METAANÁLISIS

Fibrinolytic therapy in left side-prosthetic valve acute thrombosis. In depth systematic review

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Summary

Background: Limited data are available on the impact and safety of fibrinolytic therapy (FT) in left – side prosthetic valve acute thrombosis (PVAT). Study objective: To improve our knowledge about the FT role in left –side PVAT. **Design:** Bibliographic search and analysis. **Methods:** MEDLINE search from January 1970 to January 2007. Studies were classified according to the evidence level recommendations of the American College of Chest Physicians and included if they had objective diagnosis of left-side PAVT and FT efficacy assessment (hemodynamic, echocardiographic or fluoroscopic improvement). New York Heart Association class was used to establish functional state. Data on clinical characteristics, diagnosis strategy, anticoagulation status, fibrinolytic and heparin regimens, cardiovascular adverse events, outcome, and follow-up were also required. **Results:** A systematic search produced a total of 900 references. Each abstract was analyzed according to the predetermined criteria. Thirty-two references with 904 patients constitute the subject of this analysis. Only one trial had evidence III and thirty-one evidence V. FT was more used in young female patients (64%) with prosthetic mitral valve thrombosis (77%), and clinical instability (82%). Transesophageal echocardiogram had a higher thrombus detection rate

Resumen

TERAPIA FIBRINOLÍTICA EN EL CORAZÓN IZQUIERDO

Antecedentes: Son limitados los datos disponibles sobre el impacto y seguridad de la terapia fibrinolítica (TF) en trombosis vascular aguda de válvulas protésicas izquierdas (TVA). Objetivo del estudio: Mejorar nuestro conocimiento en relación al papel de la TF en TVA de válvulas izquierdas. **Diseño:** Análisis e investigación bibliográfica. **Métodos:** Investigación a través del MEDLINE de enero de 1970 a enero de 2007. Los estudios se clasificaron de acuerdo a las recomendaciones del nivel de evidencia del "American College of Chest Physicians" y se incluyeron si tenían un diagnóstico objetivo de TVA de prótesis válvula izquierda y valoración de la efectividad de la TF (mejoría hemodinámica, ecocardiográfica o fluoroscópica). Se utilizó la clase funcional de la "New York Heart Association" para evaluar la clase funcional. También se requirieron datos de las características clínicas, abordaje de diagnóstico, estado de anticoagulación, regímenes de heparina y del fibrinolítico, eventos adversos cardiovasculares, evolución y seguimiento. **Resultados:** a través de una investigación sistematizada se obtuvo un total de 900 referencias. Cada resumen se analizó de acuerdo a los criterios predeterminados. Treinta y dos referencias que incluyeron

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(100%). Although several fibrinolytic regimens were used in a first or second course, streptokinase was the most frequent agent (61%). Clinical improvement was observed in 86% of the patients, objective success in 78%, and failure in 14%. Rescue fibrinolysis was done in 17%. Complications: peripheral and cerebral embolism rate was 5% and 4%, respectively. Major bleeding 4% and intracranial hemorrhage 1%. **Conclusions:** The available evidence demonstrates that in PVAT fibrinolytic therapy improves the outcome in younger, more ill patients, especially females, independently of the fibrinolytic regimen used with a low complications rate.

