# Appropriate use of drug-eluting stents: balancing the reduction in restenosis with the concern of late thrombosis

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*Lancet* 2008; 371: 2134–43

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**Restenosis is a serious occurrence that can lead not only to recurrent angina and repeat revascularisation but also to acute coronary syndromes. Drug-eluting stents revolutionised interventional cardiology owing to their pronounced ability to reduce restenosis compared with bare-metal stents. Attention has now shifted to safety of these devices because of evidence suggesting an association with late stent thrombosis. Findings of randomised clinical trials have not shown that drug-eluting stents result in excess mortality after 4–5 years of follow-up. Current recommendations are that individuals with a drug-eluting stent should receive at least 12 months of uninterrupted dual antiplatelet treatment; patients must understand the importance of this long-term regimen. Patients' assessment should focus on bleeding abnormalities, pre-existing disorders that need anticoagulation treatment, and possible future surgical procedures, since these factors could all contraindicate use of drug-eluting stents. Many people will do well with a bare-metal stent, whereas for individuals with a high likelihood of restenosis and late thrombosis, medical management or surgical revascularisation might be preferred options.**

## Introduction

Use of drug-eluting stents increased exponentially after their clinical introduction in 2002, including in settings in which they had not been studied extensively.[1] Enthusiasm for their use was fuelled by a pronounced ability to reduce restenosis and target lesion revascularisation,[2] which had previously been referred to as the Achilles' heel of interventional cardiology. Attention has since turned to the safety profile of drug-eluting stents, since they might augment risk for late stent thrombosis compared with bare-metal stents.[3] In view of this concern, the US Food and Drug Administration convened a 2-day meeting in late 2006 to try to resolve the safety issues of paclitaxel-eluting stents and sirolimus-eluting stents.[4]

Since findings of initial clinical trials were reported, many meta-analyses and pooled analyses with patient-level data have been published. Here, we aim to summarise these second-generation data for drug-eluting stents compared with bare-metal stents. From this framework, doctors will be able to better inform patients of their options for coronary revascularisation.

## Selection of studies and analysis of data

We systematically selected meta-analyses and pooled analyses that compared paclitaxel-eluting stents or sirolimus-eluting stents with bare-metal stents. We additionally required that adverse cardiovascular outcomes—defined as all-cause mortality, cardiovascular mortality, Q-wave myocardial infarction, non-Q-wave myocardial infarction, and stent thrombosis—were available beyond 12 months. Outcomes were reported in a cumulative fashion from stent implantation to the extent of follow-up. Very late stent thrombosis and late mortality were defined as cumulative events starting at 12 months until the extent of follow-up, unless specified otherwise. Stent thrombosis was also reported according to protocol definition and the Academic Research Consortium definition (panel). With our selection criteria, we identified 30 meta-analyses. We excluded 20 studies for the following reasons: fewer than 12 months of follow-up reported (n=13),[2,5–16] comparison only of paclitaxel-eluting stents with sirolimus-eluting stents (n=3);[17–19] assessment of experimental drug-eluting stents (n=2);[20,21] comparison of drug-eluting stents with angioplasty (n=1);[22] and outcomes not reported reliably (n=1).[23]

We tabulated frequencies and risk ratios for patients given either drug-eluting stents or bare-metal stents for every outcome from every study. Missing data were calculated from event data by the Mantel-Haenszel method. One study was a network meta-analysis that included trials of drug-eluting stents versus bare-metal stents; however, these researchers also extrapolated findings from studies of paclitaxel-eluting stents versus sirolimus-eluting stents to construct summary risk ratios.[24] Since head-to-head trials were included in this analysis, outcome frequencies were not available.

### Search strategy and selection criteria

We searched Medline from January, 1996, to September, 2007, and combined the exploded MeSH search terms "stent" plus "paclitaxel" and "stent" plus "sirolimus". We systematically selected meta-analyses and pooled analyses reported in the English language that included randomised comparisons of paclitaxel-eluting stents versus bare-metal stents or sirolimus-eluting stents versus bare-metal stents. We additionally required that adverse cardiovascular outcomes were available beyond 12 months. Titles were scanned and supplemented with a review of the abstract and full manuscript where applicable. To increase the sensitivity of our search, the references of all included manuscripts were reviewed. We also screened prominent cardiology websites (American Heart Association, American College of Cardiology, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics).

*Panel:* **Definitions of stent thrombosis**

**Protocol definition**

Acute coronary syndrome with angiographic evidence of stent thrombosis
Myocardial infarction within the stented vessel
Intervening revascularisation procedures censor later stent thromboses

**Academic Research Consortium definition**

Definite: acute coronary syndrome with angiographic or autopsy evidence of stent thrombosis
Probable: myocardial infarction within stented vessel
Possible: unexplained death after 30 days
Intervening revascularisation procedures do not censor later stent thromboses

## Characteristics of identified trials

Table 1 shows the ten meta-analyses available for inclusion in our Review.[3,24–32] Two reports contained findings that were available publicly,[3,32] whereas the remaining studies included patient-level data.[24–31] The largest study with the longest duration of follow-up was by Stettler and colleagues,[24] who reported outcomes in more than 18 000 people with up to 4 years of follow-up. In most meta-analyses, outcomes were recorded in stable patients with simple native lesions—so-called on-label use. Notable exceptions include the report by Schampaert and co-workers,[31] in which a high proportion of unstable angina and multivessel disease was noted, and the work by Kastrati and colleagues,[26] in which myocardial infarction, chronic total occlusions, bypass grafts, and complex lesions were frequent.

