closure time values were still longer than pre-firefighting closure time compared

with placebo. These results are consistent with previously noted studies showing that aspirin supplementation only partially interferes with exercise-induced platelet activation. Importantly, however, although chronic aspirin supplementation does not prevent the change in platelet closure time with firefighting, it does result in a more favorable platelet aggregability profile post-firefighting compared with placebo. Our findings are consistent with those of Hostler et al,[9] who examined platelet activation in firefighters who completed a treadmill protocol designed to simulate firefighting activity. In that laboratory-based study, mean maximal core temperature (~38.5 °C) and heart rate (~175 beats·min^{-1}) were similar to physiological responses recorded in the live-fire conditions of this study. The researchers showed that platelet closure time decreased following exercise, but low-dose aspirin supplementation blunted platelet activation compared with placebo.

While aspirin clearly reduces the risk for cardiovascular events in susceptible individuals, aspirin use also increases the risk for gastrointestinal bleeding events and possibly hemorrhagic strokes.[24] The U.S. Preventive Services Task Force has recommended against the use of aspirin for *cardiovascular disease prevention* in men younger than 45 years, and for its use in men 45–79 years of age only when the potential benefit for reducing myocardial infarctions outweighs the potential harm of an increase in gastrointestinal hemorrhage.[25] Furthermore, there has been some evidence that aspirin may result in increased risk of heat stress in some individuals.[26] Thus, low dose aspirin is the most efficacious treatment, maximizing benefits while minimizing the risk of untoward events. Firefighters are an occupational group that is at risk for job-related injuries that may increase bleeding risk. Firefighters and their physicians should carefully consider the risks and benefits of low dose aspirin supplementation in light of their overall cardiovascular risk profile before making a decision about low dose aspirin use for prevention of

cardiac events. This was a hypothesis generating study and the present results do not provide sufficient evidence to indicate whether low dose aspirin is beneficial for firefighters. Additional clinical studies are warranted to evaluate therapeutic implications of the present findings.

Acknowledgements

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Disclosures

The authors have no conflicts of interest to declare.

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List of Figure Legends

Figure 1. Mean platelet closure time (± standard error) for blood stimulated with adenosine 5´-diphosphate by Supplementation Timeframe (panel a) and Firefighting (panel b).

Figure 2. Mean platelet closure time (± standard error) for blood stimulated with epinephrine by Supplementation Timeframe (panel a) and Firefighting (panel b).

Table 1

Table 1

Descriptive characteristics of participants (n=23)

Variable	Mean±SD	Range
Age (years)	48.2±5.9	40–59
Height (m)	1.83±5.8	1.73–1.96
Weight (kg)	94.3±13.8	72.7–118.2
Body mass index ($kg \cdot m^{-2}$)	28.2±3.5	21.4–36.6
Waist circumference (cm)	100±11	83–123
Systolic blood pressure (mmHg) (n=20)	127±12	106–154
Diastolic blood pressure (mmHg) (n=20)	81± 9	62–94
Resting heart rate (bpm) (n=20)	70±10	57–96
Maximal oxygen uptake (METs) (n=22)	11.8±2.7	7–17.7
Total cholesterol ($mg \cdot dL^{-1}$) (n=22)	201±36	109–287
Low-density lipoprotein cholesterol ($mg \cdot dL^{-1}$) (n=21)	129±34	52–206
High-density lipoprotein cholesterol ($mg \cdot dL^{-1}$) (n=21)	47±12	30–77

Table 2

Table 2

Classification by risk factors

Risk factor	Frequency (*n* (%))
Body mass index[a] ($kg \cdot m^{-2}$)	
18.5–24.9	5 (22%)
25.0–29.9	9 (39%)
≥ 30	9 (39%)
Total cholesterol[b] ($mg \cdot dL^{-1}$) (n=22)	
< 200	11 (50%)
200–239	9 (41%)
≥ 240	2 (9%)
Low density lipoprotein[b] ($mg \cdot dL^{-1}$) (n=21)	
< 100	4 (19%)
100–129	6 (29%)
130–159	7 (33%)
160–189	3 (14%)
≥ 190	1 (5%)
High density lipoprotein[b] ($mg \cdot dL^{-1}$) (n=21)	
< 40	8 (38%)
40–59	10 (48%)
≥ 60	3 (14%)
Physical activity[c]	
Does not meet physical activity guidelines	18 (78%)
Meets/Exceeds physical activity guidelines	5 (22%)
Smoker	3 (13%)

Family history of cardiovascular disease[d] (n=22)	1 (5%)

[a] Classification based on established categories.[15]

[b] Classification based on established criteria.[14]

[c] Physical activity guidelines: 30–60 min·d^{-1} (150 min·wk^{-1}) of purposeful moderate exercise, or 20–60 min·d^{-1} (75 min·wk^{-1}) of vigorous exercise, or a combination of moderate and vigorous exercise.

[d] Immediate family member died of cardiovascular incident prior to 45(men)/55(women).

Table 3

Table 3

Coagulation and fibrinolytic variables (mean±standard deviation).

