Figure 3. *ITPA* rs1127354 genotypes and the time-dependent incidence of RBV dose reduction.

The time to the first reduction of the RBV dose due to any reason (3a) or due to anemia (3b) is shown stratified by the rs1127354 genotypes. Solid and broken lines indicate patients with the AA/CA and CC genotypes, respectively. The AA/CA genotype protected against the requirement for RBV dose reduction. Patients were standardized according to the baseline Hb and CLcr (3c). Even after standardization by baseline Hb and CLcr , the AA/CA genotype protected against the requirement for RBV dose reduction.

Figure 4. Combination of the *ITPA* rs1127354 genotype, baseline Hb level, and baseline CLcr level is predictive of severe anemia (Hb <10 g/dl) during the therapy.

Patients with rs1127354 genotype CC (a) and AA/CA (b) were further stratified by the baseline Hb and CLcr levels. The percentage of patients with Hb concentrations of <10g/dl at any time point during therapy is shown for the subgroups of patients. Patients with baseline Hb levels of <14 g/dl and CLcr levels of <95 ml/min had a higher incidence of severe anemia among patients with the rs1127354 genotype CC (Hb <14 g/dl and CLcr

≤95 ml/min vs. Hb ≥14 g/dl and CLcr >95 ml/min, $p < 0.0001$; Hb <14 g/dl and CLcr ≤95 ml/min vs. Hb <14 g/dl or CLcr ≤95 ml/min, $p = 0.0036$).

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Tables

Table 1. Clinical characteristics of the study population

Age	57.5 (9.5)
Sex (M/F)	50/82
Baseline platelet count (10^9/L)	150.4 (55.8)
Baseline Hb (g/dl)	14.0 (1.5)
Baseline creatinine clearance (ml/min)	94.8 (24.1)
Baseline liver fibrosis (F0-2/F3-4)	102/30
Initial ribavirin dose (n, %)	
600 mg/day	91 (69%)
800 mg/day	38 (29%)
1000 mg/day	3 (2%)
Dose reduction of ribavirin (n, %)	58 (43%)
Hb reduction at week 4 (g/dl) (n, %)	2.2 (1.4)
Hb reduction >3.0 g/dl at week 4	37 (28%)
Severe anemia (Hb <10 g/dl) at week 4 (n, %)	21 (16%)
Severe anemia (Hb <10 g/dl) at any time point (n, %)	57 (43%)
ITPA rs1127354: AA/CA/CC	4/33/95
ISDR mutation: ≤1	96/114 (84%)
Core70 mutant type	42/105 (40%)

Continuous variables were described as mean (standard deviation) and categorical variables were described as frequency and percentage.

ISDR: Interferon sensitivity determining region

Table 2. Clinical characteristics of patients according to *ITPA* genotype

	rs1127354		p value
	AA/CA	CC	
Age	56.0 (10.9)	58.1 (8.8)	0.316
Sex (M/F)	17/20	33/62	0.239
Baseline platelet count (10^9/L)	153.3 (48.5)	149.2 (58.5)	0.711
Baseline Hb (g/dl)	14.3 (1.4)	13.8 (1.5)	0.132
Baseline creatinine clearance (ml/min)	93.4 (23.3)	95.3 (24.5)	0.692
Baseline liver fibrosis (F0-2/F3-4)	33/4	69/26	0.063
ISDR mutation: ≤1	26/30 (87%)	70/84 (83%)	0.777
Core70 mutant type	11/27 (41%)	31/78 (40%)	1.000

Continuous variables were described as mean (standard deviation).

Table 3. Multivariable regression analysis of factors associated with severe anemia (Hb < 10 g/dl) during therapy.