## Cardiovascular outcomes

All-cause mortality was reported in seven studies. In no report did this outcome—nor the other cardiovascular outcomes that were investigated, except stent thrombosis—differ with use of drug-eluting stents (figure 1). Data for stent thrombosis and very late stent thrombosis were presented in seven studies (figure 2). No increase in overall risk for stent thrombosis was noted; however, most point estimates seemed to show a rise in overall risk for thrombosis with drug-eluting stents versus bare-metal stents. The frequency of very late stent thrombosis was low for drug-eluting stents and bare-metal stents, although in several studies, an increased relative risk for late drug-eluting stent thrombosis was noted according to protocol definition.

## Selecting a drug-eluting stent

Despite concerns about late stent thrombosis, 4–5 years of follow-up from initial clinical trials has not indicated an increased risk for cardiovascular outcomes with drug-eluting stents compared with bare-metal stents. The reason that late stent thrombosis has not resulted in excess mortality is unknown, although the substantial benefit of drug-eluting stents in prevention of acute coronary syndromes (which would have otherwise arisen due to restenosis) could partly account for this finding.[33,34] Since a few patients could have adverse outcomes from a drug-eluting stent, we should use them selectively in those who are ideal candidates.[35]

In the next sections, we propose a decision-making process for drug-eluting stents so that their effectiveness can be retained and their potential harm reduced. Some patients with stable angina or late presentation after acute myocardial infarction, who are deemed to be low risk, might undergo initial medical management.[36,37] In most people scheduled for coronary angiography, ample opportunity is available to do a thorough precatheterisation assessment to establish an individual's appropriateness for a drug-eluting stent.

## Precatheterisation assessment

### Patients' adherence

The strongest predictor of stent thrombosis is premature termination of dual antiplatelet treatment. Stopping clopidogrel within 6 months of stent implantation has been associated with a 25–90-fold increased hazard for stent thrombosis,[38,39] which typically arises a few days after cessation of the antiplatelet regimen.[40] Poor response to clopidogrel has also been associated with late adverse cardiovascular events, and in the future this factor might be used to provide additional risk stratification.[41] Assessment of patients' adherence is fairly easy to do in the outpatient setting, by contrast with the urgent nature of acute coronary syndromes (figure 3).

Drug-eluting stent implantation during an acute coronary syndrome has been associated with increased stent thrombosis and mortality, which is at least partly attributable to suboptimum patients' adherence. The PREMIER registry (prospective registry evaluation myocardial infarction: events and recovery) reported a high rate of clopidogrel termination after discharge from hospital, which subsequently translated into increased mortality.[42] By 30 days, 14% of individuals who had received a drug-eluting stent were no longer taking clopidogrel. 1-year mortality was 7·5% in patients who discontinued clopidogrel compared with 0·7% in those who remained on dual antiplatelet treatment (hazard ratio 9·02, p=0·02). This finding shows that there might not be adequate time during an acute coronary syndrome to assess fully patients' understanding and adherence to cardiovascular drugs.[43]

### Bleeding risk

Since dual antiplatelet treatment raises risk for major bleeding,[44] patients should be assessed for bleeding abnormalities before stent implantation, which could pose a contraindication to use of a drug-eluting stent (figure 3). Known bleeding disorders that would favour use of a bare-metal stent include a history of severe gastrointestinal bleeding or any hereditary or acquired

bleeding abnormality. Individuals with atrial fibrillation, a mechanical heart valve, or a hypercoagulable state that needs lifelong anticoagulation with warfarin already have enhanced baseline risk for bleeding.[45] In such patients, the bleeding risk from additional long-term dual antiplatelet treatment would also tend to favour use of a bare-metal stent.

### Need for elective surgery

Many cardiac patients will need future surgical procedures and undergo preoperative coronary angiography, despite findings of the CARP (coronary artery revascularisation prior to elective major vascular surgery) and DECREASE-V (Dutch echocardiographic cardiac risk evaluation applying stress echo) trials, which showed that preoperative revascularisation might not be necessary.[46,47] Nonetheless, individuals who undergo percutaneous revascularisation before an elective surgical procedure should receive a bare-metal stent, which would only need 2–4 weeks of dual antiplatelet treatment, even though the preferred option would be to extend the duration to 6 weeks or longer if possible.[48,49]

