Determinants of coronary stent thrombosis, a decade monocentric experience

Déterminants de la thrombose de stent coronaire, une décennie d'expérience monocentrique

Ahmed Romdhane, Mehdi Slim, Saeb Ben Saad, Houssem Thabet, Marwen Kacem, Anis Ghariani, Rym Gribaa, Aymen Hraiech, Elyes Neffati

Cardiology department, Sahloul University Hospital Sousse

Summary

Introduction: Despite technological and pharmacological progress, stent thrombosis remains a dreadful complication of PCI and appears to be a multifactorial disease.

Objectives: Our study aims to review the determinants of this pathology in our local environment.

Methods: Retrospective monocentric study in Sahloul hospital. We collected data about all stent thrombosis between 2007 and 2017 and studied a similar number of controls. Our research consists in a comparative case-control study.

Results: Urgent PCI, thrombus, overriding stents, hemodynamic instability and poor TIMI flow increase the risk of stent thrombosis. Multivariate analysis shows a significant link between stent thrombosis, hemodynamic instability during procedure (P=0.037) and an abnormal preprocedural TIMI flow (P <0.001).

Conclusion: We highlight the impact of an abnormal TIMI flow and hemodynamic instability in the occurrence of stent thrombosis.

Key words: stent, thrombosis, coronary artery.

Keywords

stent, thrombosis, coronary artery

Résumé

Introduction : Malgré les progrès technologiques et pharmacologiques, la thrombose de stent reste une complication redoutable de l'angioplastie et apparaît comme une maladie multifactorielle.

Objectifs : Notre étude a visé à faire le point sur les déterminants de cette pathologie dans notre environnement local.

Méthodes : il s'agissait d'une étude rétrospective monocentrique à l'hôpital de Sahloul. Nous avons recueilli les données sur toutes les thromboses de stent entre 2007 et 2017 et on a étudié un nombre similaire de témoins. Notre travail est une étude comparative cas-témoins.

Résultats : L'angioplastie urgente, le thrombus, les stents antérieurs, l'instabilité hémodynamique et le mauvais flux TIMI augmentent le risque de thrombose du stent. L'analyse multivariée a montré un lien significatif entre la thrombose du stent, l'instabilité hémodynamique au cours de la procédure (P = 0,037) et un flux TIMI pré-procédural anormal (P <0,001).

Conclusion : On a mis en évidence l'impact d'un flux TIMI anormal et d'une instabilité hémodynamique dans la survenue d'une thrombose de stent.

Mots-clés

stent, thrombose, artère coronaire

Correspondance

Ahmed Romdhane

Service de cardiologie CHU Sahloul Sousse.

Email : romdhane.ahmed1990@gmail.com

INTRODUCTION

Cardiovascular diseases were responsible of up to 30% of total deaths in Tunisia in 2009 [1]. Percutaneous coronary interventions developed as an answer to this issue. The use of coronary stents resulted in better outcomes when compared to balloon angioplasty, yet implanting these devices could lead to severe complications such as stent thrombosis. The bad prognosis of the latter allowed improvements in stent materials and preventive pharmacological therapy with the elaboration of new antiplatelet agents of greater potency than clopidogrel, e.g, Ticagrelor and Prasugrel [2]. Various elements can cause stent thrombosis, some of which are related to the patient, the pharmacological environment, the procedure and the stents themselves. Despite its decreasing rates, stent thrombosis is associated with hard clinical events including death. Data on this pathology are scarce in our local environment. In this regard, we sought to identify the determinants of stent thrombosis in our daily practice

METHODS

Our study is a retrospective monocentric survey in the cardiology department of Sahloul hospital, Sousse, Tunisia, encompassing all patients hospitalized between 2007 and 2017 with a diagnosis of stent thrombosis. Our work consists in a comparative case-control study to assess the determinants of stent thrombosis. We included all patients hospitalized with a definite diagnosis of stent thrombosis as stated by The Academic Research Consortium [3]. We enrolled an identical number of controls with similar sex proportion and period of implantation of stents before the occurrence of stent thrombosis. We seized and analyzed data using SPSS STATISTICS 20 software.

