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Letter to the Editor

No correlation of intensity of phlebotomy regimen with risk of thrombosis in polycythemia vera: evidence from ECLAP and CYTO-PV clinical trials

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The natural history of polycythemia vera (PV) is marked by arterial and venous thromboembolism and evolution into myelofibrosis and/or acute myeloid leukaemia/myelodysplastic syndrome.

One of the major goals of treatment is to reduce the thrombotic events which account for 40% of causes of mortality. Several trials have investigated the outcomes of various therapeutic approaches and underscored the importance of therapeutic phlebotomy (TP). The first PVSG prospective trial[1] randomized 431 patients to receive either TP alone or TP combined with chlorambucil or radioactive phosphate (^{32}P) and patients were then followed for 20 years. The median survival was 13, 11 and 9 years for patients randomly assigned to treatment with TP alone, radioactive phosphate and chlorambucil plus TP as needed, respectively. The study also showed an increased incidence of thrombosis among the group treated with TP alone, especially during the first 3 years (23% compared to 16% in the ^{32}P treatment arm). However, compared to patients given myelosuppressive therapy, patients who were treated with TP alone, had a lower incidence of hematological malignancies and solid tumors. The authors concluded that TP provides the best overall survival but at the cost of increased risk of thrombosis during the first 3 years. One interpretation of these unexpected finding was attributed to the occurrence of thrombocytosis, a relative frequent event after initiating TP. Then, PVSG conducted a trial[2] in which phlebotomized patients were given high-dose aspirin and dipyridamole with the aim to reduce thrombosis, but the trial failed due to an increased incidence of gastrointestinal hemorrhage. In 2004, the antithrombotic role of aspirin was demonstrated by the European collaboration on low-dose aspirin in polycythemia vera (ECLAP) placebo-controlled randomized clinical trial[3] showing that low-dose aspirin can safely prevent thrombotic complications in patients with PV who have no contraindications to such treatment. Currently, hydroxyurea (HU) is recommended[4,5] in patients who are at high risk of thrombosis, progressive disease or in those who cannot tolerate frequent therapeutic phlebotomies. Other therapeutic options include treatment with interferon-alpha,[6] or ruxolitinib as shown in 2 recent randomized clinical trials.[7,8]

Furthermore, there is now evidence from the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) randomized clinical trial,[9] that therapeutic TP, aimed at keeping hematocrit (HCT) threshold <45%, represents the cornerstone in the therapeutic armamentarium of PV either alone in low-risk PV or as supplement of cytoreductive therapy in high risk patients. However, a recent retrospective study in a large cohort of PV patients,[10] raised the issue that in patients receiving HU, frequent TP (>3 per year) enhanced the risk of major thrombosis. This finding may be relevant for clinical practice and, if confirmed, may support the use of second line therapy with JAK2-inhibitors drugs or interferon-alpha to reduce the thrombotic risk associated with higher frequency of TP. Therefore, we reviewed the ECLAP and CYTO-PV database in which information on the frequency of phlebotomies and vascular events was available.

In the ECLAP database, a subgroup of 793 patients (48%) out of 1638 included in the ECLAP study, was treated with hydroxyurea for a median follow-up of 28 months. In these patients, clinical outcomes, treatments, and laboratory values during the follow-up were recorded at follow-up visits at 12, 24, 36, 48, and 60 months. For the purpose of this study, we calculated the total number of TP/time of follow-up and the number of TP per year, in HU treated patients and looked at the correlation between frequency of TP and thrombosis. Three groups were created: NO TP (n=313, 39%), 1-2 TP per year (n=340, 43%), 3 or more TP per year (n=140, 18%). Time to first thrombotic event from HU start was calculated in each group, censoring patients with no event at last visit or at time of HU discontinuation, whichever occurred first. A total of 79 major thrombosis were observed during the follow-up of these patients while receiving HU. As reported in **Figure 1**, the cumulative incidence of thrombosis was superimposable in the 3 groups prospectively evaluated. In the patients submitted up to 2 TP per year *versus* 3 or more TP per year, HCT median values were 44.73% (IQR: 41.05% - 47.00%) and 46.03% (IQR: 44.35% - 48.63%), respectively (p=0.102), but this small difference did not impact on the rate of incident thrombosis. Of note, in those patients requiring 3 or more TP per year, only 6 received more than 5 TP on annual basis and, in these latter cases, the incidence of thrombosis was not different in comparison with those treated with less than 4 TP per year (Log-rank test, p=0.802).