No guidelines currently exist on how to manage patients who have already received a drug-eluting stent and need an urgent or elective surgical procedure; however, such individuals should be managed with a cardiologist. Some degree of antiplatelet treatment should be continued perioperatively if the surgical procedure allows. In coronary artery bypass grafting, perioperative use of aspirin is not only safe but also associated with enhanced survival.[50] Since risk for thrombosis is so high with premature termination of antiplatelet treatment (<6 months after implantation), use of an in-hospital bridge—consisting of a glycoprotein IIb/IIIa inhibitor, heparin or low-molecular-weight heparin, or both—might be considered for patients at very high risk, such as those with a recent unprotected left main bifurcation stent. If this type of regimen is used, a short-acting glycoprotein IIb/IIIa inhibitor such as eptifibatide or tirofiban could be considered.[51,52] Such an approach, however, is so-called off-label use, which needs to be assessed prospectively with a randomised clinical trial. In the future, intravenous adenosine diphosphate receptor antagonists might fill this niche.

## Angiographic assessment

### Risk for restenosis

Restenosis generally results in gradual onset of anginal symptoms, which can prompt individuals to seek medical attention; however, it is not always a benign disorder. In up to a third of patients, restenosis can culminate as an acute coronary syndrome or even death.[33,53] Furthermore, development of in-stent restenosis might predict a higher risk for late mortality,

| | Characteristics | Primary outcome | Patients | Follow-up (years) | Vessel diameter (mm) | Total stent length (mm) | Stents per patient | Diabetes mellitus (%) |
|---|---|---|---|---|---|---|---|---|
| Stettler[24] | Network meta-analysis of DES vs BMS trials and also head-to-head trials. Includes 25% myocardial infarction and some chronic total occlusions | All safety and efficacy outcomes | 18 023 in 38 trials (6331 with PES, 6771 with SES, and 4921 with BMS) | 1–4 | .. | .. | .. | 27* |
| Stone[25] | Stable patients<br>Simple native lesions | All safety and efficacy outcomes | 3513 in five PES trials | 2–4 (94–100%) | 2·7 | 24 | 1·2 | 23 |
| | | | 1748 in four SES trials | 4 (95–98%) | 2·7 | 23 | 1·4 | 22 |
| Kastrati[26] | Includes 24% myocardial infarction and some chronic total occlusions, bypass grafts and complex lesions | All-cause mortality | 4958 in 14 SES trials | 1–4·9 | .. | .. | .. | 28 |
| Mauri[27] | Stable patients<br>Simple native lesions | Stent thrombosis (ARC definition) | 2797 in four PES trials | 3·9 | 2·7 | 24 | 1·2 | 25 |
| | | | 1748 in four SES trials | 4·9 | 2·7 | 23 | 1·4 | 22 |
| Spaulding[28] | Stable patients<br>Simple native lesions | All-cause mortality | 1748 in four SES trials | 4 | 2·7 | .. | .. | 22 |
| Holmes[29] | Stable patients<br>Simple native lesions | All-cause mortality | 1748 in four SES trials | 2–3 (96%) | 2·7 | .. | 1·4† | 22 |
| Ellis[30] | Includes 32% unstable angina and 28% overlapping stents | Stent thrombosis (protocol definition) | 3445 in four PES trials | 1–3 (94–97%) | 2·7 | 25 | .. | 23 |
| Schampaert[31] | Includes 57% unstable angina and 40% multivessel disease | Late revascularisation and stent thrombosis | 1510 in three SES trials | 2 (98·7%) | 2·5–3·5 | 15–32 | .. | 25 |
| Nordmann[32] | Includes 17% non-polymeric stents | Mortality | 5470 in ten PES trials | 1–3 | 2·7–3·2 | .. | .. | 23 |
| | | | 3032 in eight SES trials | 1–4 | 2·2–2·9 | .. | .. | 27 |
| Bavry[3] | Stable patients<br>Simple native lesions | Late stent thrombosis (protocol definition) | 6675 in 14 DES trials | <1–4 (>93%) | 2·2–3·0 | .. | .. | 25 |

ARC=Academic Research Consortium. BMS=bare-metal stent. DES=drug-eluting stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent. *Drug-eluting stent *vs* bare-metal stent cohort. †Sirolimus-eluting stent and bare-metal-stent survivors.

