CORONARY STENTS:
CLINICAL EXPERIENCE
AND COST-EFFECTIVENESS
CORONARY STENTS: CLINICAL EXPERIENCE AND COST-EFFECTIVENESS

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EXECUTIVE SUMMARY

Coronary stents are of value for the treatment of acute or threatened coronary artery closure complicating PTCA. Short-term clinical and angiographic outcomes are comparable with different stent designs for acute or threatened closure. Coronary stents reduce the likelihood of both angiographic restenosis and the need for repeat revascularization in particular groups of patients compared to PTCA alone. New antithrombotic therapies after stent implantation have the potential to lower its procedural costs by reducing stent-related vascular complications and length of hospital stay. Coronary stenting is an evolving technology and data from more randomized controlled trials will be required for more robust conclusions. Economic analyses to date have primarily been limited to the experience of a single U.S. group. Canadian clinical and economic data on coronary stents will be needed before informed predictions can be made on its cost-effectiveness in our health care system.
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OBJECTIVES

The purpose of this report is to provide an overview of published information on the clinical experience with and cost-effectiveness of coronary stents in the treatment of coronary artery disease. This overview is an update of the review by the Conseil d’évaluation des technologies de la santé du Québec (CÉTS) in June 1996 on clinical experience with coronary stents (Appendix 1). This assessment was requested by a provincial health ministry for policy/program development on coronary stents.
INTRODUCTION

Despite impressive technical refinements of equipment and technique during the past two decades, percutaneous transluminal coronary angioplasty (PTCA) remains plagued by two major limitations: acute or threatened vessel closure during intervention and restenosis during follow-up. Newer angioplasty devices such as atherectomy (direct, rotational, extraction) and laser angioplasty, although proven to be feasible techniques, have to date shown null or marginal utility (Conseil d’évaluation des technologies de la santé du Québec, 1996).

Coronary stents have gained substantial recent popularity in the field of interventional cardiology as a means of overcoming these limitations. Since the first stent implant in human coronary arteries by Sigwart and colleagues in 1986 (Sigwart et al., 1987), perseverance of certain investigators with this technique has led to considerable progress in coronary stenting. At the 45th Annual Scientific Session of the American College of Cardiology held in March 1996, in addition to reports on refinements to existing designs, investigators from France, Israel, Japan and other countries reported on at least three new stent designs, including ones that are self-expandable (American College of Cardiology, 1996).

At present, six coronary stents have been approved by the Health Protection Branch of Health Canada: the Cordis (Cordis Corp.), Freedom (Global Therapeutics, Inc.), Gianturco-Roubin (Cook Inc.), Multi-Link (Advanced Cardiovascular Systems), Palmaz-Schatz (Johnson and Johnson Interventional Systems), and Wiktor (Medtronic Inc.). (Table 1)

The Gianturco-Roubin and Palmaz-Schatz stents have received approval by the Food and Drug Administration (FDA) of the United States for specific indications. The FDA has approved the Gianturco-Roubin stent for acute or threatened closure (“bailout”), and the Palmaz-Schatz stent for restenosis after angioplasty. The Palmaz-Schatz stent is the most studied and the most widely used stent in the world. The BENESTENT-I (BElgium and NEtherlands STENT study) (Serruys et al., 1994) and STRESS-I (STent RESTenosis Study group) (Fischman et al., 1994) trials were carried out with this stent, and a follow-up trial (BENESTENT-II Pilot Study) (Serruys et al., 1996) is being carried out with second-generation Palmaz-Schatz stents.
METHODOLOGY

Literature Search

Published literature was obtained through searches (January, 1992 to July, 1996) on the following bibliographic databases: MEDLINE, Health Planning & Administration, EMBASE, SciSearch and HSTAR. Non-human studies were excluded. The keywords used in the main search included: “coronary” or “endovascular” or “restenosis” with “stent” (truncated term). Additional search terms included the names of particular types of stents, and names of the groups involved in stent trials. These terms were then combined with sub-sets of additional terms which divided the search into three parts: trials, reviews and costs. Because the CÉTS report had been completed relatively recently (literature review up to March, 1995), review of trials literature was restricted to articles published from January, 1995, and reviews literature to studies from January, 1996. No restrictions were applied to the search of the costs literature with respect to publication dates. Additional literature was retrieved based on subsequent suggestions by reviewers of this report.

