Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial

*Giora Weisz, Philippe Généreux, Andres Iñiguez, Aleksander Zurakowski, Michael Shechter, Karen P Alexander, Ovidiu Dressler, Anna Osmukhina, Stefan James, E Magnus Ohman, Ori Ben-Yehuda, Ramin Farzaneh-Far, Gregg W Stone, for the RIVER-PCI investigators**

Summary

Background **Incomplete revascularisation is common after percutaneous coronary intervention and is associated with increased mortality and adverse cardiovascular events. We aimed to assess whether adjunctive anti-ischaemic pharmacotherapy with ranolazine would improve the prognosis of patients with incomplete revascularisation after percutaneous coronary intervention.**

Methods **We performed this multicentre, randomised, parallel-group, double-blind, placebo-controlled, event-driven trial at 245 centres in 15 countries in Europe, Israel, Russia, and the USA. Patients (aged ≥18 years) with a history of chronic angina with incomplete revascularisation after percutaneous coronary intervention (defined as one or more lesions with ≥50% diameter stenosis in a coronary artery ≥2 mm diameter) were randomly assigned (1:1), via an interactive web-based block randomisation system (block sizes of ten), to receive either twice-daily oral ranolazine 1000 mg or matching placebo. Randomisation was stratified by diabetes history (presence *vs* absence) and acute coronary syndrome presentation (acute coronary syndrome *vs* non-acute coronary syndrome). Study investigators, including all research teams, and patients were masked to treatment allocation. The primary endpoint was time to first occurrence of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation. Analysis was by intention to treat. This study is registered at ClinicalTrials.gov, number NCT01442038.**

Findings **Between Nov 3, 2011, and May 27, 2013, we randomly assigned 2651 patients to receive ranolazine (n=1332) or placebo (n=1319); 2604 (98%) patients comprised the full analysis set. After a median follow-up of 643 days (IQR 575–758), the composite primary endpoint occurred in 345 (26%) patients assigned to ranolazine and 364 (28%) patients assigned to placebo (hazard ratio 0·95, 95% CI 0·82–1·10; p=0·48). Incidence of ischaemia-driven revascularisation and ischaemia-driven hospitalisation did not differ significantly between groups. 189 (14%) patients in the ranolazine group and 137 (11%) patients in the placebo group discontinued study drug because of an adverse event (p=0·04).**

Interpretation **Ranolazine did not reduce the composite rate of ischaemia-driven revascularisation or hospitalisation without revascularisation in patients with a history of chronic angina who had incomplete revascularisation after percutaneous coronary intervention. Further studies are warranted to establish whether other treatment could be effective in improving the prognosis of high-risk patients in this population.**

Funding **Gilead Sciences, Menarini.**

Published **Online** October 13, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00459-6

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(15)00458-4

*See appendix for a full list of study investigators

Shaare Zedek Medical Center, Jerusalem, Israel (G Weisz MD); **New York Presbyterian Hospital, Columbia University Medical Center, New York, NY, USA** (G Weisz, Prof G W Stone MD); **Cardiovascular Research Foundation, New York, NY, USA** (G Weisz, P Généreux MD, O Dressler MD, O Ben-Yehuda MD, Prof G W Stone); **Hôpital du Sacré-Coeur de Montreal, Université de Montreal, Montreal, QC, Canada** (P Généreux); **Hospital de Meixoeiro, Vigo, Spain** (A Iñiguez MD); **American Heart of Poland SA, Katowice, Poland** (A Zurakowski MD); **Chaim Sheba Medical Center, Tel Hashomer, Israel** (M Shechter MD); **Duke Clinical Research Institute and Duke University, Durham, NC, USA** (Prof K P Alexander MD, Prof E M Ohman MD); **Gilead Sciences, Foster City, CA, USA** (A Osmukhina PhD, R Farzaneh-Far MD); **and Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden** (Prof S James MD)

Correspondence to: Dr Giora Weisz, Department of Cardiology, Shaare Zedek Medical Center, Jerusalem 91031, Israel
weiszg@szmc.org.il

