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CLINICAL INVESTIGATIONS

Use of ticagrelor alongside fibrinolytic therapy in patients with ST-segment elevation myocardial infarction: Practical perspectives based on data from the TREAT study

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Primary percutaneous coronary intervention (PCI) is the preferred reperfusion method in patients with ST-segment elevation myocardial infarction (STEMI). In patients with STEMI who cannot undergo timely primary PCI, pharmacoinvasive treatment is recommended, comprising immediate fibrinolytic therapy with subsequent coronary angiography and rescue PCI if needed. Improving clinical outcomes following fibrinolysis remains of great importance for the many patients globally for whom rapid treatment with primary PCI is not possible. For patients with acute coronary syndrome who underwent primary PCI, the PLATO trial demonstrated superior efficacy of ticagrelor relative to clopidogrel. Results in the predefined subgroup of patients with STEMI were consistent with the overall PLATO trial. Patients who received fibrinolytic therapy in the 24 hours before randomization were excluded from PLATO, and there is thus a lack of data on the safety of using ticagrelor in conjunction with fibrinolytic therapy in the first 24 hours after STEMI. The TREAT study addresses this knowledge gap; patients with STEMI who had symptom onset within the previous 24 hours and had received fibrinolytic therapy (of whom 89.4% had also received clopidogrel) were randomized to treatment with ticagrelor or clopidogrel (median time between fibrinolysis and randomization: 11.5 hours). At 30 days, ticagrelor was found to be non-inferior to clopidogrel for the primary safety outcome of Thrombolysis in Myocardial Infarction (TIMI)-defined first major bleeding. Considering together the results of the PLATO and TREAT studies, initiating or switching to treatment with ticagrelor within the first 24 hours after STEMI in patients receiving fibrinolysis is reasonable.

KEYWORDS

fibrinolysis, reperfusion therapy, ST-segment elevation myocardial infarction, ticagrelor, TREAT study

1 | INTRODUCTION

1.1 | Reperfusion therapy for patients with ST-segment elevation myocardial infarction

Guidelines for the treatment of patients with ST-segment elevation myocardial infarction (STEMI) recommend primary percutaneous coronary intervention (PCI) as the preferred reperfusion therapy, if it can be performed in a timely manner.[1,2] In patients with STEMI who cannot undergo timely primary PCI, however, early fibrinolysis also provides effective reperfusion.[3–6] If treatment with primary PCI is delayed by 2 hours or more relative to treatment with fibrinolysis, then similar mortality outcomes are observed for both treatment options.[7,8] Thus, if primary PCI cannot be performed within 2 hours of

STEMI diagnosis, pharmacoinvasive treatment is recommended, comprising immediate fibrinolytic therapy with subsequent coronary angiography and either rescue PCI, if there is no evidence of clinical reperfusion, or elective PCI within 2 to 24 hours, in case of successful reperfusion.[1,2] The efficacy of the pharmacoinvasive treatment strategy is supported by the results of the STREAM trial.[3,9] Routine PCI in asymptomatic patients more than 48 hours after symptom onset is not recommended.[2]

In real-world settings, access to primary PCI can be delayed or made impossible by geographical and economic hurdles, such as long distances to PCI centers, difficulties with traffic and transportation, and PCI centers not being open overnight or over weekends, or not being available at all.[10] Delays to providing reperfusion therapy are common: in two large prospective observational studies, EPICOR (NCT01171404) and EPICOR Asia (NCT01361386), recruiting 11 559 patients with STEMI from 773 hospitals in 28 countries across Europe, Latin America, and Asia, the overall median time from symptom onset to reperfusion therapy was 5.8 hours for primary PCI (interquartile range [IQR]: 3.2-13.5 hours) and 3.5 hours for fibrinolysis (IQR: 2.0-6.0 hours).[11] There were large regional variations, with median time from symptom onset to primary PCI ranging from 3.9 hours in Southern and Northern Europe, South Korea, Hong Kong, and Singapore, to 20.9 hours in India, and median time to fibrinolysis ranging from 2.4 hours in Southern Europe to 6.3 hours in India (Figure 1). Data from the United States indicate that fewer than half of patients who require transfer from a referral center to a STEMI receiving-center receive primary PCI within 2 hours of presentation at the referral center if the interhospital drive time is longer than 30 minutes.[6] Registry data from Arabian Gulf countries (Saudi Arabia, Bahrain, Qatar, Oman, and United Arab Emirates) show a median time from symptom onset to hospital arrival for patients with STEMI of between 2.5 and 2.9 hours, with most patients requiring emergency transfer between treatment centers.[12–14]