In the Italian randomized CYTO-PV trial, we assessed the benefit/risk profile of cytoreductive therapy with TP or HU aimed at maintaining HCT < 45% versus maintaining HCT in the range 45%–50% in 365 patients meeting the 2008-WHO criteria of PV. For all patients, exposure to (and dose of) hydroxyurea, as well as exposure to (and number of) phlebotomies, were available every 6 months from randomization until the end of follow-up. The arm maintained at HCT target less than 45%, had a significant 4 times lower rate of cardiovascular death and major thrombosis than did the arm with a hematocrit target of 45 to 50%. According to the therapy administered during the follow-up period, 3 categories were created: stable patients not requiring TP nor HU (n=36), patients on TP alone (n=92), and patients on HU alone or in combination with TP (n=237). As shown in **Figure 2**, the frequency of TP during follow-up in the 365 patients (cohort A) was significantly higher in the low-HCT arm (p<0.000) than in high-HCT arm. The same trend was documented when analysis was restricted to patients under HU treatment alone or in combination with TP (cohort B) (p<0.000). In contrast, the dose of HU was not statistically different in the two arms of the study. Thus, more TP were needed to keep the threshold HCT<45% and in this way a 3 fold lower thrombotic events were registered.

The effect of frequent TP on the risk of thrombosis was estimated by a multivariable Cox proportional-hazard model, adjusted for HCT arm and high-risk category (age of 65 years or older and/or previous thrombosis) and fitted in the cohort A and in cohort B (**Table 1**). Since the number of TP changed over time, a TP was treated as a time-dependent covariate (updated in the model every six months), to assess whether the increase in the number of phlebotomies during the follow-up was associated with the probability of having a thrombotic event. In the whole cohort (A), for every additional phlebotomy performed, no increased risk of thrombosis was seen (HR=0.92, 95% CI 0.67-1.26). Conversely, patients in the low-HCT arm (with higher median frequency of TP), had a 62% lower risk of thrombosis (HR=0.38, 95% CI 0.17-0.87) if compared with those in high-HCT arm. The same results were obtained in the cohort B, in which the HR of low-HCT arm was 0.37 (95% CI 0.13 - 1.04), not reaching the full statistical significance due to the smaller number of available events.

In a separate analysis of the two arms of the trial, the results were similar to those of the whole cohort. In particular, for every additional phlebotomy, the risk of thrombosis did not change neither in low-HCT arm (HR=1.18, 95% CI 0.81-1.73) nor in high-HCT arm (HR=0.71, 95% CI 0.42-1.22). This was also seen in the subgroup of patients receiving HU (in low-HCT arm: HR=0.72, 95% CI 0.26-1.96 and in high-HCT arm: HR=0.99, 95% CI 0.61-1.64), confirming the lack of association between the requirement of additional phlebotomies and the risk of thrombotic events.

~~All~~ These results, based on a more powerful analysis in PV patients treated with HU in the settings of controlled prospective trials, do not confirm those recently reported by Alvarez-Larran et al,[10] who showed in an observational cohort a correlation between the number of TP and a higher incidence of thrombosis in HU treated patients. It should be underscored that the median value of HCT in the group treated with 3 or more phlebotomies (46.03%) of ECLAP study was lower than the median value of hematocrit in high-HCT arm of Cyto-PV trial (always above 47.5%) and that this latter value was comparable to the group treated with 3 or more phlebotomies of the Spanish cohort in which higher risk of thrombosis was reported. Clearly, the increased number of phlebotomies is obviously related to the need of reaching the target hematocrit level. Thus, it could be argued that the higher risk of thrombosis, might be related to an uncontrolled hematocrit value, rather than to the use of phlebotomies *per se*.

In conclusion, our results indicate that the frequency of phlebotomies in PV patients on HU does not represent a risk factor for future thrombosis in PV patients and do not support the need to shift from HU plus TP to second line drugs, and indirectly reinforce that a low HCT is the key variable to reduce the thrombotic risk in PV patients.

