# Press review

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## Target haematocrit in the treatment of polycythaemia vera

*Marchioli R, Finazzi G, Specchia G,* et al.
**Cardiovascular events and intensity of treatment in polycythemia vera**
N Engl J Med 2013; **368**: 22-33.

Thrombotic events are the most common severe complication of polycythaemia vera and are the cause of death in 30% of the patients with this disorder. In this disease, thrombophilia is believed to be caused primarily by the high haematocrit values, which are the main target of cytoreductive therapy. However, the threshold haematocrit value, if any, which should be the objective of the treatment, is not clear and current recommendations are not based on solid evidence.

This article reports the results of a prospective randomised clinical trial conducted by the Cytoreductive Therapy in Polycythaemia Vera (CYTO-PV) Collaborative Group, which includes 26 centres in Italy. The trial compared two target haematocrit levels: <45% (low haematocrit) and 45 to 50% (high haematocrit). Eligible patients were adults who had received a diagnosis of polycythaemia vera according to WHO diagnostic criteria but had no substantial liver or renal disease, were not addicted to drugs or alcohol, had no condition believed to shorten life expectancy, and had not previously experienced side effects from hydroxyurea. After randomisation, the choice of the therapy (phlebotomy, cytoreductive drugs, or both) was left to the investigator. However, hydroxyurea was recommended in the case of a high risk of thrombosis or progressive thrombocytosis or splenomegaly. Low-dose aspirin was advised for all patients without contraindications. The control of additional cardiovascular risk factors was encouraged. Phlebotomy was performed twice or thrice a week until the target haematocrit was reached. The initial dose of hydroxyurea (0.5-1 g/day) was adjusted to lower the platelet count to below under $400\times10^9$/L but maintain a leucocyte count higher than $3.5\times10^9$/L. The primary outcome was the occurrence of a thrombotic event (including stroke, acute coronary syndrome, transient ischaemic attack, pulmonary embolism, abdominal thrombosis, deep vein thrombosis, or peripheral arterial thrombosis) or death from a cardiovascular cause. Secondary outcomes were the occurrence of the primary outcome or superficial vein thrombosis, incidence of cancer, progression to myelofibrosis, myelodysplasia or leukaemic transformation, major or minor haemorrhage.

The study should have enrolled 1,000 patients with a follow up of 5 years, but it was stopped earlier because after 4 years the rate of recruitment had become very low. In total, 365 patients were allocated to the experimental groups (182 low haematocrit, 183 high haematocrit). Before randomisation, the patients had been stratified for previous occurrence of thrombosis, age (<65 years or ≥65 years), and referring medical centre. There were no significant differences in the baseline characteristics between the groups. Two thirds of the patients were considered at high risk of thrombosis because of previous thrombotic events (60% arterial thrombosis) or age ≥65 years. Hypertension was found in 55% of patients. The majority of patients were being treated with phlebotomy (68%) and/or hydroxyurea (53%). Other cytoreductive drugs were used in 7% of patients.

The patients were followed for 29±11 months. In the first 6 months of follow up of the low haematocrit group, phlebotomy was initiated in 8% of the patients and phlebotomy rates increased by 36% in the others. In the high haematocrit group, phlebotomy was interrupted in 28% of patients. The treatment with hydroxyurea underwent modest changes (around 4-6%) in the same direction as phlebotomy. During the study, the median haematocrits of the low and high haematocrit groups were 44.4% and 47.5%, respectively. After the first 6 months, three-quarters of patients were always maintained within their correct haematocrit range. The statistical analysis was performed according to intention to treat. The leucocyte counts in the two experimental groups differed significantly (P <0.001): throughout the study, the average counts ranged from 7.7 to $8.6\times10^9$/L in the low haematocrit group and from 8.6 to $9.5\times10^9$/L in the high haematocrit group. Platelet counts were not significantly different.

