was positively associated [odds ratio (95% confidence interval, p value)] with current e-cigarette [2.40 (2.18 to 2.64, <0.001)], and marijuana use [1.77 (1.48 to 2.12, <0.001)], but inversely associated with smokeless tobacco [0.65 (0.60 to 0.70, <0.001)] and cigarette use [0.88 (0.84 to 0.91) <0.001)] .

In a contemporary and nationally representative U.S. cohort, we found that Internet users were more likely to use e-cigarettes and marijuana, and less likely to use cigarettes and smokeless tobacco. The widespread use of Internet and social media has likely resulted in newer avenues for advertisements and marketing,[3] with many states allowing online sales of e-cigarettes and marijuana products. The heterogeneity of state-specific legislature in regulating the online sale and use of these products, and the void created by the declining rates of traditional cigarette use could explain the rise in e-cigarettes and marijuana. Further, social media platforms like Instagram, Facebook, and Snapchat have many images of individuals, including celebrities, smoking marijuana, vaping etc. which may influence susceptible individuals such as young adults, to start using such products. These findings are important for health policymakers and healthcare providers alike as an avenue for primary prevention, and should be reported.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Comparison of Oral P2Y12 Inhibitors in Acute Coronary Syndrome

Baldetti et al[1] have performed a network meta-analysis to compare oral P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in acute coronary syndrome. Seven randomized trials, along with some observational studies, were analyzed. The main efficacy end-point was a composite of major adverse cardiovascular events (MACE) at 12 months including cardiovascular death, myocardial infarction, and stroke (Table 5[1]). Other end points of efficacy (e.g., all-cause death at 1 year) were also evaluated. The odds ratio (OR) was the outcome measure. As regards 1-year all cause death, the results of this network meta-analysis favored prasugrel and ticagrelor compared with clopidogrel; prasugrel also reduced myocardial infarction rate compared with clopidogrel (Table 4[1]). The other end-points of efficacy (e.g., the MACE composite end-point) showed no significant differences among the 3 agents.

A wide literature has recently focused on some important disadvantages of both the hazard ratio and the OR (which are both relative outcome measures) particularly because, in pairwise comparisons, they tend to overemphasise the difference in favor of the more effective treatment.[2,3] Network meta-analyses are known to accentuate this tendency of OR.

In a separate report,[2] we have presented the narrative results that we obtained by analyzing the same 7 randomised trials assessed by Baldetti et al (15 patient cohorts; data from page 17 of the Supplementary Appendix[1]). Our rankings in effectiveness (based on event-free rates at 12 months; event = MACE) were estimated by simple arithmetic ordering. Since these results separately rely on the 15 patient cohorts, they lost their linkage with the inclusion criteria of the 7 trials and with the effects of randomisation.

The results in these 15 cohorts were the following: prasugrel ranked 1st, 4th, 6th, 9th and 13th; clopidogrel ranked 2nd, 7th, 8th, 14th and 15th; ticagrelor ranked 3rd, 5th, 10th, and 12th. The message arising from these results is that the effectiveness of clopidogrel, prasugrel, or ticagrelor has clearly a random distribution; hence, a network meta-analysis is unable to provide any meaningful information beyond the one provided by this narrative analysis. It should be noted that the assumptions of our reanalysis (e.g., transitivity of outcomes) are the same as those implicitly adopted by Baldetti et al[1] in their network meta-analysis.

As pointed out by Westafer and Schriger,[3] all network meta-analyses are based on the transitivity property and therefore assume that participants and trials are similar enough so that patients could have been randomized to any of the treatment arms. This allows the direct and indirect comparison to be made in any combination of between-treatment comparisons. Although meta-analyses are sometimes considered the ultimate form of evidence, the results are only as good as the underlying studies.[3] Ideally, any meta-analysis would include only those studies that are conducted on similar populations and use similar interventions; this is particularly important in network meta-analysis for the treatment effects to be transitive and determine reliable indirect estimates.

Coherence and/or network consistency is a unique component to evaluation of a network meta-analysis. So, network meta-analyses must be scrutinized for inconsistency, heterogeneity of trials or patient populations and potential sources of bias.

The overall picture emerging from our narrative analysis (in particular, our rankings) is a message of heterogeneous effectiveness across clopidogrel, prasugrel, or ticagrelor thus emphasising the potential inconsistencies of these 7 randomized trials. Although Baldetti et al presented a conclusion about comparative effectiveness favoring prasugrel, this conclusion is not supported by our results. In our view, our narrative analysis is simpler and more reliable than the unavoidably

complex network meta-analysis that suffers from the methodological biases typical of this statistical technique.

Declaration of interests

The authors declare no conflicts of interests.

