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Platelet count and the risk for thrombosis and death in the elderly

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Abstract

Aim—Our aim was to examine the association between platelet count and the incidence of myocardial infarction, ischemic stroke, hemorrhagic stroke, venous thrombosis, and mortality.

Methods and results—Platelet count was measured at baseline in 1989–1990 and at three years follow-up, or at baseline (for a newly recruited group) in 1992–1993 in 5766 community-dwelling individuals aged 65 years and older (mean age at baseline, 73 years). During 12 to 15 years of follow-up, there were 821 incident myocardial infarctions, 807 ischemic strokes, 161 hemorrhagic strokes, 159 venous thrombotic events, and 3413 participants died. Platelet count was not associated with the occurrence of myocardial infarction, ischemic or hemorrhagic stroke, venous thrombosis, or cardiovascular mortality. Non-cardiovascular mortality was higher among both participants with low and with high platelet count. Adjusted non-cardiovascular mortality rates for platelet counts below 100, 100 to 199, 200 to 399, and above 400 $\times 10^9/l$ relative to the reference mortality rate in participants with platelet count values between 200 and 299 $\times 10^9/l$ were 1.89 (1.21–2.96), 1.08 (0.98–1.20), 1.20 (1.06–1.37), and 1.47 (1.14–1.90), respectively.

Comment—Platelet counts were not associated with vascular outcomes but low and high platelet counts were associated with non-cardiovascular mortality including cancer mortality.

Introduction

Platelets are anucleate megakaryocyte fragments circulating in the blood. They are involved in the cellular mechanisms of primary hemostasis leading to the formation of blood clots. A normal platelet count ranges from 150,000 to 400,000 platelets per cubic millimeter (150 to 400 $\times 10^9/l$). [1] Low numbers of circulating platelets as well as platelet dysfunction increase the risk of bleeding. In patients with myeloproliferative disorders such as essential thrombocythemia, high levels of platelets have been associated with thrombotic and, to a lesser extent with hemorrhagic complications, mostly at platelet counts exceeding 600 $\times 10^9/l$. There are, however, a few reports of such conditions at considerably lower platelet levels. [2–4] It is not clear whether these conditions can be ascribed to the high platelet counts or to other conditions associated with platelet count changes in these patients.

Our aim was to examine the association between platelet count and the incidence of myocardial infarction, ischemic stroke, hemorrhagic stroke, venous thrombosis and mortality in a cohort of elderly individuals.

Methods

Study design and population

The Cardiovascular Health Study (CHS) is a longitudinal cohort of adults over the age of 65 years. CHS study design and participant recruitment are described in detail elsewhere.[5] Briefly, 5201 individuals from random samples of Medicare eligibility lists in four US communities were recruited in 1989–1990. In 1992–1993, a supplemental cohort of 687 self-identified African-Americans was recruited. Eligible were persons who were 65 years or older at the time of examination, were non-institutionalized, were expected to remain in the area for the next three years, and were able to give informed consent and did not require a proxy respondent at baseline. Individuals who were receiving radiation therapy or chemotherapy for cancer at baseline, wheelchair-bound in the home or receiving hospice treatment were excluded. The study was approved by institutional review boards at each site, and the participants gave informed consent. Participants were excluded from the present analysis if platelet count had not been measured (n=122) leaving 4861 white, 868 black, and 37 ‘other-race’ participants.

Measurements and follow-up

Participants underwent annual evaluations including assessment of cardiovascular risk factors, measurement of seated blood pressure and venipuncture, performed after an overnight fast. [5] Platelet counts were measured in 1989–1990 and in 1992–1993. Platelet counts and white blood cell counts were measured at field center laboratories by Coulter counters. Hypertension was defined as systolic blood pressure ≥ 140 , or diastolic blood pressure ≥ 90 , or a physician diagnosis of hypertension along with use of antihypertensive medication. Diabetes mellitus was defined as diabetes according to the 1997 American Diabetes Association criteria (fasting glucose ≥ 126 mg/dL or receiving diabetes medications).[6]

The clinic visits alternated with phone contacts every six months for up to eleven years of follow-up. Hospital records were obtained for all hospitalizations, and cardiovascular events and deaths were adjudicated by committee. Autopsy and coroner reports, when available, were also obtained for fatal events. Films and ECG tracings were forwarded to the appropriate CHS Events Committee for incident and fatal events for interpretation. The CHS Events Committee reviewed and classified all deaths according to the underlying cause.[7] A coronary event was defined as incident fatal or non-fatal myocardial infarction, ischemic stroke as incident fatal or nonfatal ischemic stroke, hemorrhagic stroke as incident fatal or nonfatal hemorrhagic stroke, deep venous thrombosis[8;9] as incident deep venous thrombosis or fatal or nonfatal pulmonary embolism, mortality as all cause death, cancer mortality as deaths due to cancer, and non-cardiovascular mortality as all deaths due to non-cardiovascular causes.

