Review: Drug-eluting stents for coronary artery disease do not reduce mortality more than bare-metal stents

Nordmann AJ, Briel M, Bucher HC. **Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis.** Eur Heart J. 2006; 27:2784-814.

Clinical impact ratings: Cardiology ★★★★★★☆

QUESTION

In patients with coronary artery disease who are receiving percutaneous coronary intervention and stent placement, are drug-eluting stents (DESs) more effective than bare-metal stents (BMSs) in reducing mortality?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Web of Science, and the Cochrane Library (to April 2006); UpToDate (version 2005); Clinical Evidence Concise (2004, issue 12); Web sites; experts in the field; and reference lists.

Study selection and assessment: Randomized controlled trials (RCTs) that compared DESs (using sirolimus or paclitaxel) with BMSs in patients with coronary artery disease and reported mortality after a follow-up of ≥ 1 year. Trials involving stents in nonnative coronary arteries were excluded. 17 RCTs (n = 8221) (mean age range 56 to 67 y, 56% to 89% men) met the selection criteria: 8 RCTs (n = 3032) using sirolimus DESs and 10 RCTs (n = 5470) using paclitaxel DESs (1 RCT used both). Antiplatelet therapy with clopidogrel, ticlopidine, or cilostazol was recommended in all trials for ≥ 2 to 6 months after stent placement in addition to aspirin indefinitely. Quality assessment included allocation concealment, blinding, and follow-up.

Outcomes: Total, cardiac, and noncardiac mortality and stent thrombosis.

MAIN RESULTS

DESs and BMSs did not differ for total mortality or cardiac mortality at any follow-up interval (Table). Treatment effect for these outcomes did not differ between trials using sirolimus or paclitaxel DESs. At 2 years, noncardiac mortality was increased with DESs more than with BMSs (Table); this increase was observed in 5 RCTs using sirolimus DESs (odds ratio [OR] 2.7, 95% CI 1.2 to 6.1) but not in 7 RCTs using paclitaxel DESs (OR 1.2, CI 0.6 to 2.5). Groups did not differ for noncardiac mortality at other follow-up intervals (Table). Groups did not differ for early (≤ 30 d) or late (> 30 d) stent thrombosis (Table).

CONCLUSIONS

In patients with coronary artery disease, drug-eluting stents are not more effective in reducing mortality than bare-metal stents up to 4 years after implantation. Drug-eluting stents, especially those with sirolimus, may increase the risk for noncardiac mortality after the first year.

Sources of funding: Santésuisse and Gottfried Bangerter-Rhyner-Foundation.

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Drug-eluting stents vs bare-metal stents in coronary artery disease at 1 to 4 years*

Outcomes	Follow-up	Number of trials (n)	Odds ratio (95% CI)
Total mortality	1 y	17 (8221)	0.9 (0.7 to 1.3)
	2 y	12 (4631)	1.1 (0.8 to 1.6)
	3 y	9 (4105)	1.3 (0.9 to 1.7)
	4 y	2 (1293)	1.5 (0.9 to 2.3)
Cardiac mortality	1 y	17 (8221)	0.8 (0.5 to 1.4)
	2 y	12 (4631)	0.7 (0.4 to 1.2)
	3 y	9 (4105)	1.0 (0.6 to 1.6)
	4 y	2 (1293)	1.2 (0.6 to 2.4)
Noncardiac mortality	1 y	17 (8221)	1.1 (0.6 to 1.8)
	2 y	12 (4631)	1.7 (1.01 to 2.9)
	3 y	9 (4105)	1.5 (0.9 to 2.3)
	4 y	2 (1293)	1.7 (0.9 to 3.1)
Stent thrombosis	≤ 30 d	17 (8221)	1.2 (0.6 to 2.1)
	> 30 d	16 (7395)	1.3 (0.7 to 2.6)

*CI defined in Glossary.

COMMENTARY

DESs have dramatically decreased the need for coronary artery bypass graft (CABG) surgery and repeated PCI. However, late stent thrombosis is a small but important risk with DESs because it is commonly associated with sudden death or acute MI.

The clinical occurrence of stent thrombosis after stent implantation can be defined as acute (< 24 h), subacute (1 to 30 d), late (30 d to 1 y), or very late (> 1 y). The clinical diagnosis of stent thrombosis can be defined as "definite" if proven angiographically or pathologically, "probable" if an MI occurs in the distribution of the stented artery, or "possible" if death is unexplained (1). Risk for subacute stent thrombosis is about 1% for both DESs and BMSs, but risk for very late stent thrombosis continues for at least 4 years with DESs at a rate of 2 to 4 events/1000 patients per year (1–3). The presumed cause is delayed or incomplete endothelialization of the stent struts. The unanswered question is whether the decrease in risk for death and MI from avoiding CABG, restenosis, or repeated PCI is greater than the risk for death or MI from late stent thrombosis.

Pfisterer and colleagues compared the incidence of late clinical events among patients assigned to either a DES or a BMS. The study suggested an early reduction in death or MI from less TVR with DESs but a late increase in death or MI from stent thrombosis after discontinuation of clopidogrel therapy. The meta-analysis by Nordmann and colleagues, as well as several subsequent reports that have been used to support current DES labeling (1–3), showed no long-term increase in death or MI rates with 3 to 6 months of dual antiplatelet therapy. Therefore, the small increase in risk for stent thrombosis with DES implantation does not outweigh its benefit compared with BMS implantation. However, ambiguity remains regarding the role of off-label DES implantation in complicated patients (e.g., those with diabetes, acute MI, or multivessel coronary disease) and for patients with complex coronary lesions (e.g., those with longer length, smaller diameter, bifurcations, or vein grafts) in which risk for late stent thrombosis is increased. Furthermore, because there has been no controlled clinical trial examining DESs in these complicated circumstances, no comparative data exist regarding risk for death or MI with such alternative treatments as CABG or BMS.