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Meta-Analysis Comparing Angiography-Guided Versus FFR-Guided Coronary Artery Bypass Grafting

Fractional flow reserve (FFR) is the ratio of mean distal coronary artery pressure to the simultaneous mean aortic pressure at maximal hyperemia. FFR provides an objective assessment of the flow in a coronary artery and is the gold standard for physiological stenosis severity assessment. An FFR cutoff of ≤ 0.80, indicating the mean hyperemic coronary pressure is reduced by at least 20% from the theoretical maximum value, is used in contemporary practice to define a physiologically significant stenosis. FFR-guided decision making for percutaneous coronary intervention (PCI) has showed improved outcomes compared with angiography alone.[1] It remains unknown if such an approach can improve outcomes for coronary artery bypass grafting (CABG). The goal of this meta-analysis is to determine if FFR-guided CABG has better outcomes compared with angiography guidance alone.

We searched multiple databases for studies comparing FFR-guided versus angiography-guided CABG. We used the aggregated odds ratio (OR) and corresponding 95% confidence interval (CI) for measuring outcomes. Statistical analyses were performed using Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014).

There were 5 studies included in this meta-analysis (2 randomized control trials, 2 prospective observational studies, and 1 retrospective propensity matched observational study).[2–6] Studies were done from 2007 to 2019. The follow-up ranged from 6 to 85 months. The total number of patients included in the analysis was 898. A total of 3,317 grafts were placed. Graft anatomy was described in 4 studies (2,882 grafts, FFR-1,126, angiography-1,756). There were 1,629 arterial and 1,253 venous grafts. The mean age in the studies ranged from 62.4 years to 67. There were 72.5% men, 33.6% with diabetes mellitus, 69.2% with hypertension, 74.1% with hyperlipidemia, 40.9% smokers, and 21.4% with history of PCI.

There was no statistical difference between the FFR-guided group and the angiography-guided group for all-cause mortality (6.3% vs 10.6%, OR 0.59 CI 0.33 to 1.04, $p = 0.07$, I^2 0%), myocardial infarction (3.6% vs 6.7%, OR 0.54 CI 0.26 to 1.11, $p = 0.09$, I^2 0%), target vessel revascularization (5% vs 4.9%, OR 1.0 CI 0.51 to 1.95, $p = 1.0$, I^2 0%), and CCS class II-IV angina (24.6% vs 38.7% OR 1.1, 95% CI 0.21 to 5.82, $p = 0.91$, I^2 86%; see Figure 1) FFR group was more likely to have a greater proportion of arterial grafts compared with the angiography group (61% vs 53%, OR 1.33, 95% CI 1.14 to 1.55, $p = 0.0003$). There were fewer loss of graft patency events in the FFR group compared to the angiography group (10.2% vs 22.1%, OR 0.34, 95% CI 0.12 to 0.98, $p = 0.05$, I^2 90%; see Figure 1)

This meta-analysis shows similar outcomes for the FFR and angiography groups except for graft patency. Graft patency was significantly better in the FFR group. We found FFR-guided CABG results in fewer grafts per patient and higher proportion of arterial grafts. This is the likely explanation for better graft patency with FFR-guided CABG. FFR guidance often results in a simplified grafting strategy. Coronary arteries that would otherwise be grafted based on angiography alone, may not be grafted after FFR is used to determine physiologic significance.[6] Although we found better graft patency with FFR-guided CABG, this did not translate into better clinical outcome. A functionally nonsignificant coronary artery with a graft has a higher likelihood of graft failure because of competitive flow.[4,6] Failure of such a graft may remain clinically silent as the native vessel may still be able to supply the myocardium. The findings from this meta-analysis differ from the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial. The FAME trial showed that in comparison with angiography alone, FFR-guided PCI reduced the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization.[1] PCI and CABG are different forms of revascularization and this study shows FFR guidance data from PCI cannot be extrapolated to CABG.

There are certain limitations in this analysis. The follow-up is not uniform, and some studies did not have a long follow up. A prolonged follow-up could show different results. Subgroup analysis for arterial and venous grafts could not be done. The overall sample size is modest despite meta-analysis. The p values for individual adverse outcomes are of borderline significance and it is possible that the study is underpowered. Given the very small number of subjects in randomized controlled trials, heterogeneous study designs were included in this meta-analysis. In addition, certain endpoints, namely loss of graft patency and angina have high heterogeneity. Future randomized trials assessing angiography-guided versus FFR-guided revascularization in CABG are needed. Furthermore, data on non-hyperemic indexes such as instantaneous wave-free ratio in the CABG decision making are limited and could not be assessed in this meta-analysis.

To conclude, use of FFR guidance for CABG revascularization decision making compared with angiography