	Odds ratio	95%CI	P value
At week 4			
Baseline Hb: <14g/dl	7.18	1.90-27.09	0.004
Baseline creatinine clearance: ≤95ml/min	5.30	1.39-20.26	0.015
ITPA rs1127354: CC	10.17	1.25-82.85	0.030
At any time point			
Baseline Hb: <14g/dl	7.67	3.07-19.12	<0.0001
Baseline creatinine clearance: ≤95ml/min	5.51	2.21-13.73	<0.0001
ITPA rs1127354: CC	9.66	3.11-29.95	<0.0001

Table 4. Prediction model for severe anemia and recommendation for monitoring and treatment.

ITPA genotype (rs1127354)	Baseline Hb and CLcr	Risk of anemia	Recommendation	
			Monitoring	Treatment option
CC	Hb <14 g/dl and CLcr ≤95 ml/min	High	Intensive	Consider erythropoietin
	Hb <14 g/dl or CLcr ≤95 ml/min	Intermediate	Intensive	Early dose reduction of RBV
	Hb ≥14 g/dl and CLcr >95 ml/min	Low	As usual	
AA/CA	Hb <14 g/dl and CLcr ≤95 ml/min	Intermediate	Intensive	Early dose reduction of RBV
	Hb <14 g/dl or CLcr ≤95 ml/min	Low	As usual	
	Hb ≥14 g/dl and CLcr >95 ml/min	Absent	As usual	May consider higher RBV dose

Table 5. Treatment response and ribavirin adherence in terms of *ITPA* rs1127354 genotype

	rs1127354		p value
	AA/CA	CC	
All patients			
RBV adherence > 80%	19/37 (49%)	40/95 (42%)	0.436
End of treatment response	19/37 (49%)	58/95 (61%)	0.332
Sustained virological response	13/37 (35%)	26/95 (27%)	0.401
Relapse	6/19 (32%)	32/58 (55%)	0.112
Subgroup of patients; IL28B rs8099917 TT			
RBV adherence > 80%	14/18 (78%)	28/63 (49%)	0.016
End of treatment response	16/18 (89%)	50/63 (79%)	0.501
Sustained virological response	13/18 (79%)	26/63 (41%)	0.031
Relapse	3/16 (19%)	24/50 (48%)	0.046