These difficulties and regional variations are reflected in treatments used in clinical practice. In EPICOR and EPICOR Asia, rates of primary PCI ranged from 25% in India to 66% in Northern Europe, and of fibrinolysis from 8% in China to 34% in Southeast Asia (Figure 1).[11] A large number of patients received no reperfusion therapy at all, ranging from approximately 20% in Europe, to 40% in Latin America and China, and 46% in India. Among patients who received any type of reperfusion therapy, the proportions of patients who received fibrinolysis rather than primary PCI were most substantial in Latin America (55%), India (55%), and Southeast Asia (44%). Similarly, in aggregated survey data from 37 European Society of Cardiology affiliated countries, rates of primary PCI and fibrinolysis varied widely, with many patients with STEMI not receiving any reperfusion therapy.[10] In other settings, treatment options may be even more limited: an observational study conducted in predominantly rural centers in China suggests that the proportion of patients with STEMI receiving early reperfusion therapy in this setting is only about 35% (compared with 60% in the centers included in EPICOR Asia).[15] In Arabian Gulf countries and Egypt, 55% to 69% of registry patients with STEMI received thrombolytic therapy and 10% to 37% underwent PCI.[12,16–18] In contrast, in France, data from the French FAST-MI registry show that 6% of patients with STEMI received intravenous fibrinolysis and 71% underwent primary PCI.[19] In Norway, 19% of patients with STEMI aged less than 80 years were treated with fibrinolysis and 76% with primary PCI in 2016; the proportion of patients receiving fibrinolytic therapy was higher in rural than urban centers.[20]

1.2 | Antiplatelet therapy following reperfusion

Adjunct dual antiplatelet therapy with aspirin and the $P2Y_{12}$ antagonist clopidogrel is used to support reperfusion with fibrinolytic therapy,[1,2] based on results from the CLARITY (NCT00714961) and COMMIT (NCT00222573) trials.[21,22] In CLARITY, patients who presented within 12 hours of STEMI symptom onset were randomized to clopidogrel (300 mg loading dose followed by 75 mg daily) or placebo, received fibrinolytic therapy and underwent an angiogram after 2 to 8 days. Compared with placebo, treatment with clopidogrel resulted in a 36% reduction in the odds of an infarct-related artery occlusion, death, or recurrent myocardial infarction by the time of angiogram (the primary endpoint).[22] In COMMIT, patients who presented within 24 hours of an acute myocardial infarction were randomized to clopidogrel (75 mg daily, no loading dose) or placebo; approximately half of the patients also received fibrinolytic therapy. Compared with placebo, treatment with clopidogrel resulted in a 9% proportional reduction in death, re-infarction, or stroke during the treatment period (mean 15 days in survivors).[21] No significant excess risk was observed with clopidogrel for the composite of fatal bleeds, cerebral bleeds, or bleeding requiring transfusion.[21]

For patients who experience an acute coronary syndrome with or without ST-segment elevation who receive primary PCI, the PLATO trial (NCT00391872) has demonstrated that the $P2Y_{12}$ antagonist ticagrelor is superior to clopidogrel in preventing recurrent myocardial infarction, stroke or death from vascular causes over 12 months (primary endpoint; hazard ratio: 0.84; 95% CI: 0.77-0.92; $P < 0.001$).[23] In patients with STEMI and across various other predefined subgroups, efficacy results were consistent with the overall PLATO trial.[23,24] The use of ticagrelor did not significantly increase the overall risk of major bleeding relative to the use of clopidogrel, although ticagrelor was associated with significantly higher rates of major bleeding not related to coronary-artery bypass grafting, including fatal intracranial bleeding.[23]