See **Online** for appendix

Introduction

Percutaneous coronary intervention is one of the most common medical procedures, done in 954 000 patients in the USA in 2010.[1] Despite substantial improvements in technique and technology of percutaneous coronary intervention, incomplete revascularisation is present in 17–85% of patients after the procedure (partly depending on the definition),[2–4] and has been strongly associated with increased rates of repeat hospitalisation, repeat revascularisation, and mortality.[2,3,5–16]

Ranolazine, a piperazine derivative, is a late sodium-current blocker that reduces intracellular calcium overload during ischaemia.[17] Ranolazine has no negative inotropic, chronotropic, or dromotropic effects and has been shown to be safe and effective for the management of patients with chronic stable angina.[18–21] In a post-hoc subgroup analysis from the MERLIN-TIMI 36 trial,[22] patients who presented with acute coronary syndromes with a history of angina and were treated with percutaneous coronary intervention had lower rates of cardiovascular death, recurrent ischaemia, and the composite of cardiovascular death, myocardial infarction, or recurrent ischaemia when given ranolazine than when given placebo. In view of the high incidence of incomplete revascularisation, ischaemia, and angina after percutaneous coronary intervention,[2–4,23,24] ranolazine might reduce the incidence of hospitalisation after percutaneous coronary intervention due to angina and ischaemia, and could reduce the need for repeat revascularisation. We therefore did the RIVER-PCI study to assess the use of ranolazine in patients with a history of

Research in context

Evidence before this study

We searched PubMed between January, 2000, and December, 2014, to identify studies investigating the outcomes of patients with versus without complete revascularisation after percutaneous coronary intervention. We found that incomplete revascularisation is very common, reported to occur in 17–85% of patients. Incomplete revascularisation after percutaneous coronary intervention has been strongly associated with increased rates of repeat hospitalisation, repeat revascularisation, and mortality in several studies. We did not identify reports of studies that specifically examined the management of patients with incomplete revascularisation. In a subgroup analysis from the MERLIN-TIMI 36 study, patients with a history of angina who presented with acute coronary syndromes and were treated with percutaneous coronary intervention had lower rates of cardiovascular death, recurrent ischaemia, and the combination of cardiovascular death, myocardial infarction, or recurrent ischaemia when given ranolazine than when given placebo. Thus, we postulated that adjunctive pharmacotherapy with ranolazine—an anti-ischaemic drug that inhibits the late sodium current—would be effective in reducing recurrent ischaemic events in patients with a history of chronic angina who had incomplete revascularisation after percutaneous coronary intervention.

Added value of this study

RIVER-PCI was a large-scale, prospective, randomised, double-blind, placebo-controlled trial, which tested the use of ranolazine in patients with a history of chronic angina who had incomplete revascularisation after percutaneous coronary intervention. No other pharmaceutical treatments have been assessed systematically in patients with incomplete revascularisation after percutaneous coronary intervention. We found that, compared with placebo, ranolazine did not result in lower rates of the composite primary efficacy endpoint of ischaemia-driven revascularisation or hospitalisation without revascularisation during a median follow-up duration of 1·8 years. There were also no differences between the treatment groups in the prespecified secondary endpoints of sudden cardiac death, cardiovascular death, or myocardial infarction. Use of ranolazine was not associated with major safety issues, but did result in minor adverse reactions (eg, dizziness, constipation, and nausea), which led to discontinuation more frequently than placebo. Major adverse cardiovascular events were also more common in patients aged 75 years or older.

Implications of all the available evidence

Our findings show that routine use of ranolazine does not reduce the composite rate of ischaemia-driven revascularisation or hospitalisation in patients with a history of chronic angina who had incomplete revascularisation after percutaneous coronary intervention. Further studies are warranted to establish whether other treatments could be effective in improving the prognosis of high-risk patients in this population.

chronic angina who had incomplete revascularisation after percutaneous coronary intervention. We postulated that ranolazine treatment would improve the prognosis of this patient population.

Methods

Study design and patients

We performed this multicentre, randomised, parallel-group, double-blind, placebo-controlled, event-driven trial at 245 centres in 15 countries in Europe, Israel, Russia, and the USA (appendix). The design and rationale of the RIVER-PCI trial have been previously reported.[25] The appendix provides a summary of the study design.