The primary outcome occurred in 2.7% and 9.8% of the low and high haematocrit groups, respectively. The hazard ratio (HR) in the high haematocrit group was 3.91, with a 95% confidence interval (CI) of 1.45 to 10.53 (P =0.007). There were four deaths from cardiovascular causes, all in the high haematocrit group. The Authors calculated that in the same group the incidence of the primary outcome was four times higher (4.4 *vs* 1.1 per 100 person-years). When superficial vein thrombosis was also included, thrombotic events occurred in 4.4% and 10.9% of the low and high haematocrit groups, respectively (HR, 2.69; 95% CI, 1.19 to 6.12; P =0.02). The two experimental groups did not differ in the other outcomes or in the frequency of adverse events. The Authors also performed subgroup analyses (age, sex, previous thrombosis, platelet and leucocyte counts, splenomegaly, previous cytoreductive treatment, anti-platelet or anticoagulant medication), which did not, however, reveal any significant interaction.

The results of this study are surprising. A four-fold increase in major thrombotic events does not seem easily attributable to a mere 3% difference in haematocrit.

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A difference, moreover, between two average values which are largely within the normal range. In the general population, haematocrit is associated with stroke, but the association disappears when hypertension and smoking are considered (*Kannel WB, Gordon T, Wolf PA, McNamara P.* Stroke 1972; **3**: 409-20). Another prospective study confirmed that high haematocrit (≥51%) is an independent risk factor for stroke, but in hypertensive men only (*Wannamethee G, Perry IJ, Shaper AG*. J Intern Med 1994; **235**: 163-8). The Authors of the present study rightly point out that other conditions characterised by erythrocytosis but without thrombocytosis and leucocytosis show increased rates of thrombosis but far lower than those observed in polycythaemia vera. Part of the same Authors had previously shown that leucocytosis is a major thrombotic risk factor in those patients (*Landolfi R, Di Gennaro L, Barbui T et al.* Blood 2007; **109**: 2446-52). Conversely, thrombocytosis is not associated with major vessel thrombosis, but rather with microvascular occlusion causing erythromelalgia, headache and other nervous system symptoms (*Spivak JL*. Blood 2002; **100**: 4272-90).

It seems plausible, therefore, that at least part of the difference in the rate of thrombosis should be attributed to leucocytosis, rather than the higher haematocrit. The origin of the difference in the leucocyte counts is not, however, clear. It appears that the investigators managed the target haematocrits mainly through phlebotomy, which should not change the leucocyte counts appreciably. As far as regards hydroxyurea, this drug should decrease both the leucocyte and the platelet counts, but the latter were not significantly different between the experimental groups. Perhaps, the increased rate of phlebotomy in the low haematocrit group induced a more severe iron deficiency and mild leucopaenia is not uncommon in that condition. It would be interesting to collect more data on this aspect.

Two controversial statements were made by Spivak in an accompanying editorial (*Spivak JL*. N Engl J Med 2013; **368**: 76-8), namely that aspirin and hydroxyurea should not be routinely prescribed for the prevention of thrombosis in polycythaemia vera, and that in women the target haematocrit should be <42%. As regards aspirin, low-dose aspirin reduced the frequency of thrombotic events but not mortality (*Landolfi R, Marchioli R, Kutti J et al.* N Engl J Med 2005; **353**: 33-45). To the best of my knowledge, a different target haematocrit for men and women has almost no factual basis. That, too, could be an interesting topic for further research.

In conclusion, I doubt that the results of this study should be taken at face value. However, they certainly show that reducing the haematocrit to less than 50% and the platelet count to less than $400\times10^9$/L is not sufficient to prevent major thrombotic events in patients with polycythaemia vera.

## Iron, atherosclerosis and blood donation

*Germain M, Delage G, Blais C,* et al.
**Iron and cardiac ischaemia: a natural, quasi-random experiment comparing eligible with disqualiÞed blood donors**
Transfusion 2013; ahead of print (doi: 10.1111/trf.12081).