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Tables

Table 1. Hazard Ratio (HR) of time to thrombotic events, and 95% confidence intervals (CI), estimated by a multivariable Cox proportional-hazard model fitted in the whole cohort (*column A*) and among patients treated with hydroxyurea alone or in combination to phlebotomies (*column B*)

	All cohort (A) **N = 365** **HR (95% CI)**	**p**	**HU +/- TP (B)** **N = 237** **HR (95% CI)**	**p**
N° of TP[*]	0.92 (0.67 - 1.26)	0.611	0.88 (0.57 - 1.38)	0.587
Low-HCT arm	0.38 (0.17 - 0.87)	0.023	0.37 (0.13 - 1.04)	0.060
High risk category[**]	1.79 (0.71 - 4.47)	0.215	1.96 (0.45 - 8.58)	0.370

HR: Hazard Ratio; 95% CI:95% Confidence Interval

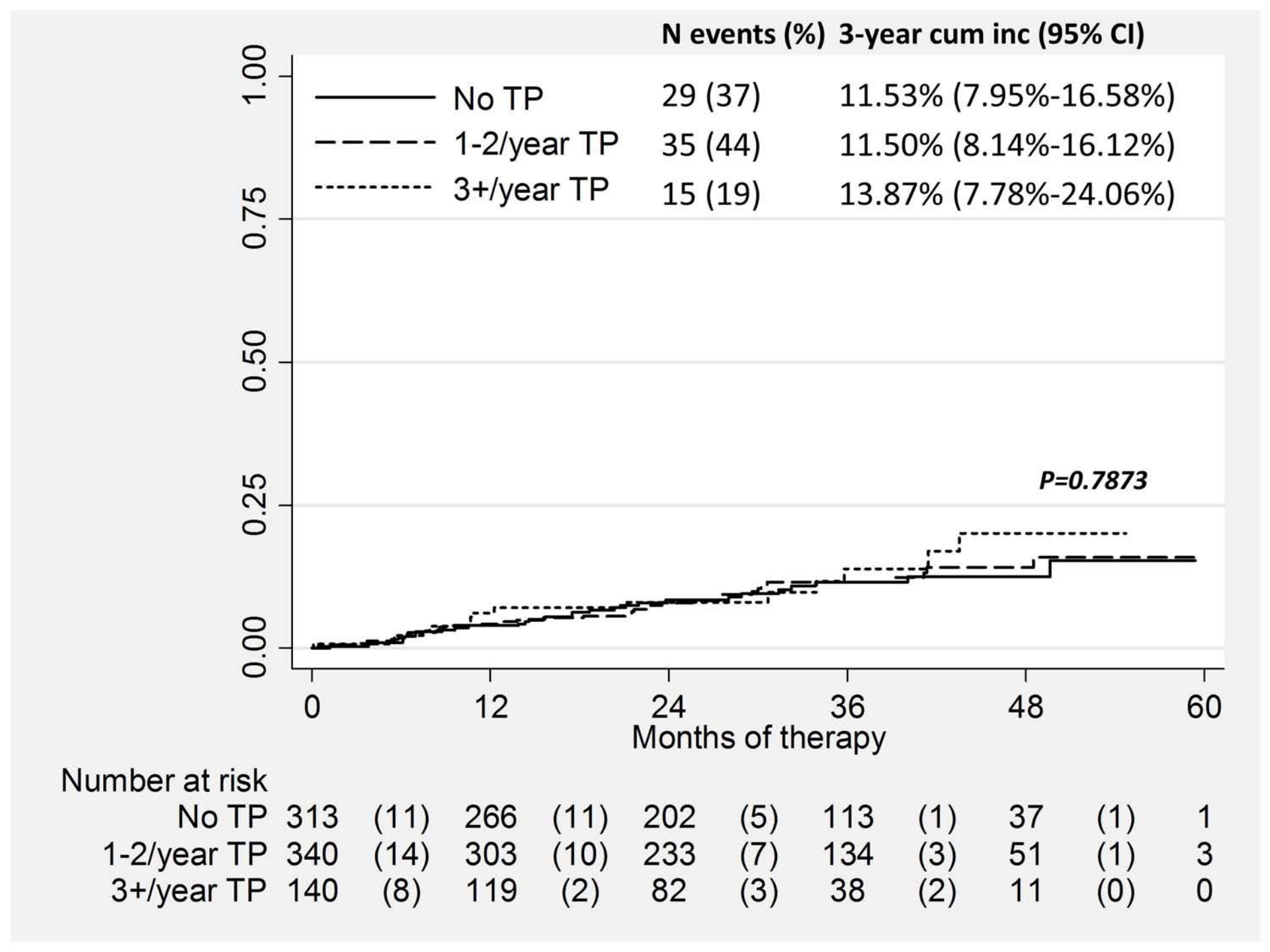
[*]The number of phlebotomies (TP) during follow-up was included in the model as a time-dependent variable