Figure 1a

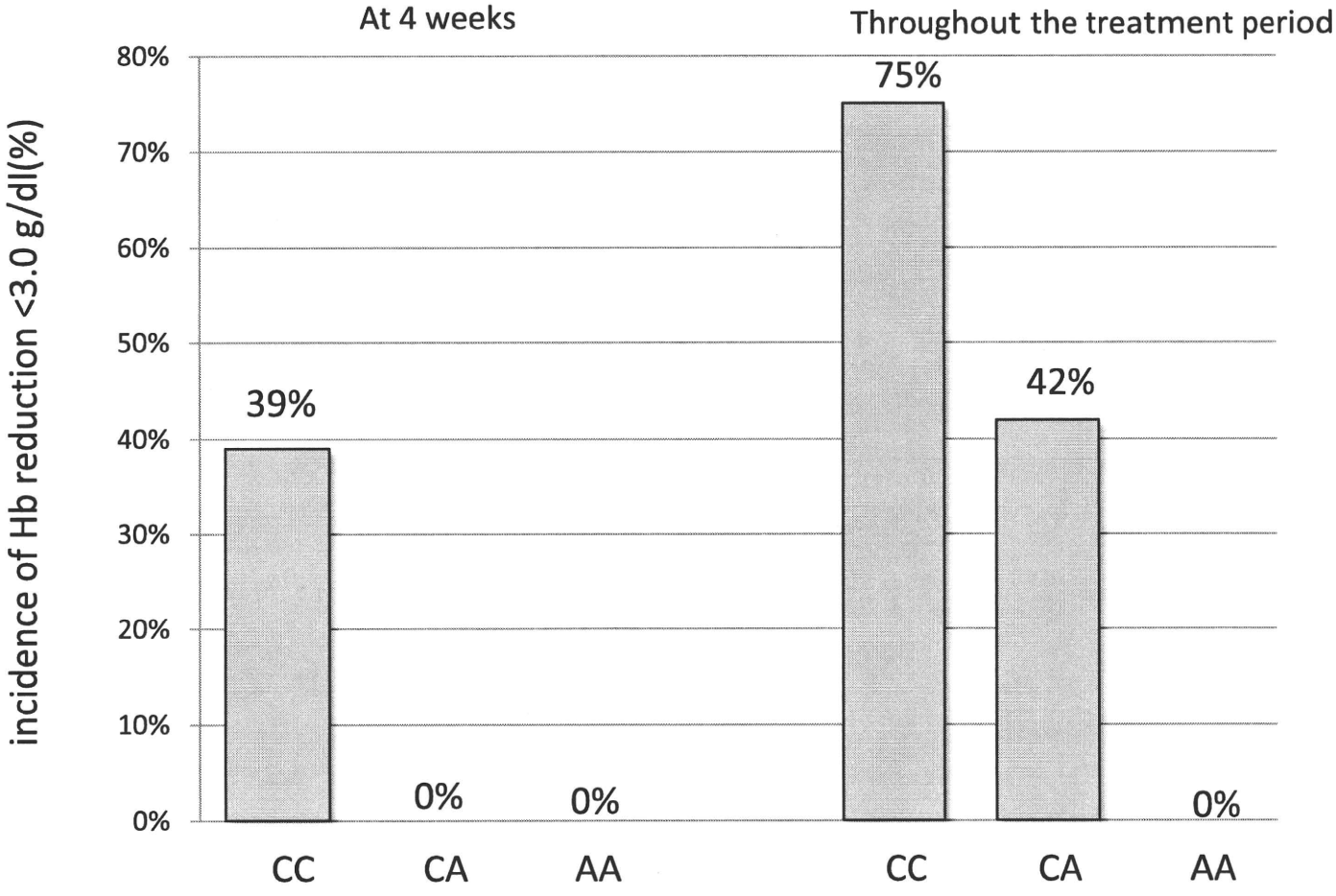

At 4 weeks
Throughout the treatment period
incidence of Hb reduction <3.0 g/dl(%)
80%
70%
60%
50%
40%
30%
20%
10%
0%
39%
0%
0%
75%
42%
0%
CC
CA
AA
CC
CA
AA

