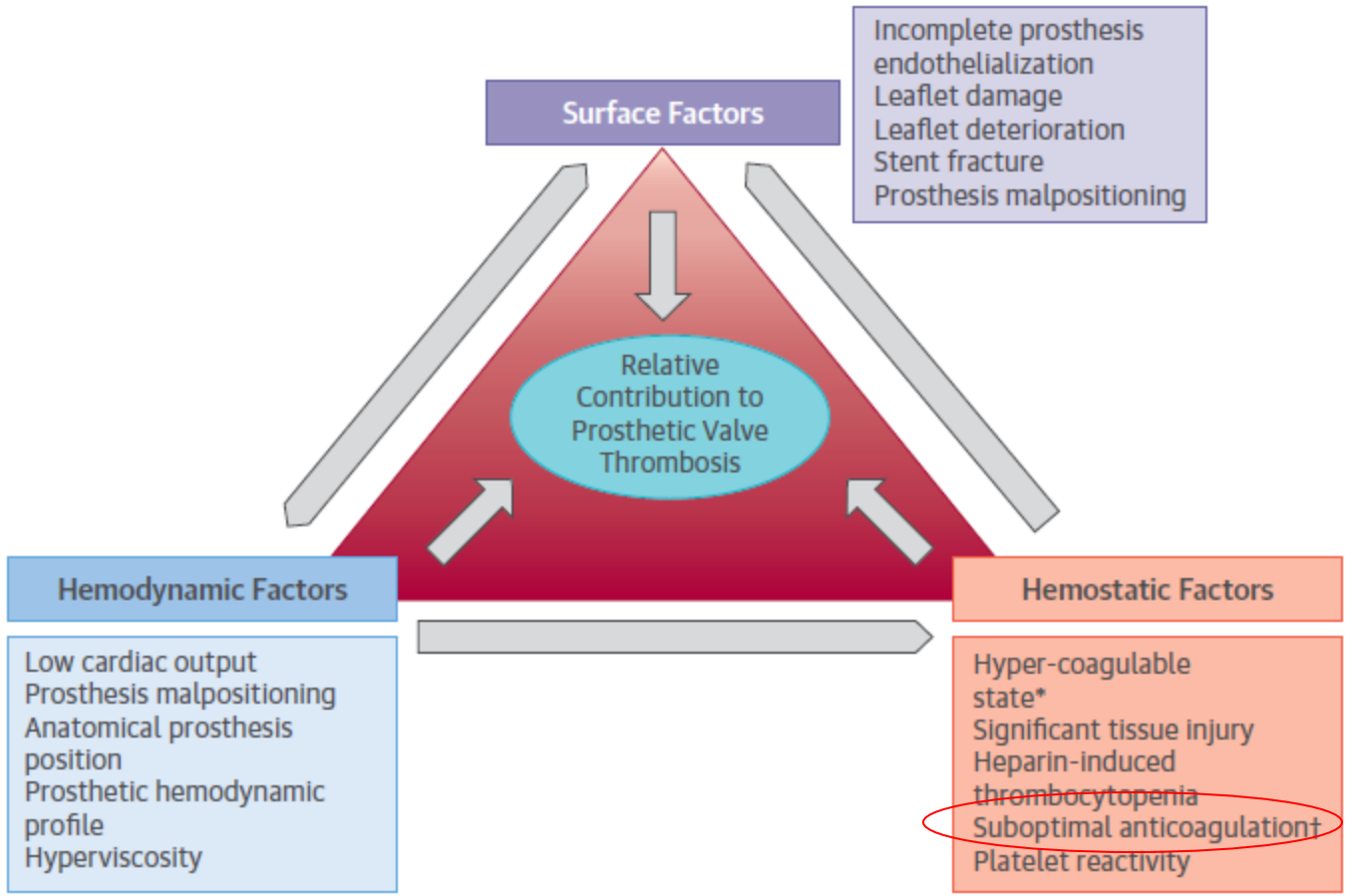
Protesi valvolari cardiache

Efficacia e sicurezza dei trattamenti anticoagulanti

Daniela Poli

Cremona 10 marzo 2017

FIGURE 2 Mechanisms of Prosthetic Valve Thrombosis



Dangas, JACC 2016

European Heart Journal (2012) 33, 2451–2496
doi:10.1093/eurheartj/ehs109

Guidelines on the management of valvular heart disease (version 2012)

Table 17: Choice of the aortic/mitral prosthesis. In favour of a mechanical prosthesis.

