

Supporting information

Table S1 Doses in on-demand regimens of bypassing agents per bleeding site and severity.

Bleeding site	Severity	Average daily dose			
		aPCC		rFVIIa	
		Adults	Children	Adults	Children
Joints	Mild/moderate	75 U/kg	75 U/kg	180 µg/kg	195 µg/kg
	Severe	103 U/kg	103 U/kg	167 µg/kg	171 µg/kg
Muscle and soft tissues	Mild/moderate	67 U/kg	67 U/kg	150 µg/kg	160 µg/kg
	Severe	102 U/kg	116 U/kg	234 µg/kg	237 µg/kg
Mucocutaneous tissues	Mild/moderate	50 U/kg	50 U/kg	135 µg/kg	150 µg/kg
	Severe	96 U/kg	96 U/kg	234 µg/kg	240 µg/kg
Subcutaneous	Mild/moderate	50 U/kg	50 U/kg	180 µg/kg	210 µg/kg
Intracranial	Severe	106 U/kg	106 U/kg	229 µg/kg	230 µg/kg
Other areas	Mild/moderate	50 U/kg	50 U/kg	135 µg/kg	150 µg/kg
	Severe	103 U/kg	103 U/kg	167 µg/kg	171 µg/kg

aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII

References: Summary product characteristics (aPCC [18] and rFVIIa [19]), and Jiménez-Yuste et al. 2018 [17].

Table S2 Drug costs.

	Amount per vial	Ex-factory price (vial)	Ex-factory price-discount (unit)*
Emicizumab	30 mg	€2,486.00	€76.65/mg
	60 mg	€4,971.00	€76.64/mg
	105 mg	€8,700.00	€76.64/mg
	150 mg	€12,429.00	€76.65/mg
aPCC	500 U	€380.98	€0.70/U
	1000 U	€761.95	€0.70/U
rFVIIa	1000 µg	€558.51	€0.52/µg
	2000 µg	€1,117.63	€0.52/µg
	5000 µg	€2,889.26	€0.53/µg

aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII

Note: *Ex-factory price discounted according to Royal Decree Law 8/2010 deduction rate. Reference: Botplus [26]; Royal Decree Law 8/2010 deduction rate [27].

Table S3 Healthcare unit costs.

	Unit cost
Primary care physician visit	€50.06
Maxillofacial surgery	€88.30
Ultrasound	€63.75
Nurse visit	€45.72
Pharmacy visit	€88.30
Physiotherapy visit	€19.00
Hematology visit	€88.30
Hemogram and biochemistry	€57.30
Hospitalization	€212.90
Neurology visit	€88.30
Psychology visit	€88.30
X rays	€20.76
Rehabilitation visit	€88.30
Abdominal computerized tomography	€219.24
Cranial computerized tomography	€219.22
Chest-abdomen-pelvis computerized tomography	€312.33
Coagulation test	€4.77
Red blood cell transfusion	€110.55
Traumatology visit	€88.30
Emergency room visit	€182.25

References: Median value of the unit costs for Autonomous Communities [28], National Statistics Institute [24] and Ministerio de Sanidad, Consumo y Bienestar Social [29].

Table S4 Sensitivity analyses results of prophylactic treatments.

	Adult				Children			
	Minimum		Maximum		Minimum		Maximum	
	Value (€)	Change (%)	Value (€)	Change (%)	Value (€)	Change (%)	Value (€)	Change (%)
Emicizumab								
Length of bleeding events	522,741.57	-3.74	563,384.41	3.74	182,517.96	-0.14	183,010.90	0.14
Cost of visits, tests, and hospitalizations	542,871.36	-0.03	543,254.62	0.03	182,601.93	-0.08	182,926.93	0.08
Dose of aPCC	-	-	543,062.99	0.00	-	-	182,764.43	0.00
Patients' weight	489,518.70	-9.86	597,072.38	9.95	166,087.37	-9.15	199,679.33	9.28
Employed patients (adults)	-	-	543,106.62	0.01	-	-	182,764.43	0.00
Annual bleeding rate	532,858.39	-1.88	553,267.59	1.88	182,639.84	-0.07	182,889.02	0.07
Caregiver salary	542,614.91	-0.08	543,511.07	0.08	179,892.15	-1.54	185,636.71	1.54
aPCC								
Length of bleeding events	622,651.71	-5.11	689,637.52	5.11	251,542.08	-4.69	276,243.15	4.69
Cost of visits, tests, and hospitalizations	655,804.48	-0.05	656,484.75	0.05	263,408.87	-0.17	264,376.36	0.17
Dose of aPCC	-	-	831,592.85	26.75	-	-	331,127.65	25.55
Patients' weight	591,179.49	-9.91	721,197.65	9.92	239,454.36	-9.29	288,685.65	9.42
Employed patients (adults)	-	-	656,309.51	0.02	-	-	263,892.61	0.00
Annual bleeding rate	639,250.81	-2.57	673,038.42	2.57	257,581.81	-2.39	270,203.42	2.39
Caregiver salary	655,696.54	-0.07	656,592.69	0.07	261,020.33	-1.07	266,764.89	1.07
rFVIIa								
Length of bleeding events	767,079.18	-6.62	875,752.36	6.62	299,899.79	-6.24	339,753.39	6.24
Cost of visits, tests, and hospitalizations	821,075.63	-0.04	821,755.91	0.04	319,342.84	-0.14	320,310.33	0.14
Dose of aPCC	-	-	821,415.77	0.00	-	-	319,826.59	0.00
Patients' weight	742,552.26	-9.60	901,478.11	9.75	289,841.92	-9.40	349,859.60	9.41
Employed patients (adults)	-	-	821,588.44	0.02	-	-	319,826.59	0.00
Annual bleeding rate	794,100.12	-3.33	848,731.42	3.33	309,727.65	-3.16	329,925.52	3.16
Caregiver salary	820,967.70	-0.05	821,863.85	0.05	316,954.31	-0.88	322,698.87	0.88

aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII.

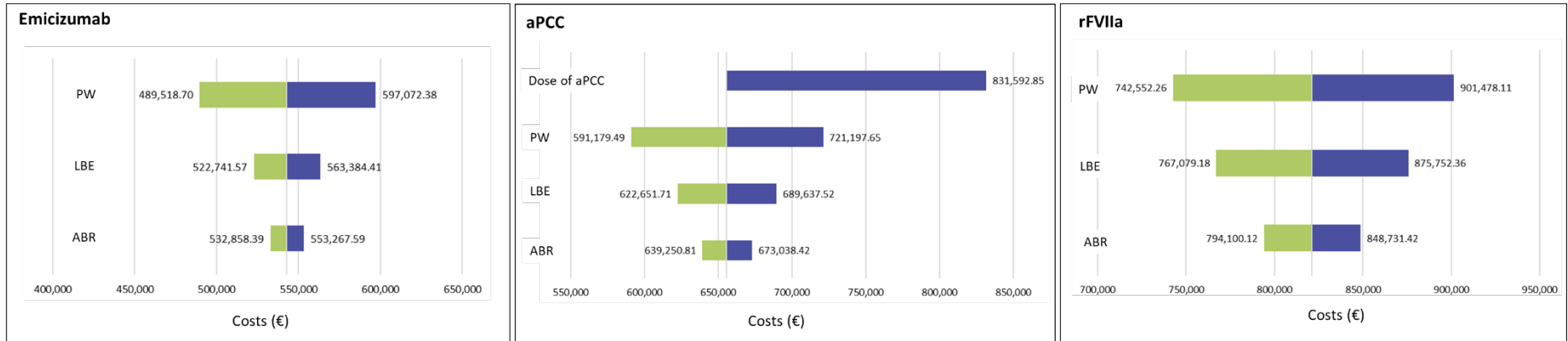
Table S5 Sensitivity analyses results of on-demand treatments.

	Adult				Children			
	Minimum		Maximum		Minimum		Maximum	
	Value (€)	Change (%)	Value (€)	Change (%)	Value (€)	Change (%)	Value (€)	Change (%)
aPCC								
Length of bleeding events	427,721.13	-19.73	637,692.54	19.73	138,066.81	-17.67	196,979.29	17.67
Cost of visits, tests, and hospitalizations	532,176.45	-0.09	533,237.22	0.09	166,935.01	-0.32	168,111.09	0.32
Dose of aPCC	-	-	532,706.84	0.00	-	-	167,523.05	0.00
Patients' weight	480,311.89	-9.84	585,173.72	9.86	152,810.86	-8.82	182,448.38	8.95
Employed patients (adults)	-	-	533,005.36	0.05	-	-	167,523.05	0.00
Annual bleeding rate	479,876.38	-9.92	585,537.29	9.92	152,555.09	-8.97	182,491.01	8.97
Caregiver salary	532,258.76	-0.08	533,154.91	0.08	164,650.77	-1.69	170,395.33	1.69
rFVIIa								
Length of bleeding events	633,029.19	-19.81	945,654.63	19.81	194,692.13	-18.36	281,917.29	18.36
Cost of visits, tests, and hospitalizations	788,811.52	-0.06	789,872.30	0.06	237,716.67	-0.23	238,892.75	0.23
Dose of aPCC	-	-	789,341.91	0.00	-	-	238,304.71	0.00
Patients' weight	713,552.96	-9.61	867,572.67	9.92	216,629.72	-9.13	259,610.43	8.97
Employed patients (adults)	-	-	789,640.43	0.04	-	-	238,304.71	0.00
Annual bleeding rate	710,847.95	-9.95	867,835.87	9.95	216,258.59	-9.27	260,350.83	9.27
Caregiver salary	788,893.83	-0.06	789,789.98	0.06	235,432.43	-1.18	241,176.99	1.18

