Changes in the safety paradigm with percutaneous coronary interventions in the modern era: Lessons learned from the ASCERT registry

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Abstract
In the past, comparative effectiveness trials evaluating percutaneous coronary interventions (PCI), using either balloon angioplasty or bare metal stent (BMS) implantation, versus coronary artery bypass surgery (CABG) found similar survival rates at long-term follow-up with both revascularization strategies. Two major meta-analyses of these trials reported 5- and 6-year comparative effectiveness between PCI and CABG: one included only four trials that compared PCI with BMS implantation versus CABG whereas the largest one also included trials using balloon angioplasty. In these studies, the authors observed no survival differences between groups although a significant survival advantage was seen in diabetics treated with CABG and this benefit was also perceived in elderly patients. In both reports, number of involved vessels, presence of left anterior descending artery stenosis or poor left ventricular ejection fraction were no predictors of poor survival with PCI. Therefore, extent of the coronary artery disease (CAD) was not associated with poor outcome after PCI in the pre-drug eluting stent (DES) era. Recently, the ASCERT (Database Collaboration on the Comparative Effectiveness of Revascularization Strategies) registry found higher mortality rate with PCI in patients ≥65 years old in comparison with CABG, and advantages of surgery were seen in all subgroups including those at low risk. In this registry, PCI was accomplished by implantation of the first type of DES designs in 78% of cases. The intriguing observation of high mortality rate with PCI, including for non-diabetics and patients with two-vessel CAD, meaning a lack of clinical benefit with DES implantation, had not been seen previously. The study was not randomized, although its results are largely strengthened by its sample size. In this manuscript, the authors describe other registries and randomized trials reporting similar results supporting the findings of the aforementioned study and explore the reasons for these results, while also searching for potential solutions.

Key words: Percutaneous coronary interventions; Coronary artery bypass surgery; Drug eluting stents; Coronary artery disease; Elderly patients

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COMPARATIVE EFFECTIVENESS BETWEEN PERCUtANEOus CORONARY INTERVENTIONS AND CORONARY BYPASS SURGERY IN THE PRE-DRUG ELUTING STENT ERA

In the past, comparative effectiveness trials evaluating percutaneous coronary interventions (PCI), either using balloon angioplasty or bare metal stent (BMS) implantation, vs coronary artery bypass surgery (CABG) found similar survival at long-term follow-up with both revascularization strategies. However, in three of these trials some outcome differences between PCI and CABG were found: firstly, the bypass angioplasty revascularization investigation (BARI) trial reported higher mortality in diabetic patients with PCI; secondly, the stent or surgery (SoS) trial observed higher non-cardiac mortality with PCI; and finally, the estudio randomizado argentino angioplastia vs cirugia de bypass coronario II (ERACI) trial had higher mortality and myocardial infarction (MI) with CABG in the first 30 days and at one year after the procedure, advantages for PCI that were present but diminished at five years. Accordingly, two major meta-analyses from those trials reported 5-year comparative effectiveness between PCI and CABG: one included only four trials that compared PCI with BMS implantation vs CABG, whereas the largest one also included trials using balloon angioplasty. In the first meta-analysis, in patients with multiple vessel disease randomized either to BMS or CABG, 5-year follow-up outcome showed similar incidence of death, MI or cerebrovascular accident (CVA). In this analysis, patients with diabetes had no safety advantage with CABG. Hlatky et al. in the other meta-analysis, which included 10 trials, observed no survival differences between groups although a significant survival advantage was seen in diabetes treated with CABG. In this study, a survival benefit with CABG was also perceived in elderly patients (≥ 65 years). In both reports, number of vessels, presence of left anterior descending artery stenosis or poor left ventricular ejection fraction were not predictors of poor survival with PCI. Therefore, extent of the coronary artery disease (CAD) was not associated with poor outcome for PCI in the pre-drug eluting stent (DES) era.

The introduction of different DES designs during PCI compared to BMS significantly reduced the incidence of angiographic restenosis and target lesion and vessel revascularization (TLR and TVR, respectively). It is important to mention that these efficacy advantages were sustained at 5 years of follow-up. However, increased frequency of very late stent thrombosis and requirements for a long-term period of dual antiplatelet therapy, mandatory for at least one year after implantation with the first DES designs, could decrease this advantage.