Patients who had received fibrinolytic therapy in the 24 hours before randomization were excluded from PLATO[23] so there is thus a lack of data on the safety of using ticagrelor in conjunction with fibrinolytic therapy in the first 24 hours after STEMI. The 2013 American College of Cardiology/American Heart Association guidelines for the management of STEMI highlighted this data gap, noting that the coadministration of $P2Y_{12}$ antagonists other than clopidogrel with fibrinolytic therapy has not been prospectively studied.[1] As a result, the European label for ticagrelor currently cautions against the concomitant use of other medicinal products that may increase bleeding risk, including fibrinolytics, within 24 hours of ticagrelor dosing.[25] The European guidelines for the treatment of STEMI recommend clopidogrel immediately after fibrinolysis; however, after a safety period, set at 48 hours, no grounds are found to consider that a more potent $P2Y_{12}$ inhibitor would increase the risk of bleeding, or fail to exert a clinically relevant benefit in line with the results of PLATO.[2] Thus, for

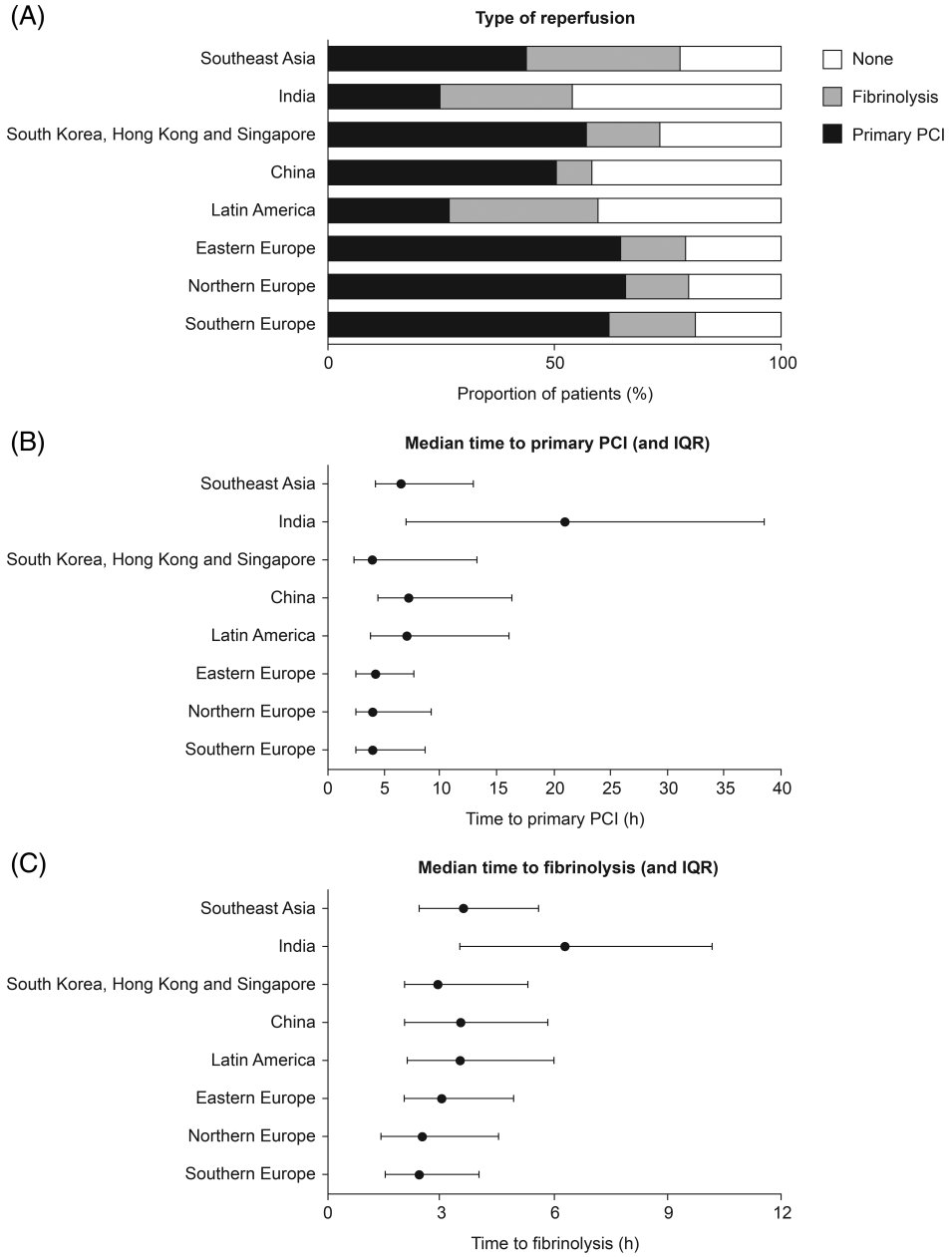

FIGURE 1 Results of the global EPICOR and EPICOR Asia studies. A, Use of reperfusion therapy; B, median time to primary PCI; and C, median time to fibrinolysis. Reproduced from Rossello et al. 2017.[11] Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention

patients who receive fibrinolysis and subsequently undergo PCI, the guidelines note that a switch from clopidogrel to prasugrel or ticagrelor may be considered 48 hours after fibrinolysis.

2 | TREAT STUDY

2.1 | Design and methodology

