Stent Thrombosis: A Poor Man's Disease?
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**ABSTRACT:**

**Background:** Stent thrombosis is a rare but devastating complication of coronary stent implantation. The incidence and potential predictors were assessed in a "real world" single center.

**Objectives:** To examine whether socioeconomic status indeed affects the occurrence of stent thrombosis.

**Methods:** We searched our database for cases of "definite" stent thrombosis (according to the ARC Dublin definitions). Each case was matched by procedure date, age and gender with three cases of stenting that did not result in stent thrombosis. Demographic and clinical parameters were compared and socioeconomic status was determined according to a standardized polling and market survey database.

**Results:** A total of 3401 patients underwent stent implantation in our hospital during the period 2004–2006. Their mean age was 63 ± 11 years, and 80% were males. Twenty-nine cases (0.85%) of "definite" sub-acute/late stent thrombosis were recorded. Mortality at 30 days was recorded in 1 patient (3.5%). Thrombosis occurred 2 days to 3 years after stent implantation. All patients presented with acute myocardial infarction. Premature clopidogrel discontinuation was reported in 60%. Patients with stent thrombosis had significantly higher rates of AMI at the time of the initial procedure (76 vs. 32%, P < 0.001) and were cigarette smokers (60 vs. 28%, P < 0.001). Drug-eluting stents were used less in the stent thrombosis group. There was no difference in stent diameter or length between the two groups. Socioeconomic status was significantly lower in the stent thrombosis group, 3.4 ± 2.4 vs. 5.4 ± 2.6 (mean ± SD, scale 1–10, P < 0.01).

**Conclusions:** The incidence rate of stent thrombosis is at least 0.85% in our population. It appears in patients with significantly lower socioeconomic status and with certain clinical predictors. These results warrant stricter follow-up and support the policy of healthcare providers regarding patients at risk for stent thrombosis.

**KEY WORDS:** stent thrombosis, low socioeconomic status, myocardial infarction, angioplasty

Stent thrombosis has emerged recently as a serious safety concern after stent implantation. An ongoing controversy exists as to whether the use of drug-eluting stents is associated with increased risk for stent thrombosis. Other possible predictors for this condition include technical aspects of stenting such as underexpansion, malapposition and dissection [1,2], and patient-related factors such as advanced age, smoking, diabetes and hypertension, and the presenting clinical syndrome [3,4]. Thienopyridine therapy significantly reduces the risk for stent thrombosis [5] and hence early discontinuation is associated with an increased risk for stent thrombosis [4]. The need for prolonged therapy may expose patients of lower financial means and of low compliance to the increased thrombosis risk.

The present study examined whether socioeconomic status indeed affects the occurrence of stent thrombosis. Socioeconomic status as well as potential clinical predictors were investigated in affected patients and matched controls in a "real world" single-center cohort.

**PATIENTS AND METHODS**

**STUDY DESIGN AND PATIENT POPULATION**

A database of 3401 consecutive patients who underwent angioplasty from January 2004 to July 2006 was searched for cases that were readmitted to our center and diagnosed with stent thrombosis. Only cases of "definite" stent thrombosis according to the ARC Dublin definitions [6], determined by both angiographic findings of stent occlusion and acute myocardial infarction in the area provided by this artery, were included in this analysis. Thus, patients with "possible" or "probable" stent thrombosis were not studied. Demographics, angiographic and procedural data were analyzed according to medical records and angiograms of the index procedure. Each case was matched by procedure date, age and gender. Three angioplasty cases did not result in stent thrombosis for at least 6 additional months. Demographic, clinical and procedural parameters were compared between the thrombosis and the control group.

Socioeconomic status was determined according to a Geocartography™ nationwide, a highly detailed demographic and socioeconomic and information system (Geocartography Data Base) in which the smallest unit of information is a building. There are about half a million...
buildings in Israel with respect to which socioeconomic data exist in the system. Thus, matching patients’ addresses with the GDB information system yielded the socioeconomic status of the patients. This unique Information system utilizes advanced GIS Free-Space analytical-mapping models for social research. GDB combines Geocartographic theory and models, and field-lab techniques, including software (developed by Prof. A. Degani, Tel Aviv University). This information system is continuously updated to reflect the real geostatistical situation in Israel.

Further analysis was conducted to compare between patients who were on Plavix® and/or aspirin therapy at the time of stent thrombosis.

STATISTICAL ANALYSIS
An unpaired t-test was used to compare between continuous variables, and the Pearson chi-square test was used for categorical parameters. A P value of < 0.05 was considered statistically significant.