904 pacientes constituyen la base de este análisis. Sólo un estudio tuvo un nivel de evidencia III y en 31 el nivel de evidencia fue V. La TF se utilizó principalmente en pacientes jóvenes del sexo femenino (64%) con trombosis en prótesis mecánicas en posición mitral (77%) y con inestabilidad clínica (82%). El ecocardiograma transesofágico tuvo el mayor porcentaje de detección de trombo (100%). Aunque varios regímenes fibrinolíticos fueron utilizados en una primera o segunda infusión, la estreptoquinasa fue el fibrinolítico más utilizado (61%). Se observó mejoría clínica en el 86% de los pacientes, éxito objetivo en el 78% y falla en el 14%. Una TF de rescate se realizó en el 17%. Complicaciones: embolia periférica o cerebral se observó en el 5 y 4%, respectivamente. Hemorragia mayor en el 4% e intracraneal en el 1%. **Conclusiones:** La evidencia disponible demuestra que la TF en TVA mejora la evolución en pacientes jóvenes graves, especialmente del sexo femenino, independientemente del régimen fibrinolítico utilizado con una baja incidencia de complicaciones.
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Key words: Thrombolysis. Fibrinolytic therapy. Cardiac valve thrombosis. Valve prosthesis.
Palabras clave: Trombólisis, Terapia fibrinolítica. Trombosis de válvula cardíaca. Prótesis valvular.

Although left-side prosthetic valve acute thrombosis (PVAT) is not a health problem, it is a serious and potentially lethal complication of heart valve replacement surgery. The conventional surgical treatment has a high mortality rate in urgent and emergency cases and is available only in few very specialized centers.[1] The advent of fibrinolytic therapy (FT) has improved the outcome among properly selected acute myocardial infarction[2] high-risk pulmonary embolism,[3,4] acute ischemic stroke,[5] and complicated hemothorax or empyema patients.[6] In the setting of left-side PVAT,[1,7,8] FT has been considered an alternative for high-risk surgical patients. However, even after the earliest FT successful report[9] and guidelines recommendations,[10,11] this therapeutic approach is sometimes considered harmful and several questions still remain unsolved.[12] In the era of evidence-based medicine and of the new antithrombotic and fibrinolytic drugs, we performed a 37-year systematic literature review attempting to improve our knowledge about FT role in PVAT.

Methods

Study identification: a MEDLINE search on FT and PVAT was undertaken (National Library of Medicine: PubMed: http://www.ncbi.nlm.nih.gov). The literature was scanned by formal searches of electronic databases with the terms: "cardiac valve thrombosis", or "prosthetic valve obstruction", or "prosthetic heart valve" and "thrombolysis" were entered in the search field. Only English-published abstracts were considered.

Study eligibility: two investigators abstracted the data (ERC, TAA) and disagreements were resolved by discussion with another investigator (CJS). No attempts were made to contact the authors for information. Investigators were not blinded to journal, author o institution. Case reports (arbitrary limit < 3 cases) and patients younger than 13 year old were not included.

Trial selection: full text studies were included if they met all of the following criteria, decided a priori: a) clinical characteristics, b) NYHA functional class, c) diagnostic work-up, d) objective approach for the diagnosis of PVAT, e) FT efficacy assessment, f) fibrinolytic regimens, g) cardiovascular adverse events (hemorrhagic com-

plications, embolization, cardiac failure, rethrombosis or cardiovascular death), h) and description of at least one of the following data: age, anticoagulation status, heparin regimens, outcome and follow-up. Acute pulmonary edema and cardiogenic shock were considered as NYHA IV class. Evidence level: studies were classified according to the American College of Chest Physicians recommendations:[13] level I, based on randomized trials with high power; level II, randomized trials with lower power; level III, non-randomized cohort studies with treated and untreated groups; level IV, non-randomized historical cohort studies with treated and untreated groups; level V, case series without control subjects. Fibrinolytic therapy assessment definition: a) objective success (hemodynamic measurements, echocardiographic or fluoroscopic parameters with gradient flow improvement, thrombus size reduction and/or opening angle improvement), b) clinical success (baseline clinical characteristics improvement) and c) non-success (failure to improve clinical, echocardiographic, or fluoroscopic baseline findings or death).

We did not have any support for this study from pharmaceutical companies or government agencies.

