Hematologische afwijkingen bij de oudere: Anemie

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Definitie van anemie

Table 2. Cut-off to Define Anemia[5]

Source	Men, g/dL	Women, g/dL	Effect of Race
WHO (Blanc et al)[2]	13	12	Not provided
Jandl[58]	14.2	12.2	Discussed
Williams (Beutler et al)[59]	14	12.3	Not provided
Wintrobe (Lee et al)[60]	13.2	11.6	Not provided
Rapaport[61]	14	12	Not provided
Goyette[62]	13.2	11.7	Blacks' hemoglobin 0.5 g/dL lower
Tietz[63]	13.2	11.7	Not provided
Hoffman et al[64]	13.5	12	Not provided

Cappellini et al. Seminar hematol 2015; 261-269

Prevalentie van anemie bij ouderen

Table 7. Anemia Prevalence in Elderly

Study	Age (yr)	Population	Prevalence (%)
Guralnik et al (2004)[11]	≥65	Community-dwelling elderly Americans	10.6
Ferrucci et al (2007)[21]	>70	Community-dwelling elderly Americans	11
Denny et al (2007)[55]	≥71	Community-dwelling	24
Joosten et al (1992)[56]	≥65	Hospitalized	24
Artz et al (2004)[57]	Most ≥65	Nursing home	48
Robinson et al (2007)[23]	≥65	Nursing home	59.6
MIgone de Amicis et al (2014)[22]	≥65	Hospitalized	48

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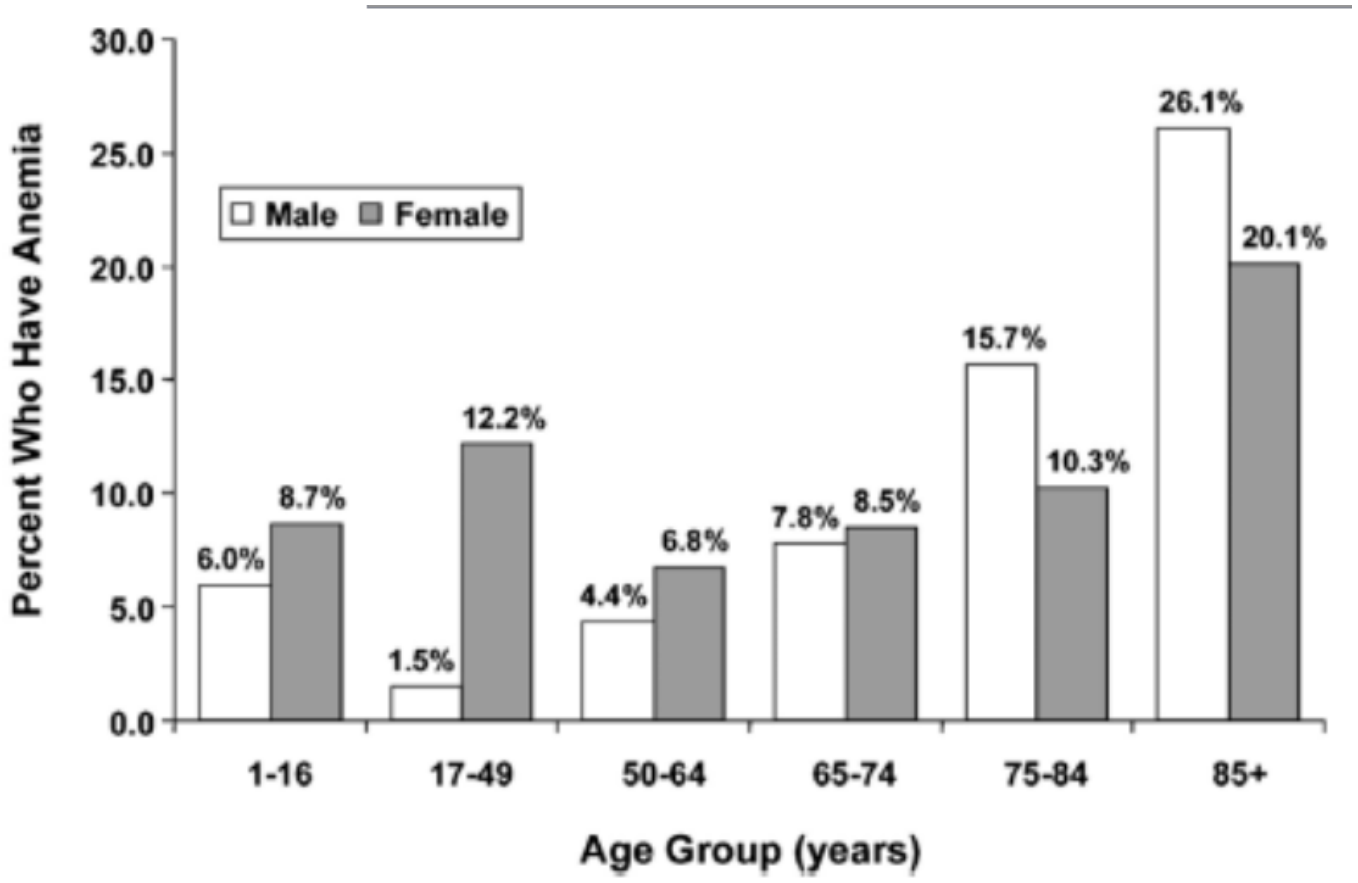


Guralnik et al. Blood 2004;104:2263-68
Mayo Clin Proc. 2007;82(8):958-966

Gevolgen van anemie bij ouderen

- Verminderde overleving
- Moeheid en verminderde functionaliteit
- Verhoogd risico op iatrogene complicaties
- Verhoogd risico op coronaire dood/ congestief hartfalen
- Verhoogd risico op dementie

Table 2. Age- and Sex-Adjusted Mortality Risks in Persons With Anemia Compared With Persons With a Normal Hemoglobin Concentration in the Periods 0 to 5 Years and 5 to 10 Years After Blood Sampling*

	0-5 y Mortality Risk (95% Confidence Interval)	5-10 y Mortality Risk (95% Confidence Interval)
Anemia		
All	1.84 (1.50-2.25)	0.99 (0.56-1.76)
Microcytic	1.84 (1.01-3.35)	. . .
Normocytic†	1.86 (1.51-2.31)	0.90 (0.52-1.79)
Macrocytic	1.52 (0.78-2.96)	. . .
Anemia, adjusted for disease‡	1.84 (1.49-2.27)	0.91 (0.50-1.64)
Anemia, adjusted for functional impairment§	1.74 (1.41-2.15)	1.07 (0.74-2.33)
Anemia, in persons without clinical disease	2.21 (1.37-3.57)	0.64 (0.15-2.68)

*World Health Organization criteria for a normal hemoglobin concentration: for women, 7.5 to 10.0 mmol/L (120-160 g/L); for men, 8.1 to 11.2 mmol/L (130-180 g/L). Ellipses indicate data not calculated because of small numbers.
†Defined as 80 to 100 fL.
‡Diseases at baseline associated with anemia: malignant neoplasm, infectious disease, thyroid disease, peptic ulcer, renal failure, and rheumatoid disease.
§Functional impairment defined as any according to dependency in activities of daily living and cognitive impairment as measured by a Mini-Mental State Examination score below 24 points.