The TREAT study (NCT02298088) has been designed to provide evidence regarding the safety of ticagrelor relative to clopidogrel in patients with STEMI treated with fibrinolytics.[26,27] TREAT is an international, phase 3 study run by the Research Institute of the Hospital do Coração, São Paulo, Brazil. It was started in August 2015 and enrolled 3799 patients from participating centers in Argentina, Australia, Brazil, Canada, China, Colombia, New Zealand, Peru, Russia, and Ukraine.

Patients aged between 18 and 75 years with STEMI who had symptom onset within the previous 24 hours and had received fibrinolytic therapy were randomized to treatment with ticagrelor or clopidogrel (Figure 2). The maximum time of 24 hours from symptom onset was chosen to fill the existing data gap, because patients who had received fibrinolytic therapy in the previous 24 hours were excluded from the PLATO trial. Patients received a loading dose of the study medication (ticagrelor: 180 mg; clopidogrel: 300-600 mg) as early as possible after the index event and not more than 24 hours after the event, and then received maintenance doses thereafter (ticagrelor: 90 mg twice daily; clopidogrel: 75 mg once daily). Patients who had received clopidogrel at the time of fibrinolysis prior to randomization were still eligible to participate, and if randomized to the

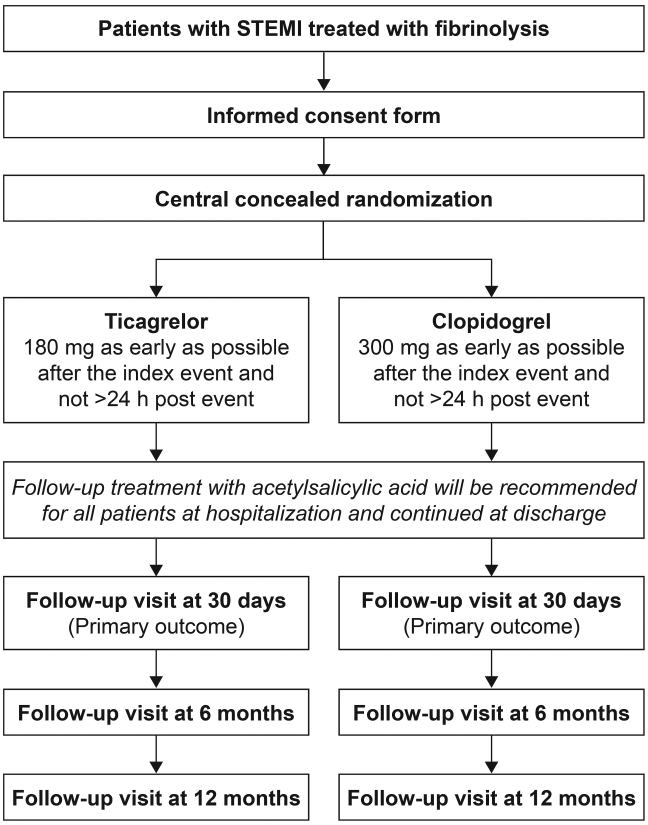

FIGURE 2 TREAT study design. Reproduced from Berwanger et al. 2018.[27] Abbreviations: STEMI, ST-segment elevation myocardial infarction

clopidogrel arm of the study could be given an additional loading dose at the discretion of the investigating physician. Follow-up visits were scheduled at hospital discharge or on the seventh day after discharge, and then at 30 days, 6 months, and 12 months after randomization.

