Prasugrel Superior to Ticagrelor in Acute Coronary Syndromes

Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med. 2019;381:1524-1534.

Study Overview

Objective. To assess the relative merits of ticagrelor compared to prasugrel in patients with acute coronary syndromes who will undergo invasive evaluation.

Design. Multicenter, open-label, prospective randomized controlled trial.

Setting and participants. A total of 4018 patients who presented with ACS with or without ST-segment elevation.

Intervention. Patients were randomly assigned to receive either ticagrelor or prasugrel.

Main outcome measures. The primary end point was the composite of death, myocardial infarction, or stroke at 1 year. The secondary end point was bleeding.

Main results. At 1 year, a primary end point event occurred in 184 of 2012 patients (9.3%) in the ticagrelor group and 137 of 2006 patients (6.9%) in the prasugrel group (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.09-1.70; P = 0.006). In the comparison between ticagrelor and prasugrel, the individual components of the primary end point were as follows: death, 4.5% versus 3.7%; myocardial infarction, 4.8% versus 3.0%; and stroke, 1.1% versus 1.0%, respectively. Definite or probable stent thrombosis occurred in 1.3% of patients assigned to ticagrelor and 1.0% in patients assigned to prasugrel. Major bleeding was observed in 5.4% of the patients in the ticagrelor group and 4.8% in the prasugrel group (HR, 1.12; 95% CI, 0.83-1.51, P = 0.46).

Conclusion. In patients who presented with ACS with or without ST-segment elevation, the incidence of death, myocardial infarction, or stroke was significantly lower among those who received prasugrel as compared to those who received ticagrelor, and incidence of major bleeding was not significantly different.

Commentary

Dual antiplatelet therapy combining an adenosine disphosphate (ADP) receptor antagonist and aspirin is standard treatment for patients presenting with ACS. The limitation of clopidogrel has been its modest antiplatelet effect, with substantial interpatient variability. The newer generation thienopyridine prasugrel and the reversible direct-acting oral antagonist of the ADP receptor ticagrelor provide consistent and greater antiplatelet effect compared to clopidogrel. It has been previously report-

ed that these agents are superior in reducing ischemic events when compared to clopidogrel.[1,2] Therefore, current guidelines recommend ticagrelor and prasugrel in preference to clopidogrel.[3,4] However, there has been no large randomized controlled study comparing the effect of ticagrelor and prasugrel. In this context, Shupke et al investigated this clinical question by performing a well-designed multicenter randomized controlled trial in patients presenting with ACS. At 12-month follow-up, the composite of death, myocardial infarction, and stroke occurred more frequently in the ticagrelor group compared to the prasugrel group (9.3% versus 6.9%; HR, 1.36; 95% CI, 1.09-1.70; $P < 0.01$). The incidence of major bleeding was not significantly different between the 2 groups (5.4% versus 4.8%; $P = 0.46$).

The strengths of this current study include the randomized design and the large number of patients enrolled, with adequate power to evaluate for superiority. This was a multicenter trial in Europe with 23 participating centers (21 from Germany). Furthermore, the interventional technique used by the operators reflects more contemporary technique compared to the previous studies comparing each agent to clopidogrel,[1,2] with more frequent use of radial access (37%) and drug-eluting stents (90%) and reduced use of GPIIb/IIIa inhibitors (12%).

There are a few important points to consider due to the differences between the 2 agents compared in this study. First, the loading dose of ticagrelor and prasugrel was administered differently in patients presenting with ACS without ST elevation. Ticagrelor was administered as soon as possible prior to the coronary angiogram, but prasugrel was administered after the coronary anatomy was defined prior to the intervention, which is how this agent is administered in current clinical practice. Therefore, this trial was an open-label study that compared not only different medications, but different administration strategies. Second, ticagrelor and prasugrel have different side-effect profiles. The side effects unique to ticagrelor are dyspnea and bradycardia. On the other hand, a contraindication unique to prasugrel is patients with a history of transient ischemic attack or stroke due to increased risk of thrombotic and hemorrhagic stroke.[1] In addition, prasugrel has increased bleeding risk in patients older than 75 years of age and those with low body weight (< 60 kg). In this study, the overall medication discontinuation rate was higher in the ticagrelor group specifically due to dyspnea, and the reduced dose of 5 mg of prasugrel was used in patients older than 75 years or with low body weight.