Figure 1. Mortality Risk by Hemoglobin Concentration in Women Aged 85 Years and Older 0 to 5 Years After Blood Sampling

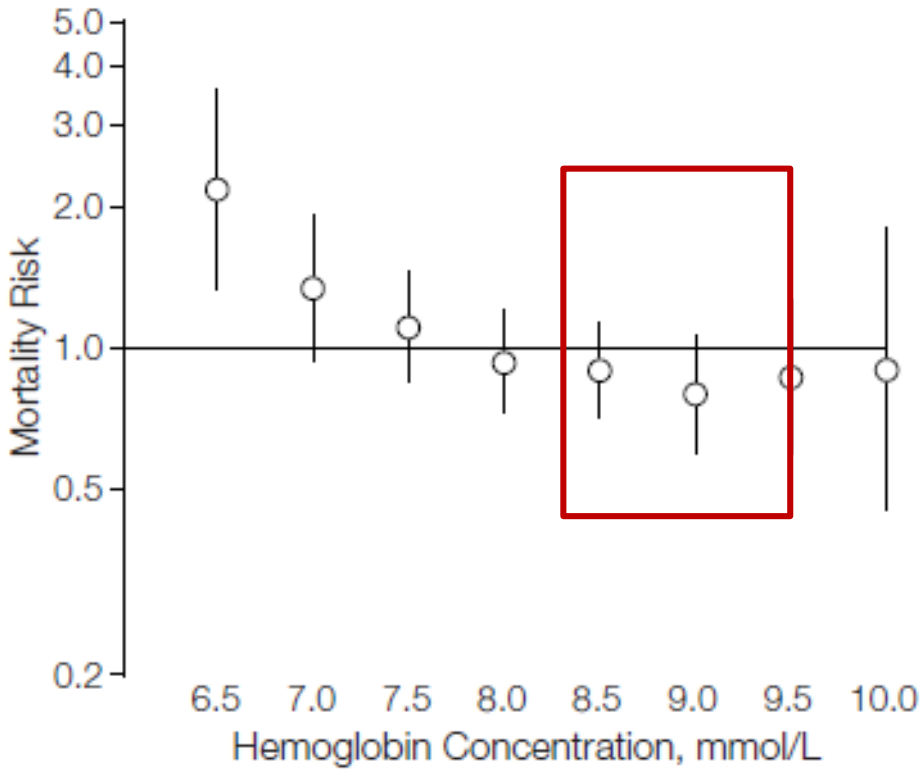
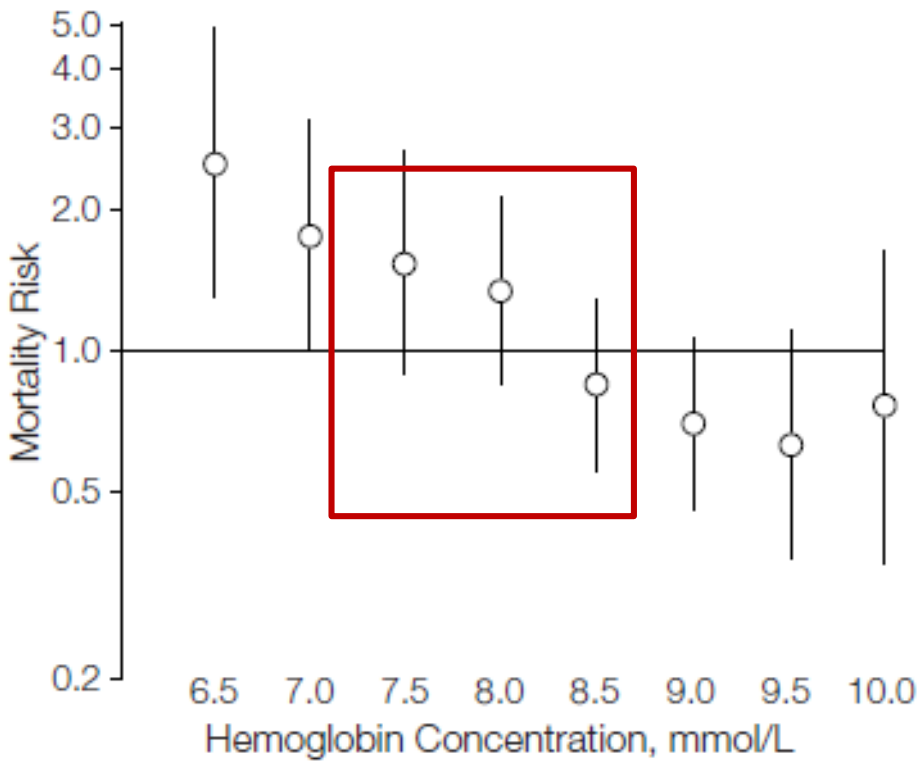
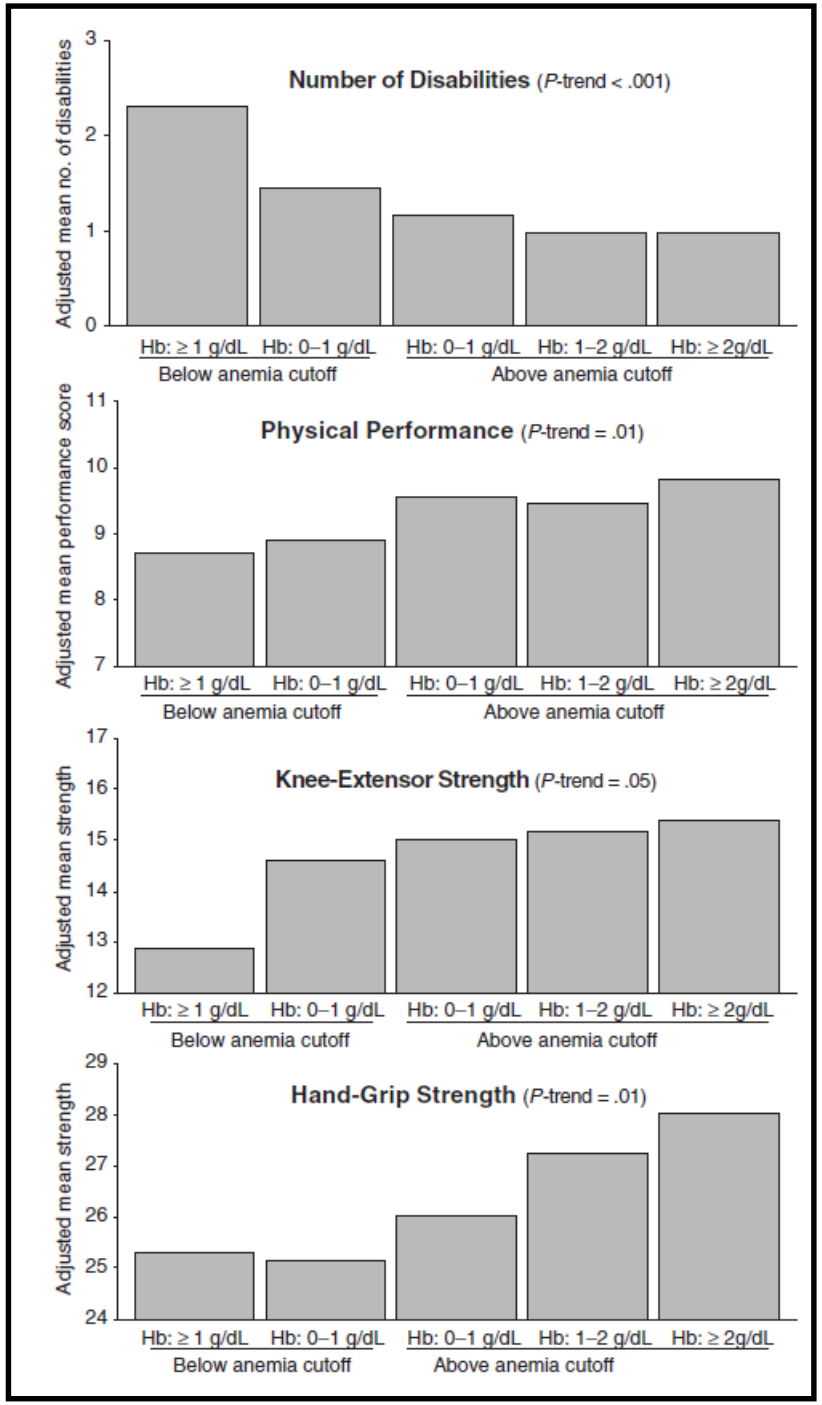