	Class [a]	Level [b]
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contraindications for long-term anticoagulation.[c]	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration.[d]	I	C
A mechanical prosthesis is recommended in patients already on anticoagulation as a result of having a mechanical prosthesis in another valve position.	I	C
A mechanical prosthesis should be considered in patients aged <60 years for prostheses in the aortic position and <65 years for prostheses in the mitral position.[e]	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy,[f] for whom future redo valve surgery would be at high risk.	IIa	C
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to high risk of thromboembolism.[g]	IIb	C

Vahanian A, 2012

CARDIAC PROSTHETIC VALVES

Mechanical valves

NEED for ANTICOAGULATION
HIGHER THROMBOEMBOLIC RISK

Biological valves

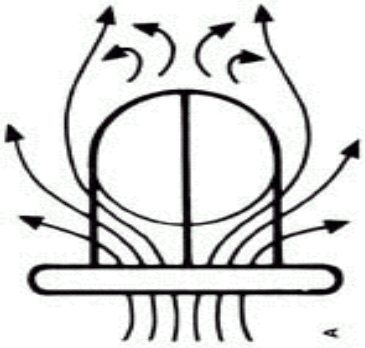
STRUCTURAL VALVE DETERIORATION
mitral > aortic prosthesis
risk of reoperation slightly higher than first operation

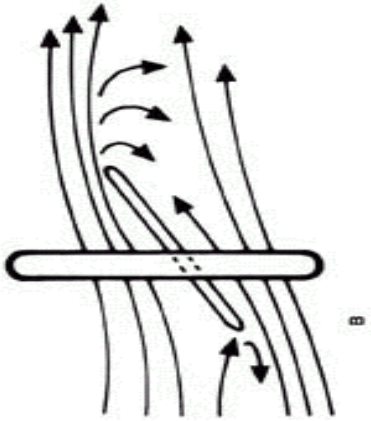
MECHANICAL PROSTHESES

Starr-Edwards

Medtronic-Hall

SJM-Regent





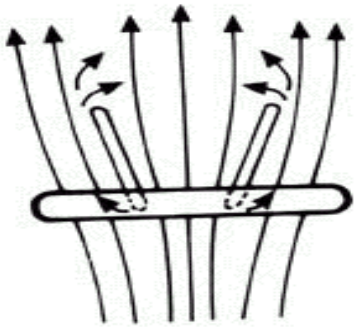


Table 20 Target international normalized ratio (INR) for mechanical prostheses

Prosthesis thrombogenicity[a]	Patient-related risk factors[b]	
	No risk factor	Risk factor ≥1
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

[a]Prosthesis thrombogenicity: Low = Carbomedics, Medtronic Hall, St Jude Medical, ON-X; Medium = other bileaflet valves; High = Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley and other tilting-disc valves.
[b]Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; left ventricular ejection fraction <35%.

Vahanian A, 2012

OPTIMAL ORAL ANTICOAGULANT THERAPY IN PATIENTS WITH MECHANICAL HEART VALVES

S.C. CANNEGIETER, M.D., F.R. ROSENDAAL, M.D., A.R. WINTZEN, M.D., F.J.M. VAN DER MEER, M.D., J.P. VANDENBROUCKE, M.D., AND E. BRIËT, M.D.