Following this strategy, twelve reports of clinical studies of stenting were retrieved and reviewed. Five publications dealing with costs and/or cost-effectiveness issues were also retrieved. The following review is based on the CÉTS report and these 17 publications.
CLINICAL EXPERIENCE

Acute or Threatened Closure

Acute or threatened vessel closure (AVC or TVC) after PTCA remains an unpredictable event that causes an increased rate of in-hospital death, myocardial infarction (MI), and increased need for coronary artery bypass grafting (CABG). AVC is defined as thrombolysis in myocardial infarction (TIMI) grade 0 or 1 flow after PTCA, and TVC is defined as including one of the following: >50% residual stenosis, dissection ≥15 mm in length, extraluminal contrast, angina or electrocardiographic (ECG) changes of ischemia (Pepine et al., 1996). The pathologic process and the complications associated with acute and threatened closure are described elsewhere.¹

Due to a lack of adequate studies of alternative procedures (e.g., prolonged balloon inflation) for AVC or TVC within the date limits of the literature review, the impact of stenting on clinical outcomes cannot be more objectively assessed. A number of observational and randomized studies for “bailout” indications with different stent types and designs, however, have been reported since the CÉTS report.

(i) Randomized Study

In a prospective, randomized study (Goy et al., 1995), rates of successful implantation and complications were similar with both the articulated Palmaz-Schatz and Wiktor stents. 65 patients, with AVC or TVC following PTCA, were randomly assigned to one of these stent types. Stenting was technically feasible in all but one patient assigned to the Palmaz-Schatz stent, and immediately successful in reverting ischemia and vessel closure in 60 patients (92%). Angiographic restenosis² rates and clinical outcomes with both devices were generally comparable at hospital discharge and on 6 months follow-up (Table 2). Based on these findings, Goy et al. (1995) conclude that the choice whether to use a Wiktor or Palmaz-Schatz stent for acute or threatened closure may probably be left to the discretion of the operator and his or her particular experience with one device.

(ii) Observational Studies

Robinson et al. (1995) comparing clinical outcomes of a full (articulated) Palmaz-Schatz stent implanted as both an elective and “bailout” procedure for AVC and TVC, have reported low complication rates following stents inserted for TVC. In-hospital complication rates in the “bailout” procedure were higher in the treatment of AVC as compared to TVC.

¹Based on the 1985-1986 U.S. National Heart, Lung, and Blood Institute PTCA registry data reviewed in the CÉTS report (p.4), for example, abrupt closure during angioplasty was associated with a 5% mortality, 40% MI, and 50% combined urgent and elective CABG. Due to changes in clinical practice in subsequent years, these rates may be different at the present time.

²Angiographic restenosis (≥50% residual diameter restenosis) after PTCA of large arteries with restenotic lesions occurs in 30% to 50% of patients by six months’ follow-up, and repeat revascularization is required in ~20% to 30% of all PTCA cases (Pepine et al., 1996).
Over a 6 month follow-up period, however, out-of-hospital rates were comparable and infrequent in both, with no patient in either “bailout” category dying or undergoing CABG (Table 2). These findings, albeit limited by study design (non-randomized, uncontrolled) and a small series of patients at a single referral center, suggest the need for early stent implantation prior to the development of intracoronary complications associated with acute vessel closure (Robinson et al., 1995).

Mehan et al. (1995) have reported on their findings in 102 patients with use of the half (disarticulated) Palmaz-Schatz stent. “Bailout” stenting was performed in 97 patients, the others receiving half stents for elective indications. Implantation success rate was 98%. Major complications included one procedural death, and one Q-wave MI. None of the study patients required emergency CABG (Table 2). The investigators recommend the use of the half Palmaz-Schatz stent in situations where a full stent may not be ideally suited (e.g., thrombotic and aorto-ostial lesions). According to the authors, use of half a stent, by reducing the amount of implanted metal in the coronary artery, has the potential to lower the risk of stent thrombosis, and to cut the costs in half. They, however, caution operators with regard to the extra care required in the mounting and delivery of the half stent, since its short length does not allow any leeway in placement (Mehan et al., 1995).