Figure 2. Mortality Risk by Hemoglobin Concentration in Men Aged 85 Years and Older 0 to 5 Years After Blood Sampling





JAGS 2004; 52:719–724

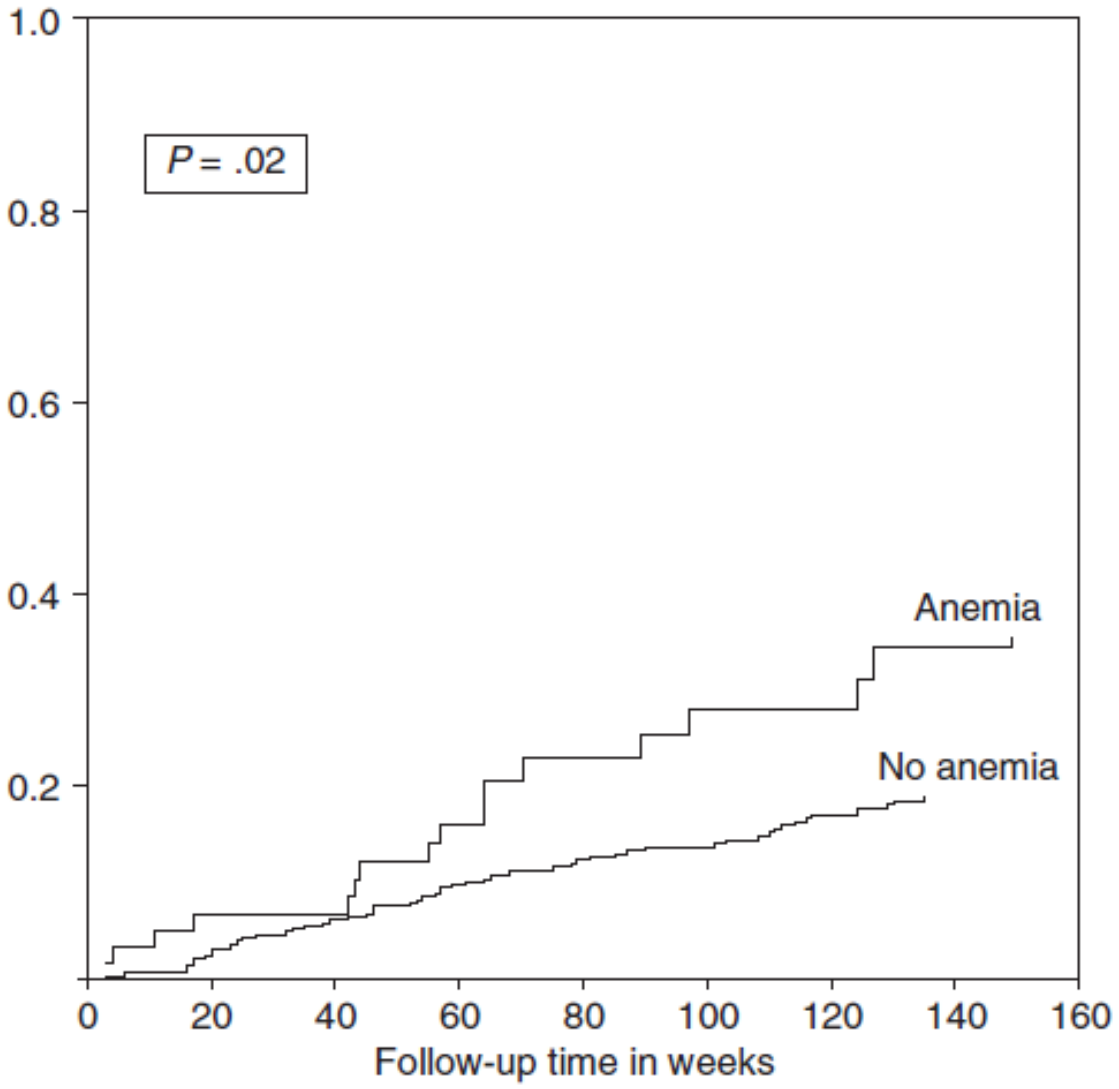


Figure 1. Adjusted hazard curve for cumulative probability to develop recurrent falls during 3 years of follow-up by anemia status. Adjusted for sex, age, body mass index, heart disease, diabetes mellitus, lung disease, joint disease, and serum creatinine level.

J Am Geriatr Soc 2005;53:2106–2111
J Am Med Dir Assoc 2004; 5:395-400

Table 3. Association of Postoperative Delirium with Intraoperative Blood Loss and Postoperative Hematocrit*

	Delirium (n = 117)	No Delirium (n = 1,224)	Odds Ratio	95% Confidence Interval	*P* Value
Mean intraoperative blood loss (cc) (odds ratio per 1,000 cc)	1,150 ± 1,860	510 ± 710	1.6	1.4–1.9	<.001†
Blood transfusions (units) (odds ratio per unit)	3.3 ± 5.6	1.2 ± 1.8	1.3	1.2–1.4	<.001†
Lowest postoperative hematocrit					
Hematocrit (%) (odds ratio per 1%)	29 ± 4	30 ± 5	0.93	0.9–0.98	.001†
Hematocrit‡					
>32%	22 (19%)	351 (31%)	—		
30–32%	12 (10%)	161 (14%)	1.2	1.1–1.3	
28–30%	25 (21%)	194 (17%)	2.0	1.3–3.3	
25–28%	42 (36%)	305 (27%)	2.2	1.3–3.8	
<25%	16 (14%)	138 (12%)	1.8	1.2–2.8	.004§
Hematocrit <30%					
Yes	83 (71%)	637 (55%)	2.0	1.3–3.0	
No	34 (29%)	512 (45%)			.001‖

* Lowest postoperative hematocrit before the onset of delirium in patients who developed delirium and throughout the entire postoperative period in those who did not. Postoperative hematocrit values were obtained in 1,266 of 1,341 patients enrolled in this study, including all 117 patients who developed delirium.