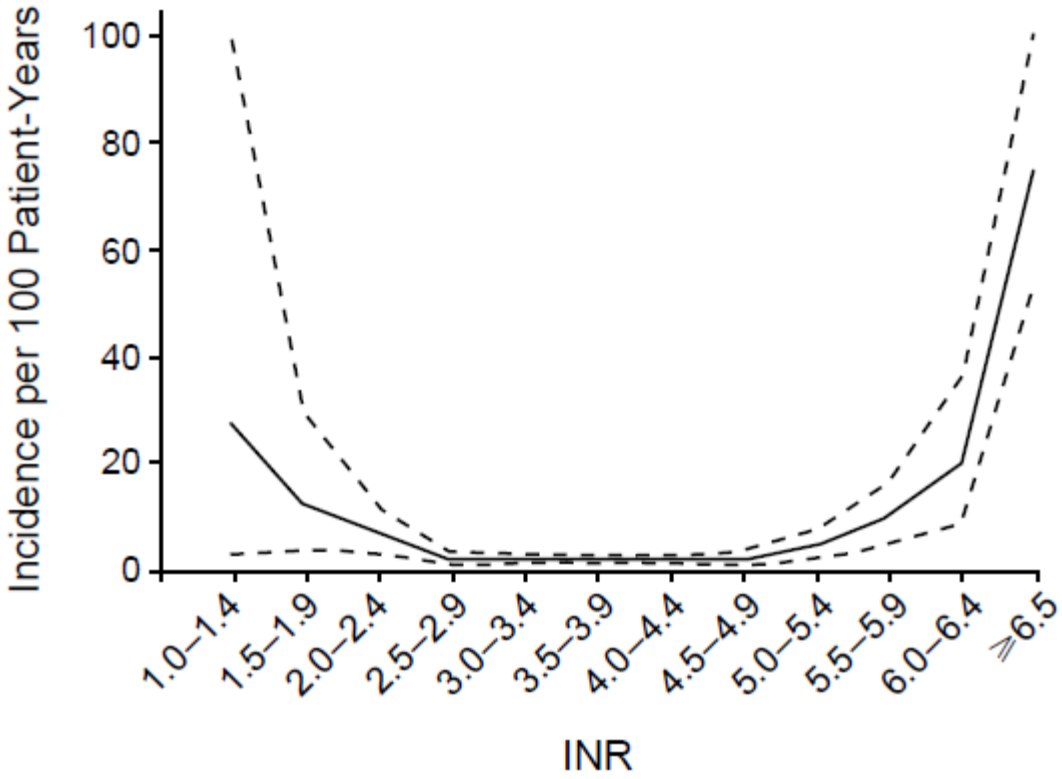


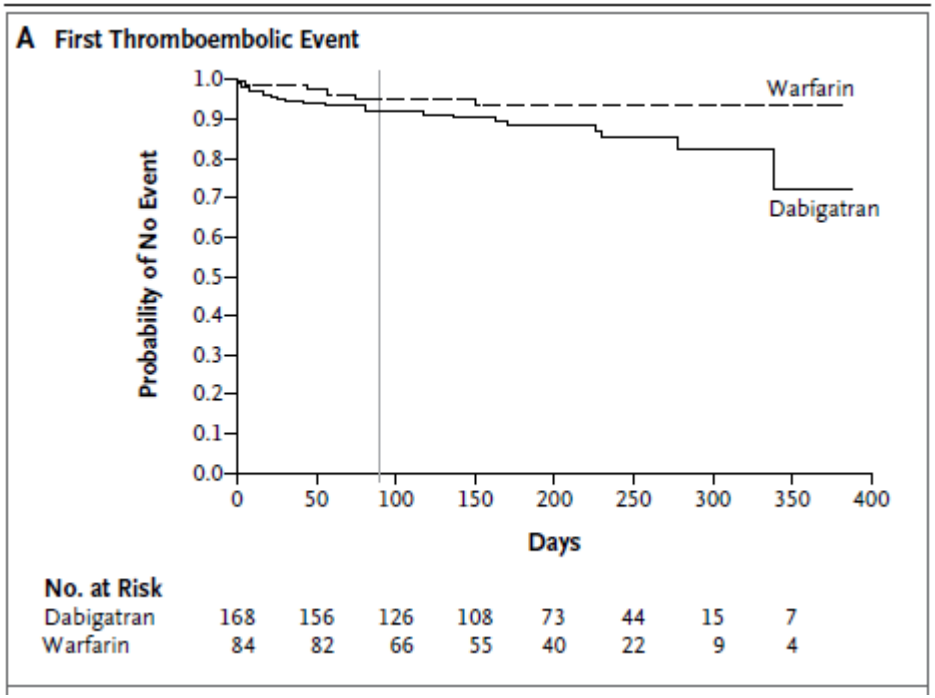
Figure 3. INR-Specific Incidence of All Adverse Events (All Episodes of Thromboembolism, All Major Bleeding Episodes, and Unclassified Stroke).