Results

From January 1970 to January 2007 a systematic MEDLINE/PubMed search produced a total of 900 references with abstracts. Thirty-two[12,14-34,43-52] studies with 904 cases met all of the inclusion criteria and constitute the subject of this analysis. Only one trial25 had evidence III and the other 31 were case series (evidence V). A composite list of the baseline characteristics of 904 patients is shown in Table I. The majority were young females with prosthetic mitral valve thrombus location, cardiovascular symptoms, and severe clinical instability. A low rate of auscultatory and neurologic findings was found. PVAT was observed in patients with or without therapeutic INR values. The list of the different types of prosthetic heart valves is shown in Table II.

Diagnostic procedures: the most common diagnostic approach was transthoracic echocardiogram (TTE) in 86%. Cinefluoroscopy and transesophageal echocardiograms (TEE) were done in 27% and 33% respectively. The baseline echo and cinefluoroscopy characteristics, as well as the diagnostic yield of the procedures, are summarized in Table III. TEE had a better thrombus detection rate as compared to TTE and cinefluoroscopy (Table III).

Fibrinolytic therapy: in 904 patients, 1,015 fibrinolytic regimens were used as a first course or rescue fibrinolysis. Indications: most studies included critically ill patients who were too sick to undergo immediate surgery (severely hemodynamically compromised) (Table I). Fibrinolytic regimens: table IV summarizes the main fibrinolytic regimens and repeated FT administrations used throughout the study period. Streptokinase was the most used fibrinolytic agent (63%) [12-24,26,30,33,34,45,47,49,50-52] compared to urokinase (15%)[14-16,21-23,26,29,45,49-51] and alteplase (18%).[21,23,25,27,28,31,34,44,46,48–50] Bolus administration followed by long-term infusions was used in the majority of the cases. The infusions of strep-

Table I. Demographic characteristics.

Variable	(n = 904)	%
Age (817 cases)	47.5 ± 13 (range 15–91)	
Gender		
Female	521	64
Male	297	36
Position of PVT		
Mitral	616	77
Aortic	178	22
NYHA Class		
I-II	177	26
III	250	37
IV	226	34
(APE 153 and shock 37 pts)		
Cardiovascular symptoms		
Atrial fibrillation	205	41
Dyspnea	235	79
Peripheral embolism	57	6
Chest pain (angina-like)	20	5
Acute myocardial infarction	2	0.4
Ventricular arrhythmias	2	0.4
Cardiac arrest	2	0.4
Auscultatory findings		
Abolished click	60	14
New murmur	29	7
Diminished click	25	6
Neurologic symptoms		
Cerebral emboli	16	4
Transient ischemic attack	6	1
Syncope	1	0.2
Nonspecific symptoms		
Fever	10	2
Asthenia	10	2
Incidental PHVT diagnosis		
None symptoms	10	5
INR status (766 pts)		
Therapeutic	306	40
Subtherapeutic	465	60
Drug default	55	13

APE: acute pulmonary edema; pts: patients

Table II. Prosthetic heart valve types.

Type	Model	n = 437	%
Mechanical			
Caged-ball	Starr-Edwards	11	3
Single-tilting-disk	Bjork–Shiley	91	21
	Medtronic Hall	12	3
	Sorin Monoleaflet	7	2
	Ultracore Monoleaflet	5	1
	Lillehei-Kaster	7	2
	Single-tilting-disk	44	10
Bileaflet-tilting-disk	St. Jude Medical	63	14
	Carbomedics	57	13
	Duromedics	7	2
	Sorin Bileaflet	4	1
	Bileaflet-tilting-disk	66	15
	Sorin	13	3
	Kaster Omniscence	11	3
Bioprosthetic			
Heterograft	Carpenter-Edwards	1	0.2
	Liota	1	0.2
No reported		37	8