RESULTS

These results are related to the 'cases' arm. Data about our controls are shown in the following comparative section.

A- Patients characteristics

63 patients were admitted for stent thrombosis between 2007 and 2017, most of them were hypertensive, smokers and diabetics. Table I reports the distribution of cardiovascular risk factors.

Table I. Prevalence of cardiovascular risk factors and comorbidities

Pathology	Percentage of patients
Hypertension	52.4%
Current smoking	49.2%
Diabetes mellitus	39.7%
Dyslipidemia	25.4%
Renal failure	15.9%
Evolving carcinoma	1.58%
Coronary heredity	7.9%
Heart failure	23.8%
Bleeding history	7.9%

B- Peri-interventional data

Most of our patients underwent PCI in the context of ACS. Lesions were thrombotic in most procedures with an abnormal TIMI flow. We observed a greater propensity of LAD involvement and type B lesions. PCI strategy was heterogeneous, with direct stenting being the preferred approach. The result was optimal in 90% of the procedures. Table 2 summarizes our findings.

Echocardiographic characteristics

Context of stent implantation before stent thrombosis, angiographic data and procedural aspects of angioplasty.

Table 2. Context of stent implantation before stent thrombosis, angiographic data and procedural aspects of angioplasty

Presentation	Percentage of patients (or number when applies)
STEMI	49%
NSTEMI	13%
CCS	38%
Cardiogenic shock	24.5%
Angiographic analysis	
TIMI flow < 3	53%
Presence of thrombus	43%
Left main stenosis	7.3%
LAD stenosis	81.8%
Circumflex stenosis	56.4%
Right coronary stenosis	50.9%
Bifurcation lesion	12%
Plaque dissection	8%
Plaque calcification	6%
Chronic total occlusion	6%
Lesion type according to ACC/ AHA classification	
A type lesion	12%
B type lesion	68%
C type lesion	20%
Course of angioplasty	
Predilatation	40%
Postdilatation	20%
Thromboaspiration	12%
Direct stenting	60%
Average number of stents implanted	2
Average stent length (millimeters)	21.29
Average stent diameter (millimeters)	2.95
Use of bare metal stents	66%
Use of drug eluting stents	34%
Overriding stents	15.3%
Result of the procedure	
Final TIMI flow = 3	90%
Coronary dissection	4%
Stent malapposition	2%
Residual stenosis <30% in stent edges	10%

C- Comparative case-control section

Significant findings related to ST in univariate analysis include revascularization in an emergent setting (p<001), bleeding events (p=0.02), hemodynamic instability during PCI (p=0.006), the presence of thrombus (p=0.017) and pre procedural TIMI flow < 3 (p < 0.001) (Table 3).

Table 3. Univariate analysis

Univariate analysis	Percentage		Odds ratio	P value
Cardiovascular risk factors and comorbidities	**Cases**	**Controls**		
Smoking	49%	69%	0.42	0.22
Hypertension	52.4%	39.7%	1.67	0.15
Diabetes	39.7%	33%	1.31	0.45
Dyslipidemia	25.4%	16.1%	1.77	0.2
Renal failure	16.4%	21%	0.56	0.24
Heart failure	23.8%	25.4%	0.91	0.83
Bleeding	7.9%	0	-	0.02
Coronary heredity	7.9%	3.2%	2.58	0.44
Context of stent implantation and angiographic data	**Cases**	**Controls**		
Angioplasty for STEMI	49%	34.9%	1.8	0.12
Emergency revascularization	41.5%	11.1%	5.67	<0.001
Hemodynamic instability	24.5%	6.34%	4.8	0.006
Presence of thrombus	43.1%	22.2%	2.65	0.017
Initial TIMI flow <3	52.9%	17.5%	5.32	<0.001
Final TIMI flow <3	9.8%	3.2%	3.26	0.29
Calcified plaques	5.8%	7.9%	0.72	0.95
Plaque dissection	8%	4.7%	1.74	0.74
CTO	5.9%	1.6%	3.8	0.2
Bifurcation angioplasty	12%	20.6%	0.52	0.22
Thromboaspiration	12%	1.59%	8.45	0.059
Iatrogenic coronary dissection	4%	0%	-	0.69
Residual cronary stenosis	10%	7.9%	1.29%	0.7
Overriding stents	15.3%	6.3%	2.68	0.11

