Drug-eluting coronary stents in clinical practice: lessons from the «BAsel Stent Kosten-Effektivitäts Trials» (BASKET)

A review of the BASKET trials

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Summary

In this review of the BAsel Stent Kosten-Effektivitäts Trial (BASKET) the trials and their impact on coronary stenting practice were examined, basing the clinical questions of each study on the findings of the previous study. Are the new drug-eluting stents (DES) cost-effective compared to standard bare-metal stents (BMS) if used in all patients? No. Are there specific subgroups of patients with a particular benefit? Yes. A "targeted stent use" was proposed for daily practice. What is the long-term safety of DES? Unexpected safety problems were observed. Was this a chance finding? No. However, with improved stenting techniques, newer stents and intensified antiplatelet regimens late problems were minimised as shown in the BASKET-PROspective Validation Examination (BASKET-PROVE). Further stent developments? Wait and see! – Many additional questions were raised and answered or are still under investigation. Obviously, answers were not always simple and needed a closer look and this is discussed. The BASKET trials proceeded not only from one question to the other, but also in size and methodology. From the restricted single-centre "local" BASKET study to multicentre international long-term trials, all prospective, randomized and investigator-driven. Their relevance was acknowledged by publications in major medical journals as well as by their impact on US and European practice guidelines and on DES research. These aspects are summarised in the present review, highlighting lessons learned from each study and commenting on the possibilities and difficulties of performing such clinical research in Switzerland.

***Key words:** percutaneous coronary intervention; drug-eluting stent; bare-metal stent*

With their introduction in interventional cardiology, drug-eluting stents (DES) were welcomed enthusiastically because they promised to "eliminate" the "Achilles heal" of coronary stenting with bare-metal stents (BMS), namely in-stent restenosis. This benefit of DES was confirmed in many trials [1–3] and a first all-comer registry suggested that DES could be used in all patients [4]. However, DES costs were two to three times higher than those for BMS, and the reason why many clinicians and hospitals were worried about cost explosion.

Therefore, the question "c*an we afford to use DES in all our patients, i.e. is the use of DES in all patients cost-effective?"* formed the basis for the original BAsel Stent Kosten-Effektivitäts Trial (BASKET):

BASKET was set up as a prospective real-world trial in unselective consecutive patients undergoing angioplasty and stenting during a one year period [5]. The only exclusion criteria were vessel diameter of >4.0 mm (sirolimus-eluting stents of that size were not available), in-stent restenosis and no patient consent. Thus, 826 patients were randomized 2:1 to DES versus BMS. Two DES had market approval: the sirolimus-eluting Cypher® stent (Cordis; Johnson and Johnson, Miami Lakes, Florida, USA) and the paclitaxel-eluting Taxus® stent (Boston Scientific Corporation, Natick, Massachusetts, USA). Patients randomized to DES were sub-randomized 1:1 to Cypher® and Taxus®. The BMS used was the "3rd generation" Vision® stent (Guidant Corporation, Indianapolis, Indiana, USA). All patients were followed clinically for six months. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel was prescribed for six months in all patients irrespective of stent type. Individual costs for stents, hospital days, medications, follow-up visits and interventions were put in relation to the effectiveness, defined as reduction in major adverse cardiac events (MACE, i.e. cardiac death, myocardial infarction (MI) and target-vessel revascularisation [TVR]). The primary endpoint was the incremental cost-effectiveness of DES versus BMS after six months.

DES proved to be effective by reducing TVR by 43% without significant differences in death/MI rates between DES and BMS patients. This was true for all lesion types and subgroups analysed. However, costs of DES were so high that cost-effectiveness for the entire patient population

was not achieved. Cost differences were mainly driven by differences in stent costs. Over the six month observation period, the incremental cost-effectiveness ratio for DES versus BMS came to 18,311 Euro to prevent one MACE per patient, resulting in costs per quality of life years gained of >50,000 Euro. Thus, the higher stent costs of DES were not compensated for by lower costs for lower follow-up visits or repeat interventions. The cost-effectiveness ratio was better in higher risk patients such as elderly patients with three-vessel disease, with more than one segment treated, particularly in small vessels or bypass grafts and with stent lengths >20 mm.