Statistical analyses

Platelet count was categorized in five categories: 48 (lowest observed value) to $99 \times 10^9/l$, 100 to $199 \times 10^9/l$, 200 to $299 \times 10^9/l$, 300 to $399 \times 10^9/l$, and 400 to 1223 (highest observed value) $\times 10^9/l$. In addition, platelet count was categorized according to quintiles of the distribution of platelet count in the total study population; findings from the latter analyses are presented in the appendix. Hazard rate ratios (HR), and 95% confidence intervals (CI) were calculated using Cox proportional hazards models with platelet counts and potential confounders modeled as time-varying exposures, updated at the follow-up visit in 1992–1993. Depending on the endpoint studied, participants were censored at (1) death attributable to

causes other than the one studied in the particular analysis, (2) loss to follow-up ($n = 237$ (4.0 % of 5888) after 12-15 years of follow-up), or (3) June 30, 2005 for all endpoints except venous thrombotic events where Dec 31 2001 was the censoring date. Multivariate models included sex, race (white versus non-white), and time-dependent variables for age, body mass index, current smoking, hypertension, use of aspirin (more than twice during the last two weeks), total cholesterol, HDL cholesterol, triglycerides, white blood cell count, and C-reactive protein (CRP), to provide adjusted hazard rate ratios. We presumed platelet count could be elevated as a marker of inflammation. We therefore examined the association between platelet count and non-cardiovascular mortality in models both with and without white blood cell count and CRP. Because of the observed differences in platelet count of men and women, we separately examined the association between platelet count and non-cardiovascular death among men and women and tested whether interaction terms for sex and categories of platelet count were statistically significant, with a 0.05 type I error.

For the analysis of each end point, we excluded participants with a history of that end point at baseline; 549 participants had a history of myocardial infarction, 240 had a history of stroke (ischemic or hemorrhagic), and 344 had a history of venous thrombosis.

Results

Platelet count and cardiovascular risk factors

In the 5766 participants included in the analysis, platelet counts ranged between 48 and 1223 $\times 10^9/l$; the mean was 250 $\times 10^9/l$, and 95 percent of platelet counts were between 102 to 398 $\times 10^9/l$. 3977 participants had a second platelet count measurement three years after baseline. Pearson's correlation coefficient between first and second measurement was 0.69, $p < 0.001$. 65% of all patients with two platelet count measurement remained in the same category.

Women had higher platelet counts than men, mean 264 $\times 10^9/l$ (95% confidence interval (CI) 261 to 266 $\times 10^9/l$) and mean 232 $\times 10^9/l$ (CI 229 to 235 $\times 10^9/l$) respectively. Table 1 presents levels of thrombotic risk factors according to categories of baseline platelet counts. Smokers had higher mean platelet counts than non-smokers, 261 (CI 255 to 267) $\times 10^9/l$ and 249 (CI 247 to 251) $\times 10^9/l$, respectively. High total, LDL and HDL cholesterol levels were all associated with increased platelet counts (Table 1). High C-reactive protein levels were associated with increased platelet counts; participants with C-reactive protein concentrations between 0 and 1, 1 to 2, 2 to 3 and higher than 3 mg/l had mean platelet counts of 238, 243, 249 and 259 $\times 10^9/l$, respectively. There was no difference in platelet count between participants who used aspirin and those who did not use aspirin, and age was not associated with platelet count.

Platelet count and incident thrombotic events

During 12 to 15 years of follow-up, there were 821 incident myocardial infarctions, 807 ischemic strokes, 161 hemorrhagic strokes, and 159 venous thrombotic events, and 3413 participants died. Table 2 presents the association between platelet count and the occurrence of these outcomes. Platelet count was not associated with occurrence of myocardial infarction, ischemic stroke, hemorrhagic stroke, or venous thrombotic events.