† *t* test.

‡ Odds ratios calculated with hematocrit >32% group as the reference.

§ Chi-square test for trend.

‖ Chi-square test.

Am J Med 1998; 105(5): 380-384

Table 2 Relative risks for different outcome measures in anemic and non-anemic patients

	Anemic	Non-anemic	RR (CI)	P-value
	n = 536	*n = 726*		
Mortality				
In-hospital	30 (5.6)	31 (4.3)	1.17 (0.90-1.52)	0.277
3-month	113 (21.1)	87 (12.0)	1.42 (1.23-1.64)	< 0.001
3-12 month	60 (11.2)	71 (9.8)	1.09 (0.89-1.33)	0.415
12-month	173 (32.3)	158 (21.8)	1.34 (1.18-1.53)	< 0.001
Delirium	162 (30.3)	155 (21.3)	1.29 (1.13-1.48)	< 0.001
LOS > 11 days	272 (50.7)	368 (50.7)	1.00 (0.88-1.14)	0.984
Discharge to a NH	277 (51.7)	285 (39.3)	1.33 (1.17-1.51)	< 0.001
90-day readmission rate	69 (12.9)	65 (9.0)	1.24 (1.04-1.49)	0.025

Values are given as number (percentage), RR = relative risk, CI = confidence interval, LOS = length of stay, NH = nursing home

J Am Geriatr Soc 2005;53:2106–2111
J Am Med Dir Assoc 2004;5(6):395-400

Table 1
Ischemic outcomes at 30 days in patients with ST-segment elevation myocardial infarction stratified by baseline hemoglobin

End Point	Hemoglobin on Admission, g/dL									
	<10 (n = 191)	10–11 (n = 288)	11–12 (n = 962)	12–13 (n = 2,502)	13–14 (n = 5,077)	14–15 (n = 6,926)	15–16 (n = 5,702)	16–17 (n = 2,783)	>17 (n = 968)	p Value
Cardiovascular death, % (106 events)	14.7	11.9	10.1	7.1	4.8	3.3	2.8	2.8	4.2	<0.001
Congestive heart failure, % (2,041 events)	12.7	12.5	12.5	10.8	8.8	6.8	7.1	6.8	8.9	<0.001
Composite, % (2,744 events)	21.6	19.2	18.4	15.1	12.2	9.0	8.8	8.7	11.2	<0.001

Adapted with permission from *Circulation*.[11]

Table 2
Ischemic outcomes at 30 days in patients with non-ST-segment elevation acute coronary syndromes stratified by baseline hemoglobin

End Point	Hemoglobin on Admission, g/dL											
	<8 (n = 137)	8–9 (n = 306)	9–10 (n = 342)	10–11 (n = 343)	11–12 (n = 976)	12–13 (n = 2,331)	13–14 (n = 3,520)	14–15 (n = 3,390)	15–16 (n = 2,130)	16–17 (n = 812)	>17 (n = 216)	p Value
Cardiovascular death, % (248 events)	3.7	2.3	2.3	3.8	2.4	1.8	1.7	1.5	1.3	1.5	0.9	<0.001
Myocardial (re)infarction, % (591 events)	5.1	2.9	5.3	5.8	4.7	4.0	3.9	4.4	3.2	4.5	3.7	0.191
Recurrent ischemia, % (1,879 events)	37.2	25.8	27.1	15.6	12.8	12.8	11.7	11.7	12.0	13.6	16.7	<0.001
Composite, % (2,347 events)	40.2	27.5	29.2	19.2	16.8	15.5	14.8	15.0	14.5	17.0	19.9	<0.001

Adapted with permission from *Circulation*.[11]