LESSONS FROM ASCERT (DATABASE COLLABORATION ON THE COMPARATIVE EFFECTIVENESS OF REvascularization STRATEGIES) REGISTRY

Recently, a large registry found a higher mortality rate with PCI in patients ≥ 65 years old in comparison with CABG and advantages of surgery were seen in all subgroups, including those at low risk. In this registry, PCI was accomplished by implantation of the first DES designs in 78% of cases. The observation of higher mortality rates with PCI, including for non-diabetics and patients with two-vessel CAD, were not seen in previous studies in the non-DES era. The study was not randomized, although its results are largely strengthened by its sample size. The study included two prospective registries from 64 centers in the USA over the years 2004 to 2008. Almost 190 000 patients were included in both groups and, despite the nature of the study, differences in favor of CABG still remained after a matched comparison in 86 300 patients.

The lack of clinical improvement with DES in this subgroup has been a surprise for our interventional cardiology community and concerns have been raised in an accompanying editorial about the non-randomized nature of the study which could be related to these unexpected results.

It is true that randomized clinical trials are the gold standard to assess results of different clinical and surgical therapies, although it is also well known that they have a limitation driven by patient selection; therefore, large prospective registries which allow us to include more complex and real world populations are also an important tool to assess these clinical results. Therefore, both randomized trials and registries should be taken into account to evaluate revascularization outcomes.

In the study carried out by Weintraub et al., the authors recognized that “...a single unmeasured confounder could produce survival differences only if it increased the long-term risk of death by a factor of approximately two or if the long-term risk of death was three to five times as high in the PCI group as in the CABG group”; therefore, unmeasured confounder factors can be linked with different survival outcomes reported by such a study. However, survival advantages with CABG remained after the authors adjusted for clinical and angiographic variables (Figure 1). Furthermore, results were still in favor of CABG after propensity-matched comparisons and these results agree with other contemporary studies such as the New York database for PCI and CABG and the ERACI III registry. In the New York registry, they also found a survival advantage with CABG and this advantage also included subgroups defined as low risk.
In the ERACI III registry, there was an increased incidence of death and MI with DES beyond the first year in comparison with BMS or CABG groups, differences still significant at 5 years of follow-up; as we can see in Figure 2, at one year in ERACI III, the DES group had a significantly lower incidence of any death, MI, stroke and TVR (major adverse cardiovascular events: MACCE) compared with either BMS or CABG groups. Death and MI were similar between BMS and DES groups but significantly lower than the CABG group. On the other hand, at 3 years, MACCE rate became similar in these three groups by an increased rate of cardiac events in the DES group, and additionally at 5 years significantly higher rates of death and MI in the ERACI III DES group of patients compared with the BMS group were seen, meaning a significantly late loss of their initial advantage (Figure 2).

In conclusion, in the ERACI III registry, patients treated with DES had higher than expected risk of serious cardiac events over the subsequent five years compared with patients treated with a BMS, despite a substantial reduction in the rate of repeat coronary revascularization procedures. These differences do not appear to be explained by different adverse risk profiles among DES-treated patients, as multivariable statistical adjustment for baseline factors did not materially affect the results in this study. However, as we discussed previously, all registries have a common limitation of non-randomized nature;
consequently we need to find randomized studies sharing similar results.

**COMPARATIVE EFFECTIVENESS BETWEEN PERCUTANEOUS INTERVENTIONS AND BYPASS SURGERY IN THE DES ERA: LESSONS FROM RANDOMIZED CLINICAL TRIALS**

The SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial, which is nowadays the largest randomized study comparing PCI with DES implantation (Taxus, Boston Scientific Corp, Natick, Massachusetts) vs CABG in the modern era, has already reported one-, three- and four-year follow-up results. This study included patients with unprotected left main stenosis and three-vessel CAD.

If we discard from this trial the subgroup of left main patients, inclusion and exclusion criteria from ASCERT and SYNTAX are quite similar. Both studies included only patients with multiple vessel disease, whereas in both patients were excluded with cardiogenic shock, MI in the previous 7 d, single-vessel CAD, and previous CABG.

If we analyze SYNTAX trial data at one year of follow-up, patients treated with PCI or CABG had similar incidence of death, MI and the composite of death/MI and CVA, although CVA was significantly higher in the CABG group; repeat revascularization procedures (TVR) were higher in PCI (Figure 3), and this was the only disadvantage in the PCI group during the first year of follow-up.

However, these numbers change at the third and fourth year of follow-up (Figure 3); death, MI and the composite of death/MI/CVA are all significantly higher in the PCI group of patients. Additionally, these results were also seen in the subgroup of patients with three-vessel disease, which is a comparative population to the ASCERT registry. In this cohort at 3 years of follow-up, death (5.7% vs 9.5%, P = 0.048), MI (3.3% vs 7.1%, P = 0.005), death/MI/CVA (10.6% vs 14.8%, P < 0.04) and MACCE (18.8% vs 28.8%, P < 0.001) were all significantly higher with PCI.