***Table 1:*** **Baseline characteristics and duration of follow-up of included meta-analyses**

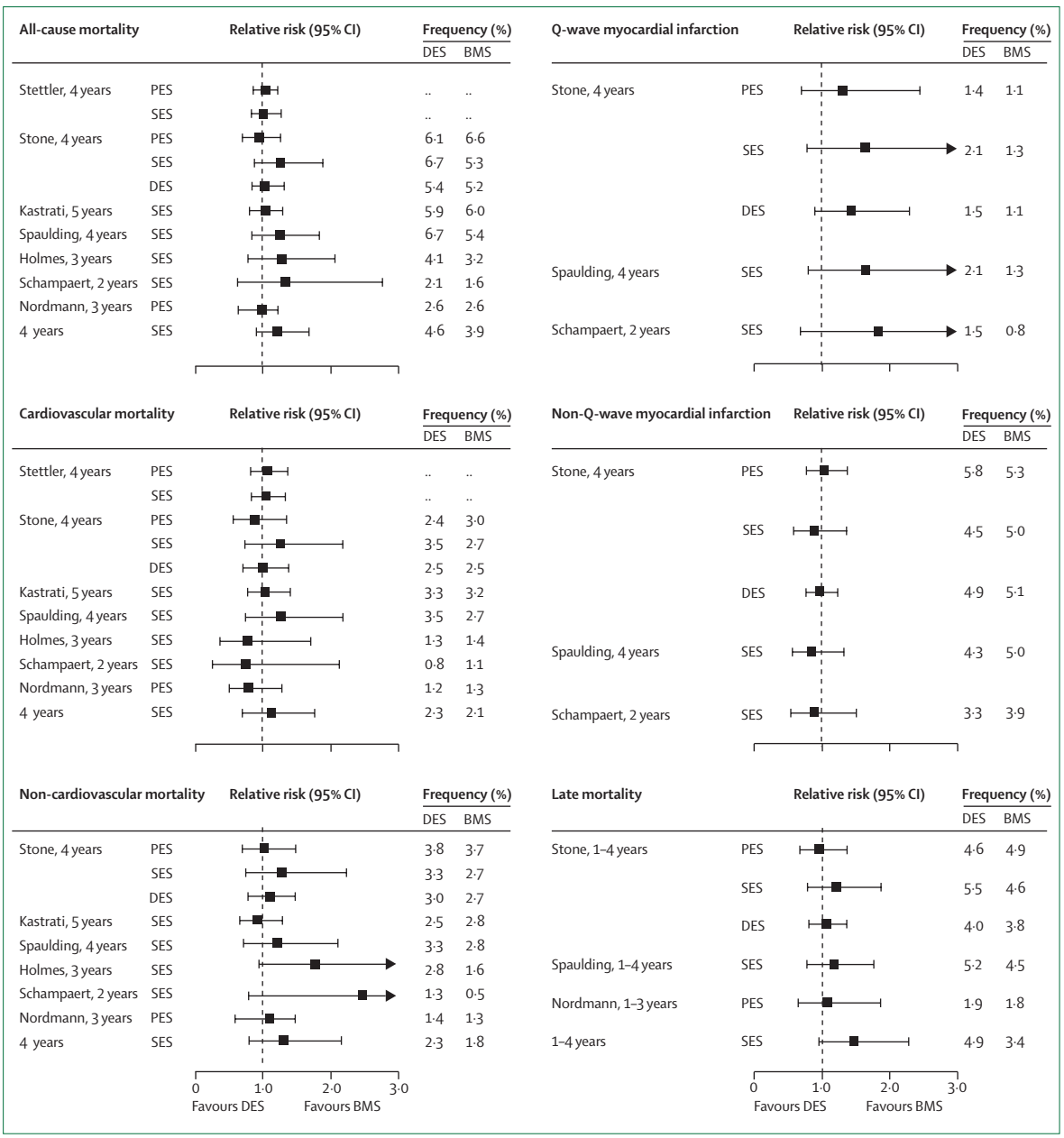


***Figure 1:*** **Effect of drug-eluting stents versus bare-metal stents on important cardiovascular outcomes**
Frequencies are not available for the Stettler analysis since this study derived risk ratios from drug-eluting stent versus bare-metal stent studies and from paclitaxel-eluting stent versus sirolimus-eluting stent studies. BMS=bare-metal stent. DES=drug-eluting stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent. See table 1 for references of included meta-analyses.

including in people with diabetes.[54–56] Restenosis also results in need for repeat coronary angiograms and revascularisation procedures, which exposes the patient to increased morbidity and mortality from small but inherent risks of percutaneous coronary intervention and, particularly, open heart surgery.[57] Restenosis substantially lowers the effectiveness of percutaneous coronary intervention compared with surgical revascularisation. By contrast with coronary artery bypass graft surgery, individuals who undergo percutaneous revascularisation are more likely to need repeat procedures to control anginal symptoms.[58]

Various characteristics of patients and lesions increase risk for restenosis after percutaneous coronary intervention. Presence of diabetes mellitus enhances risk for target lesion revascularisation by about 40–50%.[59,60] This factor could account for why people with diabetes and multivessel coronary disease had worse outcomes (including survival) after balloon angioplasty compared with surgical revascularisation.[61] Other characteristics