RESULTS
A total of 3401 patients underwent stent implantation in our cathlab during the study period, and of these, 29 cases (0.85%) of “definite” sub-acute/late stent thrombosis were recorded. Patient characteristics are presented in Table 1. The patients’ mean age was 63 ± 11 years and 80% were males. All patients presented with acute myocardial infarction. Thrombosis occurred 2 days to 3 years after stent implantation. Premature clopidogrel discontinuation (less than 1 month following bare metal stenting and less than 6 months treatment following use of a drug-eluting stent) was reported in 60% of thrombosis patients. During the study period the use of a DES was approximately 30% of the total number of stents, and was used mainly for in-stent restenosis, long lesions, chronic total occlusions, and in diabetic and chronic renal failure patients. The occurrence of stent thrombosis was similar in patients who underwent implantation of a bare metal stent (23 of 2583, 0.89%) and those who received a DES (7 of 818 subjects, 0.7%). No differences for either a particular brand DES or BMS were observed in this series. There was no difference in the time interval between the initial procedure and the occurrence of stent thrombosis between BMS and DES cases. Median time to stent thrombosis was 20 ± 11 and 27 ± 11 days, respectively. Of note is that the three cases of late stent thrombosis (>1 year) occurred in patients in whom bare metal stents (two cases) and PTFE (polytetrafluoroethylene, teflon)-covered stent (one case) were implanted. No case of late post-DES stent thrombosis was recorded in this series.

Comparing thrombosis patients with matched controls revealed a significantly higher rate of AMI at the time of the initial procedure (76 vs. 32%, < 0.001). Stent thrombosis patients also had a higher rate of cigarette smoking (60 vs. 28%, < 0.001). No differences were found in stent diameter or length between the two groups. Surprisingly, there was a lower rate of DES use in the stent thrombosis group as compared to the control (25 vs. 44%, respectively, < 0.05).

Ten patients were not taking aspirin and 18 patients were not treated with Plavix® at the time stent thrombosis occurred. Two of the patients were not taking aspirin due to allergy while the others could not provide a reasonable reason for cessation of therapy other than poor compliance.

Analysis for socioeconomic status according to the patient’s permanent residence address revealed a significantly lower socioeconomic level of stent thrombosis patients as compared to the control matched group, 4 ± 0.6 vs. 5.4 ± 0.3, respectively (mean ± SE, scale 1–10, < 0.05) [Figure 1]. Exclusion of the two patients who discontinued aspirin due

<table>
<thead>
<tr>
<th>Stent thrombosis (n=29)</th>
<th>Control (n=87)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62.5 ± 7.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Non-insulin-dependent diabetes mellitus</td>
<td>54</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 ± 3.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>60 ± 4.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Culprit lesion (%)</td>
<td></td>
<td></td>
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<tr>
<td>Left main artery</td>
<td>68 ± 4.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Anterolateral descending artery</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>24 ± 3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>3 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>1.3 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>No. of stents/procedure</td>
<td>1.32 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Stent ≥18 mm (%)</td>
<td>42 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Stent length (mm, mean ± SD)</td>
<td>16±5.7</td>
<td>17.1±8.5</td>
</tr>
<tr>
<td>Stent diameter (mm, mean ± SD)</td>
<td>3.16±0.47</td>
<td>3.2±0.48</td>
</tr>
<tr>
<td>DES use</td>
<td>25% ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AMI at presentation (%)</td>
<td>53 ± 2.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

GDB = Geocartography Data Base

Figure 1. Socioeconomic status of patients with stent thrombosis (ST) and of matched controls. Scale of 1–10, error bars denote standard error, * P < 0.05
to allergy further increased the difference to 3.5 ± 0.45 vs. 5.4 ± 0.3, respectively, \( P < 0.01 \).

**DISCUSSION**

Acute, sub-acute and late thromboses following implantation of intracoronary stents are major complications of this widely used procedure. Late stent thrombosis following implantation of a BMS was rarely reported prior to the introduction of DES [7]. However, recent data suggest that this problem was probably overlooked in the past [8,9]. Controversy still exists with regard to whether DES use is associated with an increased rate for late and very late stent thrombosis in comparison with bare metal stents.

The present series is too small to contribute any data to the ongoing debate whether DES use is associated with an increased risk for stent thrombosis. Our center’s policy during the study period did not support the use of DES in patients with AMI. AMI appears in our series as well as in other series [3,10] as associated with an increased risk for subsequent stent thrombosis. At the present time it seems that only randomized controlled trials and their meta-analyses will solve this question.

The incidence of stent thrombosis in our series was 0.85%. Only patients with “definite” stent thrombosis according to the ARC criteria were included in this analysis. The strict criteria in addition to the very low rate of mortality recorded in our series may indicate that the true rate of stent thrombosis is actually higher. Alas, the goal of this study was not to record the rate of stent thrombosis but rather to define its associated characteristics and risk factors. For such a study we believe that a stricter approach for stent thrombosis definition is required.

