The Association of White Blood Cell Count and Bleeding in Acute Coronary Syndrome: An Insight Into the ATLAS ACS 2 – TIMI 51 Trial

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Background

- An elevated white blood cell (WBC) count has been associated with an increased risk of ischemic events in patients with acute coronary syndrome (ACS).
- When treating patients with ACS, there is a need to balance the therapeutic efficacy of antithrombotic medication with their increased bleeding risk.
- There have been reports of an association between WBC and bleeding in patients after percutaneous coronary intervention (PCI) and in those with non-ST elevation myocardial infarction (NSTEMI).
- We hypothesized that an elevated WBC count would be associated with an increased bleeding risk in a more general population of patients with ACS.

Method

- ATLAS ACS 2 – TIMI 51 was a randomized, double blinded, placebo controlled trial that enrolled 15,526 subjects with an ACS to either placebo or rivaroxaban.
- A subset of patients had their WBC count measured at baseline.
- The association between baseline WBC count and a composite of Thrombolysis in Myocardial Infarction (TIMI) major bleeding or TIMI minor bleeding at 30 days was assessed in a univariate Cox proportional hazard model.

Method

- A multivariable Cox proportional hazard model was also developed using backward selection. Variables with a p <0.2 in the univariate analysis were included as possible parameters in the selection process. Exit criteria was set at p >0.2.
- Additionally, subjects were dichotomized by leukocytosis status (WBC ≤11 x 10^9/L vs > 11 x 10^9/L) and included in a multivariable analysis with the same parameters selected in the previous model.

Results

- Of the 15,526 subjects randomized at baseline, 14,231 subjects (91.7%) had a baseline WBC measurement with 9,468 subjects (66.5%) randomized to rivaroxaban and 4,763 subjects (33.2%) randomized to placebo.
- Out of the 14,231 subjects in the sub-study, 60 subjects (0.4%) experienced the composite outcome. Of those patients, 33 had a TIMI major bleeding event and 28 had a TIMI minor bleeding event.
- Baseline WBC was associated with an increased risk of the composite bleeding outcome in the univariate model (HR = 1.09 per 1 x 10^9/L increase, 95% CI: 1.01-1.18, p = 0.024).
- The final multivariable model included baseline WBC count, treatment group (rivaroxaban vs. placebo), baseline creatinine clearance, age, baseline hemoglobin level, diabetic status, smoking status, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use at baseline, and percutaneous coronary intervention (PCI) at baseline.

Results

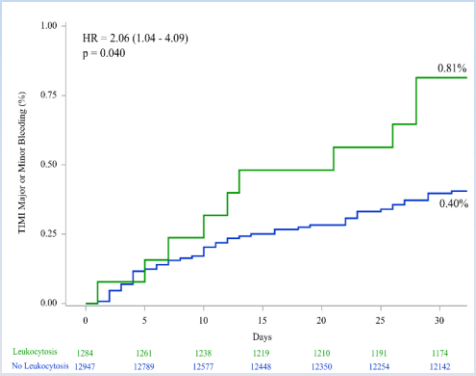
- In the multivariable model, baseline WBC count was associated with an increased risk of the composite bleeding endpoint by 30 days (HR = 1.08 per 1 x 10^9/L increase, 95% CI: 1.01-1.17, p=0.019) (Table).
- When dichotomized (WBC ≤11 x 10^9/L vs. > 11 x 10^9/L), a higher WBC count was also associated with an increased risk of bleeding by 30 days (HR 2.06, 95% CI: 1.04–4.09, p=0.040) (Figure).

Table. Multivariable Cox proportional hazard model of the composite outcome of TIMI major and minor bleeding by 30 days

Variable	HR (95% CI)	p-value
Baseline WBC count (per 1 x 10^9/L)	1.08 (1.01 – 1.17)	0.019
Rivaroxaban use	2.25 (1.14 – 4.21)	0.019
Creatinine clearance (per ml/min)	0.99 (0.98 – 1.00)	0.127
Age (per year)	1.04 (1.00 – 1.08)	0.034
Hemoglobin level (per g/dl)	0.98 (0.96 – 1.00)	0.012
Percutaneous coronary intervention at index event	1.61 (0.91 – 2.85)	0.103
Diabetes	0.56 (0.29 – 1.09)	0.086
Smoking	2.41 (1.41 – 4.15)	0.001
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker use	0.69 (0.39 – 1.19)	0.181

Results

Figure. Cumulative Incidence of TIMI major or TIMI minor bleeding at 30 Days



Conclusions

- An elevated baseline WBC count was associated with an increased risk of TIMI major or TIMI minor bleeding by 30 days.
- Further studies are required to understand the underlying mechanism and to determine whether this association is causal.

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