[**]Patients were in the high-risk category if they were aged more than 65 years and/or if they had previous thrombosis

Legend to Figures

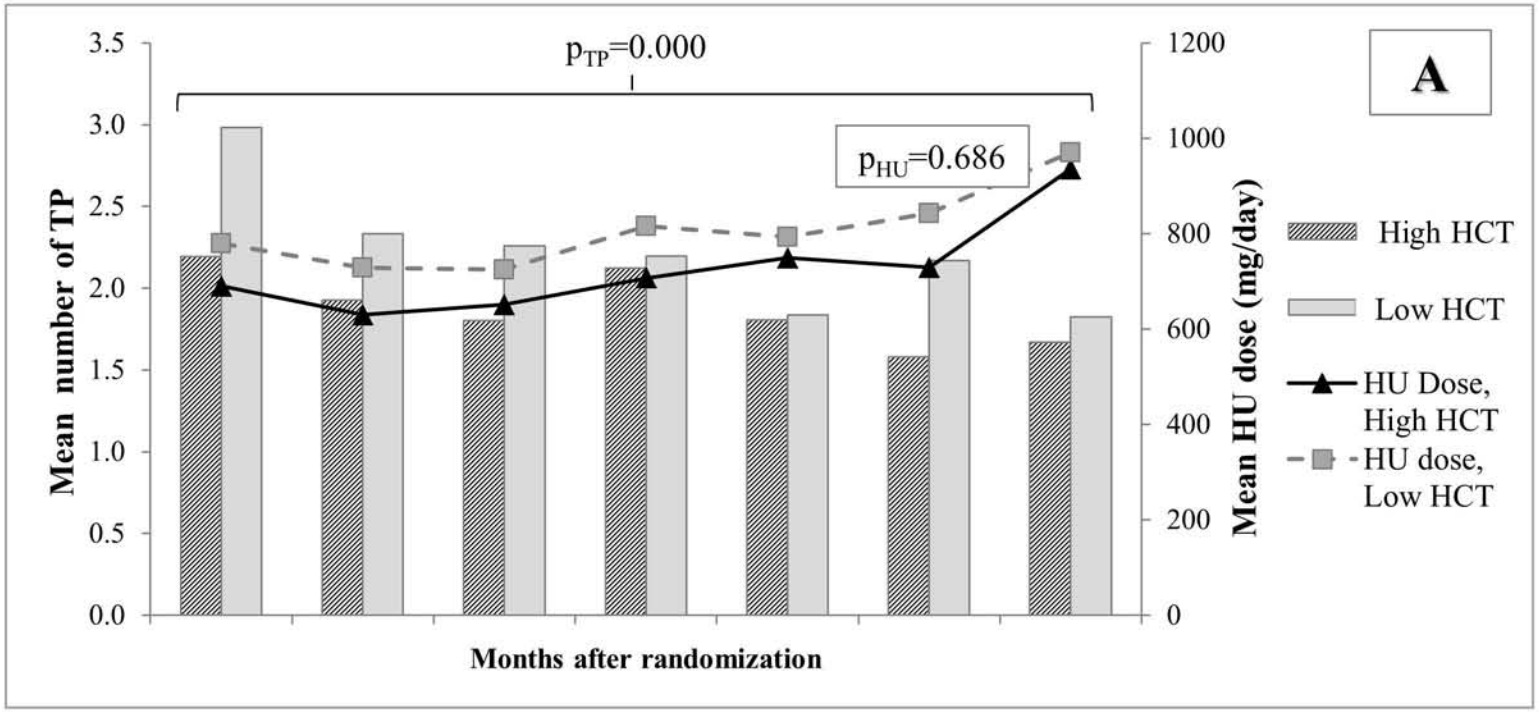
Figure 1. Cumulative incidence of major thrombosis in PV patients under hydroxyurea (HU) treatment by number of therapeutic phlebotomies (TP) per year. In parenthesis are quoted number of events for each period. Test for trend of the failure function across three ordered groups are performed and the relative p-value reported.

Figure 2. Mean number of therapeutic phlebotomies (TP) and doses of hydroxyurea (HU) during follow-up in the low/high-hematocrit (HCT) arm. (A) Whole cohort; (B) Patients treated with hydroxyurea alone or in combination with phlebotomies. The difference between the high/low-HCT arms in the number of TP or HU dose over time was assessed using a repeated-measures mixed model (p_{TP}: p-value for difference in the number of TP; p_{HU}: p-value for difference in HU dose).