The main lesson of BASKET was that if "current" DES were used in all patients, then DES were not cost-effective compared to BMS. Cost-effectiveness could only be achieved in certain subgroups of patients at increased risk of restenosis.

Discussion of BASKET findings revealed several important points. Since the cost difference of the stents was driving this result, lower DES prices could tip the balance more in favour of DES. In fact, reductions of DES prices soon came into effect. However, BMS prices fell at the same time. In addition, the limited follow-up of six months in BASKET was questioned because restenoses had been described up to nine months after stenting, although at a low rate. Thus cost-effectiveness should be assessed up to a later date to capture the benefit of DES more completely. On the other hand, DAPT was recommended for only one month after BMS, whereas all patients received it up to six months in BASKET, also affecting overall costs and bleeding complications during follow-up.

Thus, new questions arose: What would the incremental cost-effectiveness ratio between DES and BMS treated patients after 18 months be? Would there be specific patient groups with greater benefit? How would changing stent prices affect results (in specific sensitivity analyses)?

Therefore, all BASKET patients surviving the initial six months were followed for a further year, up to 18 months after stenting [6]. Overall results were similar to early findings. Despite 35% less TVR in patients treated with DES, the mean costs were still significantly higher in the DES group after 18 months (11'808 versus 10'450 Euro/patient). Subgroup analyses revealed significant differences in MACE rats between DES and BMS groups only in high risk, but not in low risk patients. As regards cost-effectiveness, 75% of low risk DES patients were in the "less effective and more expensive" zone of the cost-effectiveness plane while in the high risk subgroup 71% of the DES patients fell in the "more effective and less expensive" zone. In the overall population, cost-effectiveness was sensitive to stent cost. Cost-effectiveness could be achieved by a reduction of DES stent costs of (an unrealistically low) 29% (at a threshold of 10'000 Euro to prevent one MACE). Interestingly, cost-effectiveness was not sensitive to a reduction in DES costs in the low risk subgroup,where even substantial reductions in DES costs would not have resulted in a cost-effective scenario.

Lessons from this expanded cost-effectiveness analysis impacted on the use of DES in many hospitals and countries worldwide. Particularly in the United Kingdom, these results, together with simulations of registry data from Liver-

pool and Sweden pointing in the same direction, were used to restrict the use of DES to high risk patients, but not to ban them entirely as initially intended by the National Institute of Clinical Excellence (NICE).

The 18 month follow-up of clinical events resulted in the surprising observations published as BASKET Late Thrombotic Events (BASKET LATE) [7]. Although the reduction in TVR by DES compared to BMS was maintained, an increased rate of cardiac death and non-fatal MI in DES- compared to BMS-treated patients (4.9% vs 1.3%, formally significant) was found between months six to 18 after stenting. A detailed analysis showed that during this time period particularly late stent thromboses and related clinical events were twice as frequent after DES as after BMS implantation (2.6% versus 1.3%). It should be noted that DAPT was stopped in all patients after six months, but that the thrombotic events occurred randomly between 15 and 362 days after stopping clopidogrel, with no clustering early on.

The main lesson from BASKET LATE was that there was a danger of late stent thrombosis with related death or MI >6 months after DES implantation. This was not seen after BMS implantation and may have been related to the discontinuation of DAPT. These observations, first presented at a HotLine Session during the Annual Meetings of the American College of Cardiology early 2006, were confirmed in the Swedish Coronary Artery Angioplasty Registry (SCAAR) [8] and a Duke University registry study [9]. Together with two independent Swiss metaanalyses suggesting a late excess in mortality after DES implantation [10, 11], this led to the "fire-storm" at the Annual Meeting of the European Society of Cardiology 2007. However, this excess mortality was never confirmed. Finally, this resulted in the advice of the US Food and Drug Administration (FDA) panel [12]: DES should only be used in high risk patients and DAPT should be prolonged up to 12 months after DES use. BASKET LATE became one of the most cited papers in the cardiology literature of those years and was even commented on in the Wall Street Journal. The use of DES dropped markedly worldwide and research into new DES without such problems was enforced.

The next obvious questions were: which patients are at particular risk of late stent thrombosis? And: can nuclear imaging identify those patients non-invasively?