We used multivariate analysis to determine the impact of the following parameters: Emergent versus elective revascularization, hemodynamic instability during PCI, TIMI flow before and after procedure and the presence of thrombus. Only hemodynamic instability (p=0.037) and an altered pre-procedural TIMI flow (p<0.001) emerged as significant predictors of stent thrombosis

DISCUSSION

I- Patient's characteristics

Cardiovascular disease risk factors

We found more diabetics in our ST patients, this finding was not statistically significant in our study but the increased rates of ST in diabetics are reported in numerous publications [4],[5]. The RESTART [6] and HORIZON-AMI [7] studies show similar results and pinpoint the need for insulin as an additional risk factor.

In one study Kerieiakes and al. found a greater proportion of hypertension among patients receiving drug eluting stents and presenting with stent thrombosis, but as in our data this finding was statistically insignificant [8].

Paradoxically we found more smokers in the "controls" arm. We hypothesize that this could be related to declaration bias. J-CYPHER Japanese registry enrolled 12812 patients treated with a Sirolimus stent for a 5-year follow-up and found an association between smoking and very late stent thrombosis [9]. Another publication of Tsuyoshi Honda links smoking to subacute ST with a fivefold relative risk compared to non-smokers [10].

Malignant disease

An article by C. Michael Gross published in JACC and addressing a population of 108 patients with malignancy found a ST rate of 5.56% versus 0.78% for 7081 other patients free of malignant disease, P value was <0.000001 [11]. We notice similar findings in the German ST registry [12]. An interesting publication focuses on the effect of malignancy treatments and finds that chemotherapy is associated with delayed stent endothelialization, which could lead to stent thrombosis [13].

II- Clinical presentation, angiographic findings and procedural aspect of angioplasty related to stent thrombosis

A- Context of stent implantation

A publication of Neville Kukreja shows that stenting in the context of acute coronary syndromes is favorable to the development of stent thrombosis [14]. An explanation would be that plaque rupture and necrotic lipid cores abound in this context, especially for STEMI [15],[16]. Holmes et al detected delayed intimal healing and covering of stent struts lying above necrotic corps [17]. Our results show that 49% of ST victims underwent angioplasty for STEMI treatment. In univariate analysis, urgent revascularization was a predictor of ST ($p< 0.001$). Cardiogenic shock appears to be strongly associated to ST even in multivariate analysis ($P=0.03$). A paper published by Iqbal et al concludes that with an odds ratio of 11.7 and P value <0.001, cardiogenic shock is the first determinant of stent thrombosis [18].

B- Complexity of lesions

In our 'cases' arm, 88% of lesions were B or C type according to the ACC/AHA classification, the percentage in the 'controls' arm was 80.9%. We also found more CTO in the ST group but none of our findings were significant. A paper written by Tomohisa Tada shows that B2 and C type lesions are independent risk factors of ST [19]. Zuzana Motovska found that long multiple lesions and multivessel disease favor stent thrombosis [20]. The Spanish registry highlights the proportional relation between lesions length and ST [21]. A meta-analysis of 221066 patients and 4276 ST incriminates CTO and bifurcation lesions [22]. A study by Pedro Dardas suggests less stent thrombosis when calcified lesions are pre-treated with rotablation [23]. A study of Georgios Sianos reveals that the presence of thrombotic lesions is strongly and independently associated to death and stent thrombosis [24] and a publication in the Scandinavian cardiovascular journal demonstrates that an initial TIMI flow < 2 lead to more ST, essentially in the acute and subacute setting [25]. In his work Juergen Kammler analysed the impact of a final TIMI flow < 3 and noticed a higher trend toward MACCE and ST [26]. In our study TIMI flow < 3 prior to stenting emerged as the strongest predictor of ST in multivariate analysis ($P <0.001$).