The hypothesis that excess iron causes atherosclerosis and cardiovascular disease is particularly intriguing, as the incidence of ischaemic heart disease parallels body iron stores throughout life and across sexes. Several decades of research have neither definitely confirmed nor disproved this hypothesis. Blood donors are ideal candidates for testing it but previous retrospective studies have been inconclusive and fraught by the so-called "healthy donor effect": namely the fact that donors lead a healthier life-style than the general population and show less morbidity. The healthy donor effect also appears between active and lapsed donors (*Atsma F, Veldhuizen I, Verbeek A et al*. Transfusion 2011; **51**: 1820-8). It would seem that only a prospective study could overcome this limitation, but the Authors of the present study had a different and brilliant idea: to compare, retrospectively, active donors with those discarded because of a false-positive transmissible disease marker.

It is well known that false-positive blood donors do not have a higher risk of infection. The Authors reasoned that the occurrence of a false positive result depends on casual events, such as the change of a testing platform, and therefore equates to randomisation. They included in their study all false-positive donors ("disqualified") who presented for whole blood donation between June 1990 and March 2007 in the province of Quebec. For each of them, up to four control donors ("eligible") were matched for decade of age, sex, Þrst-time or repeat donor status, date of donation (±30 days), and region of residence. The primary outcome was hospitalisation or death due to coronary heart disease. Hospital admissions were traced into the provincial hospital discharge database, searching for codes I20 to I25 of the ICD-10 or codes 410 to 414 of the ICD-9 classification system, which correspond to ischaemic heart diseases. Deaths were recorded in the provincial death registry, with the causes similarly coded by the ICD-9 or -10 system. A 2-year delay after the inclusion date was applied, in order to allow sufficient time for a difference in iron stores to arise. The possible confounding by such factors as age, number of previous donations, year of entry in the study, sex, and region of residence, was evaluated by Cox regression analysis.

Of 13,753 disqualified donors and 54,957 eligible donors, 90% or more were traced within the health insurance registry and included in the study. The average follow up lasted about 10 years in both groups. The primary outcome occurred at a rate of 3.60 cases and 3.52 cases per 1,000 person-years in disqualified and eligible donors, respectively (rate ratio [RR]: 1.02; 95% conÞdence interval [CI], 0.92-1.13; not significant). Eligible donors had a rather low donation rate (0.36 per year) and 34% never donated during the follow up. Excluding these latter subjects did not, however, change the results. The Authors also attempted to study assiduous donors only, by limiting the analysis to those who had donated at least four times in the 2 years preceding the date of inclusion.

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In this analysis, the eligible donor group had a donation rate of 1.37 per year during the follow up. However, there was still no significant difference between disqualified and eligible donors in the incidence of the primary outcome. Similarly, adjusting for possible confounding factors did not modify the lack of association.

The Authors commented that previous retrospective studies which reported significant differences between donors and non-donors or frequent and occasional donors were probably influenced by the healthy donor effect. In fact, even in the present study, a comparison within eligible donors of those with or without four donations or more, resulted in an apparently different incidence of coronary heart disease (RR, 0.61; 95% CI, 0.55-0.67).

The results of this study do not disprove the iron hypothesis entirely, as it is still possible that the initial damage takes place early during life and is not responsive to iron depletion afterwards. However, they confirm the results of a prospective trial of phlebotomy in patients with symptomatic peripheral arterial disease (*Zacharski LR, Chow BC, Howes PS et al*. JAMA 2007; **297**: 603-10), i.e. that a reduction of body iron stores does not protect against coronary heart disease significantly.

Several decades ago, discussing the iron hypothesis with other colleagues, we imagined with amusement long queues of middle-aged men in blood collection sites, eager to reduce their iron stores and their susceptibility to ischaemic heart disease. The present study, unfortunately, puts an end to such hopes.

## Transfusion threshold in acute gastrointestinal bleeding

*Villanueva C, Colomo A, Bosch A,* et al.
**Transfusion strategies for acute upper gastrointestinal bleeding**
N Engl J Med 2013; **368**: 11-21.