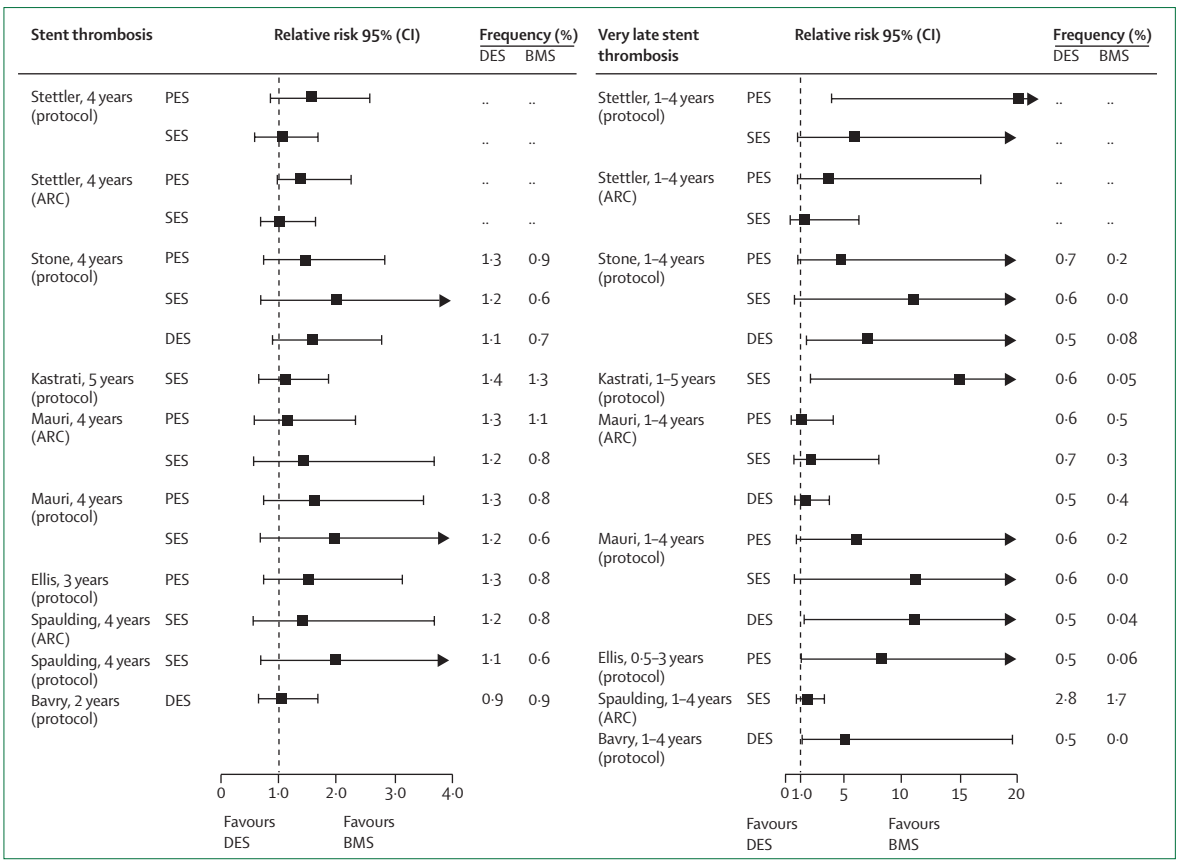


***Figure 2:*** **Effect of drug-eluting stents versus bare-metal stents on stent thrombosis**
Frequencies are not available for the Stettler analysis (see figure 1). ARC=Academic Research Consortium. BMS=bare-metal stent. DES=drug-eluting stent. PES=paclitaxel-eluting stent. SES=sirolimus-eluting stent. See table 1 for references of included meta-analyses.

that raise risk for restenosis include small-vessel diameter, long lesion length, bifurcation lesions, and multiple stents.[59] The presence of multiple coexisting risk factors can further potentiate risk for restenosis. In patients with diabetes and small vessels and complex lesions, an older generation bare-metal stent was associated with a frequency of restenosis of about 50%.[62]

Strut thickness is an important determinant of restenosis. In the ISAR-STEREO (intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome) trial,[63] researchers investigated the effect of a 50-μm versus a 140-μm stent strut on restenosis in native coronary arteries greater than 2·8 mm in diameter. A third of participants had unstable angina, three-quarters had multivessel disease, and just under a fifth had diabetes. A 42% reduction in angiographic restenosis (p=0·003) and a 38% decrease in clinical restenosis (p=0·03) was recorded with use of the thin strut bare-metal stent compared with the thick strut bare-metal stent. Although effective in large vessels, the benefit of a thin strut bare-metal stent seems to be lost for vessels smaller than 2·8 mm in diameter.[64]

In small vessels, a sirolimus-eluting stent was superior to a thin strut bare-metal stent at reducing restenosis;[65] however, this benefit was strikingly attenuated in vessels larger than 2·8 mm. Characteristics that raise risk for restenosis after implantation of a drug-eluting stent in small vessels include long stent length and treatment of in-stent restenosis with an additional stent. A greater than threefold increased risk for restenosis was noted with additional stent placement.[66]

Tung and colleagues[67] have criticised drug-eluting stent trials in which thick strut (130–140 μm) bare-metal stents were used as the control. This study design could have biased findings against the bare-metal stent group, which subsequently showed a high rate of restenosis. So-called real-world use of contemporary bare-metal stents has noted repeat revascularisation rates of about 10% at 9–12 months,[68–71] which is lower than rates recorded in patients from landmark trials.[2,67] For individuals at very low risk for restenosis, the difference between a drug-eluting stent and a currently available thin strut bare-metal stent could be low.