The primary outcome of the TREAT study is safety as a measure of time to Thrombolysis In Myocardial Infarction (TIMI)-defined first major bleeding at 30 days, with a margin for non-inferiority set at an absolute difference of 1.0% (one-sided α: 2.5%). Secondary endpoints are other bleeding events according to TIMI, PLATO or Bleeding Academic Research Consortium (BARC) definitions, and exploratory endpoints include a composite of recurrent myocardial infarction, stroke or death from vascular causes, the same composite outcome with the addition of recurrent ischemia, transient ischemic attack or other arterial thrombotic events, individual components of the composite efficacy outcome, and all-cause mortality.

2.2 | Results overview

Detailed 30-day results of the TREAT study have been published.[26] Briefly, ticagrelor was found to be non-inferior to clopidogrel for the primary outcome of TIMI-defined major bleeding at 30 days. The median time between fibrinolysis and randomization to ticagrelor or clopidogrel treatment was 11.4 hours (ticagrelor: 11.4 hours; clopidogrel: 11.5 hours), and 89.4% of patients had received clopidogrel prior to randomization. The mean age of patients was 58.0 years (SD: 9.5), and baseline characteristics were well balanced between the two groups. The proportions of patients receiving different fibrinolytic therapies were: 39.6% tenecteplase, 19.7% alteplase, 16.8% reteplase, 7.0% prourokinase, 6.9% urokinase, 5.7% streptokinase, and 4.2% other. At 30 days, TIMI major bleeding had occurred in 0.73% of patients receiving ticagrelor and 0.69% of those receiving clopidogrel (absolute difference: 0.04%; 95% CI: −0.49-0.58; $P < 0.001$ for non-inferiority) (Figure 3). Non-inferiority was similarly demonstrated for major bleeding defined according to the PLATO trial and for BARC types 3 to 5 bleeding. Patients in the ticagrelor and clopidogrel groups experienced similar rates of fatal bleeding (0.16% vs 0.11%, respectively; $P = 0.67$) and intracranial bleeding (0.42% vs 0.37%, respectively; $P = 0.82$). For other categories of bleeding events, statistically significantly higher rates of total bleeding (5.38% vs 3.82%, respectively; $P = 0.02$) and PLATO-defined minimal bleeding (3.24% vs 2.01%, respectively; $P = 0.02$) were seen for ticagrelor relative to clopidogrel, and rates of TIMI minimal bleeding were also numerically higher with ticagrelor than with clopidogrel (2.46% vs 1.59%, respectively; $P = 0.06$). The rates of bleeding in the ticagrelor and clopidogrel groups are consistent with findings from several smaller trials comparing ticagrelor and clopidogrel in patients with STEMI treated with fibrinolytics, as reported in a recently published systematic review and meta-analysis.[28–32]

Regarding efficacy, the study lacked statistical power to detect a significant difference at 30 days. The composite outcome of death from vascular causes, myocardial infarction or stroke occurred at a similar rate at 30 days in patients receiving ticagrelor and those

Safety outcomes	Number of patients (%) Ticagrelor (n = 1913)	Number of patients (%) Clopidogrel (n = 1886)	Difference in percentage points (95% CI)	*P* value
TIMI major bleeding	14 (0.73)	13 (0.69)	0.04 (–0.49 to 0.58)	<0.001
PLATO major bleeding	23 (1.20)	26 (1.38)	–0.18 (–0.89 to 0.54)	0.001
BARC type 3–5 bleeding	23 (1.20)	26 (1.38)	–0.18 (–0.89 to 0.54)	0.001