In addition to AMI at presentation, several factors were identified to be associated with stent thrombosis including diabetes. This association is in accord with previous reports [3,4,11-13] and suggest that endothelial dysfunction and defective vascular repair may contribute to the pathogenesis of thrombosis. An additional risk factor that is significantly associated with the condition is cigarette smoking. This may come as no surprise since smoking is a known predictor of AMI and is associated with increased thrombogenicity and impaired thromboregulation [14,15].

Premature discontinuation of antithrombotic therapy and especially cessation of thienopyridines is a strong predictor of stent thrombosis [3-5,8]. Spertus et al. [16] studied the prevalence and predictors for premature discontinuation of thienopyridine therapy in 500 AMI patients who were treated with DES in the PREMIER registry. At 30 days after percutaneous coronary intervention cessation of treatment was recorded in 13.6% of cases in the registry. This high rate of discontinuation was associated with significantly higher morbidity and mortality. Lack of a high school diploma was significantly related to premature discontinuation. Other variables including older age, lack of instructions during discharge, and avoiding medical care due to cost were also related with early thienopyridine cessation.

Social inequality is associated with increased mortality [17]. Several variables may underlie this grim difference, including limited resources, unhealthy behavior (cigarette smoking, sedentary lifestyle, etc.), low utilization of available screening and prevention measures, low compliance, communication problems, and inadequate attitude of health personnel.

The present report further emphasizes the association of low socioeconomic status with increased morbidity. While we cannot modify all the above variables, special precautions should be used to address those that are modifiable, such as low compliance, appropriate attitude, and a rigorous attempt to improve lifestyle habits.

In conclusion, the occurrence of stent thrombosis in our center is at least 0.85%. It occurs in patients of significantly lower socioeconomic status and with previously described clinical predictors including AMI at presentation, diabetes and cigarette smoking. The association of low socioeconomic status with the severe clinical syndrome of stent thrombosis warrants a socioeconomic evaluation of patients admitted for either elective or emergency PCI and a stricter follow-up, and supports the policy of healthcare providers regarding patients at risk for stent thrombosis.

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**References**


**PCI** – percutaneous coronary intervention
A human colonic commensal promotes colon tumorigenesis

The intestinal flora may promote colon tumor formation. Wu and co-researchers explored immunological mechanisms of colonic carcinogenesis by a human colonic bacterium, enterotoxigenic Bacteroides fragilis (ETBF). ETBF that secretes B. fragilis toxin (BFT) causes human inflammatory diarrhea but also asymptomatically colonizes a proportion of the human population. The results indicate that whereas both ETBF and non-toxigenic B. fragilis (NTBF) chronically colonize mice, only ETBF triggers colitis and strongly induces colonic tumors in multiple intestinal neoplasia (Min) mice. ETBF induces robust, selective colonic signal transducer and activator of transcription-3 (Stat3) activation with colitis characterized by a selective T helper type 17 (TH17) response distributed between CD4+ T cell receptor-α(β)+ and CD4–8–TCRγδ+ T cells. Antibody-mediated blockade of interleukin-17 (IL-17) as well as the receptor for IL-23, a key cytokine amplifying TH17 responses, inhibits ETBF-induced colitis, colonic hyperplasia and tumor formation. These results show a Stat3- and TH17-dependent pathway for inflammation-induced cancer by a common human commensal bacterium, providing new mechanistic insight into human colon carcinogenesis.

Eitan Israeli

Alternatively spliced vascular endothelial growth factor receptor-2 is an essential endogenous inhibitor of lymphatic vessel growth

Disruption of the precise balance of positive and negative molecular regulators of blood and lymphatic vessel growth can lead to myriad diseases. Although dozens of natural inhibitors of hemangiogenesis have been identified, an endogenous selective inhibitor of lymphatic vessel growth has not been previously described. Albuquerque et al. report the existence of a splice variant of the gene encoding vascular endothelial growth factor receptor-2 (Vegfr-2) that encodes a secreted form of the protein, designated soluble Vegfr-2 (sVegfr-2), which inhibits developmental and reparative lymphangiogenesis by blocking Vegf-c function. Tissue-specific loss of sVegfr-2 in mice induced, at birth, spontaneous lymphatic invasion of the normally alymphatic cornea and hyperplasia of skin lymphatics without affecting blood vasculature. Administration of sVegfr-2 inhibited lymphangiogenesis but not hemangiogenesis induced by corneal suture injury or transplantation, enhanced corneal allograft survival and suppressed lymphangioma cellular proliferation. Naturally occurring sVegfr-2 thus acts as a molecular uncoupler of blood and lymphatic vessels. Modulation of sVegfr-2 might have therapeutic effects in treating lymphatic vascular malformations, transplantation rejection and, potentially, tumor lymphangiogenesis and lymphedema.

Eitan Israeli

“Speech: a constant stratagem to cover nakedness”

Harold Pinter (1930-2008), English playwright, screenwriter, actor, director, political activist and poet. He was among the most influential British playwrights of modern times and in 2005 was awarded the Nobel Prize for Literature