C- Angiographic aspects

Stéphane Cook analyzed thrombosed stents using intravascular imaging and found frequent stent malaposition [27]. Alfonso et al observed severe stents under-expansion in a group of patients presenting with ST despite that the procedure fulfilled the criteria of an optimal angioplasty [28]. A publication describes 39% of stent overriding in the

ST group versus 8% for the controls suggesting a cause-effect relation to stent thrombosis ($p<0.001$) [29]. The EXAMINATION study finds more ST in patients with overriding stents particularly in the subgroup of bare metal stents [30].

Peter Sick collected data about 2523 angioplasties with a 6-month follow-up and found a greater number of stent thrombosis in the presence of residual coronary stenosis in the stent edges [31]. A meta-analysis of Cutlip et al enrolled 6186 patients and showed a strong bond between per-procedural coronary dissections and the occurrence of ST with an odds ratio of 3.8 and a confidence interval of [1.9-7.7] [32]. An Italian study analyzed 4630 lesions and found significantly more ST in the group of patients having coronary dissection with a percentage of 6.3% versus 1.3% ($p=0.011$) [33]. Our own data is limited but it supports these allegations

D- Stents properties

A study published in the JACC showed that stent polymers alter arterial healing in animal models [34], another publication found similar safety profile in terms of mortality and occurrence of ST between bare metal stents and drug eluting stents with bioresorbable polymers [35]. Reports pointed a higher rate of ST with drug eluting stents mainly attributed to delayed endothelialization. Aloke V Finn found that this delay was the primary substratum responsible of late ST in a series of autopsies [36]. These findings changed overtime and a large cohort of 18334 patients found lower trends of ST for second generation DES and BMS when compared to first generation DES at 3 years of follow-up [19]. A meta-analysis encompassing 9673 patients found more very late ST with BMS than second general DES [37].

Stent thrombosis is proportional to stent number and length. Cutlip et al found 1.5 more stent thrombosis for every 10 more mm in stents length [32]. Cook et al [29] as well as the German ST registry [12] show correlation between ST and the number of endoprosthesis (odds ratio : 1.35, $p = 0.027$). With 882 cases of ST among 73798 patients, the Swedish cardiac catheterization registry emphasized the importance of stents diameters and concluded to a 50% reduction of risk for each supplementary millimeter [38]. Overall, our results show longer and smaller stents in patients developing ST.

CONCLUSION

We found a significant association between ST, hemodynamic compromise during PCI and alteration of TIMI flow during coronary angiography.

REFERENCES

1. Saidi O, Mansour NB, O'Flaherty M, Capewell S, Critchley JA, Ben Romdhane H. Analyzing Recent Coronary Heart Disease Mortality Trends in Tunisia between 1997 and 2009. PLOS ONE. 3 mai 2013;8(5) :e63202.
2. Steg PG, Harrington RA, Emanuelsson H, Katus HA, Mahaffey KW, Meier B et al. Stent Thrombosis With Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes An Analysis From the Prospective, Randomized PLATO Trial, Circulation. 2013 Sep 3;128(10):1055-65.
3. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Van Es GA, et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation. 1 mai 2007;115(17):2344-51.
4. Wenaweser P, Daemen J, Zwahlen M, Domburg RV, Juni P, Vaina S et al. Incidence and Correlates of Drug-Eluting Stent Thrombosis in Routine Clinical Practice. J Am Coll Cardiol. Sept 2008;52(14):1134-40.
5. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet Lond Engl. 24 févr 2007;369(9562):667-78.
6. Kimura T, Morimoto T, Kozuma K, Honda Y, Kume T, Aizawa T et al. Comparisons of Baseline Demographics, Clinical Presentation, and Long-Term Outcome Among Patients With Early, Late, and Very Late Stent Thrombosis of Sirolimus-Eluting Stents: Observations From the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation. 6 juill 2010;122(1):52-61.
7. Dangas GD, Caixeta A, Mehran R, Parise H, Lansky AJ, Cristea E et al. Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in Acute Myocardial Infarction. Circulation. 26 avr 2011;123(16):1745-56.
8. Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DE, Steg PG et al. Stent Thrombosis in Drug-Eluting or Bare-Metal Stents in Patients Receiving Dual Antiplatelet Therapy. JACC Cardiovasc Interv. oct 2015;8(12):1552-62.
9. Kimura T, Morimoto T, Nakagawa Y, Kawai K, Miyazaki S, Muramatsu T et al. Very Late Stent Thrombosis and Late Target Lesion Revascularization After Sirolimus-Eluting Stent Implantation: Five-Year Outcome of the j-Cypher Registry. Circulation. 31 janv 2012;125(4):584-91.
10. Honda T, Fujimoto K, Miyao Y, Koga H, Ishii M. Current

