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Guidelines for percutaneous coronary interventions

The recently published guidelines for PCI[1] by the European task force were set out to mark a timely milestone, but missed this goal unfortunately as a result of unbalanced statements. Various peculiarities make it difficult to follow those guidelines for various reasons.

First, statements and findings from the Taxus VI trial were utilized for the paper,[2] although the stent utilized in Taxus VI has never been marketed and is not available while results from other trials are neglected.

Secondly, results from RCTs on various interesting subsets of patients with focus on in-stent restenosis, diabetes, and small vessels have not been taken into consideration; nevertheless, the authors of the guidelines are demanding such RCTs even at a time when ARTS II and TROPICAL could not use bare metal controls, but rather had to compare with historical controls for ethical reason.[3,4]

Thirdly, the authors' conclusion of equipotential effects of sirolimus and paclitaxel coated stents only on the basis on the small TAXI trial is likely to be oversimplified and more than courageous[5]; justified is only that the hypothesis of 6% MACE with sirolimus and 14% with paclitaxel were not met.

Finally, although the preamble to those guidelines claims both to present all relevant evidence on a particular issue and to be developed by an unquestionable decision-making process, none of those standards have been met. It is already late for an update.

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Guidelines for percutaneous coronary interventions: reply

The members of the ESC PCI guidelines task force appreciate the comments made by Dr Nienaber regarding our analysis and recommendations for drug-eluting stents (DES).

(1) Dr Nienaber states that our recommendations for DES should not have been based on the TAXUS-VI trial, because this trial investigated the moderate-release form of the Taxus stent which has not been marketed. First, in the TAXUS-II trial, there were no clinically or angiographically relevant differences between the marketed slow-release and the not marketed moderate-release forms in equivalent lesions. Furthermore, comparing the TAXUS-VI results with TAXUS-V also did not reveal clinically relevant differences between the slow-release and the moderate-release forms. From Dr Nienaber's point of view, we should also not have recommended the Cypher stent—at least for Germany: the currently marketed Cypher Select stent was not the one that was investigated in the SIRIUS trial (Cypher Bx Velocity). As another example, in most European countries, clopidogrel is not labelled for use after coronary stent implantation. Should the ESC PCI guidelines therefore not recommend clopidogrel after stent implantation?

(2) Regarding the use of DES for in-stent restenosis, Dr Nienaber criticizes that we demanded randomized, controlled studies before making definitive recommendations, 'even at a time when ARTS II and TROPICAL could not use bare metal controls, but rather had to compare with historical controls for ethical reason'. The ESC PCI guidelines committee strongly believes that for

such an important recommendation, randomized, controlled studies comparing DES with an accepted standard method of treatment are both necessary and ethical. The superiority of DES (Cypher and Taxus) over plain balloon angioplasty in patients with bare metal in-stent restenosis has been clearly demonstrated in the randomized ISAR-DESIRE and RIBS-II trials. However, the only evidence-based treatment of in-stent restenosis, as pointed out in our guidelines, is brachytherapy. Therefore, randomizing patients with in-stent restenosis to either brachytherapy or DES is ethical. ARTS II and TROPICAL were registries, both using historical controls—active controls in these trials were avoided not for ethical reasons, as Dr Nienaber suggests, but rather for funding or logistical concerns. The final publication of TROPICAL did not even publish the historical brachytherapy arm. Evidence-based guidelines cannot be changed on the basis of registries like ARTS II or TROPICAL with no active control group. Two randomized, prospective trials (SISR and TAXUS-V-ISR) compared DES with the gold standard for in-stent restenosis, vascular brachytherapy. At last year's Transcatheter Cardiovascular Therapeutics meeting, SISR was reported to be positive, but is not yet published; TAXUS-V-ISR has been presented at the ACC in March this year. If these trials are positive when published, then an evidence-based recommendation for the use of DES for restenosis in bare metal stents can be made.