Platelet count and mortality

Mortality was higher both in participants with low and with high platelet counts compared to those with platelet counts between 200 and 299 $\times 10^9/l$. While this association was attenuated after adjustment for potential confounders, participants with platelet counts between 300 and 399 $\times 10^9/l$, and those with counts above 400 $\times 10^9/l$ had higher mortality rates than participants

with platelet counts between 200 and 299 $\times 10^9/l$ (Hazard ratio 1.13 (CI 1.02-1.25) and 1.28 (CI 1.04-1.57), respectively).

We separately examined the association of platelet count with death due to cardiovascular causes, with death due to cancer and with death due to other (i.e. non-cardiovascular and non-cancer) causes (Table 2). The association between platelet count and mortality appeared to be completely due to an association with non-cardiovascular causes of death. Adjusted cardiovascular mortality rates for platelet counts below 100, 100 to 199, 300 to 399, and above 400 $\times 10^9/l$ relative to the reference mortality rate in participants with platelet count values between 200 and 299 $\times 10^9/l$ were 0.95 (CI 0.80-1.12), 0.91 (CI 0.77-1.08), 0.85 (CI 0.71-1.02), and 1.00 (CI 0.84-1.19), respectively. In the subgroup of 3820 participants who were not using regular aspirin at baseline, adjusted relative hazard ratios for cardiovascular death were 0.75 (CI 0.31-1.83), 1.06 (CI 0.90-1.26), 1.02 (CI 0.82-1.25), and 1.05 (CI 0.67-1.67), respectively.

After adjustment for potential confounders, non-cardiovascular mortality rates for platelet counts below 100, 100 to 199, 300 to 399, and above 400 $\times 10^9/l$ relative to the reference group of participants with platelet count values between 200 and 299 $\times 10^9/l$ were 1.89 (CI 1.21-2.96), 1.08 (CI 0.98-1.20), 1.20 (CI 1.06-1.37), and 1.47 (CI 1.14-1.90), respectively. Similar patterns were observed for deaths due to cancer and for deaths due to non-cardiovascular non-cancer causes (presented in Table 2).

Findings were similar for deaths occurring during the first three years after assessment of platelet count and deaths occurring after that period; if anything, associations with low and high platelet counts were more pronounced for deaths occurring after three years (data not shown). The association between platelet count and non-cardiovascular death was similar among men and women (data not shown).

Discussion

In this study, differences in platelet count were not associated with the risk of myocardial infarction, ischemic or hemorrhagic stroke, venous thrombosis, or cardiovascular mortality. However, both high and low platelet counts predicted non-cardiovascular mortality (including cancer mortality) independent of other risk factors including inflammation markers.

Thrombocytosis and thrombocytopenia have been associated with the risk of thrombotic and hemorrhagic events. Findings among patients with mild thrombocytosis suggested that high-normal platelet count is associated with the occurrence of thrombotic events.[2-4] Among patients with acute myocardial infarction, higher platelet counts on presentation were associated with an increased risk of adverse outcomes, and among the same patients a decrease in platelet count from baseline was associated with a higher risk of reinfarction.[10] Thrombocytopenia in patients with acute coronary syndromes treated with hirudin or heparin had a graded positive association with adverse clinical outcomes, including mortality.[11] In a large study among patients with secondary thrombocytosis, thrombotic events were restricted to the venous system and occurred only in the presence of other risk factors.[12]

A few reports of population-based studies reported that platelet count was not associated with the occurrence of cardiovascular events, but none of these studies showed detailed findings. [13-17] From these reports, it is not clear whether a non-linear association between platelet count and events was examined. Our findings in a detailed analysis suggest that both high and low platelet counts, within the normal range in otherwise healthy participants, are not related to the risk of arterial or venous thrombosis, or to the risk of hemorrhagic stroke, but that they are related to non-cardiovascular mortality.

In contrast to cardiovascular mortality, cancer mortality was associated with higher platelet counts (greater than $300 \times 10^9/l$). This observation is consistent with several studies that have demonstrated an association between thrombocytosis and poor prognosis in a number of solid tumor types including gynecological, colon, renal and gastric cancer.[18-21] At least part of the observed increase in mortality in patients with cancer is likely due to the fundamental role of platelets in promoting tumor metastasis and invasion as well as angiogenesis.(reviewed in [22;23]) In murine models, decreased platelet counts and anti-platelet agents have been found to reduce metastasis.[24;25]

The mechanism of thrombocytosis in patients with cancer is incompletely elucidated and host responses to malignancy as well tumor secretion of humoral factors and cytokines have been suggested.[26;27] In both cases, the presence of tumor is required. In our study, higher platelet counts might be interpreted as reflective of underlying, undiagnosed malignancy although we can not exclude alternate hypotheses such as an increased risk of metastasis and death when cancer develops in individuals with high platelet counts. We were unable to discern if the association between platelet count and cancer mortality is related to an increase in cancer incidence or an increase in cancer death. Nevertheless, given the increasing burden of cancer in the elderly, the association between platelet counts and cancer mortality is deserving of further and confirmatory study.

