

Supplementary Table S1 Description of patients receiving a dual-pathway treatment and a tritherapy

	Hemophilia type	Hemophilia severity (FVIII/FIX %)	Age (y)	Cardiovascular disease	Antithrombotic type	Months of DPT/TT treatment	CHA ₂ DS ₂ -VAsc	HAS-BLED	Prophylaxis	Number of major bleeding events	Change for another antithrombotic drug?
Dual-pathway treatment	A	Mild (10%)	77	AF	ASA + VKA	18	4	4	No	2	No
	A	Mild (18%)	65	AF	ASA + VKA	24	3	1	No	1	No
Tritherapy	A	Mild (20%)	60	ACS + AF	ASA + CLOPI + VKA	6	2	1	No	1	Yes with VKA

Abbreviations: AF, atrial fibrillation; ACS, acute coronary syndrome; ASA, aspirin; CLOPI, clopidogrel; DPT, dual-pathway treatment; Tritherapy, 2 antiplatelet drugs + 1 anticoagulant drug; VKA, vitamin K antagonist.

Supplementary Table S2 Influence of different antithrombotic treatments on the risk of major bleeding events in patients with mild hemophilia

	Control	COCHE AT-	COCHE AT+	COCHE SAPT	COCHE DAPT	COCHE AC	COCHE DPT	COCHE TT
Mean ABR (95% CI)	0.044 (0-0.09)	0.133 (0-0.328)	0.361 (0.293-0.463)	0.232 (0.177-0.286)	0.517 (0.324-0.711)	0.353 (0.01-0.606)	1.143 (0.793-1.492)	2 (0-7.141)
n patients	48	6	48	34	12	10	2	1
n months	822	90	732	472	116	102	42	6
Control		0.31	0.11	0.18	0.09	0.12	0.03	0.02
(95% CI)		(0.03-3.06)	(0.03-0.36)	(0.05-0.68)	(0.02-0.36)	(0.02-0.59)	(0.007-0.16)	(0.002-0.2)
p		0.3313	<0.0001	0.0111	0.0013	0.0187	0.0001	0.0277
COCHE AT-			0.35	0.58	0.27	0.37	0.11	0.06
(95% CI)			(0.05-2.59)	(0.07-4.62)	(0.03-2.37)	(0.04-3.63)	(0.01-0.99)	(0.003-1.04)
p			0.505	0.7069	0.4044	0.624	0.0353	0.1217
COCHE AT+			2.89	2.19 ^a	0.75 ^a	1.09 ^a	0.27 ^a	0.16 ^a
(95% CI)			(0.39-21.66)	(0.89-5.34)	(0.27-2.03)	(0.32-3.7)	(0.09-0.83)	(0.02-1.4)
p			0.505	0.0988	0.5754	1	0.0379	0.1752

(Continued)

Supplementary Table S2 (Continued)

	Control	COCHE AT-	COCHE AT+	COCHE SAPT	COCHE DAPT	COCHE AC	COCHE DPT	COCHE TT
COCHE SAPT	OR	1.73	0.46 ^a		0.31	0.64	0.18	0.14
	(95% CI)	(0.22–13.83)	(0.19–1.12)		(0.11–0.85)	(0.17–2.41)	(0.05–0.63)	(0.02–1.3)
COCHE DAPT	<i>p</i>	0.7069	0.0988		0.0249	0.455	0.0161	0.1642
	OR	3.68	1.34 ^a	3.24		1.36	0.39	0.21
COCHE AC	(95% CI)	(0.42–32.05)	(0.49–3.66)	(1.18–8.9)		(0.32–5.85)	(0.1–1.54)	(0.02–2.12)
	<i>p</i>	0.4044	0.5754	0.0249		0.7341	0.2297	0.2478
COCHE DPT	OR	2.7	0.92 ^a	1.56	0.73		0.29	0.15
	(95% CI)	(0.28–26.41)	(0.27–3.14)	(0.41–5.86)	(0.17–3.15)		(0.06–1.35)	(0.01–1.73)
COCHE TT	<i>p</i>	0.624	1	0.455	0.7341		0.194	0.207
	OR	9.37	3.68 ^a	5.42	2.55	3.47		0.53
COCHE SAPT	(95% CI)	(1.01–86.65)	(1.2–11.32)	(1.59–18.41)	(0.65–9.97)	(0.74–16.26)		(0.05–5.7)
	<i>p</i>	0.0353	0.0379	0.0161	0.2297	0.194		0.5032
COCHE DAPT	OR	17.8	6.37 ^a	7.06	4.84	6.6	1.9	
	(95% CI)	(0.96–328.5)	(0.72–56.8)	(0.77–64.84)	(0.47–49.57)	(0.58–75.39)	(0.18–20.57)	
COCHE AC	<i>p</i>	0.1217	0.1752	0.1642	0.2478	0.207	0.5032	
	OR	0.0277						