Eligible patients were at least 18 years old and had to meet all inclusion and exclusion criteria within 14 days after completion of percutaneous coronary intervention. Patient eligibility was determined by the investigators at each study site. Major inclusion criteria were a history of chronic angina and angiographic evidence of incomplete revascularisation after percutaneous coronary intervention. We defined history of chronic angina as two or more episodes of anginal pain or discomfort in the chest, jaw, shoulder, back, neck, or arm that was precipitated by exertion or emotional stress and relieved by rest or sublingual nitroglycerin, and occurred on at least 2 separate days between 30 days and 1 year before percutaneous coronary intervention. Patients could also have additional angina in the 30 days before percutaneous coronary intervention. We defined incomplete revascularisation as the presence of at least one lesion with stenosis of 50% or more in diameter (visually estimated) in a coronary artery with reference vessel diameter of 2·0 mm or more, whether in a percutaneous coronary intervention-treated target vessel or in a non-treated, non-target vessel. For patients who had undergone coronary artery bypass graft surgery, we defined incomplete revascularisation as the presence of one or more lesions with visually estimated stenosis of 50% or more in diameter in a non-bypassed epicardial vessel of 2·0 mm in diameter, or at least one stenosis (≥50%) in a bypass graft supplying an otherwise non-revascularised myocardial territory. Major exclusion criteria included any future planned revascularisation (including staged procedures), an unprotected left main coronary artery lesion with stenosis of 50% or more in diameter, major complications during the index percutaneous coronary intervention, New York Heart Association (NYHA) class III or IV heart failure, stroke within 90 days or history of stroke with permanent major neurological disability, estimated glomerular filtration rate of less than

30 mL/min per 1·73 m², cirrhosis, previous treatment with ranolazine for more than 7 consecutive days within 30 days, or known hypersensitivity or intolerance to ranolazine. Patients were also excluded for concomitant use of class Ia, Ic, or class III antiarrhythmic drugs (except for amiodarone), strong cytochrome P450 (CYP) 3A inhibitors, CYP3A4 or P-glycoprotein inducers, 20 mg or more of simvastatin daily, 40 mg or more of lovastatin daily, or 1000 mg or more of metformin daily. The appendix provides a complete list of all inclusion and exclusion criteria.

The ethics committee at each participating centre approved the protocol. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) within 14 days after the index percutaneous coronary intervention, via an interactive web-based block randomisation system (block sizes of ten), to receive either ranolazine or matching placebo. Randomisation was stratified by diabetes history (presence *vs* absence) and acute coronary syndrome presentation (acute coronary syndrome *vs* non-acute coronary syndrome). Study investigators, including all research teams, and patients were masked to treatment allocation.

Procedures

For the first 7 days, patients received 500 mg oral ranolazine or placebo twice daily, after which the dose was increased to 1000 mg twice daily. If the dose increase was not tolerated, the dose could be reduced back to 500 mg or temporarily discontinued and restarted. Patients were otherwise treated with standard recommended medical treatments, including antianginal drugs (other than ranolazine), at the discretion of the investigator. Follow-up in all patients was done at 1 month and 3 months post-randomisation, and every 3 months thereafter, for at least 1 year post randomisation. To assess the results of percutaneous coronary intervention and the extent of incomplete revascularisation quantitative angiographic analysis of the entire coronary tree was done by an independent core laboratory masked to treatment assignment, as previously described.[2]

Outcomes

The primary efficacy endpoint was time from randomisation to the first occurrence of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation. Three key secondary efficacy endpoints were prespecified: time from randomisation to the first occurrence of sudden cardiac death, cardiovascular death, or myocardial infarction. Safety endpoints included all-cause mortality, stroke, transient ischaemic attack, hospitalisation for heart failure, and major adverse cardiovascular events, defined as a composite of cardiovascular death, myocardial infarction, or stroke. All major endpoint events, including all repeat hospitalisations, repeat coronary angiographic procedures with or without revascularisation, myocardial infarction, stroke, transient ischaemic attack, and death were adjudicated by an independent clinical events committee masked to treatment allocation. The appendix provides definitions of the major endpoints.