Sabatine et al. Circulation 2005

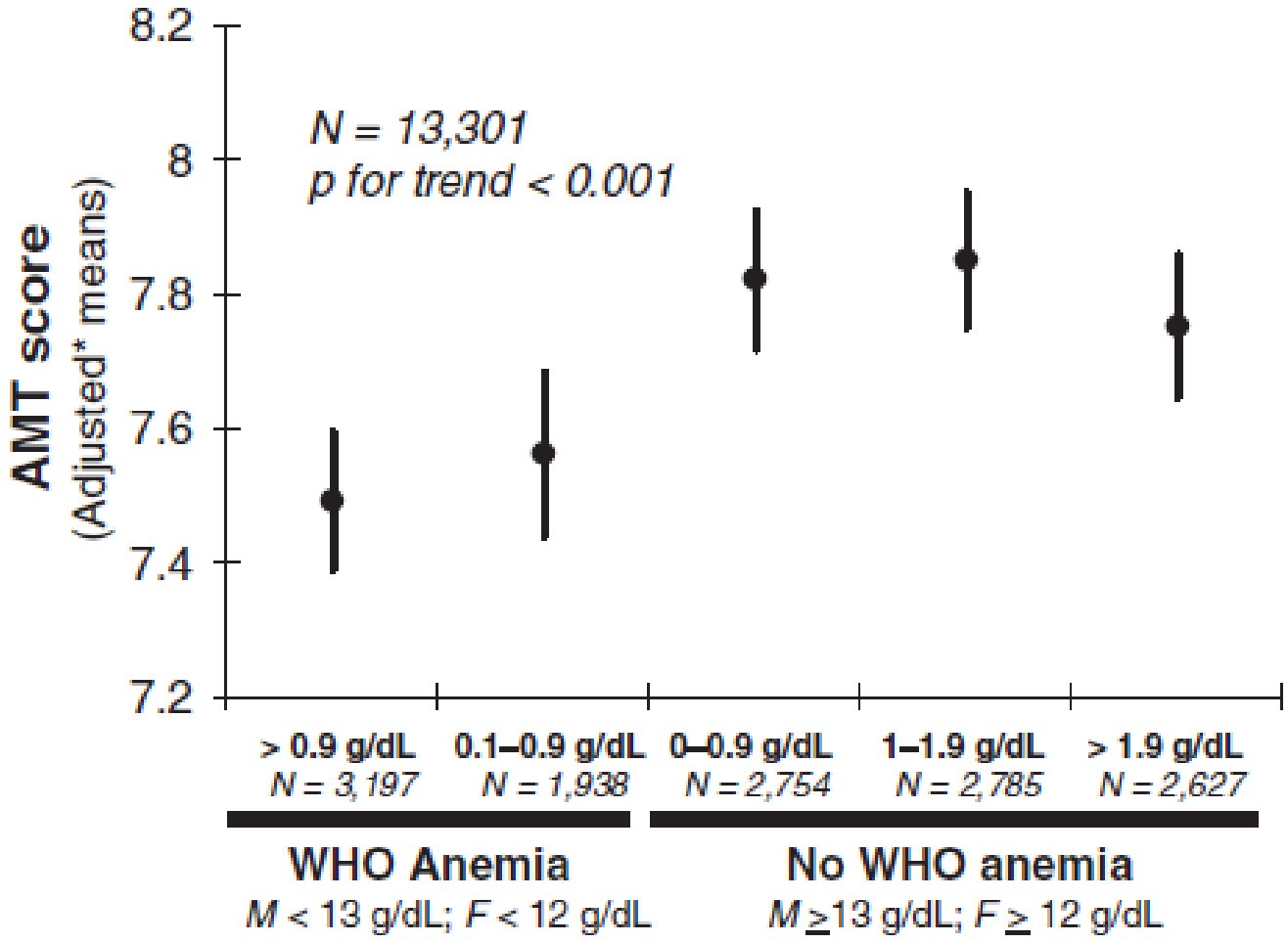


Figure 1. Adjusted* AMT mean scores (and 95% confidence intervals) for different hemoglobin levels, above and below the WHO anemia cut-points

Int J Geriatr Psychiatry 2006; 21: 529–534.

Table 2
Risk of dementia over 3 years of follow-up due to anaemia (WHO criteria)

	Dementia		HR (95% CI)		
	Anaemia, *n* (%)	Non anaemia, *n* (%)			
All subjects	25 (21.6)	170 (15.5)	1.6 (1.1–2.4)[a]	1.5 (1.0–2.3)[b]	1.3 (0.8–2.0)[c]
Subjects with MMSE score <26	9 (30.0)	78 (35.7)	0.8 (0.4–1.7)[a]	0.7 (0.4–1.5)[b]	0.7 (0.4–1.5)[c]
Subjects with MMSE score ≥26	16 (18.6)	92 (10.4)	2.1 (1.2–3.6)[a]	2.2 (1.3–3.8)[b]	2.2 (1.3–3.7)[c]

[a] Unadjusted.
[b] Sex, age, and education adjusted.
[c] Sex, age, education, and MMSE adjusted.

Am J Med 2006; 119(4):327-334

Oorzaken

- Nutritionele anemie (~15%)
  - ijzer-, foliumzuur- en vitamine B12-deficiëntie
- Anemie bij chronische aandoeningen (~10%)
  - Hartfalen
  - Maligniteiten
  - AI aandoeningen
- Anemie bij Chronische nierinsufficiëntie (~4%)
- Hematologische maligniteiten/ Myelodysplastisch syndroom (~22%)
- Thalassemie / sickle cell anemie / andere (~10%)
- Unexplained (~35%)

Unexplained

- Uitsluitingsdiagnose
- Leeftijdsgebonden progressief verlies van hematopoietische stamcelactiviteit
- Verminderde gevoeligheid van de stamcel op EPO
  - Verhoogde EPO productie bij normale veroudering
  - Lagere EPO productie bij anemie (uitz ijzerdeficiëntie)
- Chronische subklinische pro-inflammatoire status
  - Ijzerrestrictie en blunted EPO response

Welke bijkomende onderzoeken zou je plannen ?

Table 5. Classification of Anemia According to the MCV.

Low MCV (<80 fL)	Normal MCV (80-99 fL)	High MCV (>100 fL)
Thalassemic syndromes*	ACD	Folate or vitamin B_{12} deficiency
IDA	Anemia of CKD	Alcohol
IRIDA	Sickle cell disease	Chronic liver disease
Sideroblastic anemia	Myelodysplasia	MDS
	Combined deficiency (for example iron + folate)	Reticulocytosis

*β- and α-thalassemia.
ACD: anemia of chronic disease; CKD: chronic kidney disease; IDA: iron deficiency anemia; IRIDA: iron refractory iron deficiency anemia; MDS: myelodysplastic syndromes; HbE, Hb Lepore.

Reticulocytenindex

- Reticulocyten
  - 11,2 / 1000
  - RI = 0,79 (hypoproliferatief)

$$RI = \frac{\text{Reticulocytes percentage}(\%) \times \text{Ht}(\%)}{\text{Normal} \cdot \text{Ht}(\%)^{*}}$$

*(45% is usually used as a normal hematocrit).

Vitamine B12 - deficiëntie

- Prevalentie bij ouderen: 10-20% bij 60-plussers
- Gevolgen (jaren!):
  - Macrocytaire anemie
  - Neuropsychologische afwijkingen
- Oorzaken:
  - < IF deficiëntie
  - >> malabsorptie van voedsel-EW-vitamine B12-complex
    - Oorzaak: achloorhydrie, vaak in associatie met atrofische gastritis, voortvloeiend uit bestaande of doorgemaakte H. Pylori infectie

Foliumzuurdeficiëntie

- Prevalentie bij ouderen: 5-10%

- Gevolgen (4-5 maand):
  - Macrocytaire anemie

- Oorzaken:
  - Deficiënte inname
  - Alcoholabusus
  - Interactie met medicatie (trimethoprim, methotrexaat, phenytoïne)

IPSS-R Cytogenetic risk groups*,**

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

Variables (units) [usual range]	Value
Hemoglobin (g/dL) [4-20] A possible conversion for Hb values: 10 g/dL= 6.2 mmol/L, 8 g/dL= 5.0 mmol/L	10.8
Absolute Neutrophil Count ($x10^9$/L) [0-15]	2 420
Platelets ($x10^9$/L) [0-2000]	96 000
Bone Marrow Blasts (percent) [0-30]	0

Cytogenetic Category

(•) Very Good ( ) Good ( ) Intermediate ( ) Poor ( ) Very Poor

IPSS-R SCORE	1.5
IPSS-R CATEGORY	very low

Calculate

Age-adjusted calculation of risk (IPSS-RA):
(only for survival estimation)

Age 86 **Years**

IPSS-R SCORE	1.26

Table 1
Overall survival (OS) and risk of AML evolution by revised IPSS score

Risk Group	IPSS-R Score	Median OS (y)	Median Time to 25% AML Evolution (y)
Very low	<1.5	8.8	>14.5
Low	<1.5–3.0	5.3	10.8
Intermediate	>3–4.5	3.0	3.2
High	>4.5–6	1.6	1.4
Very high	>6	0.8	0.7

Abbreviation: IPSS-R, Revised International Prognostic Scoring System.

Data from Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012;120(12):2454–65.

