

Is non-cardiac death increased with an initial invasive revascularization strategy? Commentary on the ISCHEMIA trial

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In a recent issue of partner journal from the ESC Journals family, the incidence of cardiovascular adverse events at 4 years of follow-up in the ISCHEMIA trial was reported.¹ In such manuscript, authors did not find any significant differences between initial Invasive (INV) or Conservative (CON) strategies in the number of composite or individual cardiac events.

However, if we look numbers of cardiovascular death, 3.6% vs. 4.3% with INV and CON strategies, respectively $P=0.176$, and all-cause of death 5.6% in both $P=0.944$; call to our attention that incidence of *non-cardiac death* in the INV group would be significant higher compared to the CON ones 2% vs. 1.3%, respectively, $P=0.029$ and numbers of non-cardiac death are not reported in the manuscript.¹ Interestingly, most of these were due to cancer accorded to the abstract presentation reported by the same authors in the 2020 American Heart Association meeting.²

Taking in account that 74% of patients included in the INV have been treated with percutaneous coronary intervention (PCI) would be relevant to know if these findings have a relation with the sort of revascularization techniques used in the INV strategy: PCI with drug-eluting stent (DES) implantation or coronary artery bypass surgery (CABG).

High incidence of non-cardiac death with DES have been reported in randomized clinical trials, registries, and meta-analysis^{3,4} as is described in [Table 1](#) and should be matter of careful attention by those who are doing PCI in clinical practice.

Reason for the incidence of non-cardiac death in these studies has not a clear explanation yet, mis-categorization of cardiac death as non-cardiac death, requirements for long-term medication after DES implantation or related to DES biology might be the case.

In the past, in pre-DES era PCI was not linked with a rise of non-cardiac death.³

The comment of that incidence may be occurred by chance appears not to be plausible taking in account is not an isolated finding for a single study and by contrary, we are observing the same concerning data in other trials and registries as described in [Table 1](#). In all these studies, patients were followed at long term.

The authors of the ISCHEMIA trial have the chance to report very important observation on this matter splitting these findings accorded to the revascularization technique used in the INV group, PCI or CABG.

Is the increase of non-cardiac death linked with the strategy used or mainly related to one technique performed during coronary intervention?

If we have a potential problem, as increase non-cardiac death with DES, first we need to know if that's true, and if the answer is yes, we should identify the causes and search for solutions.

Introduction of DES in clinical practice significantly reduced incidence of repeat revascularization procedures, however, gap among PCI, CABG, and/or optimal medical treatment did not change in the last 20 years as is reflect by the references of this correspondence letter.^{1,3,4}

Percutaneous coronary intervention was not invented more than 40 years ago only to treat patients with a short life expectancy, with contraindication for CABG or suffering an ST-elevation myocardial infarction.

Conflict of interest: none declared.

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Table 1 Studies reporting high incidence of non-cardiac death with drug-eluting stents

Study	Design	Comparators
Stone GW, et al. EXCEL Trial Investigators. <i>N Engl J Med</i> 2019 Nov 7;381(19):1820–1830.	Randomized	DES 2 vs. CABG
Pilgrim T, et al. The BIOSCIENCE randomised trial. <i>Lancet</i> 2018 Sep 1;392(10149):737–746.	Randomized	DES 3 vs. DES2
Matsumura-Nakano Y, et al. CREDO-Kyoto PCI/CABG Registry Cohort-3. <i>Am J Cardiol</i> 2021 Apr 15;145:25–36.	Credo-Kyoto PCI/CABG Registry Cohort 3	DES 2 vs. CABG
Nordmann AJ, et al. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. <i>Eur Heart J</i> 2006 Dec;27(23):2784–814.	Meta-Analysis	BMS vs. DES 1
Gaudino M, et al. Overall and cause-specific mortality in randomized clinical trials comparing percutaneous interventions with coronary bypass surgery: a meta-analysis. <i>JAMA Intern Med</i> 2020 Dec 1;180(12):1638–1646.	Meta-Analysis	BMS vs. CABG DES 1-DES 2 vs. CABG

BMS, bare metal stents; CABG, coronary artery bypass surgery; DES1, 1st generation drug eluting stents; DES2, 2nd generation drug eluting stents; DES3, 3rd generation ultra-thin drug eluting stents.

Lead author biography



Dr Alfredo E Rodriguez MD – PhD is an author or co-author of 378 articles in peer review Journals within them first randomized comparison between PCI vs CABG (ERACI I and II trials, first randomized comparison with stents in AMI GRAMI trial). He is also an author or co-author of 17

books. Founder and Director of Cardiovascular Research Center (CECI) 1986 - to present. Director of Interventional Cardiology of Otamendi Hospital (1993- to present). He is active in Interventional Cardiology procedures since 1981 - to present.

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