Statistical analysis

The trial was designed as an event-driven study. Accrual of 720 primary endpoint events was needed to provide roughly 85% power to detect a 20% reduction in relative risk in the ranolazine group compared with placebo with a two-sided log-rank test at the 5% significance level. The 20% risk reduction was a conservative estimate based on previous differences in the rates of outcomes of patients with complete and incomplete revascularisation, and the previously reported ranolazine effect in the subset of patients undergoing percutaneous coronary intervention in MERLIN.[2,22] Assuming a 1 year placebo event rate of 20%,[2,22] exponential time-to-event distributions, identical non-informative exponential time-to-dropout distributions with a 1 year dropout rate of 5%, a recruitment period of 1·5 years, and minimum follow-up of 1 year in all patients, we anticipated enrolling about 2600 patients.

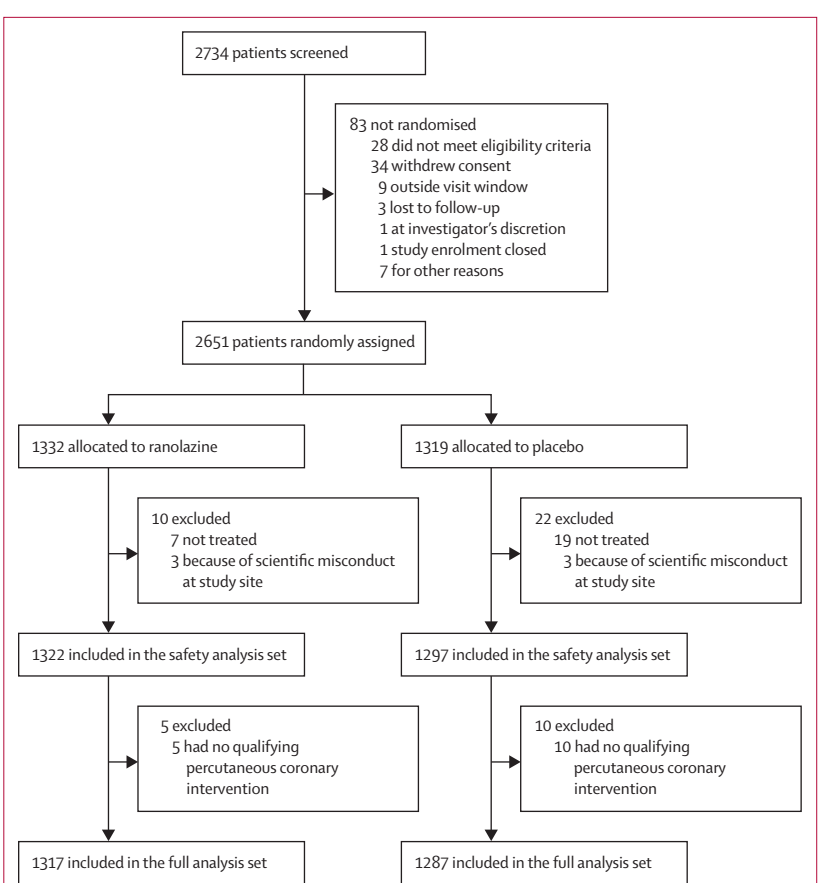

***Figure 1*: Trial profile**

	Ranolazine group (n=1317)	Placebo group (n=1287)
Age (years)	63·4 (10·5)	63·4 (10·0)
≥75	206 (16%)	192 (15%)
Sex		
Male	1043 (79%)	1030 (80%)
Female	274 (21%)	257 (20%)
Race		
White	1199 (91%)	1187 (92%)
Other	118 (89%)	100 (8%)
Body-mass index (kg/m²)	29·6 (5·5)	29·6 (5·2)
Diabetes mellitus	443 (34%)	430 (33%)
Type 1	20 (2%)	13 (1%)
Type 2	423 (32%)	417 (32%)
Hypertension	1121 (85%)	1130 (88%)
Hyperlipidaemia	1145 (87%)	1096 (85%)
Present smoker	277 (21%)	264 (21%)
Chronic kidney disease	106 (8%)	109 (8%)
Peripheral arterial disease	159 (12%)	151 (12%)
Previous myocardial infarction	614 (47%)	603 (47%)
Previous revascularisation (any)	679 (52%)	612 (48%)
PCI	593 (45%)	527 (41%)
Coronary artery bypass graft surgery	209 (16%)	196 (15%)
Previous congestive heart failure	229 (17%)	236 (18%)
Left ventricular ejection fraction (%)	54 (10·4)	55 (11·0)
Reason for PCI		
Acute coronary syndrome	433 (33%)	455 (35%)
Non-acute coronary syndrome	884 (67%)	832 (65%)
CCSC 1 month before the index PCI		
None	59 (5%)	39 (3%)
I	181 (14%)	185 (14%)
II	676 (51%)	666 (52%)
III	342 (26%)	330 (26%)
IV	56 (4%)	59 (5%)