Studies with other stent designs for AVC or TVC have also been conducted. Initial clinical experience, for example, with the Microstent (Webb et al., 1996), Multi-Link (Priestley et al., 1996) and Strecker (Hamm et al., 1995) coronary stents is generally comparable to the Palmaz-Schatz and Wiktor stents in terms of clinical outcome and angiographic restenosis (Table 2). The long-term effects of coronary stenting with these different stent types and designs, however, are not known.

Restenosis After Angioplasty

The Palmaz-Schatz stent has been the most widely used stent for primary restenosis prevention. The BENESTENT-I (n=516) and STRESS-I (n=407) trials demonstrated that the use of the Palmaz-Schatz stent as a routine adjunct to PTCA on average increased angiographic success from 91% to 94%, and reduced the rates of restenosis and repeat PTCA at 6 months from 36% to 26%, and 17% to 11% respectively. Neither trial showed, on average, any difference in mortality, Q-wave MI, or the need to perform emergency CABG either acutely or at 6 months of follow-up. Patients who received stents had a longer hospital stay (7 days for the stents group vs 3 days for the PTCA group) and a higher incidence of bleeding complications with a need for surgical repair or blood transfusion (11% for the stents group vs 3% for the PTCA group). Patients assigned to stent placement in both of these trials received intensive anticoagulation therapy (Conseil d’évaluation des technologies de la santé du Québec, 1996).

Longer-term data have been published on the Palmaz-Schatz stent to evaluate the long-term outcome of stent placement in native coronary arteries. Macaya et al., (1996) have shown, based on 1-year data from the BENESTENT-I trial, that the reduction in the rates of angiographic restenosis and repeat PTCA reported earlier from this trial are maintained to one year. No discernible differences existed between the treatment groups for mortality, Q-wave MI, or emergency CABG (Table 3). The results of this trial suggest that stenting may not only postpone restenosis but actually appears to reduce magnitude of the restenosis in new lesions in large native coronary arteries measuring 3.0 mm or more in diameter (Macaya et al., 1996). This finding is supported by Kimura et al., (1996) (Table 3) who in fact report, based on serial angiographic observations, a significant late improvement in minimal luminal diameter between six months (1.94 ± 0.48 mm) and three years (2.09±0.48 mm; p<.001) in 143 patients who underwent stenting, after an initial decrease in diameter immediately after stent placement (2.54±0.44 mm to 1.87±0.56 mm).
**Antithrombotic Therapy**

In an effort to prevent stent-associated thrombosis, most of the early trials (BENESTENT-I, STRESS-I) adopted an intensive anticoagulation regimen including heparin, dextran, aspirin, dipyridamole, and warfarin. Due to an increase in stent-associated thrombosis and bleeding complications in some patients receiving intensive anticoagulant therapy, it became clear that alternative antithrombotic approaches were needed to prevent thrombosis. New information (Neumann et al., 1996) that activation of platelets, rather than the coagulation pathway, increases the risk of stent-associated thrombosis, has stimulated investigators in recent trials to examine the role of antiplatelet therapy.

(i) Randomized Study

Schömig et al. (1996) compared antiplatelet and conventional anticoagulant therapy after the placement of Palmaz-Schatz stents in 517 patients, in a prospective, randomized trial. All patients received aspirin for four weeks. 257 (of 517) patients were assigned to receive ticlopidine (250 mg twice daily for four weeks) and 260 (of 517) patients received intravenous heparin and phenprocoumon, for 5 to 10 days and four weeks, respectively (Table 3). Schömig et al. (1996) report an 82% decreased risk of MI, an 87% decreased incidence in peripheral vascular events and a 78% decreased need for repeated interventions in patients assigned on antiplatelet therapy compared with those on anticoagulants. Occlusion of the stented vessel occurred in 0.8% of patients on antiplatelet therapy and in 5.4% of patients on anticoagulants. Cerebrovascular accidents, peripheral vascular events and death from noncardiac causes occurred in 1.2% of patients on antiplatelet therapy and in 12.3% of patients on anticoagulant therapy. Hemorrhagic complications occurred only in patients on anticoagulants. Based on these results, Schömig et al. (1996) conclude that, compared with anticoagulant therapy, antiplatelet therapy after successful placement of coronary artery stents reduces the incidence of both cardiac events, and hemorrhagic and vascular complications.

