

Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis

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EDITORIAL by Meier

RESEARCH, p 12

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STUDY QUESTION

What is the relative safety and efficacy of durable polymer drug eluting stents (DES) and biodegradable polymer biolimus eluting stents (ES) currently used to treat coronary artery disease?

SUMMARY ANSWER

The newer durable polymer everolimus-ES and Resolute zotarolimus-ES and the biodegradable polymer biolimus-ES maintain the efficacy of sirolimus-ES. For safety endpoints, however, differences become apparent with everolimus-ES and Resolute zotarolimus-ES emerging as the safest stents to date.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The efficacy and safety profile of biodegradable polymer stents compared with first and second generation durable polymer DES is controversial. There is a gradient in magnitude of effect, with everolimus and Resolute zotarolimus-ES as the safest devices to date.

Design

Network meta-analysis of all eligible trials.

Data sources and study selection

Medline, Google Scholar, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) database were searched for trials enrolling at least 100 patients comparing at least two of durable polymer sirolimus and paclitaxel-ES, newer

durable polymer everolimus-ES, Endeavor and Resolute zotarolimus-ES, and biodegradable polymer biolimus-ES.

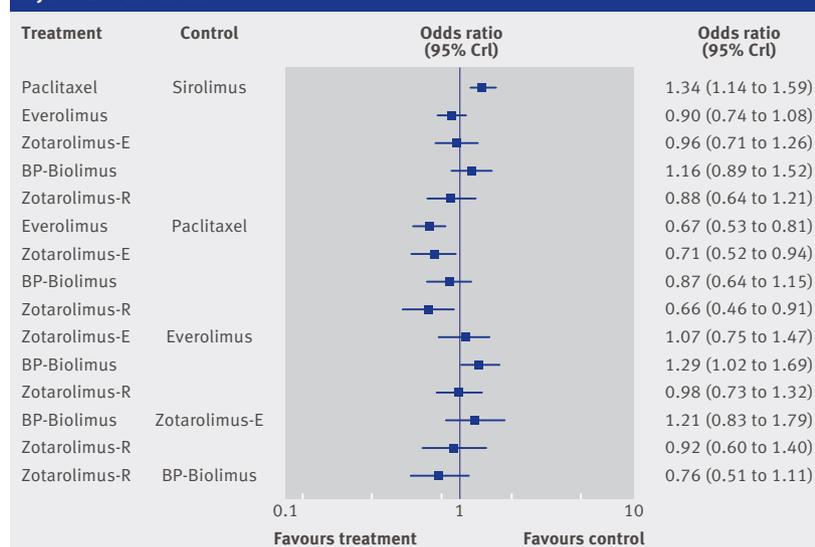
Primary outcomes

Safety endpoints were death, myocardial infarction, and definite or probable stent thrombosis. Efficacy endpoints were target lesion and target vessel revascularisation up to one year and beyond.

Main results and role of chance

Sixty randomised controlled trials were compared involving 63 242 patients treated with DES. At one year, there were no differences in mortality among devices. Endeavor and Resolute zotarolimus-ES, everolimus-ES, and sirolimus-ES, but not biodegradable polymer biolimus-ES, significantly reduced the odds of myocardial infarction by 29-34% compared with paclitaxel-ES. Compared with everolimus-ES, biodegradable polymer biolimus-ES significantly increased the odds of myocardial infarction by 29%, while Endeavor zotarolimus-ES and paclitaxel-ES significantly increased the odds of stent thrombosis. All investigated DES did not differ significantly with regard to efficacy endpoints, except for Endeavor zotarolimus-ES and paclitaxel-ES, which significantly increased the odds of target lesion and target vessel revascularisations compared with other devices. Direction of results beyond one year did not diverge from the follow-up up to one year. Bayesian probability curves showed a gradient in the magnitude of effect, with everolimus-ES and Resolute zotarolimus-ES offering the highest safety profiles.

Pooled odds ratio and 95% credible intervals determined by network meta-analysis for myocardial infarction



Bias, confounding, and other reasons for caution

Results were analysed on trial level data and not on individual data and therefore we could not assess whether all baseline characteristics were balanced among groups (although for the most part they were balanced within each trial). The patient inclusion criteria are broad, reflecting current practice, comprising both stable and unstable high risk patients.

Study funding/Potential competing interests
Some authors and their institutions have received funding for other work from Boston Scientific, Medtronic, Abbott Vascular, Micell Technologies, and Terumo Europe. See bmj.com for full details.

Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis

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EDITORIAL by Meier
RESEARCH, p 11

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STUDY QUESTION

What is the efficacy and safety of biodegradable polymer drug eluting stents (DES) compared with durable polymer DES (especially newer generation) and bare metal stents for the treatment of coronary artery disease?

SUMMARY ANSWER

Biodegradable polymer DES are superior to first generation durable polymer DES in reducing restenosis but not superior to newer generation durable polymer DES, compared with which they were associated with worse outcomes for a few endpoints (definite stent thrombosis overall and death after one year).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Biodegradable polymer DES were developed to preserve the safety of bare metal stents while maintaining the efficacy (reduction in restenosis) of durable polymer DES, but the efficacy and safety are not known. Newer generation durable polymer DES, especially the cobalt chromium everolimus eluting stent, have the best combination of efficacy and safety.

Selection criteria for studies

We searched PubMed, Embase, and Central for randomized trials comparing any of the Food and Drug Administration approved durable polymer DES (sirolimus eluting stent, paclitaxel eluting stent, cobalt chromium everolimus eluting stent, platinum chromium everolimus eluting stent, zotarolimus eluting stent-Endeavor, and zotarolimus eluting stent-Resolute) or biodegradable polymer DES, with each other or against bare metal stents. We used mixed treatment comparison (network) meta-analyses and

direct comparison meta-analyses to evaluate relative efficacy and safety.

Primary outcome(s)

Long term efficacy (target vessel revascularization, target lesion revascularization) and safety (death, myocardial infarction, stent thrombosis) outcomes were evaluated.

Main results and role of chance

From 126 randomized trials and 258 544 patient years of follow-up, biodegradable polymer DES were superior to first generation durable polymer DES (versus paclitaxel eluting stents: rate ratio 0.66, 95% credibility interval 0.57 to 0.78) for long term efficacy (target vessel revascularization) but not superior to newer generation durable polymer DES (for example, versus cobalt chromium everolimus eluting stents: 1.03, 0.89 to 1.21) and were associated with worse outcomes for long term safety (definite stent thrombosis) (versus cobalt chromium everolimus eluting stents: 2.04, 1.27 to 3.35). In landmark analysis after one year, biodegradable polymer DES were superior to sirolimus eluting stents for definite stent thrombosis (0.29, 0.10 to 0.82) but were associated with increased mortality compared with cobalt chromium everolimus eluting stents (1.52, 1.02 to 2.22). Overall, among all stent types, the newer generation durable polymer DES (zotarolimus eluting stent-Resolute, cobalt chromium everolimus eluting stents, and platinum chromium everolimus eluting stents) were the most efficacious (lowest target vessel revascularization rate), and cobalt chromium everolimus eluting stents were the safest with significant reduction in definite stent thrombosis (0.35, 0.21 to 0.53), myocardial infarction (0.65, 0.55 to 0.75), and death (0.72, 0.58 to 0.90) compared with bare metal stents.

Bias, confounding, and other reasons for caution

The study combines trial level data only. In addition, the study combined all of the biodegradable polymer DES into a single class, as the proposed benefits of these stents are for late events when the polymer has degraded and a bare metal-like stent is left. Future randomized trials are needed to evaluate whether any one biodegradable polymer DES is superior to another.

Study funding/potential competing interests

This research received no specific grant from any funding agency. SB has acted as an advisory board participant/consultant for Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Gilead, Abbott, and Abbott-Vascular. FF is a shareholder in Medtronic, Boston Scientific, and Johnson and Johnson.

Biodegradable polymer drug eluting stents in comparison with other stents and risk of events from network of all trials in landmark analysis beyond one year (late events). Values are rate ratio (95% credibility interval)

Comparison of biodegradable polymer stent versus:	Death	Myocardial infarction	Target vessel revascularization	Definite stent thrombosis
Bare metal stent	0.85 (0.61 to 1.19)	0.80 (0.53 to 1.37)	0.67 (0.45 to 0.95)*	1.02 (0.33 to 3.42)
Sirolimus eluting stent	0.89 (0.69 to 1.17)	0.69 (0.49 to 1.09)	0.79 (0.54 to 1.08)	0.29 (0.10 to 0.82)*
Paclitaxel eluting stent	0.99 (0.68 to 1.36)	0.63 (0.39 to 1.13)	0.79 (0.53 to 1.13)	0.51 (0.16 to 1.69)
Cobalt chromium everolimus eluting stent	1.52 (1.02 to 2.22)*	1.03 (0.67 to 1.95)	1.15 (0.74 to 1.72)	1.81 (0.44 to 7.09)
Platinum chromium everolimus eluting stent	2.03 (0.95 to 4.08)	0.74 (0.20 to 2.51)	1.50 (0.62 to 3.54)	1.11 (0.12 to 7.79)
Zotarolimus eluting stent-Endeavor	1.02 (0.73 to 1.46)	0.87 (0.50 to 1.59)	0.97 (0.60 to 1.46)	1.39 (0.44 to 5.62)
Zotarolimus eluting stent-Resolute	1.28 (0.71 to 2.48)	0.92 (0.42 to 3.08)	1.02 (0.53 to 2.04)	1.68 (0.20 to 15.70)

*Statistically significant comparisons.