Since the timing of administration of ticagrelor (preloading prior to coronary angiography is recommended) is similar to that of clopidogrel, and given the theoretical benefit of reversible inhibition of the ADP receptor, ticagrelor has been used more commonly in clinical practice than prasugrel, and it has been implemented in the ACS protocol in many hospitals. In light of the results from this first head-to-head comparison utilizing more contemporary interventional techniques, these protocols may need to be adjusted in favor of prasugrel for patients presenting with ACS. However, given the difference in timing of administration and the difference in side-effect profile, operators must also tailor these agents depending on the patient profile.

Applications for Clinical Practice

In patients presenting with ACS, prasugrel was superior to ticagrelor, with a lower composite of death, myocardial infarction, and stroke at 12 months. Prasugrel should be considered as a first-line treatment for ACS.

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Cardioprotective Effect of Metformin in Patients with Decreased Renal Function

Roumie CL, Chipman J, Min JY, et al. Association of treatment with metformin vs sulfonylurea with major adverse cardiovascular events among patients with diabetes and reduced kidney function. JAMA. 2019;322:1167-1177.

Study Overview

Objective. To assess whether metformin use is associated with lower risk of fatal or nonfatal major adverse cardiovascular events (MACE) as compared to sulfonylurea use among diabetic patients with reduced kidney function.

Design. Retrospective cohort study of US Veterans receiving care within the Veterans Health Administration, with data supplemented by linkage to Medicare, Medicaid, and National Death Index data from 2001 through 2016.

Setting and participants. A retrospective cohort of Veterans Health Administration (VHA) patients, aged 18 years and older. Pharmacy data included medication, date filled, days supplied, and number of pills dispensed. For Medicare and Medicaid patients, enrollees' claims files and prescription (Part D) data were obtained. In addition, dates and cause of death were obtained from vital status and the National Death Index files.

Patients with new-onset type 2 diabetes were identified by selecting new users of metformin, glipizide, glyburide, or glimepiride. These patients were followed longitudinally and the date of cohort entry and start of follow-up was the day of reaching a reduced kidney function threshold, defined as either an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 or serum creatinine level of 1.5 mg/dL for men or 1.4 mg/dL for women. Patients were excluded for nonpersistence, defined as 90 days without an antidiabetic drug; censoring, defined as the 181st day of no VHA contact; or study end date of December 31, 2016.

Main outcome measures. Primary outcome was the composite of MACE including hospitalization for acute myocardial infarction (AMI), ischemic or hemorrhagic stroke, transient ischemic attack (TIA), or date of cardiovascular death. The secondary outcome excluded TIA as part of the composite MACE event because not all patients who sustain a TIA are admitted to the hospital.

Main results. From January 1, 2002 through December 30, 2015, 67,749 new metformin users and 28,976 new sulfonylurea users who persisted with treatment were identified. After using propensity score-weighted matching, 24,679 metformin users and 24,799 sulfonylurea users entered the final analysis. Cohort patients were 98% male and 81.8% white. Metformin users were younger than sulfonylurea users, with a median age of 61 years versus 71 years, respectively.

For the main outcome, there were 1048 composite MACE events among metformin patients with reduced kidney function and 1394 MACE events among sulfonylurea patients, yielding 23.0 (95% confidence interval [CI], 21.7-24.4) versus 29.2 (95% CI, 27.7-30.7) events per 1000 person-years of use, respectively, after propensity score-weighting. After covariate adjustment, the cause-specific adjusted hazard ratio (aHR) for MACE was 0.80 (95% CI, 0.75-0.86) among metformin users compared with sulfonylurea users. The adjusted incidence rate difference was 5.8 (95% CI, 4.1-7.3) fewer events per 1000-person years for metformin compared with sulfonylurea users. Results were also consistent for each component of the primary outcome, including cardiovascular hospitalizations (aHR, 0.87; 95% CI, 0.80-0.95) and cardiovascular deaths (aHR, 0.70; 95% CI, 0.63-0.78).

Analysis of secondary outcomes, which included AMI, stroke, and cardiovascular death and excluded TIA, demonstrated similar results, with a cause-specific aHR of 0.78 (95% CI, 0.72-0.84) among metformin users compared with sulfonylurea users. The

adjusted incidence rate difference was 5.9 (95% CI, 4.3-7.6) fewer events per 1000-person years for metformin compared with sulfonylurea users.

Conclusion. For patients with diabetes and reduced kidney function, treatment with metformin monotherapy, as compared with a sulfonylurea, was associated with a lower risk of MACE.