(ii) Observational Studies

In a study intended to further examine the requirement for anticoagulant therapy Serruys et al. (1996) have investigated the use of the heparin-coated Palmaz-Schatz stent in 207 patients with stable angina resulting from a single de novo lesion in a coronary artery (BENESTENT-II Pilot Study). The BENESTENT-II Pilot Study was designed as a sequential, four-phase, uncontrolled observational trial with about 50 patients in each phase (Table 3). Patient eligibility criteria were similar to BENESTENT-I. All patients received aspirin for six months. In phases I, II, and III, heparin was given as a bolus dose at the beginning of the procedure and reinstituted as a continuous infusion 6, 12, or 36 hours, respectively, after removal of the arterial sheath. Phase IV patients received only oral ticlopidine 250 mg daily after sheath removal.

None of the 202 patients in whom stent placement was successful experienced stent thrombosis. The incidence of severe bleeding decreased progressively with each phase falling from 7.9% in phase I to 0% in phase IV. Length of in-hospital stay for patients receiving ticlopidine was half that for anticoagulated patients (Table 3). The rate of angiographic restenosis ranged from 6% to 20% and was lowest in the ticlopidine group (Table 3). At the 6-month follow-up, 84%, 75%, 94%, and 92% of the patients of phases I to IV, respectively, were free of major clinical complications (Table 3). On the basis of these findings, Serruys et al. (1996) conclude that heparin-coated stents when implanted by current techniques in patients with stable angina pectoris and one de novo lesion is a well tolerated procedure, and is associated with no (sub)acute thrombosis, and results in a favorable event-free survival at 6 months follow-up.
Despite its impressive success rates, the Pilot Study (Serruys et al., 1996) does not convincingly demonstrate that the low rate of stent thrombosis is due to the heparin coating of the stent or to some other treatment influence (Williams, 1996). For example, the technique of stent deployment in the Pilot Study (Serruys et al., 1996) differed from that used in BENESTENT-I and was not consistent throughout the Pilot Study itself. Recent investigations (Colombo et al., 1995; Karrillon et al., 1996) demonstrate that low rates of stent thrombosis can be achieved with non-heparin-coated stents, with or without ultrasound guidance. Randomized trials comparing the two kinds of stents and using similar deployment methods, and extended to other stent designs and study populations, will be required to evaluate the influence of heparin coating in interventional cardiology (Williams, 1996).

These findings on the role of antithrombotic therapy, albeit limited, provide support for a reduced anticoagulant regimen and show that antiplatelet therapy with ticlopidine and aspirin is a safe and effective alternative to intense anticoagulation after satisfactory stent deployment in a particular group of patients. The role of ticlopidine after coronary stenting, however, needs to be explored in further controlled trials in light of its important side effects (neutropenia) (Schöneberger and Schmidt, 1996).
The limited published clinical experience described above suggests that coronary stents reduce both angiographic restenosis and the need for repeat revascularization compared to PTCA. Stent-related vascular complications and an increased length of hospital stay, however, have led to concern over the cost-efficiency of widespread application of this procedure in interventional cardiology.

Cohen and colleagues (Cohen et al., 1994, Cohen and Baim, 1995) have performed a cost-utility analysis of stenting with the Palmaz-Schatz coronary stent compared with PTCA in patients with single-vessel disease. A decision-analysis model was developed to evaluate three specific strategies: (1) PTCA, (2) coronary stenting, and (3) initial PTCA followed by stenting to treat symptomatic restenosis (secondary stenting). The probability estimates for procedural success and complications were derived from a review of the literature published as of December, 1994 (e.g., from BENESTENT-I and STRESS-I trials). Since cost estimates were not available from these trials at the time of modeling, cost data were based on earlier estimates of the resource costs of the relevant procedures as measured by the investigators (Cohen et al., 1993).