To address the first question, a sophisticated analysis of the 18 months BASKET outcome data was performed [13] which identified patients in need of large vessel stenting, i.e. implantation of stents in native coronary arteries with a diameter of ³ 3.0 mm, as those patients are at particular risk of late stent thrombosis related death and MI. On the other hand, the benefit of DES was maintained at no higher risk for late stent thrombosis in patients with stenting of small native vessels or bypass grafts.

Lesson: Based on the evidence from BASKET-LATE, the proposition of a "targeted stent use" of DES in clinical practice was put forward. The main reasoning was that 1) the rate of clinically relevant restenoses is comparatively small after large artery stenting as shown earlier [2]and that 2) the probability that an occlusion of a large coronary artery would lead to an acute clinical coronary event is

much greater than an occlusion of a small coronary artery which may even remain undetected. These findings and considerations supported and paralleled those of the FDA and other researchers and were in agreement with the conclusions of the 18 months cost-effectiveness analysis of BASKET (s. above).

To assess the value of nuclear imaging to predict these late clinical events, all BASKET patients were invited to undergo a rest/stress single-photon emission computed tomography (SPECT) test six months after stenting [14]. The findings were related to 18 months outcomes. This study led to two conclusions: 1) target-vessel ischaemia assessed by SPECT imaging was significantly lower after DES compared to BMS implantation (5.4% vs 10.4%, P = 0.045) documenting the enhanced benefit of DES in addition to the reduction in TVR, and it was silent in 2/3 of cases; 2) target-vessel ischaemia was a predictor of late clinical events related to restenosis but not to late stent thrombosis. Lesson: Compared to BMS, DES not only reduced the rate of TVR but also that of clinically silent restenosis. Detection of target vessel ischaemia six months after stenting is useful in predicting restenosis-related events during further follow-up, but not events due to late stent thrombosis. Thus, the mechanisms leading to coronary vessel obstruction in acute late stent thrombosis differ fundamentally from those leading to hyperplasia-induced "restenosis".

The next question was whether the enhanced rates of late stent thrombosis, death and MI in BASKET LATE were chance findings?

To answer this question, two options were tested: 1) to perform a long-term follow-up of BASKET patients which could show whether the event curves between DES and BMS treated patients would merge over time suggesting a chance finding, or whether they would stay parallel or even diverge further underscoring the true value of the18 months results; and 2) to perform a large scale prospective randomized long term study specifically addressing the late safety of DES compared to BMS. – Both options were chosen.

Firstly, all BASKET patients surviving 18 months were followed up clinically after three years and analysed as a total group and in subgroups of large and small vessel stenting [15]. Overall results showed that the benefit of DES in reducing the rate of TVR was maintained up to three years at no increased risk of death or death/MI. However, between months 7 and 36, the curves of cardiac death/MI diverged further with a difference becoming significantly greater in disfavour of DES versus BMS (9,1% versus 3.8%, p = 0.009) indicating a late "harm" of DES regarding the combined death/MI endpoint. This was almost entirely due to findings in patients with large vessel stenting, whereas in patients with small vessel stenting the early benefit of DES in reducing death/MI rates was maintained up to three years.

Lesson: This analysis confirmed 18 month findings showing that implantation of DES in large coronary arteries carries an increased risk of late stent thrombosis related death/MI, whereas the benefit of DES persists in patients with small vessel stenting. – Together with the cost-effectiveness aspects of BASKET, these data influenced the guidelines of the European Society of Cardiology on stenting [16]

However, this was still "observational" data with results from subgroup analyses and thereby no "definitive" proof of a "late harm" of DES. Therefore, a large prospective randomized multicentre trial was conducted, BASKET PROspective Validation Evaluation (BASKET PROVE) [17].

Two specific questions were asked: 1) is the "late harm" of DES still present with current experience and medical management? 2) Are there differences in late events between a new "2nd generation" DES and a previously tested "1st generation" DES in this regard? Importantly, only patients at increased risk for late stent thrombosis related death/MI, i.e. those in need of large vessel stenting, were studied.