Like thrombocytosis, thrombocytopenia was also associated with an increase in cancer mortality. A mechanistic explanation for cancer related mortality in association with low platelet counts is likely different from that seen with high platelet counts. An association with low platelet counts might be explained by thrombocytopenia due to underlying illnesses with an increased risk of malignancy. Diseases such as myelodysplastic syndrome are not uncommon in the elderly and may transform to acute leukemia in a subset of patients. Other causes of thrombocytopenia such as underlying liver disease also carry an increased risk of malignancy, for example due to active hepatitis C. In addition, undiagnosed coagulopathies may lead to thrombocytopenia and reflect underlying malignancy prior to clinical symptoms. Alternatively, the thrombocytopenia may be reflective of medication use in the population or the presence of undiagnosed malignancy involving the bone marrow.

The strengths of this analysis include the large population-based sample of white and black participants and careful ascertainment of risk factors and cardiovascular events. Nevertheless, the number of participants with platelet counts below 100 or above $400 \times 10^9/l$ was low. We therefore base our conclusions primarily on the findings in participants with platelet counts between 100 and $400 \times 10^9/l$. Findings in the extreme groups suggest that there may be a higher risk of ischemic stroke and venous thrombosis events among participants with platelet counts above $400 \times 10^9/l$. Our study lacked the power to further investigate this. In addition, the sizes of the hazard ratios are insufficient to merit use of platelet count as a screening tool for cancer risk.

In this study of the elderly, thrombotic and cerebral hemorrhagic risks were similar across the whole range of platelet counts between 100 and $400 \times 10^9/l$. However, both low-normal and high-normal platelet counts were associated with increased non-cardiovascular mortality.

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Appendix 1: results of the analyses of quintiles of baseline platelet count

Table. Incidence and hazard ratios for myocardial infarction, stroke, venous thrombosis, and mortality according to last platelet count.

	Q1 <189	Q2 190-223	Q3 224-254	Q4 255-297	Q5 >297
Myocardial infarction					
Cases myocardial infarction(n)	187	172	169	158	135
Multivariate-adjusted [*] HR (CI)	0.95 (0.76-1.18)	0.89 (0.72-1.15)	1	0.96 (0.77-1.19)	0.88 (0.69-1.11)
Ischemic Stroke					
Cases of ischemic stroke (n)	174	169	143	166	155
Multivariate-adjusted [*] HR (CI)	1.24 (0.99-1.56)	1.19 (0.95-1.49)	1	1.19 (0.95-1.49)	1.17 (0.93-1.48)
Hemorrhagic Stroke					
Cases of hemorrhagic stroke (n)	33	33	39	30	26
Multivariate-adjusted [*] HR (CI)	0.88 (0.55-1.41)	0.83 (0.52-1.34)	1	0.76 (0.47-1.24)	0.75 (0.45-1.25)
Venous thrombosis					
Cases of venous thrombosis (n)	33	36	35	34	21
Multivariate-adjusted [*] HR (CI)	0.84 (0.52-1.37)	0.99 (0.62-1.59)	1	0.99 (0.62-1.59)	0.69 (0.40-1.20)
Total mortality					
Cases of death (n)	813	687	663	599	651
Age, race and sex adjusted HR (CI)	1.07 (0.96-1.18)	0.94 (0.84-1.05)	1	0.96 (0.86-1.07)	1.26 (1.13-1.41)
Multivariate-adjusted [*] HR (CI)	1.06 (0.96-1.18)	0.96 (0.86-1.07)	1	0.93 (0.83-1.04)	1.16 (1.03-1.29)
Cardiovascular mortality					
Cases of cardiovascular death (n)	317	287	287	235	249
Age, race and sex adjusted HR (CI)	0.95 (0.80-1.11)	0.90 (0.76-1.06)	1	0.88 (0.74-1.04)	1.12 (0.94-1.32)
Multivariate-adjusted [*] HR (CI)	0.95 (0.80-1.12)	0.91 (0.77-1.08)	1	0.85 (0.71-1.02)	1.00 (0.84-1.19)
Cancer mortality					
Cases of cancer death (n)	190	142	158	134	164
Age, race and sex adjusted HR (CI)	1.04 (0.84-1.29)	0.82 (0.66-1.03)	1	0.90 (0.72-1.13)	1.28 (1.03-1.60)
Multivariate-adjusted [*] HR (CI)	1.05 (0.84-1.30)	0.85 (0.68-1.07)	1	0.89 (0.71-1.12)	1.20 (0.96-1.50)
Non-CVD & non-cancer mortality					
Cases non-CVD/non-cancer death (n)	306	258	218	230	238
Age, race and sex adjusted HR (CI)	1.24 (1.04-1.48)	1.08 (0.90-1.29)	1	1.10 (0.91-1.33)	1.44 (1.19-1.73)
Multivariate-adjusted [*] HR (CI)	1.23 (1.03-1.45)	1.10 (0.92-1.33)	1	1.04 (0.86-1.25)	1.35 (1.11-1.63)