cigarette smoking is an independent risk factor for subacute stent thrombosis in acute myocardial infarction patients. J Cardiol. mai 2014;63(5):358-64.

11. Gross CM, Posch MG, Geier C, Olthoff H, Kramer J, Dechend R et al. Subacute Coronary Stent Thrombosis in CancerPatients. J Am Coll Cardiol. mars 2008;51(12):1232-3.
12. Van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ et al. Predictors of Coronary StentThrombosis. J Am Coll Cardiol. avr 2009;53(16):1399-409.
13. Mauri L, Yeh RW, Kereiakes DJ. Duration of Dual Antiplatelet Therapy afterDrug-Eluting Stents. N Engl J Med. 2 avr 2015;372(14):1371-4.
14. Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, Domburg R, Serruys PW. The Risk of Stent Thrombosis inPatients With Acute Coronary Syndromes Treated With Bare-Metal and Drug-Eluting Stents. JACC Cardiovasc Interv. juin 2009;2(6):534-41.
15. Nakazawa G. Stent thrombosis of drug eluting stent: Pathological perspective. J Cardiol. sept 2011;58(2):84-91.
16. Cheneau E. Leborgne L, Mintz GS, Kotani J, Pichard AD, Satler LF et al Predictors of Subacute Stent Thrombosis: Results of a Systematic Intravascular Ultrasound Study. Circulation. 23 juin 2003;108(1):43-7.
17. Holmes DR, Kereiakes DJ, Garg S, Serruys PW, Dehmer GJ, Ellis SG et al. Stent Thrombosis. J Am Coll Cardiol. Oct 2010;56(17):1357-65.
18. Iqbal J, Sumaya W, Tatman V, Parviz Y, Morton AC, Grech ED et al. Incidence and predictors of stent thrombosis: a single-centre study of 5,833 consecutive patients undergoing coronary artery stenting. Eurointervention J. EuroIntervention. 2013 May 20;9(1):62-9
19. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M et al. Risk of Stent Thrombosis Among Bare-Metal Stents, First-Generation Drug-Eluting Stents, and Second-Generation Drug-Eluting Stents. JACC Cardiovasc Interv. déc 2013;6(12):1267-74.
20. Motovska Z, Knot J, Widimsky P. REVIEW: Stent Thrombosis—Risk Assessment and Prevention. Cardiovasc Ther. 1 oct 2010;28(5):e92-100.
21. De la Torre-Hernández JM, Alfonso F, Hernández F, Elizaga J, Sanmartin M, Pinar E et al. Drug-Eluting Stent Thrombosis. J Am Coll Cardiol. mars 2008;51(10):986-90.
22. D'Ascenzo F, Bollati M, Clementi F, Castagno D, Lagerqvist B, De la Torre-Hernández JM et al. Incidence and predictors of coronary stent thrombosis: Evidence from an international collaborative meta-analysis including 30 studies, 221,066 patients, and 4276 thromboses. Int J Cardiol. Juill 2013;167(2):575-84.
23. Dardas P, Mezilis N, Ninios V, Tsikaderis D, Theofilogiannakos EK, Lampropoulos S. The Use of Rotational Atherectomy and Drug-Eluting Stents in the Treatment of Heavily Calcified Coronary Lesions. Hellenic J Cardiol. 2011 Sep-Oct;52(5):399-406
24. Sianos G, Papafaklis MI, Daemen J, Vaina S, Mieghem CA, Domburg RT et al. Angiographic Stent Thrombosis After Routine Use of Drug-Eluting Stents in ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol. août 2007;50(7):573-83.
25. Nammas W, Pietilä M, Romppanen H, Sia J, Debelder A, Karjalainen PP. Outcome of poor initial TIMI flow in patients presenting with acute coronary syndrome. Scand Cardiovasc J. 3 sept 2017;51(5):248-54.