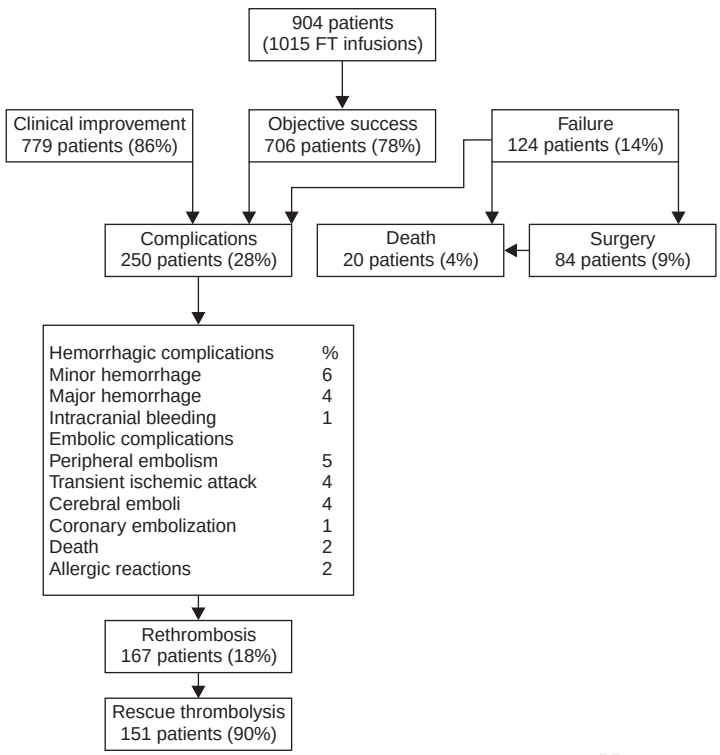

Fig. 1. Fibrinolytic therapy outcome overview.

tokinase were longer (24 to 72 hours), followed by urokinase (12 to 15 hours) and alteplase (5 hours). Short-infusions were used mainly with alteplase (90 minutes to 3 hours) and in a few cases of streptokinase (90 minutes to 1 hour) (Table IV).

Table III. Baseline diagnostic procedures.

Variable	(n = 904)	%
TTE	779	86
Diagnosis	243	74
Thrombus fixed or mobile	30	12
Cinefluoroscopy	241	27
Diagnosis	45	28
Thrombus fixed or mobile	0	0
TEE	294	33
Diagnosis	294	100
Thrombus fixed or mobile	56	41
Total baseline studies	603	

TTE: transthoracic echocardiography; TEE: transesophageal echocardiograph

The clinical response, hemorrhagic and embolic complications and mortality secondary to FT are shown in Table V. In the group with FT failure, 7% required surgery.[14-16,21,23,27,30,31,33,34,44-50,52] In patients with FT failure, rescue fibrinolysis (a second course) was done in 17%. Only 1% (11 cases) of intracranial bleeding was reported.[12,14-16,19-22,26,31,34,47,49,50] The incidence of major and intracranial hemorrhage was low and the overall hemorrhagic and embolic complications rate was 7%, embolic 70% and hemorrhagic 30%. A close relationship among hemorrhagic complications, vascular punctures, and central catheter line was found. The mortality cause secondary to FT was cerebral emboli in 13 patients, intracranial bleeding in 5, serious bleeding in 3 and peripheral hemorrhage in one patient. Most patients were under long-term (12 to 96 hours) infusions.[12,18,21,33,47,49,52] In spite of the broad use of streptokinase, a low rate of allergic reactions (1%) was reported.[19,23,26,30,50,52] The main overall mortality was cardiovascular. Fibrinolytic therapy failure was attributed mainly to re-thrombosis. When a follow-up was performed, 13% of mortality was described.[12,14-16,18,19,21-23,26,27,30,34,43,47,48–52] A FT outcome overview is shown in Figure 1.

Discussion

Available data provided a thirty-seven-year broad view and clinically relevant information about FT efficacy and safety in the setting of left-side PVAT. This result supports previous knowledge coming from American College of Cardiology and American Heart Association guidelines10,11 and identifies current evidence that could be used in the clinical practice.