## Risk for thrombosis

With the exception of coronary brachytherapy, late stent thrombosis seems to be unique to drug-eluting stents. Only a few studies have been published in which late

bare-metal stent thromboses have been reported, with limited follow-up; therefore, the true prevalence of bare-metal stent thrombosis beyond 6–12 months is unknown.[72,73] The pathophysiology of late thrombosis in drug-eluting stents seems to be attributable to delayed arterial healing characterised by persistent fibrin deposition and incomplete endothelialisation around stent struts as long as 4 years after the intervention.[74] Localised hypersensitivity vasculitis and impaired endothelial function have also been described.[75,76]

Predictors of drug-eluting stent thrombosis include renal insufficiency, diabetes, long total stent length, bifurcation stenting (including stenting across the ostium of the side-branch vessel), incomplete stent expansion, poor stent apposition, stent strut penetration into a necrotic plaque core, left ventricular dysfunction, stent implantation during an acute coronary syndrome, and treatment of diffuse in-stent restenosis (table 2).[7,38,39,74,77–82] Use of intravascular ultrasound to optimise stent deployment and high-pressure balloon inflation could lessen stent thrombosis, although this procedure adds time and expense.[80,83,84]

Unfortunately, many predictors of late thrombosis are similar to those of restenosis. This similarity makes choosing a drug-eluting stent based on these criteria alone difficult, since many patients will be at increased risk for both restenosis and thrombosis. People with diabetes are a particular example, in whom risk for both restenosis and thrombosis is high and surgical revascularisation remains an attractive option for complete revascularisation.[61]

## Duration of dual antiplatelet treatment

Currently, the ideal duration of a dual antiplatelet regimen with drug-eluting stents is unknown, although the US Food and Drug Administration advisory committee has advocated 12 months of uninterrupted treatment.[4] This proposal is supported by the American Heart Association, American College of Cardiology, and European Society for Cardiology.[85] The optimum duration of dual antiplatelet treatment must balance the benefit of reduced ischaemic events against the harm from increased bleeding episodes.

Researchers on the CREDO trial (clopidogrel for the reduction of events during observation)[86] noted that