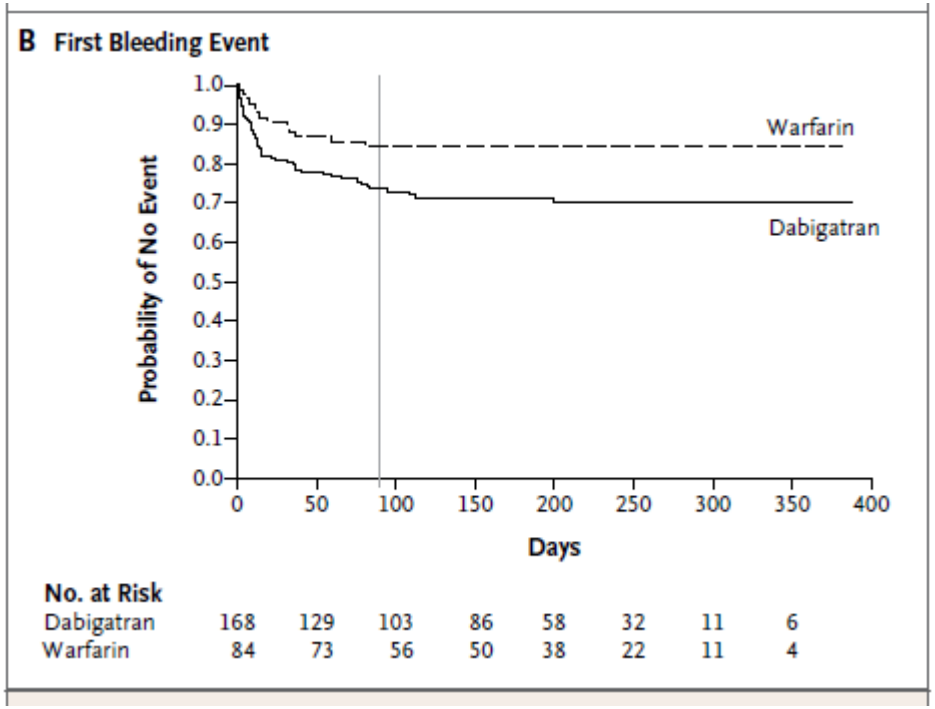
NEJM 1995

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves





Eikelboom J et al, RE-ALIGN Study, 2013

Better anticoagulation control improves survival after valve replacement

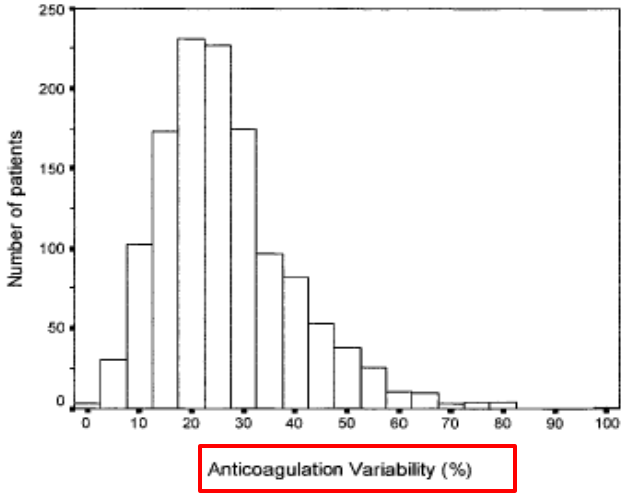


TABLE 2. Valve-related deaths by ACV grouped

	Aortic		Mitral	
	Low/medium ACV n (%/yr)	High ACV n (%/yr)	Low/medium ACV n (%/yr)	High ACV n (%/yr)
Patients	420	205	436	211
Patient-years	3454	1230	4106	1413
Stroke	5 (0.1)	8 (0.7)***	8 (0.2)	5 (0.4)
Thrombosis	0 (0)	0 (0)	1 (0.02)	1 (0.07)
Major bleeding	8 (0.2)	6 (0.5)	9 (0.2)	7 (0.5)
PVE	3 (0.09)	3 (0.2)	3 (0.07)	8 (0.6)***
Total	16 (0.5)	17 (1.4)***	21 (0.5)	21 (1.5)***

ACV, Anticoagulant variability; *PVE*, prosthetic valve endocarditis.
***$P < .001$.