^{*} adjusted for sex, race, age, current smoking, body mass index, total cholesterol, HDL cholesterol, triglycerides, body mass index, hypertension, use of aspirin, white blood cell count and C-reactive protein.

HR denotes Relative hazard rate

CI denotes 95% confidence interval

CVD denotes cardiovascular disease

References

1. Buckley MF, James JW, Brown DE, Whyte GS, Dean MG, Chesterman CN, Donald JA. A novel approach to the assessment of variations in the human platelet count. *Thromb Haemost* 2000;83:480–484. [PubMed: 10744157]
2. Regev A, Stark P, Blickstein D, Lahav M. Thrombotic complications in essential thrombocythemia with relatively low platelet counts. *Am J Hematol* 1997;56:168–172. [PubMed: 9371529]
3. Hehlmann R, Jahn M, Baumann B, Kopcke W. Essential thrombocythemia. Clinical characteristics and course of 61 cases *Cancer* 1988;61:2487–2496.
4. Fenaux P, Simon M, Caulier MT, Lai JL, Goudemand J, Bauters F. Clinical course of essential thrombocythemia in 147 cases. *Cancer* 1990;66:549–556. [PubMed: 2364366]
5. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263–276. [PubMed: 1669507]
6. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–1197. [PubMed: 9203460]
7. Ives DG, Fitzpatrick AL, Bild DE, Psaty BM, Kuller LH, Crowley PM, Cruise RG, Theroux S. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol* 1995;5:278–285. [PubMed: 8520709]
8. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, Folsom AR. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med* 2004;117:19–25. [PubMed: 15210384]
9. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med* 2002;162:1182–1189. [PubMed: 12020191]
10. Ly HQ, Kirtane AJ, Murphy SA, Buros J, Cannon CP, Braunwald E, Gibson CM. Association of platelet counts on presentation and clinical outcomes in ST-elevation myocardial infarction (from the TIMI Trials). *Am J Cardiol* 2006;98:1–5. [PubMed: 16784909]
11. Eikelboom JW, Anand SS, Mehta SR, Weitz JI, Yi C, Yusuf S. Prognostic significance of thrombocytopenia during hirudin and heparin therapy in acute coronary syndrome without ST elevation: Organization to Assess Strategies for Ischemic Syndromes (OASIS-2) study. *Circulation* 2001;103:643–650. [PubMed: 11156874]
12. Griesshammer M, Bangerter M, Sauer T, Wennauer R, Bergmann L, Heimpel H. Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count. *J Intern Med* 1999;245:295–300. [PubMed: 10205592]
13. Zakai NA, Katz R, Jenny NS, Psaty BM, Reiner AP, Schwartz SM, Cushman M. Inflammation and hemostasis biomarkers and cardiovascular risk in the elderly: the Cardiovascular Health Study. *J Thromb Haemost* 2007;5:1128–1135. [PubMed: 17388967]
14. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 1997;96:1102–1108. [PubMed: 9286936]
15. Folsom AR, Rosamond WD, Shahar E, Cooper LS, Aleksic N, Nieto FJ, Rasmussen ML, Wu KK. Prospective study of markers of hemostatic function with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation* 1999;100:736–742. [PubMed: 10449696]
16. Meade TW, Cooper JA, Miller GJ. Platelet counts and aggregation measures in the incidence of ischaemic heart disease (IHD). *Thromb Haemost* 1997;78:926–929. [PubMed: 9268196]
17. Lowe G, Rumley A, Norrie J, Ford I, Shepherd J, Cobbe S, Macfarlane P, Packard C. Blood rheology, cardiovascular risk factors, and cardiovascular disease: the West of Scotland Coronary Prevention Study. *Thromb Haemost* 2000;84:553–558. [PubMed: 11057849]