Effect of β blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records

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STUDY QUESTION

Are β blockers associated with decreased mortality in patients with COPD having a first myocardial infarction?

SUMMARY ANSWER

The use of β blockers initiated either at the time of hospital admission for myocardial infarction or before is associated with decreased mortality in patients with COPD.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Despite increasing evidence that β blockers are safe and beneficial in people with COPD, they continue to be underprescribed after myocardial infarction in this group. β blockers improve survival after myocardial infarction in patients with COPD, and they should be more widely used in this group.

Participants and setting

Patients with COPD with a first myocardial infarction from 1 January 2003 to 31 December 2008 as recorded in the UK national registry of myocardial infarction (Myocardial Ischaemia National Audit Project (MINAP)), who had no previous evidence of myocardial infarction. The primary outcome was all cause mortality after a first ST elevation or non-ST elevation myocardial infarction in patients with COPD prescribed and not prescribed a β blocker during the admission for myocardial infarction.

Design, size, and duration

A population based cohort study in England including 1063 patients with COPD in MINAP linked to the General Practice Research Database (GPRD). Smoking status, age, and sex were included in all models as likely confounders. Other confounders added cumulatively included age, sex, smoking, family history of cardiovascular disease, angina,

hypertension, dyslipidaemia, peripheral arterial disease, cerebrovascular disease, heart failure, diabetes before myocardial infarction, frequency of exacerbation of COPD, type and severity of myocardial infarction, and drug use at the time or before myocardial infarction (diuretics, anti-arrhythmia drugs, antiplatelet agents, angiotensin converting enzyme inhibitor, statins, nitrates, and calcium channel blockers).

Main results and the role of chance

β blockers initiated during the admission for myocardial infarction were associated with substantial survival benefits (fully adjusted hazard ratio 0.50, 95% confidence interval 0.36 to 0.69; $P < 0.001$; median follow-up time 2.9 years). Patients with COPD already taking a β blocker before their myocardial infarction also had a survival benefit (0.59, 0.44 to 0.79; $P < 0.001$).

Bias, confounding, and other reasons for caution

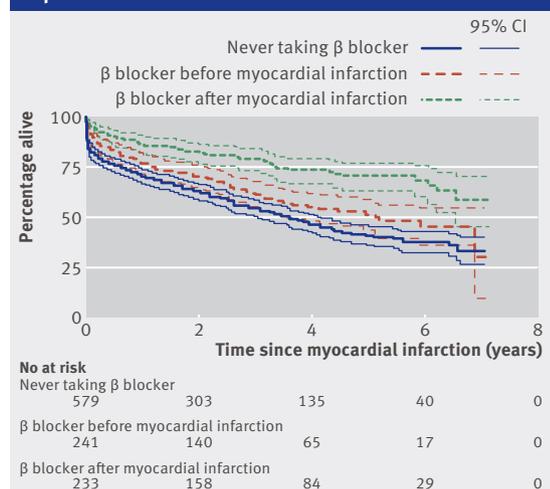
A limitation of this study is the coding of β blocker use during the hospital admission for myocardial infarction in MINAP. Patients were more likely to be coded as not being prescribed a β blocker if they died in hospital. Repeated analysis with date of discharge from hospital as the start time of follow-up confirmed the protective effect of β blockers. Over half (59%) of the patients excluded from the study were not prescribed a β blocker during the hospital admission for myocardial infarction because of contraindications, but we had no further information regarding reasons for this. Though some physicians could have thought a diagnosis of COPD was a contraindication, potentially allowing us to include those individuals in the analysis, we could not determine this and so they were excluded. This could have led to a selection bias. One of the reasons for the differences in the effect size according to start of follow-up (date of myocardial infarction or date of discharge) could be an immortal time bias. Nonetheless, the overall protective effect was still preserved when we changed the start of follow-up time. There might be some residual confounding and confounding by contraindication and a risk of healthy user bias in those patients who take any drugs, including β blockers. While the effect in reality might not be as large as observed in this study, some protective effect seems likely and, in view of these findings, it is difficult to believe that β blockers are harmful.