In BASKET PROVE, 2314 patients were included in 11 centres in Switzerland, Denmark, Austria and Italy and randomized to a 1st generation sirolimus-eluting Cypher Select® stent (Cordis, Johnson & Johnson, Miami Lakes, FL, USA), the 2nd generation Xience V® stent (Abbott Vascular, Santa Clara, CA, USA) or the BMS Vision® stent (Abbott Vascular, Santa Clara, CA, USA) [18]. The primary endpoint was cardiac death/MI after two years. Two thirds of patients presented with acute coronary syndromes, whereof half with ST-elevation MI. All patients received DAPT for 12 months irrespective of stent type used. Results of BASKET PROVE documented again the benefit of DES in reducing the need for TVR in these patients, and this was true for both DES tested. In addition, no significant differences were found in rates of death/MI between the three stents tested, neither for the entire two year follow-up nor for the late time period of months 7–24. It should be noted that overall event rates were markedly lower than in similar patients in the earlier BASKET trial.

Lessons from BASKET PROVE were the following: With current experience and medical management, including 12 months of DAPT, an excess of late death/MI with DES could no longer be detected in patients in need of large coronary artery stenting. No outcome differences between the 1st generation Cyper Select® and the 2nd generation Xience V® stent were found. Lower overall event rates in similar patients as in BASKET seem to reflect advances in medical management and greater experience in stent use (for instance higher deployment pressures used).

The findings of BASKET PROVE were reassuring for DES, although the improved overall outcomes compared to the earlier BASKET trial are not yet fully understood. However, obviously, the development of newer stents is ongoing. BMS with thinner stent struts and "bio-compatible" coatings, DES with newer metal alloys, thinner struts, "bio-degradable" polymers and lower drug doses, or even totally absorbable stents. In addition, new and more potent antiplatelet agents have been developed and introduced into the market that may reduce the rate of late stent thrombosis even further, albeit at a certain increased risk of bleeding [19].

Thus, new questions arise: 1) will newest generations of DES with a "bio-degradable" polymer have even better outcomes in MACE compared to currently "standard" 2nd generation DES? 2) Will the outcome of patients treated with newest generation BMS for large vessel stenting not be similarly good as with current DES? 3) What will these results look like in the light of modern DAPT for both stent

types, with 12 month duration of DAPT only for patients with acute coronary syndromes and/or DES?

To address these questions, another large multicentre trial has been initiated; BASKET PROVE II [20]. Here, 2400 patients in need of large vessel stenting will be randomized to a DES with a "bio-degradable" polymer (Nobori®, Terumo, Somerset NJ, USA), the standard 2nd generation Xience V® or a modern BMS with "bio-compatible" coating (Prokinetik®,Biotronik, Berlin, Germany). Patients will be treated with aspirin and prasugrel, a new potent antiplatelet agent, for 12 months, unless patients present with stable angina and receive a BMS. The primary endpoint will be 2 year rates of MACE, i.e. the combination of cardiac death/ MI and TVR. The last patient will be included by the end of 2011 and main results are expected two years later.

Lessons from BASKET PROVE II will impact on the current management of coronary stenting since it is the first large prospective comparison of currently used newest generations of DES and BMS on the background of modern DAPT, data which is currently lacking.

Several additional questions were investigated in the BASKET trial program, some of which are still ongoing. Among them are the following:

1) Are patients presenting with acute coronary syndromes, particularly ST elevation MI, at increased risk for late stent thrombosis?

Post mortem analyses in ST elevation MI patients showed delayed vessel healing at the stenting site after DES implantation, a potential substrate for an increased risk for stent thrombosis. In an analysis of the BASKET population, 210 patients with ST elevation MI were compared with 323 stable angina patients [21]. In fact, after three years of follow-up, a higher rate of stent thrombosis was found in ST-elevation MI patients. This difference occurred only during the late period, i.e. >6 months after stenting, and in patients with DES but not in those with BMS. This translated into a trend towards more clinical events, cardiac death/MI, after six months in ST elevation MI patients if treated with DES, but not if treated with BMS. The overall rate of TVR was significantly lower in DES patients. However, the difference was not significant in patients treated for ST elevation MI. These clinical observations seem to confirm post mortem findings that delayed healing occurs at DES sites as well as in patients treated for ST elevation MI. Thus, the combination of the two factors, i.e. DES implantation and ST-elevation MI may result in increased rates of late stent thrombosis.