Clin Geriatr Med 2016;155-173

Behandeling MDS

Table 2
Treatment options for older adults with MDS based on disease and patient characteristics

Disease Characteristics (IPSS-R)	Goal of Therapy	Patient Characteristics	Treatment Considerations (Comments)
Very low risk, low risk. Asymptomatic	Improve QOL	Any	Observation (evidence is lacking to support QOL or survival advantage with early therapy)
Very low/low/intermediate. Symptomatic			
5q deletion	Improve QOL	Any	Lenalidomide (understudied in vulnerable/frail patients. Dose adjust for impaired creatinine clearance)
Absence of 5q− with erythropoietin level <500 uM/mL	Improve QOL	Any	Erythropoietin ± GCSF (discontinue if no response in 8 wk) Consider lenalidomide (especially if isolated anemia)
	Improve QOL	Good PS/minimal comorbidity	Consider hypomethylating agents (observational data suggest benefit in lower risk MDS)
Intermediate/high/very high	Delay progression, extend life	Any age, good PS, absence of major comorbidity	Hypomethylating agents (strongest evidence supports use of 7-d azacitidine regimen)
	Cure	Age 60–75 y, excellent PS, absence of major comorbidity	Consider referral for RIC HSCT vs hypomethylating agents (comprehensive GA may help inform fitness, randomized data to support benefits of HCST are lacking)
	Delay progression, extend life	Poor PS and/or major comorbidity	Consider hypomethylating agents vs supportive care (absence of data in frail patients; however, given potential to improve survival and QOL, would discuss with patient)

Abbreviations: GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; PS, performance status; RIC, reduced-intensity conditioning.

Adapted from Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. J Clin Oncol 2014;32(24):2541–52.

Clin Geriatr Med 2016;155-173

Behandeling MDS

Table 3
Selected randomized treatment trials for MDS

Treatment	N	Disease Risk Category	Positive Outcomes	Toxicity
Azacitidine[16] 75 mg/m^2 SQ × 7 d Q 4 wk vs supportive care	191	IPSS Int-1/Int-2/high	Improved response rate (23% vs 5%) Improved time to AML or death (21 vs 13 mo) Decreased AML transformation (15% vs 38%) Improved QOL (physical function, symptoms, psychological state)	Grade 3–4 myelosuppression (43%–58%) Infection (20%)
Azacitidine[15] 75 mg/m^2 SQ × 7 d Q 4 wk vs conventional care (supportive, low-dose cytarabine, intensive chemotherapy)	358	IPSS Int-2 or high	OS (median 24.5 vs 15 mo)	Myelosuppression
Decitabine 15 mg/m^2 IV Q 8 h for 3 d Q 6 wk vs supportive care[20]	170	IPSS Int or high	Response rate (17% vs 0%) Improved QOL (global health, fatigue, dyspnea)	Dose reductions/delays (35%) Grade 4 myelosuppression (>50%)
Lenalidomide 10 mg/d days 1–21 vs 5 mg/d days 1–28 vs placebo on 28-d cycle[21]	205	MDS with del5q31 IPSS low or Int-1 RBC transfusion dependence	RBC transfusion independence for ≥26 wk (56.1% vs 42.6% vs 5.9%) RBC transfusion independence >8 wk associated with decreased risk of death and AML progression	Myelosuppression in first 2 cycles DVT (5.8%) in 10-mg group

Abbreviations: DVT, deep venous thrombosis; ECOG, Eastern Cooperative Oncology Group; Int, intermediate; IV, intravenous; Q, every; RBC, red blood cell; SQ, subcutaneous.

Clin Geriatr Med 2016;155-173

Behandeling MDS

- Transfusie bij anemie
  - Geen evidentie via RCT beschikbaar

Authors' conclusions—This review indicates that there is currently a lack of evidence for the recommendation of a particular transfusion strategy for bone marrow failure patients undergoing supportive treatment only. The one RCT included in this review was only published as an abstract and contained only 13 participants. Further randomised trials with robust methodology are required to develop the optimal transfusion strategy for such patients, particularly as the incidence of the main group of bone marrow failure disorders, MDS, rises with an ageing population.

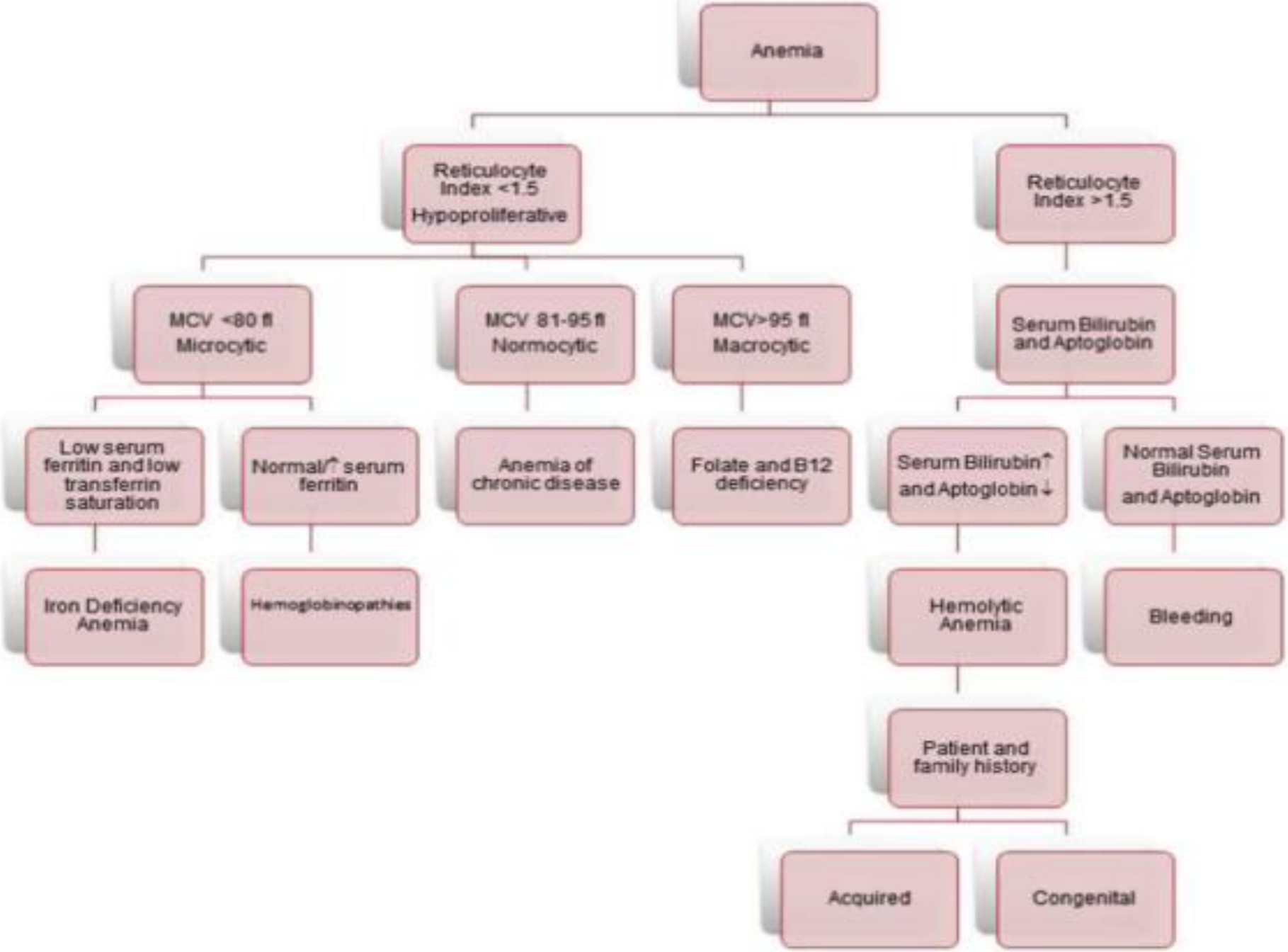
Cochrane Database Syst Rev 2015;10:CD011577