Under baseline estimates, their model predicted that a 55 year-old male with symptomatic, single-vessel coronary disease treated by PTCA alone would have a quality-adjusted life expectancy of 19.24 years and an expected lifetime treatment cost of US $52,100 (Cohen and Baim, 1995). In comparison, the strategy of initial stenting produced a slightly greater quality-adjusted life expectancy (19.27 QALYs) but at a somewhat higher lifetime cost (US $52,700), with an incremental cost-utility ratio of US $33,700 per QALY gained compared to PTCA alone (Cohen and Baim, 1995). The strategy of secondary stenting (baseline: US $72,500/QALY), in contrast, was estimated to be less effective and less cost-effective than initial stenting over a wide range of variables.

Sensitivity analyses performed by the investigators demonstrated that the cost-utility ratio was most sensitive to the relative restenosis rates for stenting and PTCA, and to the vascular complication rate with stenting. The cost-utility ratio for stenting, for example, would remain at less than US $40,000/QALY as long as the PTCA angiographic restenosis rate were greater than 31% and the PTCA abrupt closure rate were greater than 5% (Cohen and Baim, 1995).

Analysis of the economic outcome of the STRESS-I trial by Cohen et al., (1995) has subsequently demonstrated that, compared with PTCA, primary stenting was associated with significantly higher initial hospital cost (US $9,738 vs US $7,505; p <.001), mainly because of a significantly longer hospital stay (7.5 vs 4.8 days; p <.001) and higher catheterization laboratory cost (US $4,705 vs US $3,643; p <.001) (Cohen et al., 1995). However, follow-up hospital costs during the next year were lower for stenting than for PTCA (US $1,918 vs US $3,359; p =.21). Nonetheless, cumulative one-year medical care costs remained higher for patients undergoing initial stenting (US $11,656 vs US $10,865) (Cohen et al., 1995). Recent research into alternative stent deployment techniques (Kiemeneij et al., 1995), for example, demonstrate a reduced cost of initial hospitalization associated with stenting (Dfl 9,409 for the transradial bare technique vs. Dfl 14,046 for the transfemoral sheath-protected technique).

Despite providing much needed economic data for coronary stents, the above analyses have primarily been limited to the experience of one U.S. group, and on (U.S.) data from (a particular group of) patients treated between 1991-93 (STRESS-I economic study by Cohen et al., 1995). Current trends in stenting practice (e.g., antiplatelet therapy) and changes in costs further reduce the relevance of these data.
## Table 1: Stent Types Under Current Clinical Investigation

<table>
<thead>
<tr>
<th>Stent type:</th>
<th>Study:</th>
<th>Indication:</th>
<th>Delivery System (expandability):</th>
<th>Composition:</th>
<th>Configuration:</th>
<th>HPB/FDA approval/date:</th>
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<tr>
<td>Act-One</td>
<td>Nakamura et al., 1996</td>
<td>elective/bailout</td>
<td>balloon</td>
<td>nitinol</td>
<td>slotted tube</td>
<td>HPB/June, 1996</td>
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<td>Cordis</td>
<td>Hamasaki et al., 1995</td>
<td>elective/bailout</td>
<td>balloon</td>
<td>tantalum</td>
<td>single strand, continuous wire</td>
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<td>Freedom</td>
<td>Chevalier et al., 1996</td>
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<td>balloon</td>
<td>stainless steel</td>
<td>wire mesh</td>
<td>HPB/Oct, 1993</td>
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<tr>
<td>Gianturco-Roubin</td>
<td></td>
<td>bailout</td>
<td>balloon</td>
<td>stainless steel</td>
<td>flexible coil</td>
<td>FDA/June, 1992</td>
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<td>second generation</td>
<td>Marco et al., 1996</td>
<td>elective</td>
<td></td>
<td></td>
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<td>Microstent PL</td>
<td>Webb et al., 1996</td>
<td>bailout/elective</td>
<td>balloon</td>
<td>stainless steel</td>
<td>wire zigzags</td>
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<td>balloon</td>
<td>stainless steel</td>
<td>individual corrugated rings</td>
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<td>elective/bailout</td>
<td>self</td>
<td>nitinol</td>
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<td>Palmaz-Schatz</td>
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<td>balloon</td>
<td>stainless steel</td>
<td>slotted tube</td>
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<td>articulated-</td>
<td>Serruys et al., 1996</td>
<td>elective</td>
<td>balloon</td>
<td>stainless steel</td>
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<td>FDA/Aug, 1994</td>
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<td>(heparin-coated)</td>
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<td>disarticulated</td>
<td>Mehan et al., 1995</td>
<td>bailout/elective</td>
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<td>Hamm et al., 1995</td>
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<td>balloon</td>
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<td>single-wire</td>
<td>HPB/May, 1995</td>
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<td>single wire, sinusoidal helix</td>
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<td>self</td>
<td>stainless steel</td>
<td>multiple wire-braid</td>
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</table>