Butchart, 2002

Efficacy and Safety of Very Low-Dose Self-Management of Oral Anticoagulation in Patients With Mechanical Heart Valve Replacement

Heinrich Koertke, MD, PhD, Armin Zittermann, PhD, Otto Wagner, MS, Juergen Ennker, MD, PhD, Werner Saggau, MD, PhD, Falk-Udo Sack, MD, PhD, Jochen Cremer, MD, PhD, Christof Huth, MD, PhD, Maurizio Braccio, MD, PhD, Francesco Musumeci, MD, PhD, and Reiner Koerfer, MD, PhD

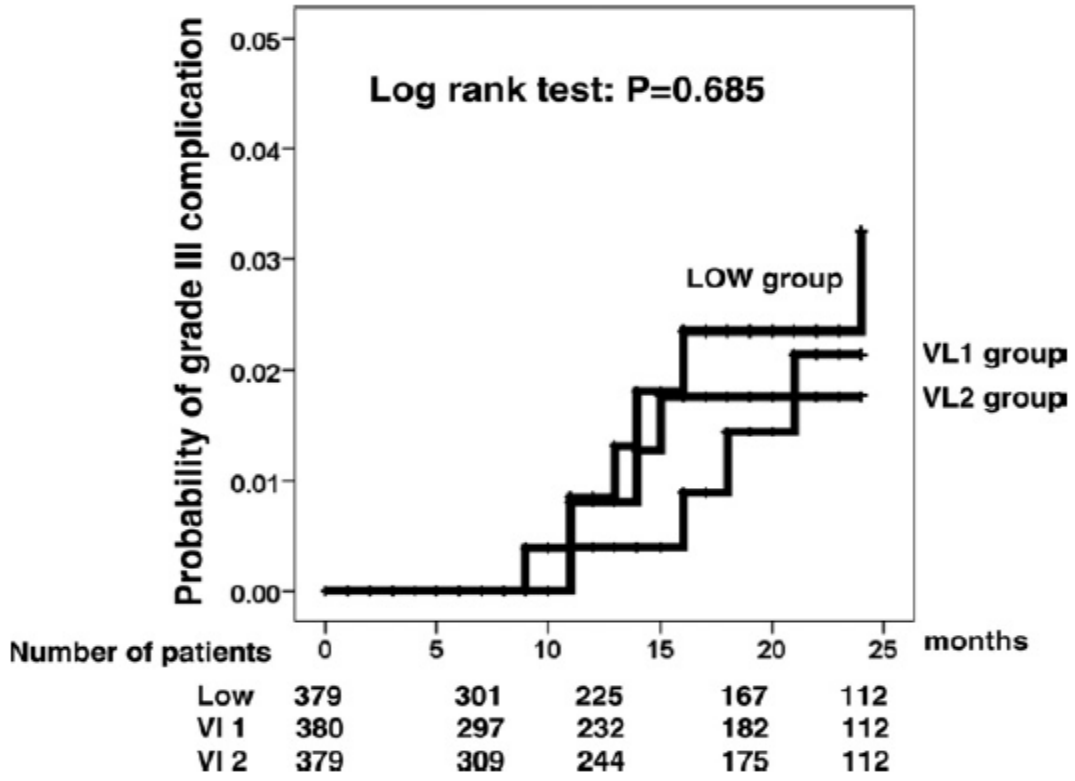


Fig 1. Freedom from grade III complications beyond postoperative month six.

low-dose group
AVR INR 1.8-2.8
MVR INR 2.5-3.5

Very low-dose groups
AVR INR 1.6-2.1
MVR INR 2.0-2.5

Ann Thorac Surg, 2010

Mechanical heart valve prosthesis and warfarin – Treatment quality and prognosis

Bartosz Grzymala-Lubanski [a,*], Ashkan Labaf [c], Erling Englund [b], Peter J. Svensson [c], Anders Själander [d]

Complications at different levels of individual TTR divided into quartiles. 95% CI indicates incidence rate of complication per 100 treatment years.