(3) Dr Nienaber's third series of questions relates to the comparison of Cypher and Taxus stents and questions our suggested equivalency of these two stents regarding patients' outcome. In the ESC guidelines, we have stated that at the time the guidelines were finished (March 2005), there was no evidence that one DES was superior to another. Until March 2005, TAXI was the only trial comparing Cypher and Taxus, which was fully published. Because TAXI did not clearly define its primary endpoint and no power calculation was provided, we did not feel it appropriate to draw evidence-based recommendations from this study. In the meantime, two superiority trials have been presented: SIRTAX and REALITY. Although SIRTAX was well conducted and met its primary clinical endpoint, the task force does not feel it is appropriate to make an important recommendation on the basis of only a dual-centre study. REALITY, the largest and the only true multicentre trial performed to date testing the hypothesis that Cypher is superior to Taxus, did not meet its primary endpoint (which was angiographic, not clinical, though there were no major clinical differences apparent between the two stents). After our guidelines were printed, two more small (200–250 patients) 1–2 centre studies comparing Cypher vs. Taxus have been fully published: ISAR-Diabetes and ISAR-SMART. Both were designed as non-inferiority studies and both did not meet their non-clinical primary endpoints. This raises the important question: if a non-inferiority study did not confirm its hypothesis, is it justified to apply the results into a retrospective superiority analysis? If one does, then, for example, for the ISAR-SMART trial, the differences between the Cypher and the Taxus stents would have a power in the range between 50 and 70%. The history of medicine is full of erroneous conclusions drawn from underpowered studies or analyses. In order to make an evidence-based statement regarding Dr Nienaber's question about the superiority of Cypher over Taxus, one would require a study as follows:

(i) superiority design
(ii) primary clinical endpoint
(iii) adequate power calculated and reached
(iv) true multicentre study
(v) external and independent CEC/DSMB committee

Not a single large-scale, true multicentre trial with an appropriate clinical endpoint has been performed to address the relative efficacy of Cypher and Taxus. Until such a trial is presented, no evidence-based recommendation about the superiority of one DES vs. another regarding patients' outcome can be made.

In conclusion, ESC guidelines are evidence-based and follow strict rules. The task force of the ESC PCI guidelines was and still is strongly committed to the scientific evidence derived from fully published studies, emphasizing the patients' clinical outcome (rather than surrogate endpoints) demonstrated in appropriately designed, large-scale, adequately powered multicentre trials. Guidelines must be based purely on scientific evidence and be independent of labelling, current or future marketing strategies, or pressures from the industries.

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Abnormal QT responses to adenosine in subjects with long-QT syndrome

In the interesting article by Viskin *et al.*,[1] adenosine-induced bradycardia was found to produce a higher increase in QT and a lower decrease in QT_c (calculated using the Bazett formula) in subjects with long-QT syndrome (LQTS) than in controls. However, a major issue in this study concerns the reliability of QT correction when large ranges of heart rates are analysed. The Bazett formula overcorrects at slow rates and undercorrects at high rates.[2] More generally, the accuracy of correction formulas is limited by the high inter-individual variability of the QT/RR relation,[3] so that they should only be used for an approximate adjustment of QT over a narrow range of heart rates.[4] In the study by Viskin *et al.*,[1] mean RR interval ranged from 580 to 1670 ms in the LQTS group, and from 550 to 2240 ms in the controls. These wide ranges suggest that caution is required in interpreting the observed between-group differences in QT_c.

Moreover, the appropriateness of QT correction during abrupt changes in heart rate should be considered critically. Most correction formulas utilize models obtained by rest electrocardiograms in subject cohorts, but do not describe the electrophysiological process of delayed adaptation of repolarization to rapid changes in heart rate, i.e. QT hysteresis. Although QT correction has been used in studies on LQTS patients under dynamic conditions such as epinephrine administration, measurements were generally taken at steady state during infusion.[5] The effect of QT hysteresis throughout the sudden adenosine-induced deceleration–acceleration sequence may be reasonably relevant. Therefore, when QT is adjusted to the preceding RR interval in these conditions, the resulting value does not represent an effectively rate-corrected QT (i.e. it does not reflect the QT expected at 60 bpm). Also, this value has controversial biological meaning, because it is derived by applying formulas calculated in steady-state conditions to data recorded in non-steady-state conditions.

An alternative analysis could be performed using the QT/RR plot obtained over a few minutes of recording during the test. This may allow (i) avoidance of bias due to QT correction over large RR ranges; (ii) quantification of QT hysteresis by evaluation of the QT/RR loop; and (iii) estimation of QT/RR slope, obtained either from raw data or after QT lag compensation by resynchronization of QT and RR changes.[6] This analysis might also be helpful in discriminating different LQTS genotypes. QT hysteresis could differ between genotypes, as shown by different dynamic responses to sympathetic stimulation.[7] Also, the higher increase in QT at maximal bradycardia in the LQTS group than in the controls is in accordance with studies showing steeper QT/RR slope in LQTS patients than in healthy subjects.[8] However, current evidence suggests that an increased QT/RR slope exists in LQT2 and particularly in LQT3 patients, but not in those with LQT1 genotype, as in these subjects, a paradoxical prolongation in QT occurs at fast rates.[9,10] On the basis of these considerations, dynamic assessment of QT rate dependence and hysteresis could be clinically intriguing and may improve the diagnostic accuracy of the adenosine challenge test.

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