This article reports the results of a randomised prospective trial comparing a restrictive red cell transfusion strategy (haemoglobin threshold, 7 g/dL; target range, 7-9 g/dL) and a liberal strategy (haemoglobin threshold, 9 g/dL; target range, 9-11 g/dL). The study was conducted in the Hospital de la Santa Creu i Sant Pau of Barcelona, from 2003 to 2009, and included adult patients with acute upper gastrointestinal bleeding, stratified for the presence or absence of liver cirrhosis. Exclusion criteria were the following: refusal of transfusion, exsanguinating bleeding requiring massive transfusion, acute coronary syndrome, symptomatic peripheral vasculopathy, stroke or transient ischaemic attack, transfusion within the previous 90 days, recent trauma or surgery, lower gastrointestinal bleeding, a "do not resuscitate" order, a low risk of further bleeding or death, and inclusion in this study less than 90 days before or inclusion more than twice. The primary outcome was death within 45 days. Secondary outcomes were further bleeding and in-hospital complications. Only complications requiring therapy or prolonged hospital stay were considered.

Of 962 eligible patients, 41 refused to participate and 32 were withdrawn, mostly because they were found, in fact, to be ineligible. At the end, 444 patients in the restrictive group and 445 in the liberal group were included in the analysis. The baseline characteristics of both groups were similar. The most important causes of bleeding were peptic ulcer (49% of cases) and gastro-oesophageal varices (24%). Liver cirrhosis was present in 31% of patients. Haemoglobin levels were checked after the transfusion of each red cell concentrate (pre-storage leucoreduced) and further transfusions given, if necessary, until the target range was reached. At admission, discharge, and after 45 days, haemoglobin levels were 9.6±2.2, 9.2±1.2, 11.6±1.7 g/dL, and 9.4±2.4, 10.1±1.0, 11.7±1.8 g/dL, in the restrictive and liberal groups, respectively (P <0.001 at discharge). The nadir haemoglobin levels were 7.3±1.4 and 8.0±1.5 g/dL in the respective groups (P <0.001). The transfusion rate was 49% *vs* 86% (P <0.001). The total number of red cell units transfused was 671 *vs* 1,638 (P <0.001). Plasma or platelets were transfused in 8% and 3% of patients, respectively, without difference between the groups.

The primary outcome (death within 45 days) occurred in 5% *vs* 9% of the patients (P =0.02). After adjustment for in-hospital bleeding, cirrhosis, age and Rockall score (a score of severity in patients with gastrointestinal bleeding), the hazard ratio (HR) in the restrictive group was 0.55 (95% confidence interval [CI], 0.33-0.92; P =0.02). Among patients with cirrhosis, mortality differed between the restrictive and liberal groups in patients with good or intermediate hepatic function (Child-Pugh classes A and B, comprising 78% of the patients, P =0.02) but not in those with poor function (Child-Pugh class C). As regards the causes of death, the incidence of uncontrolled bleeding was significantly different between the groups: 0.7% *vs* 3.1% (P =0.01). Further bleeding developed in 10% *vs* 16% of patients (P =0.01), particularly in those with cirrhosis. Emergency surgery was necessary in 2% *vs* 6% of patients with peptic ulcer (P =0.04). The restrictive group also experienced fewer adverse events (40% *vs* 48%, P =0.02): in particular, the patients in this group had fewer cardiac complications (11% *vs* 16%, P =0.04) and transfusion reactions (3% *vs* 9%, P =0.001). Among the transfusion reactions, the greatest difference was in the incidence of transfusion-associated circulatory overload (0.5% *vs* 4%, P =0.001). There were no significant differences between the groups in other therapeutic interventions, such as crystalloids and colloids, but balloon tamponade and transjugular intrahepatic portosystemic shunting were more frequent in the liberal group. The Authors concluded that the restrictive strategy significantly improved clinical outcomes.

This important prospective trial was carefully designed and conducted and is devoid of the flaws which weakened the conclusions of some other studies. In particular, more than 90% of eligible patients actually participated in the study and protocol deviations, although more frequent, as expected, in the restrictive group (9% *vs* 3%, P <0.001),

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involved a minority of the patients only.