TTR (%)	>82.9	82.9 – 71.9	71.9 – 61.6	<61.6
Number of patients	134	133	133	134
Time of treatment (yr)	464.6	446.5	454.9	448.0
All complications n(rate)	27 (5.8)	44 (9.9)	45 (9.9)	55 (12.3)
95% CI	3.6 – 8.0	6.9 – 12.8	7.9 – 12.8	9.0 – 15.5
Bleedings n(rate)	9 (1.9)	21 (4.7)	24 (5.3)	25 (5.6)
95% CI	0.7 – 3.2	2.7 – 6.7	3.2 – 7.4	3.4 – 7.8
Thromboembolic events n(rate)	9 (1.9)	16 (3.6)	20 (4.4)	19 (4.2)
95% CI	0.3 – 2.3	1.0 – 3.9	2.5 – 6.3	2.3 – 6.1
Death n(rate)	16 (3.4)	17 (3.8)	23 (5.1)	29 (6.5)
95% CI	1.8 – 5.1	2.0 – 5.6	3.0 – 7.1	4.1 – 8.8

Complications at different levels of individual TTR divided into quartiles. 95% CI indicates incidence rate of complication per 100 treatment years. The risk of complications was significantly higher with lower levels of TTR for all types of complications ($p = 0.005$), bleeding ($p = 0.01$) and death ($p = 0.018$) but not for thromboembolic events.

Thromb Res, 2014

Incidence and risk factors for thromboembolism and major bleeding in patients with mechanical valve prosthesis: A nationwide population-based study

Table III. Rate of stroke/TE and major bleeding events in relation to target INR

AVR	Stroke/TE	Rate	Major bleeding	Rate
2.0-3.0	139	1.29 (1.09-1.52)	257	2.44 (2.15-2.76)
2.5-3.5; 2.0-4.0	27	1.20 (0.79-1.75)*	67	3.07 (2.38-3.90) †
MVR				
2.0-3.0	26	1,73 (1.14-2.51)	61	4.02 (3.07-5.16)
2.5-3.5; 2.0-4.0	8	1.77 (1.03-2.83)*	29	2.98 (1.99-4.28) ‡

Rate is incidence per 100 patient-years (95% CI). * not significant; † $P = .10$; ‡ $P = .18$.

Labaf A et al, 2016

Reprospective multicentre FCSA-START –VALVOLE
PLECTRUM Study

33 Centri Partecipanti (n. pazienti)

1. TESTA SOPHIE, PAOLETTI ORIANA Centro Emostasi E Trombosi - A.O. Istituti Ospitalieri di Cremona, Cremona (420)
2. LODIGIANI CORRADO; CELESTE CINZIA; ILARIA QUAGLIA; PAOLA FERRAZZI Centro Trombosi IRCCS-HUMANITAS RESEARCH HOSPITAL Milano (365)
3. DANIELA POLI, ELISA GRIFONI, NICCOLO' MAGGINI Centro Trombosi SOD Malattie Aterotrombotiche Azienda ospedaliero universitaria AOU Careggi; Firenze (300)
4. COFFETTI NADIA ROSA MAROTTA; VARUSCA BRUSEGAN, ORAZIO BERGAMELLI Servizio di Immunoematologia e Medicina Trasfusionale ASST Bergamo Est, Seriate (67+129)
5. FACCHINETTI ROBERTO Laboratorio Analisi Sede Di Borgo Trento Ospedale Civile Maggiore Azienda Ospedaliera Universitaria Integrata Verona (163)
6. SERRICCHIO GIUSEPPINA Centro TAOASSTT-Lariana PO-CANTU' Como (160)
7. FALCO PIETRO Centro Per La Sorveglianza E Il Controllo Dei Pazienti In Terapia Anticoagulante, Poliambulatorio Specialistico Medical Pontino, Latina (148)
8. CATELLO MANGIONE; BELLOMO GIACOMO Servizio Immunotrasfusionale Presidio Ospedaliero Galatina (Le) (131)
9. MASOTTINI SERENA; COSENZA ALESSANDRA centro per la diagnosi e terapia delle malattie trombolitiche Cittadella della Salute Cagliari (120)
10. RUOCCO LUCIA U.O.Analisi Chimico Cliniche, Ambulatorio Antitrombosi CAT-TAO, Azienda Ospedaliero-Universitaria Pisana, Pisa (100)
11. CAFOLLA ARTURO Centro Trombosi - Dip. Di Biotecnologie Cellulari Ed Ematologia, Az. Policlinico Umberto I Universita' "Sapienza", Roma (95)
12. RUPOLI SERENA; MICUCCI GIORGIA Azienda Ospedaliero-Universitaria Ospedali Riuniti Di Ancona (92)
13. PEDICO PAOLO; ROTUNNO ROSA U.O. Medicina Trasfusionale Ospedale Mons. A.R. Dimiccoli Barletta (Bt) (91)
14. INSANA ANTONIO Servizio Di Patologia Clinica Dipartimento Dei Servizi - Ospedale S. Croce Moncalieri, Ospedale S. Croce, Moncalieri (To) (69)
15. SANTORO ANGELO Direttore U.O.C. Patologia Clinica e Centro Trombosi, Presidio Ospedaliero "A. Perrino", ASL Brindisi (67)