Commentary

There are approximately 30 million US adults with a diagnosis of type 2 diabetes (T2DM), of whom 20% also have impaired kidney function or chronic kidney disease (CKD).[1] Metformin hydrochloride has remained the preferred first-line treatment for T2DM based on safety and effectiveness, as well as low cost.[2] Metformin is eliminated by the kidneys and can accumulate as eGFR declines. Based on the negative clinical experience, the US Food and Drug Administration (FDA) issued a safety warning restricting metformin for patients with serum creatinine levels of 1.5 mg/dL or greater for men or 1.4 mg/dL or greater for women. The FDA recommended against starting metformin therapy in patients with CKD with eGFR between 30 and 45 mL/min/1.73 m^2, although patients already taking metformin can continue with caution in that setting.[1,3]

There are several limitations in conducting observational studies comparing metformin to other glucose-lowering medications. First, metformin trials typically excluded patients with CKD due to the FDA warnings. Second, there is usually a time-lag bias in which patients who initiate glucose-lowering medications other than metformin are at a later stage of disease. Third, there is often an allocation bias, as there are substantial differences in baseline characteristics between metformin and sulfonylurea monotherapy users, with metformin users usually being younger and healthier.[4]

In this retrospective cohort study by Roumie et al, the authors used propensity score–weighted matching to reduce the impacts on time-lag and allocation bias. However, several major limitations remained in this study. First, the study design excluded those who began diabetes treatment after the onset of reduced kidney function; therefore, this study cannot be generalized to patients who already have reduced eGFR at the time of metformin initiation. Second, cohort entry and the start of follow-up was either an elevated serum creatinine or reduced eGFR less than 60 mL/min/1.73 m^2. The cohort may have included some patients with an acute kidney injury event, rather than progression to CKD, who recovered from their acute kidney injury. Third, the study population was mostly elderly white men; together with the lack of dose analysis, this study may not be generalizable to other populations.

Applications for Clinical Practice

The current study demonstrated that metformin use, as compared to sulfonylureas, has a lower risk of fatal or nonfatal major adverse cardiovascular events among patients with reduced kidney function. When clinicians are managing hyperglycemia in patients with type 2 diabetes, it is important to keep in mind that all medications have adverse effects. There are now 11 drug classes for treating diabetes, in addition to multiple insulin options, and the challenge for clinicians is to present clear information to guide patients using shared decision making, based on each patient's clinical circumstances and preferences, to achieve individualized glycemic target ranges.

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Combination Encorafenib, Cetuximab, and Binimetinib Improves Survival in *BRAF* V600E–Mutated Metastatic Colon Cancer

Kopetz S, Grothey A, Yaeger R, et. al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med. 2019;381:1632-1643.

Study Overview

Objective. To evaluate whether the combination of encorafenib plus cetuximab with or without the MEK inhibitor binimetinib would lead to longer overall survival (OS) than standard therapy in patients with metastatic *BRAF* V600E–mutated colorectal cancer.

Design. Global, multicenter, randomized, open-label, phase 3 trial.

Intervention. Patients were randomized in a 1:1:1 fashion to 1 of 3 groups: triplet-therapy group (encorafenib 300 mg daily, binimetinib 45 mg twice daily, and cetuximab 400 mg/m^2 of body surface area initially, then 250 mg/m^2 weekly), doublet-therapy group (encorafenib and cetuximab in same doses and schedule as the triplet-therapy group), and control group (investigators choice of cetuximab and irinotecan or cetuximab and FOLFIRI). The randomization was stratified by performance status and prior irinotecan use. Treatment was given until progression or unacceptable toxicities on a 28-day cycle. No crossover was permitted.

Setting and participants. 665 patients underwent randomization: 224 patients to triplet-therapy, 220 to doublet-therapy, and 221 to the control group. Eligible patients had histologically confirmed metastatic colorectal cancer with a *BRAF* V600E mutation. Patients all had disease progression after 1 or 2 previous lines of therapy.

Main outcome measures. The primary end point of the study was OS and objective response rate (ORR) in the triplet-therapy group compared with the control group. Secondary endpoints included OS in the doublet-therapy group compared with the control group, as well as progression-free survival (PFS), duration of response (DOR), and safety. Assessments were performed every 6 weeks for the first 24 weeks and then every 12 weeks thereafter.