18. Monreal M, Fernandez-Llamazares J, Pinol M, Julian JF, Broggi M, Escola D, Abad A. Platelet count and survival in patients with colorectal cancer--a preliminary study. *Thromb Haemost* 1998;79:916–918. [PubMed: 9609220]
19. Symbas NP, Townsend MF, El-Galley R, Keane TE, Graham SD, Petros JA. Poor prognosis associated with thrombocytosis in patients with renal cell carcinoma. *BJU Int* 2000;86:203–207. [PubMed: 10930915]
20. Gucer F, Moser F, Tamussino K, Reich O, Haas J, Arikan G, Petru E, Winter R. Thrombocytosis as a prognostic factor in endometrial carcinoma. *Gynecol Oncol* 1998;70:210–214. [PubMed: 9740692]
21. Ikeda M, Furukawa H, Imamura H, Shimizu J, Ishida H, Masutani S, Tatsuta M, Satomi T. Poor prognosis associated with thrombocytosis in patients with gastric cancer. *Ann Surg Oncol* 2002;9:287–291. [PubMed: 11923136]
22. Nash GF, Turner LF, Scully MF, Kakkar AK. Platelets and cancer. *Lancet Oncol* 2002;3:425–430. [PubMed: 12142172]
23. Sierko E, Wojtukiewicz MZ. Inhibition of platelet function: does it offer a chance of better cancer progression control? *Semin Thromb Hemost* 2007;33:712–721. [PubMed: 18000800]
24. Nierodzik ML, Klepfish A, Karpatkin S. Role of platelets, thrombin, integrin IIb-IIIa, fibronectin and von Willebrand factor on tumor adhesion in vitro and metastasis in vivo. *Thromb Haemost* 1995;74:282–290. [PubMed: 8578473]
25. Pearlstein E, Ambrogio C, Karpatkin S. Effect of antiplatelet antibody on the development of pulmonary metastases following injection of CT26 colon adenocarcinoma, Lewis lung carcinoma, and B16 amelanotic melanoma tumor cells into mice. *Cancer Res* 1984;44:3884–3887. [PubMed: 6744304]
26. Estrov Z, Talpaz M, Mavligit G, Pazdur R, Harris D, Greenberg SM, Kurzrock R. Elevated plasma thrombopoietic activity in patients with metastatic cancer-related thrombocytosis. *Am J Med* 1995;98:551–558. [PubMed: 7539977]
27. Suzuki A, Takahashi T, Nakamura K, Tsuyuoka R, Okuno Y, Enomoto T, Fukumoto M, Imura H. Thrombocytosis in patients with tumors producing colony-stimulating factor. *Blood* 1992;80:2052–2059. [PubMed: 1382717]

Table 1
Baseline characteristics according to platelet count at entry into the study of all 5766 participants.

	48 - 99 *10 ⁹ /l	100 - 199 *10 ⁹ /l	200 - 299 *10 ⁹ /l	300 - 399 *10 ⁹ /l	400 - 1223*10 ⁹ /l	N
Number of participants	19	1379	3184	994	190	5766
Sex (female)	7 (37%)	553 (40%)	1906 (60%)	772 (73%)	125 (66%)	5766
Ethnicity						5766
Caucasian	16 (84%)	1149 (83%)	2672 (84%)	857 (86%)	167 (88%)	
African American	3 (16%)	226 (16%)	488 (15%)	128 (13%)	23 (12%)	
Other	0 (0%)	4 (1%)	24 (1%)	9 (1%)	0 (0%)	
Age (yrs)	76 (5)	73 (6)	73 (6)	72 (5)	72 (5)	5766
Current smoking (yes)	1 (5%)	144 (10%)	359 (11%)	147 (15%)	28 (15%)	5760
Body mass index (kg/m2)	28.8 (6.0)	26.4 (4.6)	26.8 (4.8)	26.7 (4.7)	25.6 (4.3)	5748
Hypertension (yes)	14 (74%)	763 (55%)	1884 (59%)	588 (59%)	123 (65%)	5758
Diabetes (yes)	8 (42%)	438 (32%)	939 (30%)	263 (27%)	60 (32%)	5760
Lipid lowering medication (yes)	0 (0%)	76 (5%)	161 (5%)	66 (7%)	14 (7%)	5759
Aspirin (yes)	2 (11%)	478 (35%)	1044 (33%)	345 (35%)	70 (37%)	5759
Total cholesterol (mg/dl)	183 (35)	199 (37)	213 (38)	221 (39)	216 (45)	5761
LDL cholesterol (mg/dl)	108 (33)	121 (33)	131 (35)	136 (37)	133 (39)	5682
HDL cholesterol (mg/dl)	45 (11)	51 (16)	55 (15)	56 (16)	56 (18)	5753
CRP (mg/l), median	2.2	1.7	2.5	3.0	3.3	5740