HPB = Health Protection Branch (Health Canada); FDA = Food and Drug Administration (USA)
### Table 2: Clinical Studies: Acute or Threatened Closure

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<tr>
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<td>91-93</td>
<td>32</td>
<td>58</td>
<td>(80)</td>
<td>97</td>
<td>6</td>
<td>6 -</td>
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<td>3</td>
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<td>retrospective : observational</td>
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<tr>
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<td>13</td>
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<td>6</td>
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<td>38 (of 24 Pts)</td>
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<tr>
<td>Palmaz-Schatz (disarticulated) Mehan et al., 1995</td>
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<td>93-94</td>
<td>102</td>
<td>60</td>
<td>81</td>
<td>98</td>
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<td>1</td>
<td>0 -</td>
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<td>prospective : observational (32)*</td>
<td>7-year</td>
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<tr>
<td>Multi-Link Priestley et al., 1996</td>
<td>prospective : observational</td>
<td>93</td>
<td>10</td>
<td>-</td>
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<tr>
<td>Strecke Hamm et al., 1995</td>
<td>prospective : observational</td>
<td>90-91</td>
<td>64</td>
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Pts = patients; CABG = coronary artery bypass grafting; MI = myocardial infarction; LOS = length of (hospital) stay; PTCA = percutaneous transluminal coronary angioplasty; * = “bailout” indication
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<th>Stent &amp; Study:</th>
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<th>Pts (no.):</th>
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<th>Patient Characteristics</th>
<th>Implant. Success (%):</th>
<th>Death (%):</th>
<th>Q-wave MI (%):</th>
<th>Urgent CABG (%):</th>
<th>LOS (days):</th>
<th>Follow-up Death: MI (%):</th>
<th>Follow-up Death: CABG (%):</th>
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</table>

Pts = patients; CABG = coronary artery bypass grafting; MI = myocardial infarction; LOS = length of (hospital) stay; PTCA = percutaneous transluminal coronary angioplasty
APPENDICES

Appendix 1: Specific Recommendations on Coronary Stents by the Conseil d’évaluation des technologies de la santé du Québec, (1996)

a) **Acute or Threatened Closure**
Coronary stenting is an established percutaneous technique with proven safety and efficacy in the acute treatment of abrupt or threatened closure following PTCA and it reduces the incidence of acute myocardial infarction, urgent CABG and death (strength of recommendation A; quality of evidence II). The risk of sub-acute stent thrombosis makes long term management of these patients uncertain.

b) **Stable Angina**
Coronary stenting is an innovative technique with proven safety and efficacy in the treatment of the symptoms of appropriate patients with stable angina pectoris and de novo native arterial lesions and reduces the restenosis rate compared to PTCA. Stents do not affect mortality or myocardial infarction rates, are associated with a risk of sub-acute thrombosis, do increase the length of hospital stays and peripheral vascular complications and do not as yet allow a recommendation for routine use (strength of recommendation D; quality of evidence I).

c) **Saphenous Vein Grafts and for Restenosis**
Patients at high risk of restenosis (e.g., suboptimal PTCA results or saphenous vein graft stenosis) may be considered for elective stent implantation (strength of recommendation B; quality of evidence II).

The categories for the strength of recommendations and for quality of evidence used in the CÉTS report (Conseil d’évaluation des technologies de la santé du Québec, 1996, p. 43) were derived from those recommended by the Canadian Task Force on the Periodic Health Examination (1994):

<table>
<thead>
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<th>Category</th>
<th>Definition</th>
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<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation for or against</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence to support a recommendation against use</td>
</tr>
<tr>
<td>E</td>
<td>Good evidence to support a recommendation against use</td>
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<table>
<thead>
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<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one properly randomized controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least one well-designed clinical trial without randomization, from cohort case-control analytic studies, preferably from more than one centre, from multiple time series or from dramatic results in uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
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</table>
REFERENCES