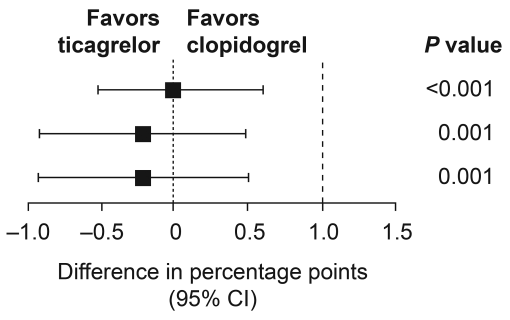

FIGURE 3 TIMI major, PLATO major and BARC type 3 to 5 bleeding at 30 days among patients receiving ticagrelor and patients receiving clopidogrel in the TREAT study. Reproduced from Berwanger et al. 2018.[26] Abbreviations: BARC, bleeding academic research consortium; CI, confidence interval; PLATO, Platelet Inhibition and Patient Outcomes; TIMI, Thrombolysis in Myocardial Infarction

receiving clopidogrel (4.0% vs 4.3%, respectively; $P = 0.57$). Similarly, no statistically significant difference was observed between the two patient groups in other individual or composite efficacy outcomes. Despite the lack of statistical power, the results from the TREAT study are consistent with those from the PLATO STEMI analysis, which suggested that clinical benefit was observed only after the first month of treatment.[24]

3 | CLINICAL IMPLICATIONS

Given the superior efficacy of ticagrelor relative to clopidogrel demonstrated in PLATO for patients receiving primary PCI, and its noninferior safety demonstrated in the TREAT study when given within 24 hours of fibrinolysis, the length of the period during which clopidogrel is recommended following fibrinolysis before switching to ticagrelor or prasugrel (currently 48 hours in the European guidelines)[2] should be reconsidered. The TREAT study provides strong evidence that the administration of ticagrelor will not increase the risk of major bleeding in patients treated with fibrinolytics, even if undertaken very soon after the thrombolytic index event. Physicians should decide on a patient-by-patient basis as to whether such a switch is likely to be of benefit.

Two aspects of the design of the TREAT study should be noted. First, dosing with the study drug did not occur immediately after the administration of fibrinolysis. The median time from fibrinolysis to randomization was approximately 11.5 hours and the majority of patients (89.4%) received un-blinded clopidogrel during this period.[26] The time from fibrinolysis to randomization was comparable to that observed in the COMMIT study (personal communication, data on file). For patients who received clopidogrel with fibrinolysis who were subsequently randomized to clopidogrel, the TREAT study protocol allowed for the administration of a second loading dose of 300 mg, at the discretion of the treating physician. The study was designed in this way to allow for questions of logistics and feasibility (transfer times from smaller receiving centers to larger study centers), while also filling the data gap following PLATO regarding the safety of the use of ticagrelor within 24 hours of fibrinolysis. It is of note that even in the subgroup of patients who were randomized within 4 hours of fibrinolysis, no significant difference was found between ticagrelor and clopidogrel for the primary safety endpoint of TIMI major bleeding ($P = 0.73$), or for PLATO major bleeding or BARC types 3 to 5 bleeding.[26] However, the smaller size of this subgroup analysis reduces the statistical power of the trial to detect such a difference.

Second, efficacy endpoints were exploratory only and the trial lacked statistical power to detect significant differences. The sample size for the trial was chosen to provide greater than 90% statistical power for the primary safety outcome, with a projected TIMI major bleeding rate at 30 days of 1.2%. Twelve-month follow-up of the TREAT study is ongoing, and will provide further information regarding the relative efficacy of the two treatments.

Given the large number of patients around the world for whom rapid treatment with primary PCI is not possible, the question of how to improve clinical outcomes following fibrinolysis remains of great importance.[11] There is growing recognition of the effectiveness of a pharmacoinvasive treatment strategy to ensure that rapid reperfusion is achieved. The wide geographic coverage and heterogeneity of the patient population in the TREAT study, which did not specify a specific fibrinolytic agent for investigation, and left several treatment decisions to the discretion of the investigating physicians, allows for a high degree of external validity.[26] The results can thus be applied to a wide range of patient populations worldwide.

A number of important questions remain to be answered, some of which may be addressed by secondary analyses of the TREAT data set, while others depend on the conduct of future randomized controlled trials. Nevertheless, the current trial results represent a significant step forward in informing the optimal treatment of patients with STEMI. Considering together the results of the PLATO and TREAT studies, initiating or switching to treatment with ticagrelor within 24 hours of receiving fibrinolysis in patients with STEMI is a reasonable approach to undertake.

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Conflict of interest

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Ricardo Iglesias: Speaking for AstraZeneca.

Sigrun Halvorsen: Speaking for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Novartis, and Sanofi.

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