Table 6
Considerations for risk stratification and treatments for older adults with AML

Patient Risk Category	Characteristics	Treatment Considerations (Clinical Trials Preferred)
Frail	Poor oncology PS (ECOG PS score ≥3) Major comorbidity (ie, HCT-CI >2) Impairment in ADLs	High treatment-related mortality (particularly for adults >75 y old) Favorable tumor biology*: consider lower intensity therapy (HMAs, low-dose Ara-C). Patients with poor PS (particularly aged 60–75 y) but without end-stage comorbidity may consider intensive treatment if risks/benefits are consistent with goals of care Intermediate/unfavorable: consider best supportive care, including palliative care consultation if available vs lower intensity therapy (HMAs, low-dose Ara-C) Clinical trials targeting frail patients are needed; randomized evidence is lacking
Vulnerable	ECOG PS score 0–2 Absence of major comorbidity (HCT-CI ≤2) Presence of: Impairment in IADLs/self-reported mobility Impaired physical performance (SPPB <9) Impaired cognition (3MS score <77) High symptom burden (fatigue, pain)	Outcomes for this subgroup are poorly defined in clinical trials because of lack of characterization. In nonrandomized studies this group is at risk for shorter survival compared with fit patients Favorable tumor biology: consider intensive therapy Intermediate/unfavorable: consider intensive therapy if risks and benefits are consistent with goals of care vs lower intensity therapies (HMAs, low-dose Ara-C) Consider enhanced supportive care targeting vulnerabilities such as early physical therapy for impaired mobility Clinical trials are needed to validate definitions of vulnerability and to test treatment and supportive care strategies to improve outcomes in this group
Fit	ECOG PS score 0–1 Minimal comorbidity (ie, HCT-CI <1) Absence of any risk factors mentioned earlier	Best evidence suggests fit older adults derive benefit from aggressive therapy Favorable tumor biology: intensive therapy should be offered Intermediate/unfavorable: consider intensive treatment with possible RIC allogeneic HSCT if risks/benefits consistent with goals of care vs lower intensity therapies (HMAs, low-dose Ara-C) Future clinical trials should compare investigational therapies with standard intensive treatment among fit older adults

Abbreviations: Ara-C, cytarabine; HMA, hypomethylating agent; IADLs, instrumental ADL; TRM, treatment-related mortality.

* Favorable tumor biology: inv(16), t(16;16), t(8;21), t(15;17). Intermediate risk: normal cytogenetics, +8 alone, t(9;11), other nondefined. Unfavorable: complex (≥3 clonal abnormalities), −5, 5q−, −7, 7q−, abnormalities of 11q, inv(3), t(3;3), t(6;9). In the normal cytogenetic category, NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation confers better risk than the presence of FLT3-ITD, which confers worse risk.



Cappellini et al. Semin hematol 2015; 261-269

Figure 1. Diagnostic work-up for anemia.

Table 8. Serum Parameters in Differential Diagnosis of Anemia of Chronic Disease, Iron Deficiency Anemia, and Both Conditions[65]

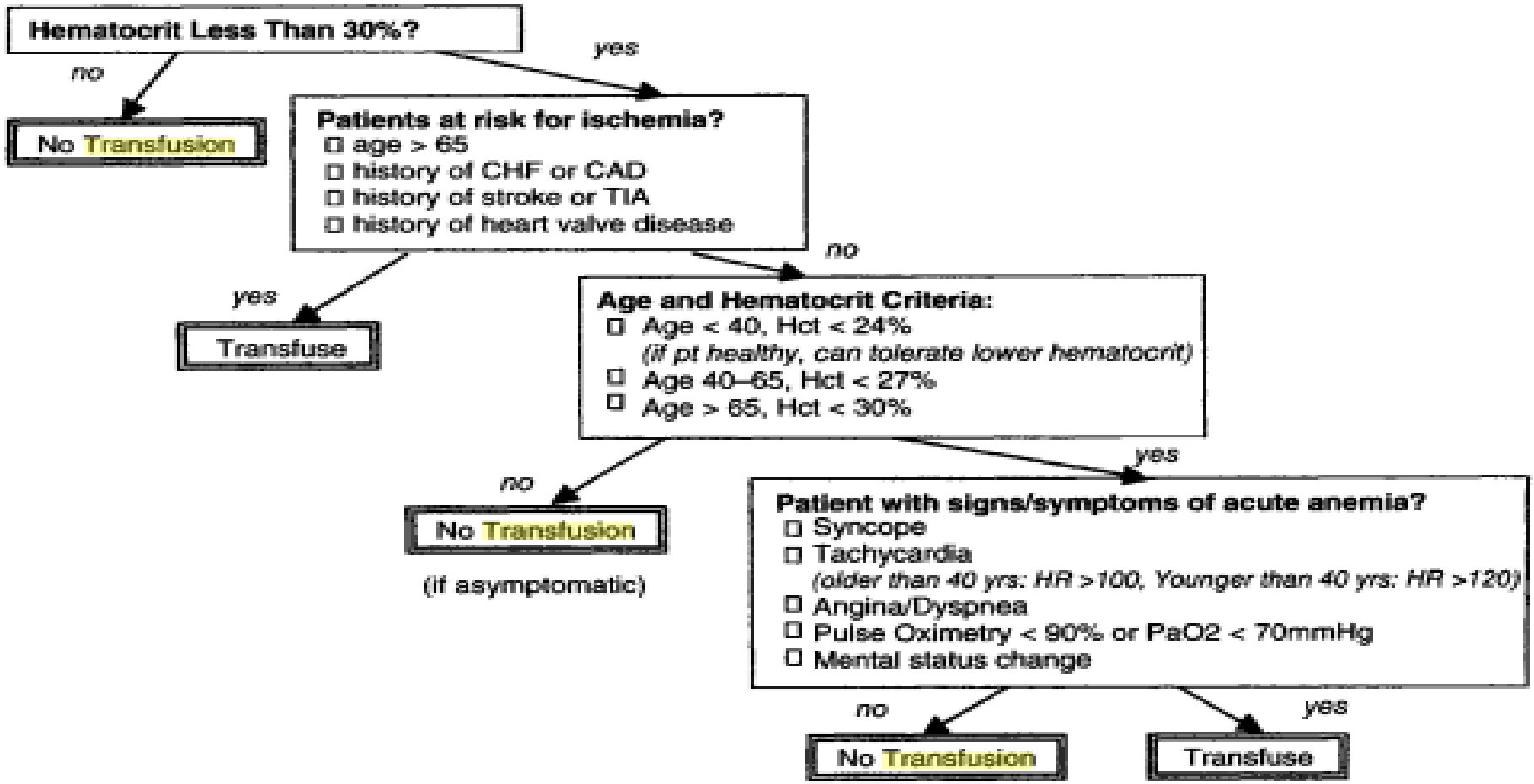
	ACD	IDA	ACD Associated to IDA
Iron	↓	↓	↓
Transferrin	↓/N	↑	↓
Transferrin saturation	↓	↓	↓
Ferritin	N/↑	↓	↓/N
sTR	N	↑	N/↑
STR/logFerritin	↓(<1)	↑(>2)	↑(>2)
Cytokine lebels	↑	N	↑

sTr: soluble transferrin receptor; ACD: anemia of chronic disease; IDA: iron deficiency anemia; N: normal.