Although, the clinical characteristics of PVAT have been clearly defined,15 the clinical profile in this study included young patients, with mitral thrombus and cardiovascular instability without co-morbidity, independently of the anticoagulation status (Table I). There is not a clear explanation for the small incidence of aortic PVAT seen in the reviewed cases. In addition, there were no differences in PVAT rate amongst old or new generation mechanical

Table IV. Fibrinolytic regimens in 437 patients.

Author	Year	Streptokinase (n = 576, 61%)	Urokinase (n = 150, 16%)	Alteplase (n = 178, 19%)
Witchitz[14]	1980	500,000 IU/30 min + 100,000 IU/12-96 h	150,000 IU/30 min + 75,000 – 150,000 IU/24 - 48 h	_ _ _ _
Leidan[15]	1986	500,000 IU/20 min + 1,500,000 IU/10 h	4,500 IU/kg/h/12 h	_ _ _ _
Lorient[16]	1987	500,000 IU/30 min + 1,500,000 IU/1 h/10 h	4,500 IU/h/12 h	_ _ _ _
Zhogbi[17]	1989	250,000 IU/30 min + 150,000 IU/h/8 h or 100, 000 IU/h/48 h	_ _ _ _	_ _ _ _
Wilkinson[18]	1989	250-500,000 IU + 100,000 IU/36 a 72 h	_ _ _ _	_ _ _ _
Dzavick[19]	1991	500-750,000 IU/30 min + 100,000 IU/34 h or 3,000 IU/4 days	_ _ _ _	_ _ _ _
Vasan[20]	1992	250,000 IU/30 min + 100,000 IU/h until achieve improvement or bleeding	_ _ _ _	_ _ _ _
Rodaut[21]	1992	500,000 IU/20 min + 1,500,000 UI/10 h	4,500/2,000 IU/kg/h/12 h	10 mg + 90 mg, 90 min
Silber[22]	1993	250,000 IU/30 min + 1,000 IU/h/72 h	4,400 IU/10-15 min + 4,000 IU/kg/h/24 h	_ _ _ _
Guerrero[23]	1993	250,000 IU + 100,000 IU/h/22-60 h	300,000 IU + 100,000 IU/h/13-64 h	100 mg/90 min
Solorio[24]	1994	250,000 IU/30 min + 100,000 IU/h/72 h	_ _ _ _	_ _ _ _
Vitale [25]	1994	_ _ _ _	_ _ _ _	10 mg bolus + 50 mg/1 h + 20 mg/2 h
Reddy[26]	1994	250,000 IU/30 min + 100,000 IU/h or 1,500,000 IU/1 h	Streptokinase plus Urokinase¨* 250,000 IU/30 min + 100,000 IU/h/2 h	_ _ _ _
Losi[27]	1995	_ _ _ _	_ _ _ _	10 mg bolus + 50 mg/1 h + 40 mg/2 h
Astengo[28]	1995	_ _ _ _	_ _ _ _	100 mg/2 h
Hernandez[29]	1998	_ _ _ _	180/250,000 IU + 240,000 IU/h/24-36 h or 5, 000 IU bolus + 100,000 IU/h/72 h	_ _ _ _
Manteiga[30]	1998	250,000 IU/20 min + 1,500,000 IU/90 min	_ _ _ _	10 mg bolus + 90 mg/90 min
Munclinger[31]	1998	_ _ _ _	_ _ _ _	10 mg bolus + 5 mg/h until improvement
Koca[32]	2000	250-500,000 IU/30 min + 100,000 UI/h/24 h	_ _ _ _	_ _ _ _
Gupta[33]	2000	250,000 IU/30min + 100,000 IU/h until improvement or 72 h	_ _ _ _	_ _ _ _
Özkan[12]	2000	1,500,000 IU/3 h/60-100,000 IU/h/15-24 h	1,500,000 IU/15 h	10 mg bolus + 90 mg/5 h
Shapira[34]	2000	150-250,000 IU/30 min + 100,000 U/h/24 h	4,400 IU/kg/30 min + 4,400 IU/kg/h/24 h	10 mg bolus + 90 mg/3 h
Sanchez[43]	2001	_ _ _ _	_ _ _ _	_ _ _ _
Azpitarte[44]	2001	_ _ _ _	_ _ _ _	100 - 200 mg
Kumar[45]	2001	250,000 IU p/30 min + 1000 U/h + hydrocortison 100 mg	4,400U/k/h 72 h	_ _ _ _
Montorsi[46]	2003	_ _ _ _	_ _ _ _	10 mg bolus + 90 mg/3 h
Ramos[47]	2003	250,000 U/30 min + 100,000 IU/h 72 h	_ _ _ _	_ _ _ _
Shapira[48]	2003	_ _ _ _	_ _ _ _	10mg bolus + 90 mg/3 h
Roudaut[49]	2003	500,000 IU/20 min + 1500,000 U/10 h (recently accelerate doses)	4,500 U/kg/h for 12 h o 2000U/kg/h for 12 h	10 mg bolus + 90 mg/90 min-3 h or 20 mg bolus + 10 mg/h for 3 h
Tong[50]	2004	12-48 h or up to 72-120 h	6-48 h	10 mg bolus + 90 mg / 2-6 h
Balasundaram[51]	2005	250,000 IU/30 min + 1,000 IU/h 96 h	4,400 U/kg/h 96 h	
Caceres[52]	2006	** 250,000 IU/ 30 min + 100,000 IU/h	_ _ _ _	_ _ _ _