	48 - 99 *10 ⁹ /l	100 - 199 *10 ⁹ /l	200 - 299 *10 ⁹ /l	300 - 399 *10 ⁹ /l	400 - 1223*10 ⁹ /l	N
Factor VIII (IU/ml)	1.20 (0.4)	1.20 (0.4)	1.23 (0.4)	1.22 (0.4)	1.22 (0.4)	5740
White blood cell count X1000/mm ³	6.1 (2.6)	5.8 (2.0)	6.3 (2.0)	6.8 (1.8)	8.0 (3.4)	5766
History of MI	3 (16%)	160 (12%)	291 (9%)	78 (8%)	17 (9%)	5766
History of stroke	1 (5%)	58 (4%)	134 (4%)	37 (4%)	10 (5%)	5766
History of VTE	1 (6%)	93 (7%)	177 (6%)	61 (6%)	12 (7%)	5554

Values are mean (standard deviation) or number (percentage of total number of participants in column).

Incidence and hazard ratios for myocardial infarction, stroke, venous thrombosis, and total mortality according to last platelet count.

Table 2

	<100 *10 ⁹ /l	100-199 *10 ⁹ /l	Reference 200-299 *10 ⁹ /l	300-399 *10 ⁹ /l	>400 *10 ⁹ /l
Myocardial infarction					
Cases myocardial infarction(n)	2	223	467	117	12
Rate per 100 personyears	0.77	1.59	1.45	1.28	0.80
Crude HR (CI)	0.52 (0.13-2.10)	1.09 (0.93-1.29)	1	0.89 (0.72-1.09)	0.56 (0.31-0.99)
Age, race and sex adjusted HR (CI)	0.43 (0.11-1.74)	0.90 (0.77-1.06)	1	1.00 (0.82-1.23)	0.64 (0.36-1.14)
Multivariate-adjusted* HR (CI)	0.40 (0.10-1.61)	0.95 (0.80-1.12)	1	0.92 (0.75-1.14)	0.55 (0.31-0.98)
Ischemic Stroke					
Cases of ischemic stroke (n)	4	216	438	124	25
Rate per 100 person years	1.49	1.43	1.29	1.30	1.71
Crude HR (CI)	1.15 (0.43-3.09)	1.11 (0.94-1.31)	1	1.02 (0.83-1.24)	1.35 (0.90-2.02)
Age, race and sex adjusted HR (CI)	1.05 (0.39-2.82)	1.05 (0.89-1.24)	1	1.09 (0.89-1.33)	1.43 (0.95-2.13)
Multivariate-adjusted* HR (CI)	0.97 (0.36-2.61)	1.13 (0.95-1.34)	1	0.98 (0.80-1.20)	1.10 (0.72-1.69)
Hemorrhagic Stroke					
Cases of hemorrhagic stroke (n)	1	40	94	23	3
Rate per 100 person years	0.37	0.26	0.28	0.24	0.21
Crude HR (CI)	1.35 (0.19-9.70)	0.96 (0.66-1.39)	1	0.89 (0.56-1.40)	0.78 (0.25-2.45)
Age, race and sex adjusted HR (CI)	1.32 (0.18-9.48)	0.97 (0.67-1.42)	1	0.94 (0.59-1.48)	0.79 (0.25-2.50)
Multivariate-adjusted* HR (CI)	1.28 (0.18-9.25)	0.97 (0.66-1.43)	1	0.91 (0.56-1.45)	0.75 (0.23-2.41)
Venous thrombosis					
Cases of venous thrombosis (n)	0	39	100	13	7
Rate per 100 person years	0	0.31	0.36	0.17	0.54
Crude HR (CI)	na	0.86 (0.59-1.24)	1	0.47 (0.27-0.85)	1.59 (0.74-3.43)
Age, race and sex adjusted HR (CI)	na	0.79 (0.54-1.15)	1	0.52 (0.29-0.94)	1.74 (0.81-3.76)
Multivariate-adjusted* HR (CI)	na	0.78 (0.53-1.16)	1	0.50 (0.28-0.91)	1.70 (0.77-3.76)
Total mortality					
Cases of death (n)	27	959	1802	525	100
Rate per 100 person years	9.0	5.8	4.9	5.1	6.0
Crude HR (CI)	1.80 (1.23-2.63)	1.20 (1.11-1.30)	1	1.07 (0.97-1.18)	1.33 (1.09-1.63)