Cappellini et al. Seminar hematol 2015; 261-269

- **In patient WITH acute blood loss, consider RBC Transfusion if...**

- **In patient WITHOUT acute blood loss, consider RBC Transfusion if...**



Surgery: Basic Science And Clinical Evidence Jeffrey A. Norton, Philip S. Barie, Randall Bollinger

Recommendations. The task force bases its recommendations on available category II-2 and II-3 evi-

that (1) transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute; (2) the deter-

fusion should be based on the patient's risk for com-

especially when the anemia is acute; (2) the determination of whether intermediate hemoglobin concentrations (6–10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation; (3) the use of a

liberate hypotension and pharmacologic agents) may be beneficial; and (5) the indications for transfusion of autologous RBCs may be more liberal than for allogeneic RBCs because of the lower (but still significant) risks associated with the former.

Anesthesiology 1996. 84: 732

Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB

- Recommendation 1: The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

- Recommendation 2: The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

Carson et al. Ann Int Med 2012;157:49-58

Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB

- Recommendation 3: The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

- Recommendation 4: The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).

Carson et al. Ann Int Med 2012;157:49-58

Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB

- The strength of the recommendations included in these guidelines is limited by the paucity of clinical trial data in certain patient populations. The results of the 3 largest trials … do not include patients from many other populations who frequently receive transfusions. Clinical trials are needed in other patient populations that include patients with the acute coronary syndrome, elderly medical patients recovering from illnesses that result in hospitalization, …

Carson et al. Ann Int Med 2012;157:49-58

KEY FINDINGS

Among chronic kidney disease (CKD) patients with iron deficiency anemia (IDA), oral heme iron polypeptide (HIP) was comparably effective compared with intravenous (IV) iron preparations or oral ferrous sulfate to improve hemoglobin levels and transferrin saturation. However, both IV iron and oral ferrous sulfate improved serum ferritin levels to a significantly higher level than HIP in CKD patients with IDA.

Canadian agency for drugs and technology in health – oral iron for anemia; 06/01/2016

EPO bij ouderen met anemie

- Mogelijke indicaties
  - CKD stadium 3 en 4
  - Hartfalen
  - Chronische aandoeningen

CKD en EPO

MAIN RESULTS: Nineteen studies (enrolling 993 participants) were included. Due to the age of the included studies (most performed prior to 2000) the risk of bias was judged to be unclear in the majority of the studies for most of the domains. There was an improvement in haemoglobin (MD 1.90 gm/L, 95% CI -2.34 to -1.47) and haematocrit (MD 9.85%, 95% CI 8.35 to 11.34) with treatment and a decrease in the number of patients requiring blood transfusions (RR 0.32, 95% CI 0.12 to 0.83). The data from studies reporting quality of life or exercise capacity demonstrated an improvement in the treatment group. Most of the measures of progression of kidney disease showed no statistically significant difference. No significant increase in adverse events was identified.

Cody et al. Cochrane 2016; 1: CD003266

Hartfalen en EPO: controversieel

Table 1 Randomized, controlled trials on ESA administration in patients with anemia and heart failure

Study	N	ESA versus control	Iron	Follow-up (months)	End point	Conclusion
Silverberg et al, 2000[40]	26	Epoetin alfa	Yes	7±5	NYHA class, LVEF, decrease in diuretic dose and hospitalizations	An increase in Hb was associated with an improvement in NYHA functional class and LVEF and a decrease in diuretic dose and hospitalization.
Mancini et al, 2003[41]	23	Epoetin alfa versus placebo	Yes	3	Exercise capacity, vasodilatatory function	EPO therapy was associated with significant increase in Hb values from 11.0±0.5 to 14.3±1.0 g/dL, with a concomitant increase in 6MWD and peak oxygen uptake (11.0±1.8 to 12.7±2.8 mL/min per kilogram, $P<0.05$).
Palazzuoli et al, 2007[42]	51	Epoetin beta versus placebo	Yes	12	Primary: LV dimensions, LVEF, Hb, Cr, BNP Secondary: cardiac events (sudden death, hospitalization, MI), weight, edema, NYHA	Hb increased; LV dimensions, volume, and mass decreased; and LVEF increased in the epoetin group with no change in the control group. The pulmonary artery pressure and BNP blood levels also decreased as well as the need for hospitalization in patients treated with EPO.
Ponikowski et al, 2007[43]	41	Darbepoetin alfa versus placebo	Yes	6	Primary: exercise capacity Secondary: change in peak VO_2, exercise duration, Hb, NYHA, QOL, BNP, weight, hospitalization	No differences were revealed regarding peak VO_2, exercise duration, BNP, and renal function between treatment groups.
van Veldhuisen, 2007[44]	165	Darbepoetin alfa versus placebo	Yes	6	Primary: rate of rise in Hb Secondary: change in LVEF, 6MWD, NYHA, QOL, PGA	The rate of Hb rise was equivalent between darbepoetin alpha weight-based and fixed dosing groups. There were nonsignificant improvements in the combined darbepoetin alfa group versus placebo for 6MWD ($P=0.074$) and PGA ($P=0.057$).
Ghali et al, 2008[45] STAMINA-HeFT	319	Darbepoetin alfa versus placebo	Yes	12	Primary: change in exercise toleration Secondary: NYHA, QOL, time to death, first HF hospitalization	Darbepoetin treatment did not significantly improve exercise duration, NYHA class, or QOL score compared with placebo
Swedberg et al, 2013[46] RED-HF	2,278	Darbepoetin alfa versus placebo	Yes	28	Primary: all-causes mortality or first HF hospitalization Secondary: death from CV cause or first HF hospitalization, MI, stroke, HF hospitalization, SCD, QOL	There was no significant difference between the darbepoetin alfa and placebo groups for the primary composite outcome of death from any cause or first HF hospitalization. An increased rate of thromboembolic events was seen in the treated patients compared with placebo.

Abbreviations: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; Cr, creatinine; CV, cardiovascu [illegible] t ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; QOL, quality [illegible]

Therapeutics and clinical practice 2014;10:641-650

Behandeling van anemie bij chronische aandoeningen

- Beschikbare behandelingen: controversieel – individueel te bepalen
  - Transfusie
  - Ijzerpreparaten
  - EPO

- Behandelingen in de toekomst:
  - Blokkeren van hepcidin formatie of activiteit
  - Stimuleren van endogene EPO productie

Weiss et al. Semin hematol 2015;52:313-320