Predictors of late ST are analysed in a separate study. Patient specific factors, i.e. more advanced coronary disease and procedure related factors contribute to the risk of this event. A new observation was made that the use of high doses of statins may have a protective effect against ST [22]. However, this needs to be verified in a dedicated prospective trial.

2) What is the bleeding risk of triple antithrombotic therapy, i.e. DAPT in patients needing oral anticoagulants for other reasons?

A special analysis of BASKET data showed that bleeding complications up to three years were increased eightfold in patients who were treated with anticoagulants and DAPT [23]. Specific risk factors for such bleeds could be identi-

fied. The main lesson was that patients in need of oral anticoagulants should not be treated with DES because of the inherent need for prolonged DAPT.

3) Are DES superior to BMS, with or without glycoprotein IIb/IIIa inhibitors, in stenting of bypass graft lesions?

A first retrospective analysis of BASKET data showed that treatment of saphenous bypass graft lesions with DES resulted in a better long term outcome than treatment with BMS. In contrast, no DES benefit was found in similarly sized native vessels regarding MACE [24]. This prompted the initiation of another prospective multicentre international trial (BASKET Saphenous Venous graft Angioplasty using Glycoprotein IIb/IIIa receptor inhibitors and drug-Eluting stents, (BASKET SAVAGE), in which 240 patients in need of bypass graft stenting are randomized to DES or BMS and followed on DAPT with aspirin and clopidogrel for 12 months. The primary endpoint is combined MACE. Half of the patients are presently included. The study will define the role of DES in bypass graft stenting.

4) What is the importance of coronary disease progression on long term outcome of patients after stenting?

Long term follow-up studies after DES implantation have been mandated by the FDA for safety reasons. However, after five years of follow up, progression of underlying coronary disease may become as relevant as stent related clinical problems. To address this question, 428 patients of the original BASKET population with successful stenting, i.e. no symptoms up to six months after stenting and no scintigraphic perfusion defects after six months, were followed up to five years [25]. The primary aim was to define the rate of remote vessel MI, revascularisation or new perfusion defects (in 5 year follow-up SPECT studies) in relation to target vessel events and perfusion defects. Results showed that close to 40% of late events and, in addition, almost 40% of new perfusion defects in the absence of events could be attributed to myocardial areas not related to target vessels. Notably, the majority of new perfusion defects were asymptomatic. Thus, progression of coronary disease is clinically relevant five years after stenting and becomes an important factor in the long term management of patients after stenting.

Concluding remarks

The BASKET trial programme started in the Division of Cardiology of the University Hospital of Basel with the simple but clinically most relevant question when the new DES became available: can we afford to treat all our coronary patients with these new, very promising but also very costly devices? The answer was: DES are not cost-effective if used in all patients, but there are patients at high risk for restenosis in whom they are even cost-saving. This led to further relevant questions, which were studied prospectively, in single and then multicentre trials, leading to clinically relevant answers, "lessons learned". This left room for new questions to be addressed. Importantly, all these questions came from the investigators, and these investigator-initiated studies and trials were conducted independently from industry. This fact added to their credibility and acceptance in the interventional cardiology community and led to publications in The Lancet (twice), the New England

Journal of Medicine, the Journal of the American College of Cardiology, the European Heart Journal (twice), the American Heart Journal (three times) and others, and thereby to the worldwide recognition of the BASKET Study Group. Of course, these BASKET trial results have to be evaluated in the context of the other stenting literature, which is done in the individual publications, but this is beyond the scope of the present BASKET review. The financial support for this evolving research programme came primarily from the Basel Cardiovascular Research Foundation, and in small parts from grants of the Swiss National Foundation of Research and the Swiss Heart Foundation. Although the budgets for this research were several times lower than that of comparable industry-sponsored trials, it proved most difficult to find sufficient money from official research foundations in Switzerland to conduct them. Thus, the completion of these studies had to be based on the hard work voluntarily performed by very dedicated investigators, who made BASKET a success. Support came also from statisticians of the Clinical Trial Unit of the University Hospital of Basel. This review demonstrates that despite these problems excellent clinical research can be performed in Switzerland successfully leading to co-operations of Swiss and international centres and impacting on the practice of medicine worldwide. In addition, it demonstrates that clinical research is not only epidemiology or drug/device testing, but may be based on relevant clinical questions originating from daily practice aiming to improve direct patient care.

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