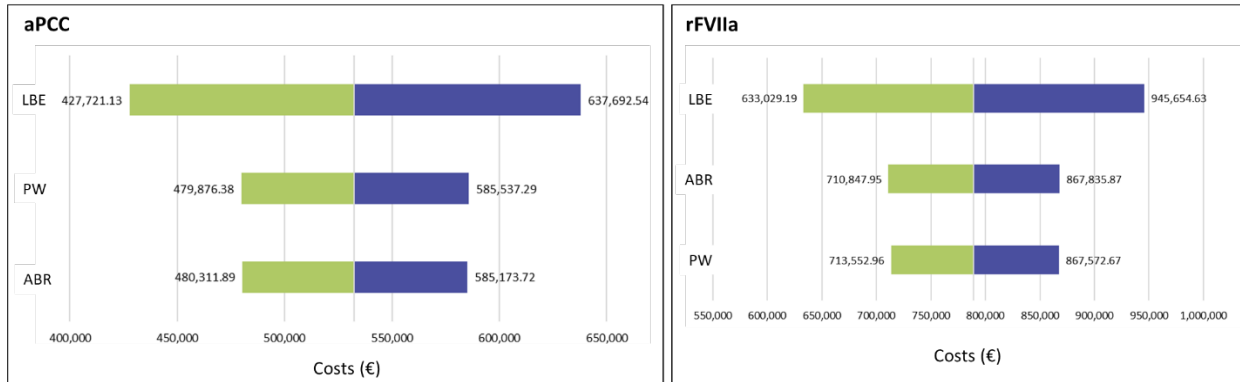
aPCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII.

Figure S1 Sensitivity analysis results in adult patients (Tornado diagrams).

PROPHYLACTIC TREATMENTS



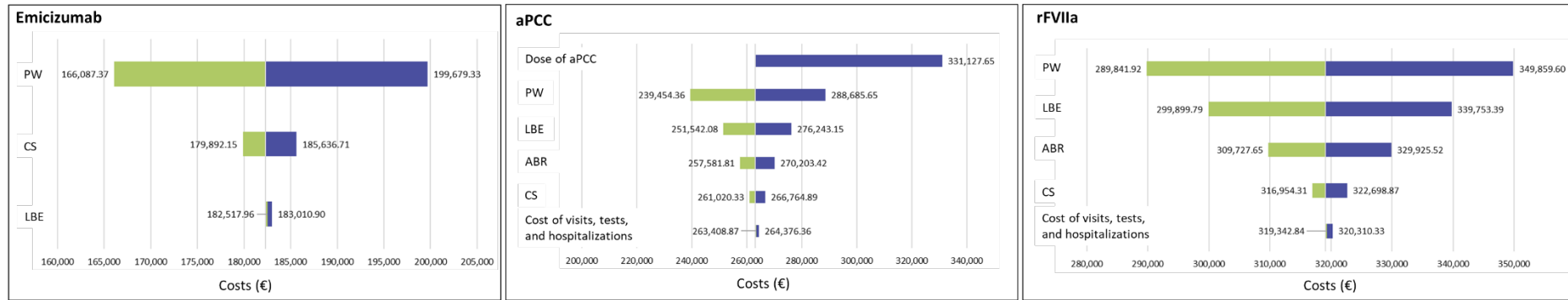
ON-DEMAND TREATMENTS



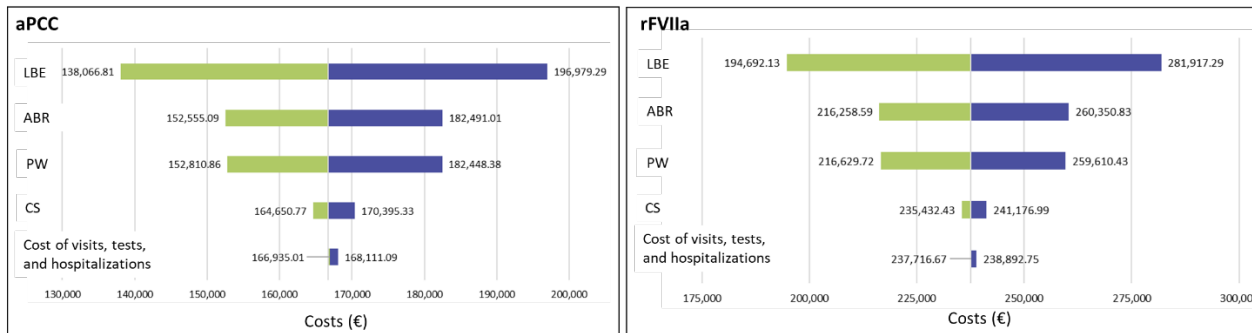
Note: Parameters that varied the base case results at least $\pm 0.1\%$. Abbreviations: aPCC: activated prothrombin complex concentrate; ABR: annual bleeding rate; LBE: length of bleeding events; PW: patients' weight. rFVIIa: recombinant activated factor VII.

Figure S2. Sensitivity analysis results in pediatric patients (Tornado diagrams).

PROPHYLACTIC TREATMENTS



ON-DEMAND TREATMENTS



Note: Parameters that varied the base case results at least $\pm 0.1\%$. Abbreviations: aPCC: activated prothrombin complex concentrate; ABR: annual bleeding rate; CS: caregiver salary; LBE: length of bleeding events; PW: patients' weight. rFVIIa: recombinant activated factor VII.