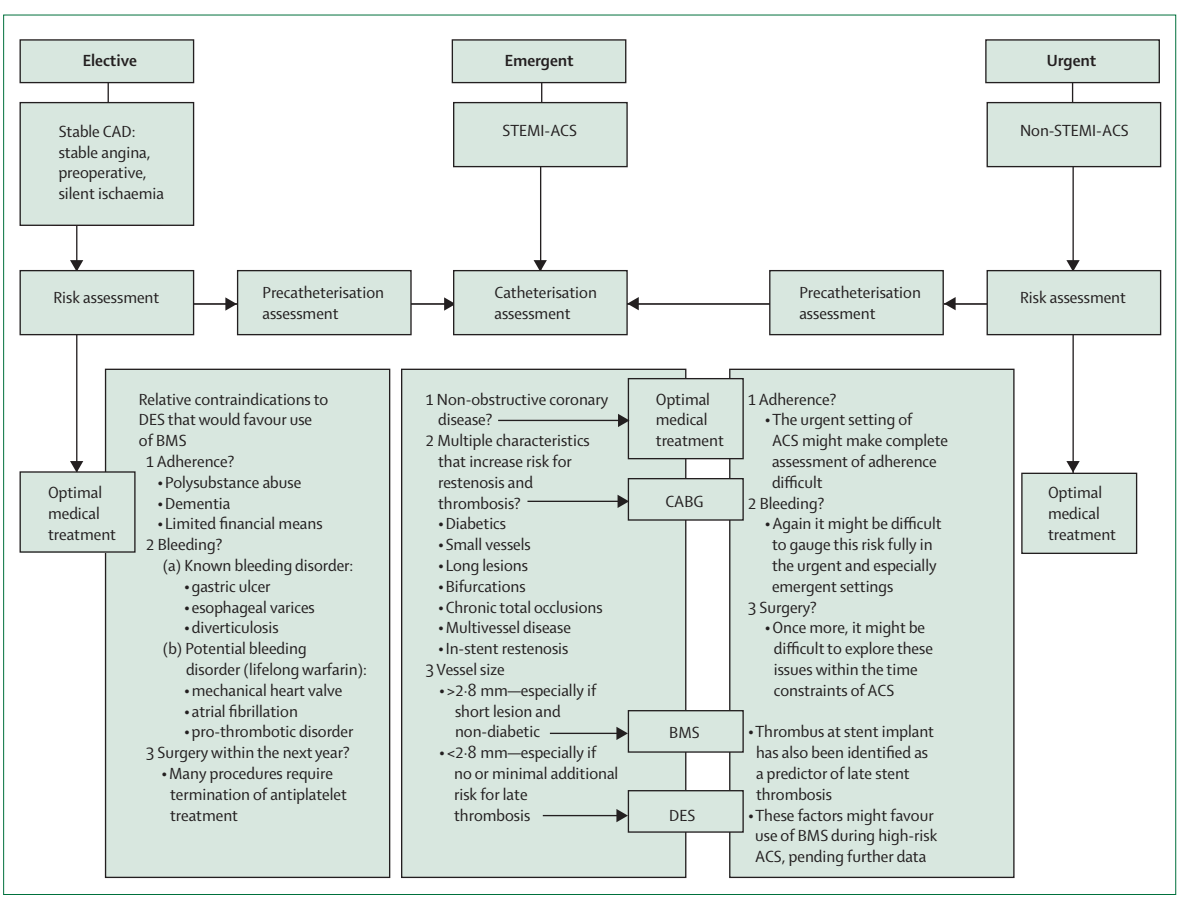


*Figure 3:* **Suggested approach to use of drug-eluting stents to boost benefit and reduce harm**
Most stable patients will be directed to conservative treatment whereas most unstable patients will be expeditiously directed to the catheterisation laboratory. ACS=acute coronary syndrome. BMS=bare-metal stent. CAD=coronary artery disease. CABG=coronary artery bypass grafting. DES=drug-eluting stent. STEMI=ST-elevation myocardial infarction.

| | Duration of clopidogrel (months) | Stent thrombosis | Myocardial infarction | Mortality | Predictors of stent thrombosis | Antiplatelet treatment at late stent thrombosis |
|---|---|---|---|---|---|---|
| Iakovou[38] (n=2229) | 3–6 | DES 1·3% at 9 months | .. | .. | Premature termination of clopidogrel*†<br>Bifurcation lesion*†<br>Left ventricular dysfunction*†<br>Diabetes† | .. |
| Park[39] (n=1911) | ≥6 | DES 0·8% at 1·6 years | .. | .. | Premature termination of clopidogrel*†<br>Renal failure*<br>ACS at index†<br>Long total stent length† | Dual therapy 36%<br>Monotherapy 27%<br>No therapy 36% |
| Pfisterer[77] (n=746) | 6 | .. | .. | After 6 months, DES increased mortality and myocardial infarction (hazard ratio 2·2 [95% CI 1·1–4·7]) | Prior myocardial infarction*<br>Need for glycoprotein IIb/IIIa inhibitor*<br>Side branch occlusion*<br>Bypass graft stenting* | .. |
| Kuchulakanti[78] (n=2974) | ≥6 | DES 1·3% at 1 year | .. | .. | In-hospital renal failure†<br>Bifurcation lesion†<br>In-stent restenosis†<br>Lack of clopidogrel† | Dual therapy 50%<br>Monotherapy 50% |
| Daemen[79] (n=8146) | 3–6 (Dutch centre) and 12 (Swiss centre) | DES 2·9% at 3 years | DES 4·1% at 3 years | DES 10·3% at 3 years | Family history of coronary disease*<br>Number of stents*<br>ACS at index†<br>Diabetes† | Dual therapy 23%<br>Monotherapy 51%<br>No therapy 26% |

ACS=acute coronary syndrome. BMS=bare-metal stent. DES=drug-eluting stent. *Late thrombotic events. †Cumulative thrombotic events.

*Table 2:* **Predictors of late stent thrombosis and frequency of adverse events from drug-eluting stent registries**

12 months of aspirin and clopidogrel provided a 27% reduction in relative risk of death, myocardial infarction, or stroke in patients undergoing percutaneous coronary intervention, compared with a 1-month regimen (p=0·02). Experience with intracoronary radiation also showed that 12 months of dual antiplatelet treatment was superior to a 6-month schedule,[87] which was better than a 1-month regimen at reduction of adverse ischaemic events.[88] The Duke study[89] deserves special mention, since this analysis focused on drug-eluting stents, and findings showed that 2-year mortality for patients treated with these devices was lowest for those who remained on clopidogrel for at least 1 year and was highest in individuals not on this drug at 1 year. Intermediate outcomes were recorded for people treated with bare-metal stents, irrespective of the duration of the clopidogrel regimen. Findings of other registry studies[77,90] have also confirmed an increase in mortality and myocardial infarction with termination of clopidogrel 6–12 months after implantation of drug-eluting stents.

Most of the bleeding risk with dual antiplatelet regimens seems to come fairly early after initiation of treatment. Data from the CHARISMA trial (clopidogrel for high atherothrombotic risk and ischaemic stabilisation, management, and avoidance)[91] noted similar rates of moderate-to-severe bleeding after dual antiplatelet treatment compared with aspirin alone after 270 days. Thus, a patient who has tolerated a dual regimen for 9–12 months, without occurrence of any bleeding episodes that led to a doctor stopping treatment or the patient discontinuing the regimen themselves, has essentially passed a so-called bleeding stress test. The CHARISMA analysis suggests that such individuals are unlikely to have an appreciable incremental bleeding risk with an extended duration of dual antiplatelet treatment compared with the baseline risk with aspirin alone.

Therefore, available data lend support to uninterrupted dual antiplatelet treatment for at least 1 year. Whether a longer regimen would provide additional benefit with acceptable bleeding risk is unknown. Only a prospective randomised clinical trial can properly address this question.