	Acute				Chronic				Significant Effects			
	Aspirin		Placebo		Aspirin		Placebo		Drug	Supple-men-tation	Fire-fighting	Drug x Supple-men-tation
	Pre	Post	Pre	Post	Pre	Post	Pre	Post				
Fibrinogen ($mg \cdot dL^{-1}$)	263.2±45.8	274.3±67.2	278.3±78.6	292.0±85.4	273.1±53.3	299.6±48.7	280.8±43.4	295.7±49.3				
Prothrombin time (s)	11.7±0.6	11.5±0.5	11.7±0.7	11.7±0.6	11.8±0.6	11.9±1.1	11.7±0.5	11.6±0.6				
Activated partial thromboplastin time (s)	28.7±2.1	25.8±2.1	29.0±2.9	26.2±1.3	28.9±1.7	26.7±2.1	29.0±2.1	26.3±1.9			<0.001	
Tissue plasminogen activator activity ($IU \cdot mL^{-1}$)	0.60±0.29	6.88±5.13	0.69±0.32	7.49±4.94	0.63±0.30	6.68±5.31	0.70±0.31	7.56±4.97			<0.001	
Tissue plasminogen activator antigen ($ng \cdot mL^{-1}$)	6.13±2.25	18.77±16.12	6.05±2.85	16.58±13.33	5.79±2.20	14.62±8.36	5.63±1.89	22.00±22.09			<0.001	
Plasminogen activator inhibitor one activity	36.4±20.5	47.8±25.9	36.2±22.5	44.3±24.5	37.1±26.0	44.0±22.2	29.9± 14.5	54.1±26.8		0.007	0.050	

(AU·mL^{-1})									
Plasminogen activator inhibitor one antigen (ng·mL^{-1})	8.5±4.1	8.8±3.7	11.1±7.2	8.0±3.8	12.2±7.6	10.8±6.3	13.5±6.2	10.2±4.9	<0.001

Figure 1

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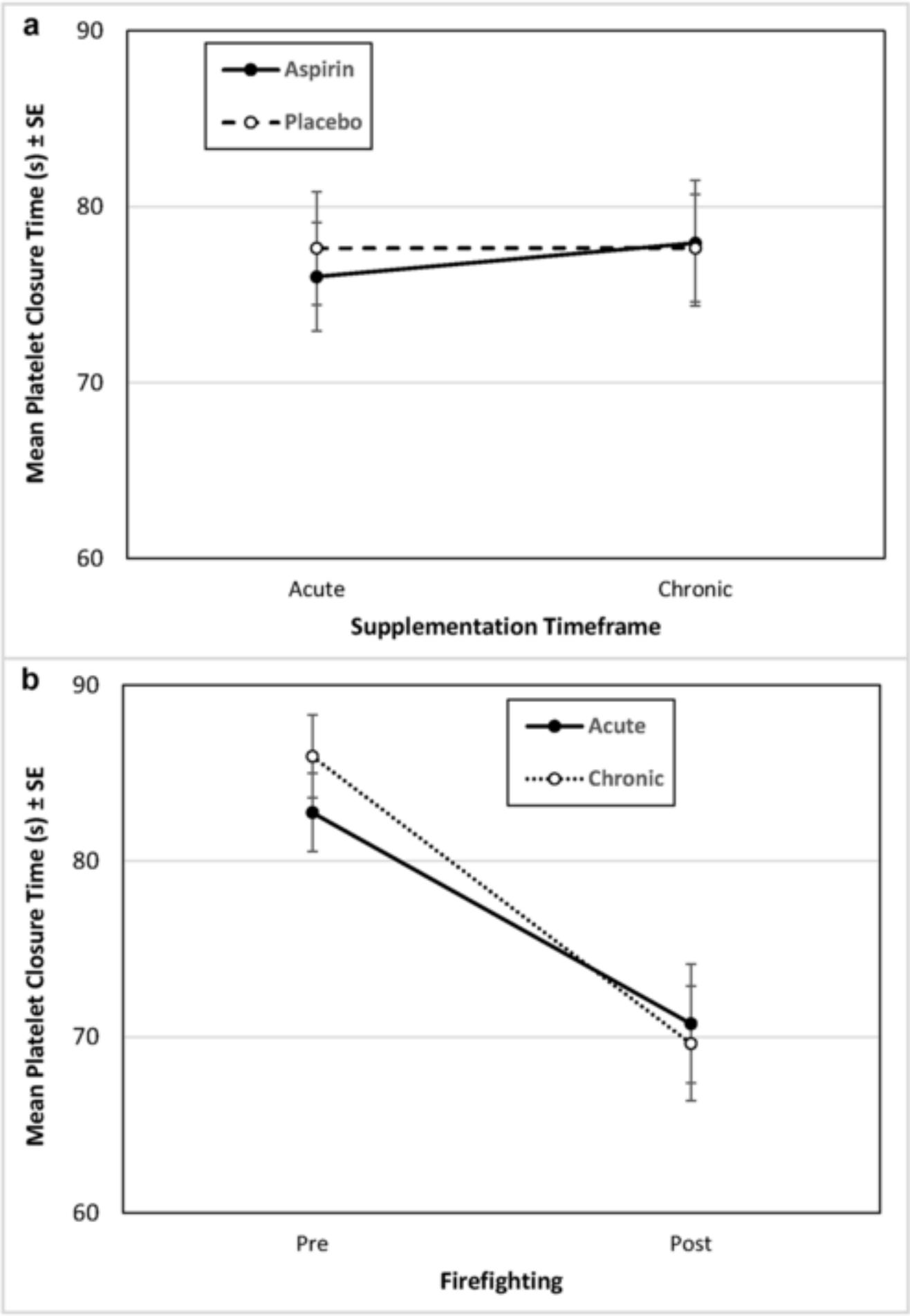

Figure 2

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