Letter by Bonassi Regarding Article, “Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials”

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To the Editor:

Recent results from a meta-analysis of 28 randomized controlled trials of patients with peripheral artery disease of the leg, reported an increased risk of all-cause death in the group treated with paclitaxel-coated devices. Despite the lack of a plausible mechanism, the strength of statistical evidence and the popularity of this procedure raised general concern about its safety. As a consequence, the pending enrollment of major ongoing randomized controlled trials in the field were temporarily halted, and the Food and Drug Administration recommended that healthcare providers improve surveillance of patients with paclitaxel-coated devices, while waiting for further investigation.

In the 28 studies evaluated by Katsanos et al no higher risk of death was found in patients treated with paclitaxel-coated devices after 1 year of follow-up (risk ratio [RR]=1.08; 0.72–1.61), and none of those studies showed significant results. The authors then evaluated those studies with extended follow-up, under the hypothesis that a longer period of observation may reveal an increased risk of death, hidden in short-term studies by the limited observation time and by the small number of events. A significant association with the risk of all-cause death in patients treated with paclitaxel-coated devices was found after 2 and 5 years of follow-up, ie, RR=1.68 [1.15 to 2.47], and 1.93 [1.27 to 2.93], respectively.

The prospective approach, which is generally robust to bias, is vulnerable to non-random losses, and whenever a systematic loss of information related to the potential factors under investigation occurs, any conclusions drawn from the study may be erroneous. Since positive results reported by the meta-analysis came only from the subset of studies with long-term follow-up, the presence of selection bias because of a selective loss of studies should be carefully considered.

To investigate the presence of non-random selection of the studies which published results from follow-ups over the first year, ie, 12 and 3 studies up to 2 and 5 years, respectively, all 28 studies selected for the meta-analysis were ranked according to the RR at the first year of follow-up (information available for all studies). Thirteen studies reported an RR≤1, 4 studies did not report events (deaths), 11 showed an RR >1 (5 of them RR >2) (see Table S1). According to this list, negative or inconclusive studies represent the 60.7% of all studies (17 out of 28), while positive studies (RR >1) represent 39.3% (11 out of 28). If the selection of those studies whose follow-up continued after the first year would have been random, negative/inconclusive studies at the first year of follow-up should approximately represent the 60% of them, while 40% should come from studies with RR >1 at the first year of follow-up. From Figures 1, 2, and 3 of the meta-analysis we see that studies which were negative at 1-year follow-up contributed to 50% (6/12) of studies which continued to the second year, and none of them (0/3) continued to the fifth year. On the contrary, positive studies (RR >1) at the first year of follow-up represented 50% (6/12) of studies with a 2-year follow-up, and the totality (3/3) of studies which continued to the fifth year. Interestingly, all 5 studies with the highest RR continued the follow-up while none of the 5 studies with the lowest RR continued after the first year. Using the absolute number of patients or changing stratification criteria did not change these figures.

The non-random selection of studies with longer surveillance—which we believe is associated to the results of the first-year follow-up—supports the conclusion that results from the article by Katsanos et al may be flawed, because of the higher propensity of research groups finding a potential association paclitaxel-mortality at the first year of follow-up to...
continue the surveillance, while groups reporting at first negative or inconclusive association in most cases did not continue the follow-up.

An additional observation coming from the comparison of results at different times shows in 2 [THUNDER [Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries] and IN.PACT.SFA [Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter in the Superficial Femoral Artery]] studies out of 3 with a 5-year follow-up that the RR is lower than that observed at the first year, further challenging the hypothesis of a risk of death growing with time.

The possibility that the results of the meta-analysis by Katsanos et al, are affected by some degree of selection bias raises doubts about the real increase of all-cause mortality in patients treated with paclitaxel-coated devices. As recommended by the Food and Drug Administration, further research is required, extending the duration of follow-up also in those studies which do not show higher risk of death in short-term analyses.

Disclosures

Dr Bonassi has received a fee (modest) from Indena SpA, Milan, Italy to review literature on Paclitaxel. There are no other disclosures to report.

References

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2. U.S. Food & Drug Administration. Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers. January 17, 2019. Available at https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm629589.htm.

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SUPPLEMENTAL MATERIAL
Table S1. Distribution of the 28 RCTs included in the Meta-analysis by Katsanos et al., (1) ranked by RR at 1st year follow-up.

| Study                     | RR at 1st YEAR | RR at 2nd YEAR | RR at 5th YEAR |
|---------------------------|----------------|----------------|----------------|
| PACIFIER                  | 0.15           |                |                |
| BIOLUX P-1                | 0.20           |                |                |
| FREEWAY                   | 0.45           |                |                |
| BATTLE                    | 0.49           |                |                |
| RAPID                     | 0.50           |                |                |
| EFFPAC                    | 0.51           |                |                |
| LEVANT I                  | 0.53, 0.85     |                |                |
| LUTONIX JAPAN             | 0.54           |                |                |
| FAIR                      | 0.62           |                |                |
| LEVANT II                 | 0.87, 1.51     |                |                |
| ILLUMENATE EU             | 0.92, 1.28     |                |                |
| RANGER SFA                | 0.96           |                |                |
| ACOART I                  | 1.00, 1.32     |                |                |
| PACUBA                    | No deaths      |                |                |
| IN.PACT SFA –JAPAN        | No deaths      | 1.76           |                |
| FINN-PTX                  | No deaths      | 2.36           |                |
| DEBELLOM                  | No deaths      |                |                |
| ZILVER-PTX                | 1.34, 1.62, 2.09 |    |                |
| DEBATE-in-SFA             | 1.67           |                |                |
| CONSEQUENT                | 1.86, 1.86     |                |                |
| DEBATE-SFA                | 1.92           |                |                |
| DRECOREST                 | 1.93           |                |                |
| ILLUMENATE Pivotal        | 2.00           |                |                |
| THUNDER                   | 2.25           | -              | 1.69           |
| FEMPAC                    | 2.80, 2.18     |                |                |
| ISAR-PEBIS                | 3.00, 7.25     |                |                |
| IN.PACT SFA               | 4.66, 8.57, 1.92 |            |                |
| ISAR-STATH                | 6.65, 6.69     |                |                |