## Limitations

Several potential limitations of our review deserve comment. First, we have presented a narrative review that is distinct from a traditional meta-analysis or guideline from a professional society. Despite this fact, we have retained the systematic approach to meta-analysis that we feel boosts the integrity and reproducibility of our findings. The study by Stettler and colleagues is unique in its network design. The decision to include it was based on the fact that it was a quality analysis of the largest reported cohort of patients to address our central hypothesis. In general, the findings from that study were consistent with those of other large traditional meta-analyses; however, the researchers did report that sirolimus-eluting stents decreased total myocardial infarction compared with bare-metal stents. Whether this finding is a true treatment effect or one that was affected by the different definition of myocardial infarction (Q-wave and non-Q-wave events), or perhaps bias from the study design, is unknown.

Second, there is substantial overlap between included studies and company sponsoring within meta-analyses.

Moreover, in one early meta-analysis, the researchers reported findings from non-polymeric drug-eluting stent studies that are regarded as experimental and could have biased the findings of that particular study. Fortunately, the meta-analyses we included with the most power are also patient-level analyses. Our report did not address paclitaxel-eluting stents compared with sirolimus-eluting stents. This leads to difficulties with assessing the effect, if any, of different polymers and stent design on outcomes.

Safety data were derived from major randomised trials; therefore, our safety findings are most applicable to patients represented in the clinical-trial population—largely on-label use. Definitive safety data with off-label use of drug-eluting stents are scarce. In work specifically addressing this population, researchers have noted off-label use in at least half of interventions.[92,93] Increased early and late adverse events and enhanced need for revascularisation with off-label versus on-label use of drug-eluting stents has been reported in these trials. Continued surveillance by creation of a tracking registry,[94] especially with off-label use, is warranted with drug-eluting stents. An alternative and perhaps preferable approach would be initiation of randomised clinical trials to study safety with off-label use and to compare the benefit of different durations of dual antiplatelet treatment and the need for an in-hospital bridge of a glycoprotein IIb/IIIa inhibitor on early termination of antiplatelet treatment. These issues will need to be debated by the cardiology community, especially with the arrival of the next generation of drug-eluting stents.

## Conclusions

To augment benefit and reduce harm of drug-eluting stents, use of these devices should be more selective than at present. Precatheterisation assessment should favour use of a bare-metal stent when patients' adherence to a drug regimen is poor, increased bleeding risk exists, or a future surgical procedure is possible. Urgent, and especially emergent, acute coronary syndromes make complete precatheterisation assessment difficult and also favour use of a bare-metal stent. Angiographic characteristics are important to ascertain a patient's candidacy for a drug-eluting stent. Individuals at very low risk for restenosis, such as someone without diabetes and with a focal lesion in a large vessel, would be expected to do well with a bare-metal stent. Those at enhanced risk for both restenosis and thrombosis might do better with surgical revascularisation. Lastly, all patients who receive a drug-eluting stent should be treated with uninterrupted and long-term dual antiplatelet treatment.

**Conflict of interest statement**

AAB has received honoraria for consulting from Boston Scientific, Genesis Associates, the Frankel Group, HRA, Propagate Pharma, and Hagen/Sinclair Research Recruiting. DLB has appeared on the speaker's bureau for Bristol Myers Squibb, Sanofi Aventis, and the Medicines Company; has received honoraria from AstraZeneca, Bristol Myers Squibb, Cardax, Centocor, Daiichi-Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Millennium, Otsuka, Paringenix, PDL, Sanofi Aventis, Schering Plough, the Medicines Company, and TNS Healthcare; has acted as a consultant for or sat on the advisory board of AstraZeneca, Bristol Myers Squibb, Cardax, Centocor, Cogentus, Daiichi-Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Medtronic, Millennium, Otsuka, Paringenix, PDL, Portola, Sanofi Aventis, Schering Plough, the Medicines Company, tns Healthcare, and Vertex; has provided expert testimony about clopidogrel; and has received research grants (to Cleveland Clinic Cardiovascular Coordinating Center) as principal investigator or co-principal investigator for CHAMPION (the Medicines Company), CHARISMA (Bristol Myers Squibb, Sanofi Aventis), CRESCENDO (Sanofi Aventis), LANCELOT (Eisai), REACH (Bristol Myers Squibb, Sanofi Aventis), and STAMPEDE (Ethicon). Cleveland Clinic Coordinating Center currently receives or has received research funding from: Abraxis, Alexion Pharma, AstraZeneca, Atherogenics, Aventis, Biosense Webster, Biosite, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardionet, Centocor, Converge Medical, Cordis, Dr Reddy's, Edwards Lifesciences, Esperion, GE Medical, Genentech, Gilford, GlaxoSmithKline, Guidant, Johnson & Johnson, Kensey-Nash, Lilly, Medtronic, Merck, Mytogen, Novartis, Novo Nordisk, Orphan Therapeutics, Proctor & Gamble Pharma, Pfizer, Roche, Sankyo, Sanofi Aventis, Schering-Plough, Scios, St Jude Medical, Takeda, TMC, VasoGenix, and Viacor.

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