	<100 *10 ⁹ /l	100-199 *10 ⁹ /l	Reference 200-299 *10 ⁹ /l	300-399 *10 ⁹ /l	>400 *10 ⁹ /l
Age, race and sex -adjusted HR (CI)	1.58 (1.09-2.32)	1.03 (0.95-1.11)	1	1.23 (1.12-1.36)	1.55 (1.27-1.90)
Multivariate-adjusted* HR (CI)	1.41 (0.96-2.07)	1.05 (0.97-1.14)	1	1.13 (1.02-1.25)	1.28 (1.04-1.57)
Cardiovascular mortality					
Cases of cardiovascular death (n)	7	381	749	204	34
Rate per 100 person years	2.33	2.32	2.03	1.98	2.06
Crude HR (CI)	1.13 (0.54-2.38)	1.15 (1.01-1.30)	1	1.00 (0.85-1.16)	1.08 (0.76-1.52)
Age, race and sex -adjusted HR (CI)	0.98 (0.47-2.07)	0.97 (0.85-1.10)	1	1.16 (0.99-1.36)	1.26 (0.89-1.78)
Multivariate-adjusted* HR (CI)	0.79 (0.37-1.66)	0.99 (0.87-1.13)	1	1.03 (0.88-1.21)	0.99 (0.69-1.41)
Cancer mortality					
Cases of cancer death (n)	12	217	399	132	28
Rate per 100 person years	3.40	1.32	1.08	1.28	1.69
Crude HR (CI)	3.60 (2.03-6.39)	1.22 (1.04-1.44)	1	1.21 (0.99-1.47)	1.65 (1.13-2.43)
Age, race and sex -adjusted HR (CI)	3.17 (1.78-5.63)	1.06 (0.90-1.25)	1	1.35 (1.10-1.64)	1.88 (1.28-2.76)
Multivariate-adjusted* HR (CI) without white blood cell count or CRP in the model	3.28 (1.84-5.85)	1.05 (0.89-1.25)	1	1.34 (1.10-1.64)	1.72 (1.15-2.56)
Multivariate-adjusted* HR (CI)	2.89 (1.62-5.17)	1.07 (0.90-1.27)	1	1.27 (1.04-1.55)	1.46 (0.98-2.19)
Non-CVD & non-cancer mortality					
Cases non-CVD/non-cancer death (n)	8	361	654	189	38
Rate per 100 person years	2.67	2.20	1.78	1.83	2.30
Crude HR (CI)	1.47 (0.73-2.94)	1.25 (1.10-1.43)	1	1.07 (0.91-1.26)	1.43 (1.03-2.00)
Age, race and sex -adjusted HR (CI)	1.32 (0.66-2.66)	1.08 (0.95-1.23)	1	1.25 (1.06-1.47)	1.68 (1.21-2.33)
Multivariate-adjusted* HR (CI) without white blood cell count or CRP in the model	1.41 (0.70-2.83)	1.08 (0.95-1.24)	1	1.22 (1.04-1.44)	1.66 (1.19-2.30)
Multivariate-adjusted* HR (CI)	1.31 (0.65-2.63)	1.11 (0.97-1.27)	1	1.18 (1.00-1.40)	1.52 (1.09-2.13)

* also adjusted for current smoking, body mass index, total cholesterol, HDL cholesterol, triglycerides, body mass index, hypertension, use of aspirin, white blood cell count and plasma C-reactive protein concentration.

HR denotes Relative hazard rate

CI denotes 95% confidence interval

CVD denotes cardiovascular disease

CRP denotes C-reactive protein