Although premature discontinuation of dual antiplatelet therapy (< 3 to 6 mo) is a risk factor for stent thrombosis and many cases of stent thrombosis occur despite therapy, the optimal duration of antiplatelet

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Drug-eluting stents increased risk for late cardiac death or myocardial infarction more than bare-metal stents

Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. **Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents.** J Am Coll Cardiol. 2006;48:2584-91.

Clinical impact ratings: Cardiology ★★★★★☆☆

QUESTION

Are drug-eluting stents (DESs) more effective than bare-metal stents (BMSs) in reducing major cardiac events in patients with coronary artery disease who discontinue antiplatelet therapy with clopidogrel 6 months after stent placement?

METHODS

Design: Cluster randomized controlled trial (Basel Stent Kosten-Effektivitäts Trial Late Thrombotic Events [BASKET-LATE]).
Allocation: {Concealed}†.*
Blinding: Blinded ({data collectors}† and outcome assessors).*
Follow-up period: 18 months.
Setting: University hospital in Basel, Switzerland.
Patients: BASKET included 826 patients (mean age 64 y, 79% men) with coronary artery disease who were being treated with percutaneous coronary intervention (PCI) and stenting. Patients with target vessel diameter ≥ 4 mm or restenotic lesions were excluded. The BASKET-LATE follow-up study analyzed data on 743 patients who survived 6 months after the procedure without a major cardiac event.
Intervention: DES (using sirolimus or paclitaxel) (n = 499) or BMS (n = 244). Patients were randomized by treatment day to 1 of the 3 stents, and all received maintenance clopidogrel, 75 mg/d for 6 months, in addition to aspirin, 100 mg/d, and statin therapy indefinitely.
Outcomes: Late (7 to 18 mo after stent implantation) major cardiac events, including cardiac death, nonfatal myocardial infarction (MI), and restenosis-related target vessel revascularization (TVR).
Patient follow-up: 98% (89% of patients in BASKET) (intention-to-treat analysis).

MAIN RESULTS

DESs reduced risk for major cardiac events in the first 6 months (Table). At 7 to 18 months, risk for cardiac death and MI was higher in the DES group than in the BMS group (Table); groups did not differ for TVR or total late major cardiac events (Table). Over the 18-month follow-up, risk for cardiac death or MI did not differ between groups, but risk for TVR was lower in the DES group (Table). Late stent thrombosis-related events (25% of total late events) were twice as likely with a DES {P = 0.23}‡ and occurred at a median 116 days (range 15 to 362 d) after discontinuation of clopidogrel.

CONCLUSION

In patients with coronary artery disease, increased risk for late cardiac death or myocardial infarction following discontinuation of antiplatelet clopidogrel therapy 6 months after stent placement may offset the early benefits of drug-eluting stents over bare-metal stents.

Source of funding: Basel Cardiac Research Foundation.

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*See Glossary.
†Information provided by author.
‡Calculated from data in article.

Drug-eluting stents (DESs) vs bare-metal stents (BMSs) in coronary artery disease at 18 months§

Outcomes	Follow-up	DESs	BMSs	RRR/RRI (95% CI)	NNT/NNH (CI)
Major cardiac event	6 mo‖	7.2%	12%	RRR: 41% (9 to 62)	NNT: 21 (11 to 120)
	7 to 18 mo	9.3%	7.9%	RRI: 18% (–29 to 96)	Not significant
Cardiac death or MI	7 to 18 mo	4.9%	1.3%	RRI: 289% (27 to 1109)	NNH: 28 (17 to 112)
	18 mo	8.4%	7.5%	RRI: 13% (–31 to 85)	Not significant
TVR	7 to 18 mo	4.5%	6.7%	RRR: 33% (–24 to 64)	Not significant
	18 mo	7.5%	12%	RRR: 36% (1 to 58)	NNT: 24 (12 to 974)

§Major cardiac event = cardiac death, nonfatal myocardial infarction (MI), or restenosis-related target vessel revascularization (TVR). Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
‖Kaiser C, Brunner-LaRocca HP, Buser PT, et al. Lancet 2005;366:921-9.

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therapy is unknown. No data exist showing the benefit of prolonged dual antiplatelet therapy after 6 months, but 12 months of therapy after DES implantation has been recommended recently, if the bleeding risk is low (4, 5). Similarly, no data exist to support indefinite dual antiplatelet therapy, an impractical general strategy given the cost and attendant risk for bleeding. Consequently, DESs should be avoided in the presence of financial barriers to continuing prolonged dual antiplatelet therapy, social barriers that may limit patient compliance, or medical issues involving bleeding risks or the need for invasive or surgical procedures in the following year that would interrupt antiplatelet therapy.

Patients should understand the benefits and risks of all treatment options and be able to commit to uninterrupted dual antiplatelet therapy for 1 year before DES implantation can be recommended. Interventionalists should thoughtfully select patients for a DES and use optimal implantation techniques. Unfortunately, industry-funded observational registry studies are not likely to clarify the issue of long-term DES safety, and the lack of randomized trials in complicated patients with complex coronary lesions further precludes evidence-based comparisons between DES and BMS, CABG, and medical therapy. The solution will probably come from newer stent iterations with antithrombotic coatings, bioabsorbable polymers, or biodegradable struts.

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