Abbreviations: ABR, annualized bleeding rate; AC, anticoagulant drug alone; AT –, no antithrombotic treatment; AT +, antithrombotic treatment; CLOPI, clopidogrel; DAPT, dual antiplatelet treatment; DPT, dual-pathway treatment; SAPT, single antiplatelet treatment; TT, tritherapy with 2 antiplatelet drugs and 1 anticoagulant drug; VKA, vitamin K antagonist.

Note: Odds ratios were measured from row subgroups vs. column subgroups with the Fischer's exact test. Significance was set at $p < 0.05$ with 95% CI.

^aSubgroups with an AT were compared with all other subgroups with AT.

Supplementary Table S3 Influence of antithrombotic monotherapies on the risk of major bleeding events in patients with mild hemophilia

	Control	VKA	DOA	ASA	CLOPI	
Mean ABR (95% CI)	0.044 (0–0.09)	0.545 (0–1.165)	0	0.262 (0.092–0.432)	0.2 (0–0.6)	
<i>n</i> patients	48	6	4	30	4	
<i>n</i> months	822	66	36	412	60	
Control	OR		0.07	0.3	0.16	0.21
	(95% CI)		0.01–0.38	0.02–5.94	0.04–0.59	0.02–2.04
	<i>p</i>		0.0061	1	0.0031	0.2387
VKA	OR	13.48		4.02	2.13	2.81
	(95% CI)	2.66–68.17		0.2–80.15	0.56–8.09	0.28–27.78
	<i>p</i>	0.0061		0.55	0.22	0.6207
DOA	OR	3.33	0.25		0.58	0.54
	(95% CI)	0.17–65.62	0.01–4.95		0.03–10.21	0.02–13.71
	<i>p</i>	1	0.55		1	1
ASA	OR	6.32	0.47	1.72		1.32
	(95% CI)	1.7–23.48	0.12–1.78	0.1–30.15		0.16–10.59
	<i>p</i>	0.0031	0.22	1		1
CLOPI	OR	4.8	0.36	1.84	0.76	
	(95% CI)	0.49–46–85	0.04–3.52	0.07–46.42	0.09–6.1	
	<i>p</i>	0.2387	0.6207	1	1	

Abbreviations: ABR, annualized bleeding rate; ASA aspirin alone; CI, confidence interval; CLOPI, clopidogrel alone; DOA, direct oral anticoagulant alone; OR, odds ratio; VKA, vitamin K antagonist alone.

Note: Odds ratios were measured from row subgroups vs. column subgroups with the Fischer's exact test. Significance was set at $p < 0.05$ with 95% CI.

Supplementary Table S4 Summary of risk factors for major bleeding in antithrombotic-treated patients with hemophilia

Risk factor for major bleedings	Comments
Severity of hemophilia	Mean ABR is directly correlated with basal clotting factor levels up to 20%
Clotting factor treatment	Prophylaxis in severe and moderate hemophilia attenuates mean ABR compared with controls
Type of antithrombotic treatment	Mean ABR is for DPT > DAPT > SAPT (with insignificantly, DAPT ≥ AC ≥ SAP). Antiplatelet drugs can promote GIB
HAS-BLED score ≥ 3	Other patient-related parameters than hemophilia can promote bleeding (e.g., arterial hypertension, age > 65 years old or liver disease)

Abbreviations: ABR, annualized bleeding rate; AC, anticoagulant drug alone; DAPT, dual antiplatelet therapy; DPT, dual pathway therapy; GIB, gastrointestinal bleeding; HAS-BLED, hypertension, abnormal liver or renal function, stroke, bleeding history, labile INR, elderly (> 65 years old) and drugs/alcohol/tobacco use; SAPT, single antiplatelet therapy.