Number at risk

No TP	313	(11)	266	(11)	202	(5)	113	(1)	37	(1)	1
1-2/year TP	340	(14)	303	(10)	233	(7)	134	(3)	51	(1)	3
3+/year TP	140	(8)	119	(2)	82	(3)	38	(2)	11	(0)	0


A
p_{TP}=0.000
p_{HU}=0.686
Mean number of TP
Mean HU dose (mg/day)
Months after randomization
High HCT
Low HCT
HU Dose, High HCT
HU dose, Low HCT
3.5
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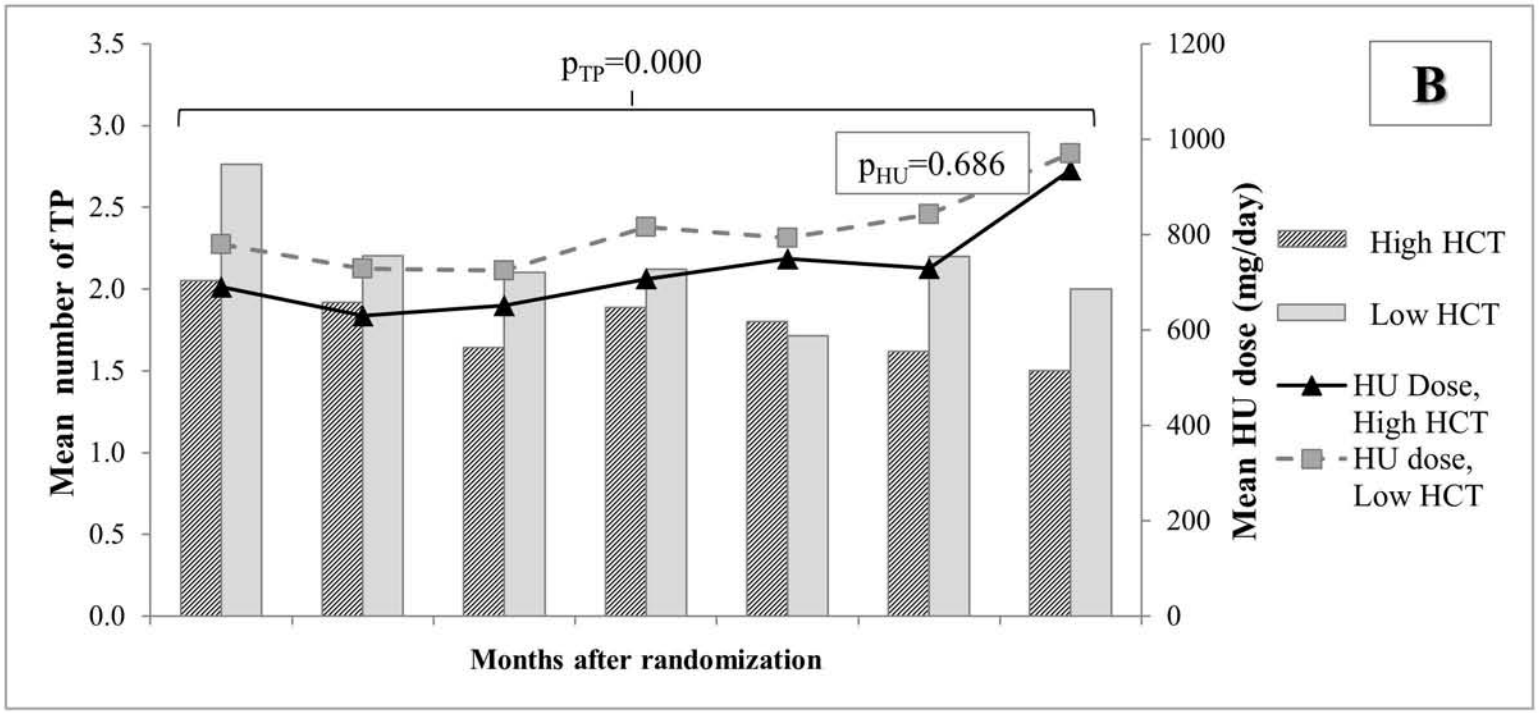
B
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Mean number of TP
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Months after randomization
High HCT
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HU dose, Low HCT
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1200
1000
800
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400
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