26. Kammler J, Kypta A, Hofmann R, Kerschner K, Grund M, Sihorsch K et al. TIMI 3 flow after primary angioplasty is an important predictor for outcome in patients with acute myocardial infarction. Clin Res Cardiol. mars 2009;98(3):165-70.
27. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R et al. Correlation of Intravascular Ultrasound Findings With Histopathological Analysis of Thrombus Aspirates in Patients WithVery Late Drug-Eluting Stent Thrombosis. Circulation. 4 août 2009;120(5):391-9.
28. Alfonso F, Suárez A, Angiolillo DJ, Sabaté M, Escaned J, Moreno R et al. Findings of intravascular ultrasound during acute stent thrombosis. Heart. déc 2004;90(12):1455-9.
29. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C et al. Incomplete Stent Apposition and Very Late Stent Thrombosis After Drug-Eluting Stent Implantation. Circulation. 23 avr 2007;115(18):2426-34.
30. Ortega-Paz L, Brugaletta S, Giacchi G, Ishida K, Cequier A, Iniguez A et al. Impact of stent overlapping on long-term clinical outcomes in patients with ST-segment elevation myocardial infarction: insights from the five-year follow-up of the EXAMINATION trial. EuroIntervention. août 2017;13(5):e557-63.
31. Sick P, Hüttl T, Niebauer J, Thiele H, Lauer B, Hambrecht R et al. Influence of residual stenosis after percutaneouscoronary intervention with stent implantation on development of restenosis and stentthrombosis. Am J Cardiol. janv 2003;91(2):148-53.
32. Cutlip DE, Baim DS, Ho KKL, Popma JJ, Lansky AJ, Cohen DJ et al. Stent Thrombosis in the Modern Era : A Pooled Analysis of Multicenter Coronary Stent Clinical Trials. Circulation. 17 avr 2001;103(15):1967-71.
33. Biondi-Zoccai GGL, Agostoni P, Sangiorgi GM, Airoldi F, Cosgrave J, Chieffo A et al. Incidence, predictors, and outcomes of coronary dissections left untreated after drug-eluting stent implantation†. Eur Heart J. 1 mars 2006;27(5):540-6.
34. John MC, Wessely R, Kastrati A, Schomig A, Joner M, Uchihashi M et al. Differential Healing Responses in Polymer- and Nonpolymer-Based Sirolimus-Eluting Stents. JACC Cardiovasc Interv. Oct 2008;1(5):535-44.
35. Yin Y, Zhang Y, Zhao X. Safety and Efficacy of Biodegradable Drug-Eluting vs. Bare Metal Stents: A Meta-Analysis from

Randomized Trials. PLoS ONE. 19 juin 2014;9(6) :e99648.

36. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK et al. Vascular Responses to Drug Eluting Stents: Importance of Delayed Healing. Arterioscler Thromb Vasc Biol. 1 juill 2007;27(7):1500-10.
37. Philip F, Stewart S, Southard JA. Very late stent thrombosis with second generation drug eluting stents compared to bare metal stents: Network meta-analysis of randomized primary percutaneous coronary intervention trials: Network Meta-Analysis of Randomized PCI Trials. Catheter Cardiovasc Interv. Juill 2016;88(1):38-48.
38. Lagerqvist B, Carlsson J, Frobert O, Lindback J, Scherstén F, Stenestrand U et al. Stent Thrombosis in Sweden: A Report From the Swedish Coronary Angiography and Angioplasty Registry. Circ Cardiovasc Interv. 1 oct 2009;2(5):401-8.