Generalisability to other populations

These data suggest that β blockers should be used more widely in COPD patients who have had a myocardial infarction. Safety to date is good in these patients, but further evaluation of the safety of β blockers in this high risk group could be required to change current prescribing practice.

Study funding/potential competing interest See bmj.com.

Kaplan-Meier survival curves



► Diabetes updates from *BMJ* <http://www.bmj.com/specialties/diabetes>

Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study

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STUDY QUESTION

What is the risk of new onset diabetes in patients with impaired glucose tolerance and other cardiovascular risk factors using diuretics, β blockers, and statins?

SUMMARY ANSWER

Among people with impaired glucose tolerance and other cardiovascular risk factors with serial glucose measurements, diuretics and statins were associated with an increased risk of new onset diabetes, whereas the effect of β blockers was non-significant.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

β blockers, diuretics, and statins have been postulated to increase the risk of new onset diabetes in high risk patients, based on their pharmacological properties and analysis of clinical datasets. Our secondary analysis of a large randomised controlled trial found that among people with impaired glucose tolerance and other cardiovascular risk factors with serial glucose measurements, diuretics and statins were significantly associated with new onset diabetes, whereas a non-significant effect of β blockers was observed.

Participants and setting

Patients who were treatment naïve to each class of drug at baseline in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.

Design, size, and duration

Using data from the NAVIGATOR trial, this study examined the relation between incident diabetes and use of β blockers, diuretics, statins, and calcium channel blockers among treatment naïve patients at enrolment (n=5640, n=6346, n=6146, and n=6294, respectively); calcium channel blocker was used as a metabolically neutral control. The relation between each treatment and new onset

diabetes was evaluated using marginal structural models for causal inference, to account for time dependent confounding in treatment assignment during a median of five years of follow-up.

Main results and the role of chance

During the study period, β blockers, diuretics, statins, and calcium channel blockers were started in 915 (16.2%), 1316 (20.7%), 1353 (22.0%), and 1171 (18.6%) patients, respectively. After adjusting for baseline characteristics and time varying confounders, diuretics and statins were both associated with an increased risk of new onset diabetes (hazard ratio 1.23, 95% confidence interval 1.06 to 1.44 and 1.32, 1.14 to 1.48, respectively), with the number need to harm 17 (95% confidence interval 9 to 68) for diuretics and 12 (8 to 29) for statins, whereas β blockers and calcium channel blockers were not associated with new onset diabetes (adjusted hazard ratio 1.10, 0.92 to 1.31 and 0.95, 0.79 to 1.13, respectively).

Bias, confounding, and other reasons for caution

We took into account changes over time in both treatments and covariates influencing treatment such as blood pressure, heart rate, smoking status, oral glucose tolerance test, glycated haemoglobin level. Documentation of the reason for initiation of new non-trial study treatment was not collected as part of the trial protocol. Although the NAVIGATOR dataset captured strong predictors of new onset diabetes, and all known factors expected to be associated with treatment utilisation, these measured confounders were not measured perfectly.

Generalisability to other populations

Our study population included high risk patients with impaired glucose tolerance and cardiovascular risk factors. The observed treatment patterns and relation to outcome may be specific to this population, although previous studies suggest similar results in a general population.

Study funding/potential competing interests

The NAVIGATOR study was designed by Novartis Pharma in collaboration with an academic executive committee. All statistical analyses relevant to this publication were performed independently by statisticians at the Duke Clinical Research Institute (Durham, NC). The authors of this manuscript are solely responsible for the design and conduct of this study, all statistical analyses, and the drafting and editing of the paper and its final contents.

Effect of time dependent drugs on progression to diabetes

Drugs	Unadjusted hazard ratio (95% CI)	MSM adjusted* hazard ratio (95% CI)	Absolute excess risk* (95% CI) at 5 years
β blockers	1.25 (1.07 to 1.46)	1.10 (0.92 to 1.31)	2.6 (-2.3 to 8.0)
Diuretics	1.36 (1.20 to 1.55)	1.23 (1.06 to 1.44)	5.9 (1.5 to 10.7)
Statins	1.30 (1.14 to 1.48)	1.32 (1.14 to 1.48)	8.1 (3.5 to 13.0)
Calcium channel blockers	1.01 (0.87 to 1.18)	0.95 (0.79 to 1.13)	-1.5 (-5.8 to 3.4)

MSM=marginal structural model.

*MSM with regression adjustment for baseline variables and inverse probability of treatment weighting for time dependent confounders; truncation of extreme weights applied at 0.25th centile and 99.75th centile.