Reprospective multicentre FCSA-START –VALVOLE
PLECTRUM Study

33 Centri Partecipanti (n. pazienti)

16. BARCELLONA DORIS Policlinico Universitario di Monserrato, Università di Cagliari; (65)
17. PENGO VITTORIO, SEENA PADAYATTIL, TISO ENRICO Istituto di Cardiologia, Policlinico Universitario, Università di Padova (58)
18. PAPARO CARMELO Centro Anti Trombosi Ospedale Maggiore, Chieri (TO) (55)
19. BUCHERINI EUGENIO Ambulatorio per il controllo della terapia anticoagulante orale, Presidio Ospedaliero di Faenza AUSLROMAGNA (53)
20. PIGNATELLI PASQUALE, PASTORI DANIELE, VICARIO TOMMASA Centro TAO Clinica Medica Policlinico Umberto I, Roma. (45)
21. MASCIOCCO LUCILLA Centro Controllo Coagulazione - S.C. Medicina Interna, Ospedale Francesco Lastaria, Lucera (FG) (41)
22. TURRINI ANNA Laboratorio Analisi Chimico-Cliniche E Di Microbiologia Ospedale Sacro Cuore Negrar (Vr) (40)
23. TOMA ANDREA UOC di Patologia Clinica Ospedale Civile, Arzignano (VI) (35)
24. PAOLO GRESELE Centro Emostasi e Trombosi Medicina Interna cardiovascolare Università di Perugia (33)
25. LA ROSA LUCIA; RINO MORALES Centro Trasfusionale e ambulatorio emostasi e trombosi; ASST VIMERCATE (30)
26. RONCHI FRANCESCO, ISU GIUSEPPE Centro Tao Servizio Di Patologia Clinica Ns Signora Di Bonaria Asl N. 6 San Gavino Monreale Cagliari (26)
27. FALANGA ANNA,LEREDE TERESA, BARCELLA LUCA Centro per la diagnosi e la terapia delle malattie emorragiche e trombotiche-USC IMMUNOEMATOLOGIA E MED TRASFUSIONALE ASSTT PAPA GIOVANNI XXIII Bergamo (25)
28. RIA LUIGI Centro Trombosi ed Emostasi U.O.C Med.Interna Gallipoli (LE) (18)
29. CRISANTEMO ROSANNA; LUCIANO SURIANO,LUCIANO LORUSSO; MARIO DE SARLO.
Servizio di Immunoematologia e Medicina Trasfusionale Ospedale L.Bonomo Andria (15)
30. CARRATO PASQUALE Ist. Polidiagnostico S. Chiara, Agropoli (Sa) (14)
31. ORICCHIO CARMINE Responsabile Centro Immunotrasfusionale, Ospedale Civile L.Curto Polla (SA) (7)
32. GRANDONE ELVIRA, COLAIZZO DONATELLA Centro Trombosi, I.R.C.C.S. Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG) (6)
33. MOLINATTI MAURIZIO Centro Trombosi e sorveglianza delle terapie Antitrombotiche Clinica Cellini Torino (1)

Reprospective multicentre FCSA-START –VALVOLE study

PLECTRUM Study

Methods

Observational retrospective multicenter study among 33 Centres affiliated to FCSA.