h: hours; min: minutes; * fibrinolytic therapy combined; ** recombinant streptokinase

Table V. Fibrinolytic therapy in 904 patients.

Variable	(n = 1,015 infusions)	%
Clinical response		
Efficacy*	779	86
Objective success*	706	78
Failure	124	14
Rethrombosis	167	18
Rescue fibrinolysis	151	17
Hemorrhagic complications		
Minor hemorrhage	54	6
Major hemorrhage	36	4
Intracranial bleeding	13	1
Total	138	15
Embolic complications		
Peripheral embolism	46	5
Transient ischemic attack	36	4
Cerebral emboli	39	4
Coronary embolization	10	1
Total	85	9
Mortality secondary to FT		
Death	22	2
Overall mortality		
Cardiovascular	88	10
FT failure	36	4

* All papers included efficacy and/or objective success

valves or in those with high or low thrombogenic profile (Table II). There is not a satisfactory explanation regarding the low incidence (3%) of PVAT in patients with Starr-Edwards in aortic or mitral position, in spite of its high thrombus risk profile. All prosthetic valve types developed thrombus, independently if patients were or not under effective oral anticoagulation. Transthoracic echocardiogram and TEE were the main tools in the diagnostic process;32 both techniques are quite specific, reproducible, and useful to diagnose left-side PVAT, and to monitor thrombus lysis. Moreover, TEE offers better resolution allowing more direct thrombus visualization (Table III).

FT represents an alternative management to surgery, with a convincing biological benefit by inducing lysis of the obstructive thrombus; the rapid improvement through "pharmacologic embolectomy" possibly reverses the clinical instability and prevents death. The high FT success rates observed, particularly in critically ill patients, support this pharmacologic action and establish this therapeutic approach as an important alternative when operative mortality could be higher than the risk of hemorrhagic or embolic complications.[12,14-34,43-52] Due to the lack of a standard regimen10,11 several infusion protocols and doses have been tried, in this setting long-term streptokinase infusion was the most frequently used regimen (Table IV); the benefit obtained with this non-fibrin specific fibrinolytic agent in the setting of severe clinical instability could be explained through its long intravascular half-life, resulting in a higher systemic fibrinolytic state than that produced by fibrin-specific agents. Although the experience with alteplase is scarce, considering its main advantages, are short half life, more fibrin specificity, less blood requirements after surgery, the capability to dissolve fresh cerebral embolus and a faster achievement of valve opening, it emerges as an important therapeutic approach in unstable patients.[34] Any comparison among fibrinolytic agents is unjustified due to the small number of courses and the nonrandomized fashion in which these agents were given.