The most interesting finding of the present study is that, in patients with acute gastrointestinal bleeding, transfusion to maintain a haemoglobin level higher than 9 g/dL seems not only unnecessary but actually detrimental. The Authors suggested that transfusion interferes with the splanchnic vasoconstriction caused by hypovolaemia, which favours the formation of clots. They noted that in their study most of the benefit of the restrictive strategy was observed in patients with portal hypertension. The liberal group showed a significant increase in hepatic venous pressure gradient between measurements performed initially and after 2-3 days, which occurred despite the administration of somatostatin. The Authors' hypothesis is also in keeping with the greater incidence of uncontrolled bleeding (which caused the higher mortality) and further bleeding in the liberal group. The Authors did consider alternative explanations (immunomodulation, storage lesion) for the detrimental effect of transfusion. However, there were no signs of an immunomodulatory effect, as infections occurred with approximately the same frequency in both groups. The transfused red cells had been stored for a median of 15 days in both groups.

The explanation offered by the Authors is also in keeping with the concept that fluid resuscitation should be administered prudently, if not delayed, until haemostasis has been reached, because otherwise bleeding will be increased, as a consequence of clot disruption and dilutional coagulopathy. In this regard, one wonders if transfused blood behaves differently from another volume expander. I suspect not. Following this line of thought, one also wonders whether the liberal group received an excessive volume of fluids: in addition to more than twice the amount of red cells during the index bleeding, they were given the same volume of crystalloids in the first 24 hours as the restrictive group. A greater volume of fluids during the whole hospital stay could be justified by the larger bleeding, but in the first phases of the stay, it looks suspicious. In addition, the liberal group experienced a much higher incidence of transfusion-associated circulatory overload (4% *vs* 0.5%), an incidence which is higher than expected in general, and even more so considering that this particular kind of patient should be more prone to hypovolaemia than hypervolaemia.

These suppositions seem plausible. If they are true, the difference between the outcomes of the two transfusion strategies could disappear or even be reversed if the total amount of fluids were to be the same in both cases. This could well be the starting point for new studies.

## Articles in brief

### Guidelines

*Milkins C, Berryman J, Cantwell C,* et al.
**Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories.**
Transfus Med 2013; **23**: 3-35.

This document from the British Committee for Standards in Haematology is a new edition of the guidelines originally issued in 1991 and successively updated in 1996 and 2004. Compared to the 2004 version, its size has more than doubled, from 16 to 33 pages. There are three new sections, on "Selection and issue of red cells", "Testing and red cell issue in non-routine situations", and "Post issue of blood components", plus 11 appendices. Part of the additional material consists of flow charts and worked examples of antibody identifications. The latter, frankly, seem more pertinent to educational texts than guidelines.

An entirely new sub-section is devoted to the remote issue of red cell concentrates, by means of computer-controlled blood refrigerators. This is a veritable sign of the times and acknowledges a situation which in my opinion is going to become increasingly widespread. Another major change is the recommendation that the blood group of a first-time patient be determined on a second sample, before issue of ABO-identical red cells. In Italy, this is a requirement that has been enforced by law for many years. Unfortunately, this level of safety cannot be achieved in urgent cases, i.e. when errors are more likely to occur.

The previous edition recommended that a new sample for compatibility testing was taken not more than 24 hours before transfusion when the patient had been transfused in the last 3-14 days; not more than 72 hours, when the last transfusion had taken place 15-28 days before; not more than a week, for a transfusion in the last 3 months; patients transfused daily had to be screened for irregular antibodies at least every 72 hours. The Authors mentioned evidence from SHOT (the British haemovigilance system) as supporting this measure. The current edition simplifies the requirement to not more than 3 days for a transfusion in the last 3 months. The Authors report that the previous requirement had been largely disregarded but there was no evidence from SHOT that this had caused delayed haemolytic reactions.

In general, the recommendations contained in these guidelines are sensible and balanced. However, I am sure that every experienced immunohaematologist would find something to add, delete or change. I will spare the reader my own choice of grumbles. However, I cannot but note that the advice to give fresh red cells to transfusion-dependent patients translates into less than 10-day-old units for patients with sickle cell disease and less than 14-day-old units for patients with thalassaemia. It is true that, in both cases, the present guidelines cite other guidelines, but the difference still strikes me as being totally unjustified.

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