The PCI policy of this study which was non-ischemia guided stent implantation leading to an excess of DES per patient/lesion implanted would be one of the reasons of these findings.

Therefore, increased serious cardiac events beyond one year with PCI appear to be a common finding in both ASCERT and SYNTAX.

Reasons of these findings are unclear, although the observation of high mortality rate in elderly patients after PCI raises the question whether this subgroup is at high risk if they are treated with PCI.

However, the ASCERT statement that high mortality was noted in all subgroups, including in patients whose clinical and angiographic criteria were more consistent with selection for PCI, should be taken with caution. In fact, we do not know if results in some of the trials mentioned previously are also related to poor late outcome in an elderly population; indeed we do not know the outcome of elderly patients in the SYNTAX trial.

Consequently, we do not know what the clinical reasons for these findings are; however, we will try to explore some hypotheses and also find potential solutions.

After introduction of the first DES designs together with the reduction of angiographic restenosis, a high rate of late and very late stent thrombosis was described and became a concern for some investigators. In spite of this, several randomized studies did not shown major safety concerns with DES implantation, while other studies reported a high rate of cardiac events at late follow-up together with the increased incidence of very late stent thrombosis in complex patient/lesion subsets such as diabetics, stent restenosis, ST elevation MI, bifurcations, etc., most of them classified as off-label indications by the Food and Drug Administration.

Therefore, at the end of the last decade concerns about the safety of the first DES designs were reduced but the debate did not disappear and persists nowadays.

There was a requirement for dual antiplatelet therapy to be prescribed with the first DES designs during the first six months post-procedure although clopidogrel therapy was recommended in most patients beyond one year. How this necessity for dual antiplatelet therapy can be linked with poor outcome in the elderly patients is unknown. However, some recent data from a small randomized study add limited, but valuable, information and strengthen the ASCERT results.

The Oral Rapamycin in Argentina III (ORAR) trial was a cost-effectiveness randomized comparison between DES versus BMS plus 14 d of oral rapamycin (OR) in the DES arm, first DES designs were used in 96.8% of cases. At 4 years of follow-up, patients included in the

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**Table 1 Drug eluting stent:Bare metal stent hazard ratios (95% confidence limits) in multivariable Cox models adjusted for baseline characteristics from ERACI II at five-year follow-up**

| Endpoint         | All patients (n = 450) | P values | Propensity score matched points (n = 242) | P values |
|------------------|------------------------|----------|------------------------------------------|----------|
| MACCE            | 0.75 (0.51-1.2)        | 0.1562   | 1.20 (0.75-0.90)                         | 0.45     |
| Death            | 1.84 (0.92-0.68)       | 0.0864   | 2.53 (1.10-0.83)                         | 0.03     |
| Death, MI or stroke | 1.66 (0.95-0.88)     | 0.0744   | 3.31 (1.62-0.76)                         | 0.001    |
| Repeat revascularization | 0.52 (0.31-0.85)     | 0.0996   | 0.84 (0.48-0.47)                         | 0.37     |

MI: Myocardial infarction; MACCE: Major adverse cardiovascular events.
OR group were at lower risk of death from any cause (DES: OR hazard risk 2.84, CI: 1.12-7.34, \( P = 0.024 \)) and the composite of death + MI + CVA (DES: OR hazard risk 2.18, CI: 1.09-4.34, \( P = 0.018 \)) without differences in TVF (\( P = 0.091 \)) or TVR (\( P = 0.162 \)) compared to the DES group.

However, as we can see in Table 2, in the group of patients who were less than 65 years of age, incidence of death (\( P = 0.32 \)), cardiac death (\( P = 0.41 \)), MI (\( P = 0.56 \)) and composite of death + MI + CVA were similar (\( P = 0.56 \)). Requirements for new hospital admissions during follow-up were also similar in both groups (45% vs 35% in OR and DES, respectively, \( P = 0.26 \)). Conversely, in the elderly group (\( \geq 65 \) years) there were significant differences in incidence of MI (\( P = 0.05 \)), death + MI + CVA (\( P = 0.03 \)) and TVF (\( P = 0.02 \)). Of note, at 4 years, elderly patients treated with DES had new hospital admittances more frequently during follow-up than those treated in the OR plus BMS group (64.6% vs 37.5%, respectively, \( P = 0.011 \)). In both groups, DES patients were more frequently taking clopidogrel therapy (Table 2).