In the setting of partial or total failure or early reocclusion after FT (16%), a second course of fibrinolysis was a successful approach with a low complication rate;[12,14-16, 19-22,26,31,34,47-52] although evidence in this field is very limited, a trend to improve initial results with repeated FT sessions has been reported.[12,34,47-52] No specific agent or regimen to obtain optimal results was identified. In addition, no information regarding new antithrombotic or fibrinolytic drugs (tecneteplase, low molecular weight heparins, platelet glycoprotein IIb/IIIa integrin receptor blockade or clopidogrel) was available in the reviewed literature.

Even in properly selected patients, independently from the vascular thrombosis location, intracranial bleeding is the most serious and feared FT complication. The low intracranial bleeding rate (1%) was similar to that observed in acute myocardial infarction[35-37] and it could be explained by the age of the patients and the broader streptokinase use, instead of fibrin-specific agents. On the other hand, long-term fibrinolytic infusions were excellent models for severe hemorrhage complications, similarly to those observed in pulmonary embolism.[38] Additionally, all patients whose mortality was attributed to FT complications were under long-term infusions. Although short-term streptokinase and alteplase infusion experience is scarce and more information is required, these regimens, by peripheral vein followed by a second course when needed, could be an attractive therapeutic option. Regarding hemorrhagic complications, the rate of

major and minor bleeding events was higher than previously reported[12] (Table V), however, a close relationship with venous invasive procedures was found. Avoiding catheter central line placement could reduce bleeding complications as has been observed in pulmonary embolism.[3,4,38] In this research, overall systemic embolism was far above predictable, however, the cerebral emboli rate was low. Recurrence and cardiovascular mortality in acute phase and follow-up were high, which is explained by the extremely serious condition of patients and the absence of intensive antithrombotic treatment to reduce recurrence. In addition, in this group of patients, the attempts to identify persistent active thrombosis through inflammation and haemostatic risk markers, as in acute coronary syndromes,[39] have been scarce.[33] Compared with a previous experience in which long-term FT regimens were used[53] our data suggesting higher FT success rates in terms of mortality. Bleeding complications were not reported.[53]

Limitations of the study

Randomized trials and homogeneity among publications were not identified.40 We did not contact the principal investigators for verification of the published data. Certainly, the trend in medicine is to publish successful cases, so it is possible that we do not know the real number of failure cases.

Evidence-based considerations

1. All prosthetic heart valves types can develop thrombus in the presence of ineffective or apparently effective oral anticoagulation.
2. More data are required in aortic PVAT, class I or II, and cardiogenic shock cases, as well as in patients with underlying co-morbidity.
3. In the PVAT diagnostic process, TTE and TEE should be considered as the main diagnostic tools.
4. Although all FT regimens were effective, long-term infusions may be harmful since they are associated to hemorrhagic complications.
5. New adjunctive or concomitant intensive antithrombotic treatments are required to avoid high recurrence rates.
6. The benefit observed in young patients overcomes the intracranial bleeding risk of FT.
7. In the setting of FT failure or early recurrence, rescue FT course was an effective and safe therapeutic approach.
8. Short-term infusions following a second FT course among properly selected patients could be an attractive regimen waiting for scientific support.
9. Direct comparison between FT and surgical therapy seems unlikely in the future, because these patients are so sick and the disease so infrequent, that probably a randomized controlled trial will never be undertaken.
10. Although there are no randomized trials and there is a conspicuous lack of homogeneity among publications, the present data confirm previous observations[10,53] regarding the efficacy and safety of FT in left-side PVAT and updates its clinical significance[41,53] and beneficial effects.[42,53]

Conclusions

The available evidence demonstrates that, in PVAT, fibrinolytic therapy improves the outcome in younger, more ill patients, especially in females, independently of the fibrinolytic regimen used with a low complications rate.

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