Figure 1b

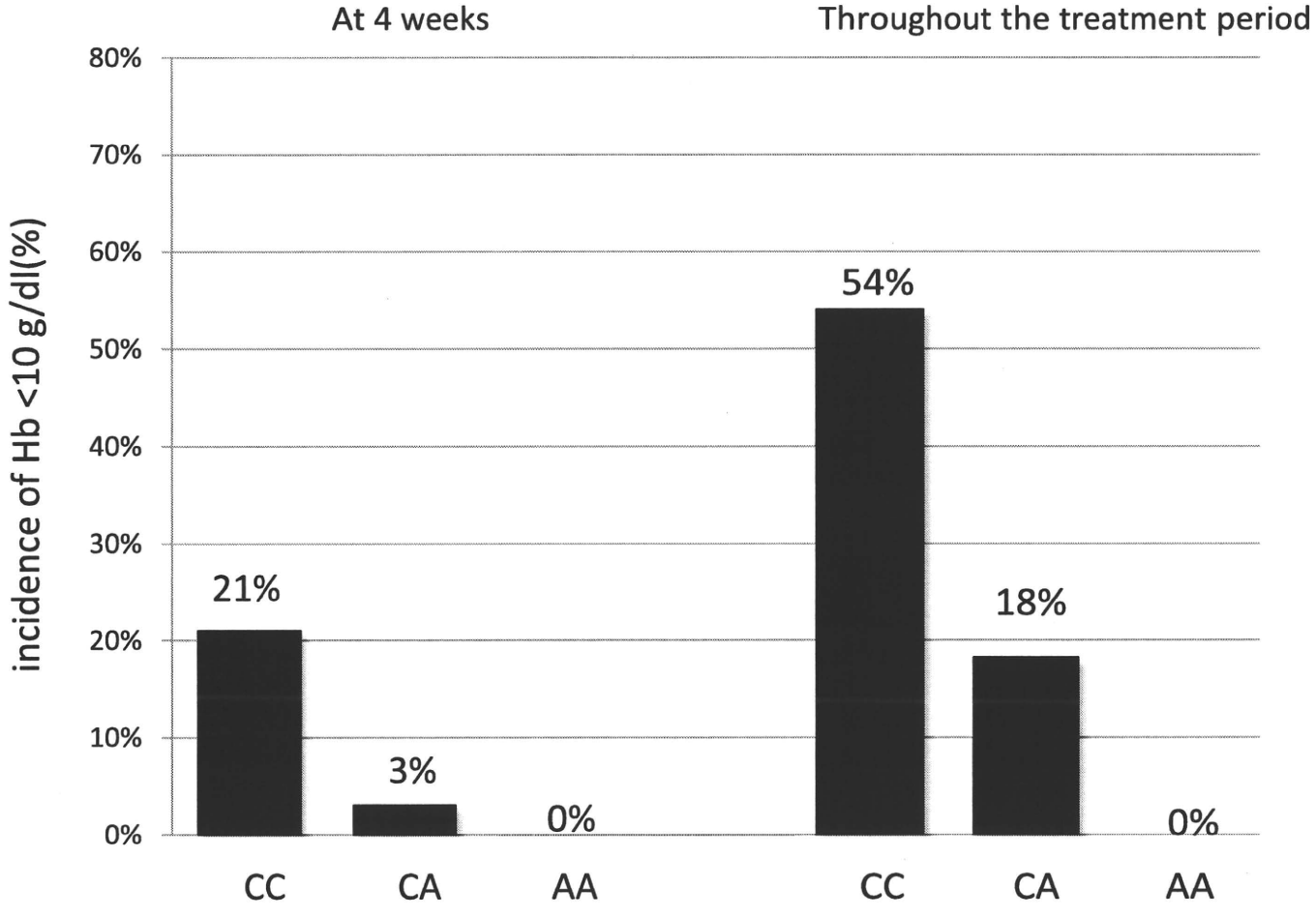

At 4 weeks
Throughout the treatment period
incidence of Hb <10 g/dl(%)
80%
70%
60%
50%
40%
30%
20%
10%
0%
21%
3%
0%
54%
18%
0%
CC
CA
AA
CC
CA
AA