The main results of this randomized study suggested that safety advantages in favor of an OR plus BMS strategy observed in ORAR III were driven by the poor outcome in patients \( \geq 65 \) years treated with DES.

Results from ORAR III agree with those reported by the ASCERT[15] registry, although clinical reasons for these findings cannot be determined due to the sample size of such a small population.

**RESULTS WITH THE LATEST DES DESIGNS**

Altogether the above-mentioned studies share a common finding: the first DES platforms with durable and non-biocompatible polymers were used with requirements for
Table 2  Comparison of oral rapamycin vs drug eluting stent treatment in patients under 65 years old and equal to or older than 65 years old at 5.1 years (4.2-5.8) of follow-up

|                    | < 65 yr | ≥ 65 yr |
|--------------------|---------|---------|
|                    | OR (n = 60) | DES (n = 52) | P value | OR (n = 40) | DES (n = 48) | P value |
| Death              | 3.3% (2) | 9.6% (5) | 0.32    | 7.5% (3) | 20.8% (10) | 0.07    |
| Cardiac death      | 0.0% (0) | 5.8% (3) | 0.19    | 5.0% (2) | 12.5% (6) | 0.22    |
| MI                 | 10.0% (6) | 13.5% (7) | 0.56    | 0.0% (0) | 12.5% (6) | 0.05    |
| Death + MI + CVA   | 10.0% (6) | 13.5% (7) | 0.56    | 7.5% (3) | 25.0% (12) | 0.03    |
| TVF                | 26.7% (16) | 28.8% (15) | 0.79    | 22.5% (9) | 45.8% (22) | 0.02    |
| TLR                | 9.3% (9/97) | 14.6% (12/82) | 0.26    | 11.5% (7/61) | 20.5% (18/88) | 0.14    |
| TVR                | 14.8% (12/81) | 17.4% (12/69) | 0.66    | 14.0% (7/50) | 21.9% (16/75) | 0.26    |
| New hospital admissions1 | 45.0% (27) | 34.6% (18) | 0.26    | 37.5% (15) | 64.6% (31) | 0.01    |
| Continue clopidogrel therapy2 | 15.5% (9/58) | 44.7% (21/47) | 0.002  | 24.3% (9/37) | 52.6% (20/38) | 0.05    |

1Patients with at least one cardiovascular or not cardiovascular hospital readmissions; 2Of surviving patients. OR: Oral rapamycin therapy and bare metal stent; DES: Drug eluting stent; MI: Myocardial Infarction; CVA: Cerebrovascular accident; TVF: Target vessel failure; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

Figure 4  Reduction of cardiac events in all subgroups from COMPARE and SPIRIT IV trials with the use of everolimus-eluting stents19,34. ACS: Acute coronary syndrome; MI: Myocardial infarction; LAD: Left anterior descending artery; RVD: Reference vessel diameter; BMI: Body mass index.

CONCLUSION

PCI is the most common myocardial revascularization strategy in the current era. However, revascularization guidelines for PCI and CABG in multiple vessel CAD, established some years ago in the pre-DES era, should be refocused according to the latest data from randomized studies and large registries. The ASCERT study was, to our knowledge, the largest registry comparing current PCI strategies vs CABG in patients with multiple vessel disease who were older than 64 years. In spite of study limitations mainly driven by the non-randomized nature, its sample size largely supported results. Furthermore, these outcomes were also observed in some randomized studies sharing similar clinical and angiographic findings.

We are unable to find clinical reasons for these results, although we cannot discard the concept that side effects linked with the first DES designs, including mandatory requirements for long-term dual antiplatelet therapy,

long periods of clopidogrel therapy which were greater than needed for the latest ones currently used and recommended18,31. Therefore, worries about the first DES designs which were largely described and debated a decade ago with the paradigm of more efficacy but perhaps less safety11,12,13 could explain the controversial PCI results of these studies15,17,21,22 observed today but with a patient recruitment period in 2004-2008.

However, nowadays newer DES designs either with biocompatible or biodegradable18,31,34-36 polymers demonstrate in randomized clinical trials a significantly lower incidence of adverse events including death, cardiac death and MI compared to the first ones17 (Figure 4). In addition, necessity for long-term clopidogrel therapy appears to be no longer than 6 mo, consequently we have new tools today to improve outcome in our patients who undergo PCI with DES implantation; as we can see in Figure 4, benefits apply to several subgroups of patient/lesion characteristics.
could be associated with this poor all-comers outcome in an elderly PCI population.

Whether new DES designs would modify these intriguing results should be determined by prospective studies.

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