Results. The baseline characteristics were well balanced between the treatment arms. At the time of data cutoff, the median duration of follow-up was 7.8 months for each group. The median OS was 9 months in the triplet-therapy group and 5.4 months in the control group (hazard ratio [HR] for death, 0.52; 95% confidence interval [CI], 0.39-0.70; $P < 0.001$). The median OS was 8.4 months for the doublet-therapy group, resulting in a significant reduction in the risk of death compared with the control group (HR, 0.6; 95% CI, 0.45-0.79; $P < 0.001$). The estimated 6-month survival was 71% for the triplet-therapy group, 65% for the doublet-therapy group, and 47% for the control group. The triplet-therapy group had a higher ORR compared with the control group (26% versus 2%, $P < 0.001$). The ORR in the doublet-therapy group was also significantly higher than that in the control group (20% versus 2%, $P < 0.001$). Complete responses were seen in 4% of patients in the triplet-therapy group, 5% of the doublet-therapy group, and no patients in the control group. PFS was significantly longer in both the triplet-therapy and doublet-therapy groups compared with the control group (median PFS: 4.3 months, 4.2 months, 1.5 months, respectively). This translated into a 62% and 60% reduction in the risk for disease progression or death in the triplet-therapy and doublet-therapy groups, respectively, compared to the control group.

The most common adverse event reported in the triplet-therapy group was gastrointestinal (GI) related (diarrhea, nausea, and vomiting), with grade 3 or higher GI toxicity seen in 10% of patients. Skin toxicity in the form of acneiform dermatitis was seen in almost 50% of those in the triplet-therapy arm; however, grade 3 or higher skin toxicity was uncommon (2%). Overall, adverse events

grade 3 or higher were observed in 58% of those in the triplet-therapy group, 50% in the doublet-therapy group, and 61% in the control group. Adverse events leading to drug discontinuation occurred in 7% in the triplet-therapy group, 8% in the doublet-therapy group, and 11% in the control group. Three deaths were considered treatment related: 1 in the triplet-therapy group (bowel perforation) and 2 in the control group (anaphylaxis and respiratory failure).

Conclusion. The triplet-combination of encorafenib, binimetinib, and cetuximab as well as the doublet-regimen of encorafenib and cetuximab improved both PFS and OS in patients with metastatic, *BRAF* V600E–mutated colorectal cancer that has progressed after 1 or 2 lines of therapy.

Commentary

The current interim analysis of the BEACON CRC trial demonstrates improved response rates, PFS, and, importantly, OS with the triplet regimen of encorafenib, binimetinib, and cetuximab in patients with metastatic *BRAF* V600E–mutated colorectal cancer compared to standard irinotecan-based therapy. Similarly, a doublet-regimen of encorafenib and cetuximab also improved outcomes compared with irinotecan-based chemotherapy, resulting in significantly higher response rates, PFS, and OS.

BRAF mutations are seen in approximately 5% to 15% of colorectal cancers and are more commonly seen in right-sided disease. *BRAF*-mutated colorectal cancer has a poor prognosis, and the presence of a *BRAF* mutation is an independent prognostic factor for decreased survival.[1] Previous work to improve outcomes in this subset of patients has been largely disappointing. For example, Kopetz and colleagues have previously shown that single-agent BRAF inhibition with vemurafenib in metastatic *BRAF*-mutated colorectal cancer did not show meaningful clinical activity.[2] Preclinical studies have suggested that single-agent BRAF or MEK inhibition alone do not lead to sustained MAPK pathway inhibition. Mechanistically, inhibition of BRAF has been shown to lead to feedback activation of EGFR; thus, inhibition of BRAF alone does not lead to cessation of proliferation.[3] In light of this, the combination of EGFR and BRAF inhibition has been an attractive therapeutic strategy. Yaeger and colleagues enrolled 15 patients in a pilot study looking at the efficacy and safety of the BRAF inhibitor vemurafenib and the EGFR antibody panitumumab in patients with *BRAF*-mutated metastatic colorectal cancer. In this cohort, combined BRAF and EGFR inhibition showed tumor regression in 10 of 12 patients.[4] This finding was validated in other subsequent studies.[5]

The current study is the first phase 3 trial to validate the efficacy of BRAF, MEK, and EGFR inhibition in patients with *BRAF*-mutant metastatic colorectal cancer. The results of this study represent a very important step forward in treating this patient cohort that has historically had very poor clinical outcomes. The combination of encorafenib, binimetinib, and cetuximab improved OS by 48% compared with standard irinotecan-based chemotherapy. In light of this, we now have a chemotherapy-free targeted combination that improves survival and likely represents the new standard of care in patients with *BRAF*-mutated colorectal cancer after progression on 1 or 2 prior lines of therapy. Ongoing trials are being pursued to investigate the efficacy of these combinations in the upfront setting, and the results of these trials are eagerly awaited.

Applications for Clinical Practice

The combination of encorafenib, binimetinib, and cetuximab improved OS in patients with *BRAF*-mutated metastatic colorectal cancer after progression on 1 or 2 prior lines of therapy. This combination represents a potential new standard of care in this patient population.

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