Figure 2

* p<0.0001

** p=0.02

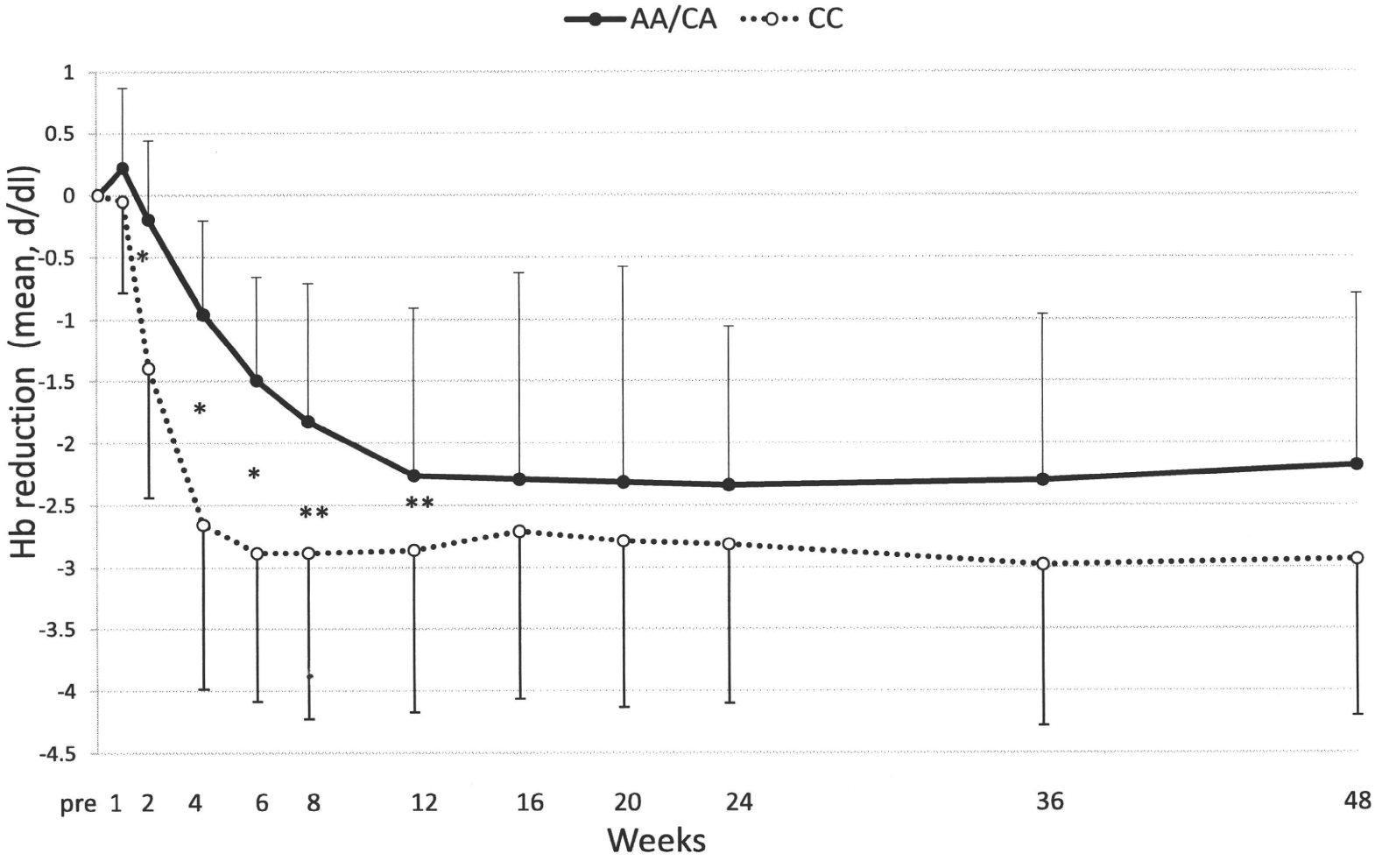


Figure 3a

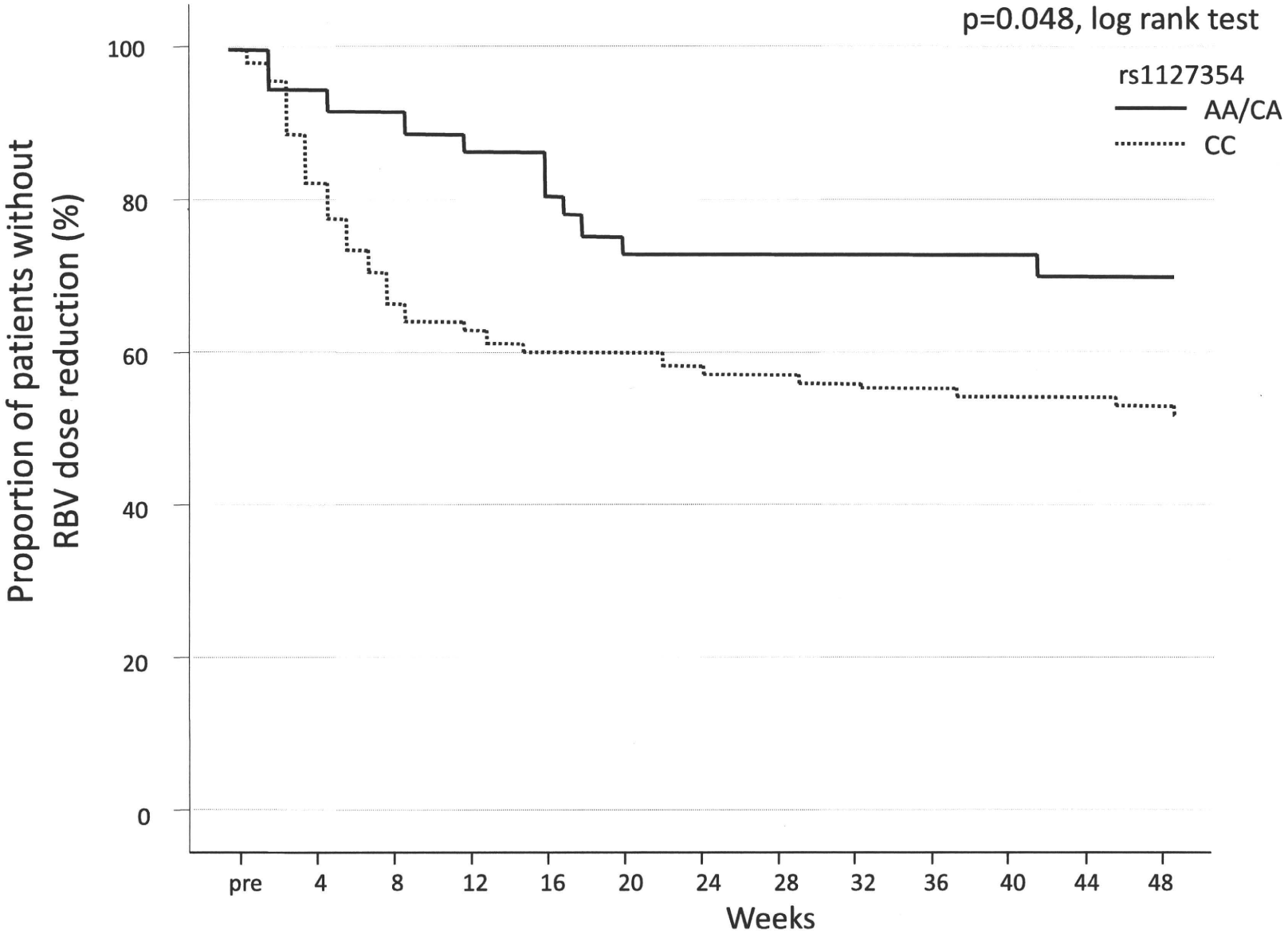

p=0.048, log rank test
rs1127354
AA/CA
CC
Proportion of patients without RBV dose reduction (%)
100
80
60
40
20
0
pre
4
8
12
16
20
24
28
32
36
40
44
48
Weeks