Centres were asked to provide information on each patient in whom a mechanical heart valve or bioprosthesis was implanted.

Quality of anticoagulation, bleeding and thrombotic events occurring during the follow-up were recorded.

Reprospective multicentre FCSA-START –VALVOLE study

PLECTRUM Study

Results

	N (%)
N	3026
Males	1664 (55.0)
Median age at implantation (IQR)	61.85 (52.3-69.1)
Follow-up (years)	27.422
Median follow-up (years) (IQR)	8.45 (3.1-13.1)
Type of heart valve	
mechanical	2357 (77.9%)
biological	669 (22.1)
Site of implantation (2980/3029)	
aortic	1790 (60.0)
mitralic	851 (28.6)
Mitro-aortic	339 (11.4)

Mechanical heart valves

Number	2357
Type of anticoagulant drug	
Warfarin	1929 (81.8)
acenocoumarole	428 (18.2)
Intensity of anticoagulation	
INR 2.0-3.0	604 (26.4)
INR 2.5-3.5	1484 (64.8)
INR 3.0-4.0	202 (8.8)
Events	
Death (%)	174 (7.4)
EMG (rate x100 pt-yrs)	243 (1.0)
Stroke/TIA/Peripheral embolism(x100 pt-yrs)	164 (0.67)
Re-implatation	77 (4%)

Mechanical heart valves

Prosthesis thrombogenicity			
Prosthetic valve position	Low n(%)	Medium n(%)	High n(%)
Aortic (%)	829 (92.3)	27 (3.0)	42 (4.7)
Mitralic (%)	371 (89.8)	25 (6.1)	17 (4.1)
Mitro-Aortic(%)	143 (95.3)	6 (4.0)	1 (0.7)

Mechanical heart valves

INR Range	Aortic n(%)	Mitralic n(%)	Mitro-aortic n(%)
2.0-3.0	560 (40.6)	35 (5.4)	9 (3.5)
2.5-3.5	786 (57.0)	517 (78.8)	181 (70.7)
3.0-4.0	34 (2.4)	104 (15.8)	66 (25.8)
TTR (IQR)	64 (51-78)	55 (44-68)	55 (42-69)

Mechanical heart valves

Range INR	**2.0-3.0**	**2.5-3.5**	**3.0-4.0**
MedianTTR (IQR)	71.5 (57.3-84.0)	58.6 (46.7-71.0)	46.0 (37.8-56.0)
Median n.INR<1.8(last year) (IQR)	1 (0-3)	0 (0-2)	0(0-1)
Major Bleeding (rate)	69 (1.4)	145 (0.98)	23 (0.8)
Stroke/TIA/SE (rate)	22 (0.43)	109 (0.36)	27 (0.9)
Valve position			
Aortic %	92.7	53.0	16.8
Mitralic %	5.8	34.8	50.5
Mitro-Aortic %	1.5	12.2	32.7
AF %	24.0	40.9	57.4
Previous stroke %	6.0	7.9	15.8

Mechanical heart valves

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Mechanical heart valves

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age at implantation	1.01 (0.99-1.02)	0.12	-	
Female sex	1.25 (0.91-1.72)	0.16	-	
Atrial Fibrillation	1.95 (1.41-2.68)	0.000	1.46 (1.01-2.09)	0.04
Previous thromboembolism	6.27 (4.27-9.20)	0.000	5.45 (3.68-8.07)	0.000
Intra-atrial thrombus	6.56 (2.78-15.44)	0.000	3.84 (1.55-9.52)	0.004
Ejection fraction <35%	1.54 (0.68-3.48)	0.29	-	
Mitral prosthesis	1.94 (1.40-2.67)	0.000	1.49 (1.04-2.15)	0.03
TTR ≤47% (25°)	1.31 (0.91-1.88)	0.14	-	

Conclusioni

I risultati di questo studio suggeriscono che una elevata intensità dell'anticoagulazione nei pazienti portatori di protesi valvolari meccaniche cardiache si associa ad una peggiore qualità del trattamento in assenza di una maggiore efficacia.