Figure 3b

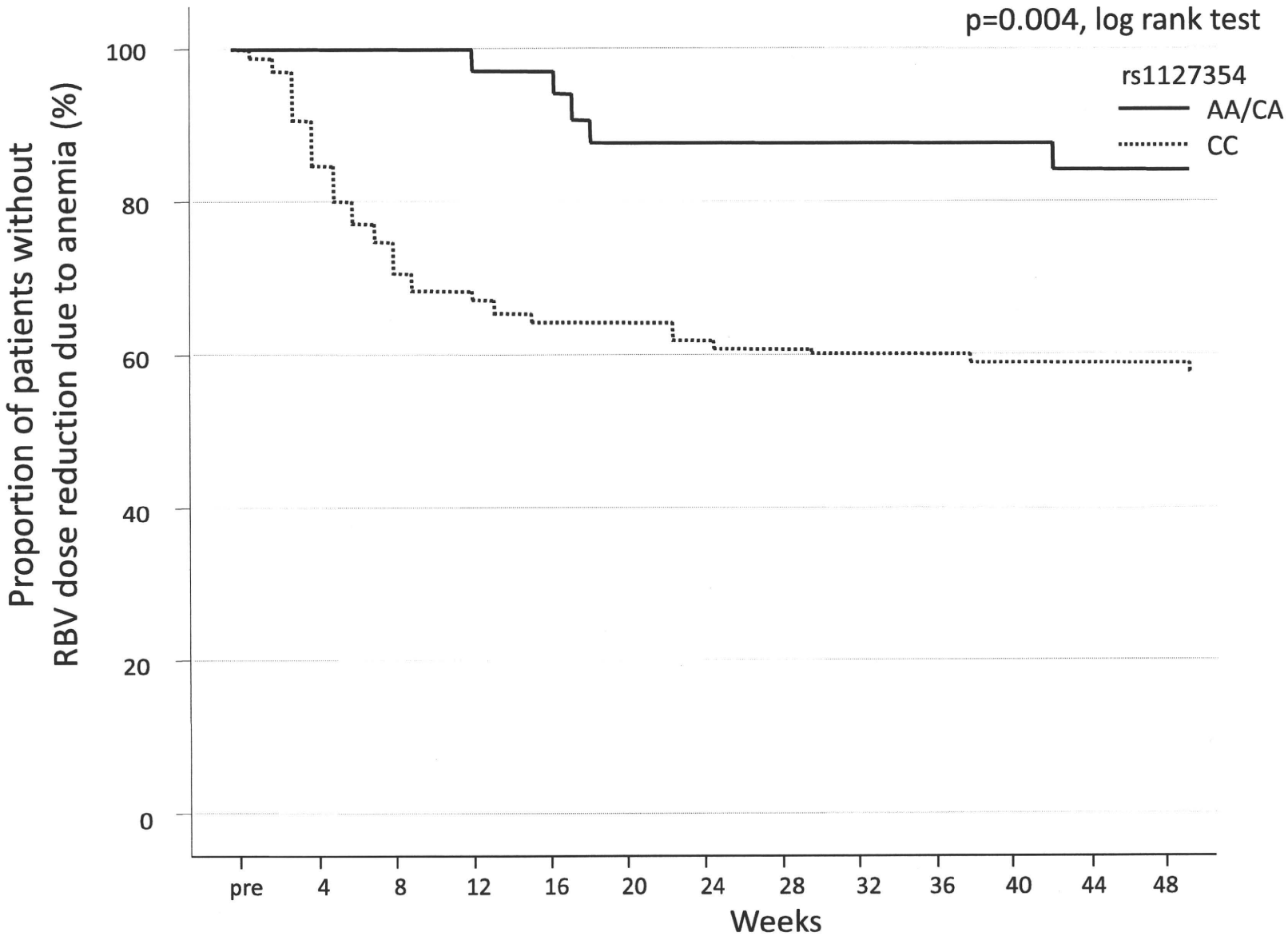
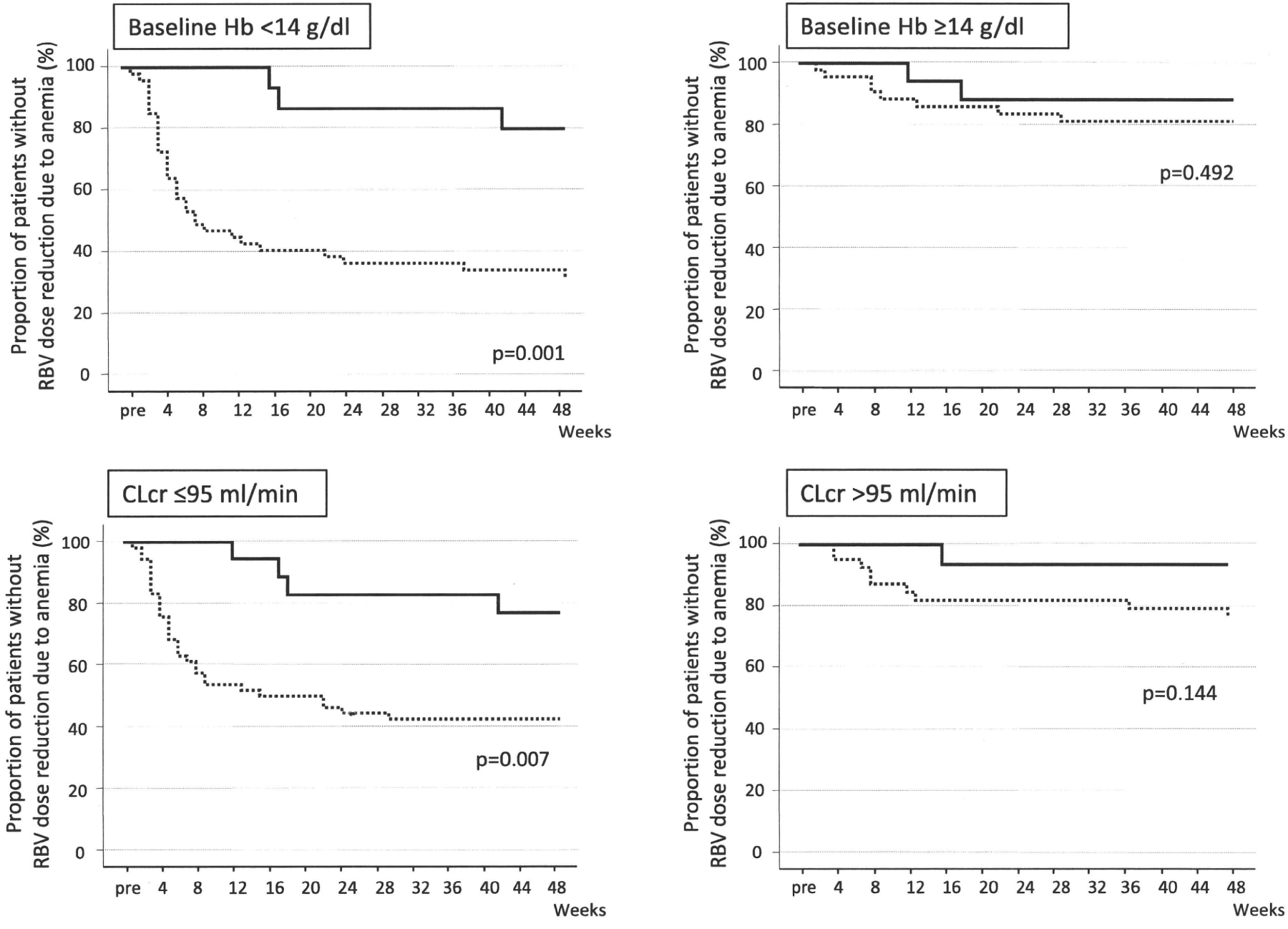

p=0.004, log rank test
rs1127354
AA/CA
CC
Proportion of patients without RBV dose reduction due to anemia (%)
100
80
60
40
20
0
pre
4
8
12
16
20
24
28
32
36
40
44
48
Weeks

Figure 3c


Baseline Hb <14 g/dl
Proportion of patients without RBV dose reduction due to anemia (%)
100
80
60
40
20
0
p=0.001
pre 4 8 12 16 20 24 28 32 36 40 44 48
Weeks
Baseline Hb ≥14 g/dl
Proportion of patients without RBV dose reduction due to anemia (%)
100
80
60
40
20
0
p=0.492
pre 4 8 12 16 20 24 28 32 36 40 44 48
Weeks
CLcr ≤95 ml/min
Proportion of patients without RBV dose reduction due to anemia (%)
100
80
60
40
20
0
p=0.007
pre 4 8 12 16 20 24 28 32 36 40 44 48
Weeks
CLcr >95 ml/min
Proportion of patients without RBV dose reduction due to anemia (%)
100
80
60
40
20
0
p=0.144
pre 4 8 12 16 20 24 28 32 36 40 44 48
Weeks