Data are mean (SD) or n (%). PCI=percutaneous coronary revascularisation. CCSC=Canadian Cardiovascular Society Classification of angina.

Table 1: **Baseline characteristics**

We analysed the efficacy and safety endpoints with a Cox proportional hazards model stratified by history of diabetes and presentation of acute coronary syndrome. Results are presented as hazard ratios (HRs) with 95% CIs and p values. We used Kaplan-Meier analysis to estimate the proportion of patients with events. The family-wise type I error rate for the primary comparison and the three secondary comparisons was controlled at 5% with a prespecified hierarchical testing sequence as previously described.[25] We did additional analyses of the primary endpoint in prespecified subgroups, including sex, age, diabetes, and presentation (acute coronary syndrome *vs* non-acute coronary syndrome). No multiplicity adjustment was done for subgroup analyses in view of their exploratory nature.

Demographic and baseline characteristics are summarised by treatment group with means and SDs for continuous variables and as numbers and percentages for categorical variables. We compared continuous data with the Wilcoxon rank-sum test and binary data with Pearson's χ^2 test. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 17.1), with reporting of each preferred term with 2% or more events in either treatment group.

We analysed the primary and key secondary efficacy endpoints in the full analysis set, which included all patients in whom a qualifying percutaneous coronary intervention was done before randomisation and who received at least one dose of study drug (intention-to-treat analysis). Safety analyses were done in the safety analysis set, which included all randomised patients who received at least one dose of study drug. We did analyses with SAS (versions 9.2 and 9.4).

Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, and data interpretation, but not the writing of the report. GW and GWS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between Nov 3, 2011, and May 27, 2013, we randomly assigned 2651 patients to receive ranolazine (n=1332) or placebo (n=1319); 2619 (99%) patients comprised the safety analysis set and 2604 (98%) patients comprised the full analysis set (figure 1). The median duration of follow-up was 644 days (IQR 575–757) for the ranolazine group and 642 days (575–761) for the placebo group (p=0·49).

Baseline characteristics were well balanced between groups (table 1). Roughly a third of patients had diabetes, a third presented with acute coronary syndrome, and more than 80% had class II–IV angina within the month before study entry (table 1). Use of non-study antiplatelet and anti-ischaemic drugs was similar between groups at the time of randomisation and follow-up, except for a slightly greater use of adenosine diphosphate receptor antagonists at 12 months in the ranolazine group (appendix). The mean time from the qualifying percutaneous coronary intervention to randomisation was 6·6 days (SD 4·4) in the ranolazine group versus 6·5 days (4·4) in the placebo group (p=0·54). Table 2 shows the extent of coronary artery disease at baseline and after percutaneous coronary intervention. The mean baseline SYNTAX score was 16·9 (SD 8·3) and the mean residual score after PCI was 10·5 (7·1); both scores were balanced between groups (table 2). The most common site-reported reasons for incomplete revascularisation were the belief that medical treatment was an accepted approach for the degree of untreated atherosclerosis, that, angiographically, any residual lesions were unlikely to be clinically significant, and that percutaneous coronary intervention would have a low likelihood of acute success (appendix).

	Ranolazine group (n=1317)	Placebo group (n=1287)
Number of diseased coronary arteries		
One-vessel disease	115 (9%)	120 (9%)
Two-vessel disease	574 (44%)	554 (43%)
Three-vessel disease	579 (44%)	573 (44%)
Number of treated lesions	1·5 (0·8)	1·5 (0·8)
Untreated chronic total occlusion*	441 (34%)	423 (33%)
Untreated small-vessel or diffuse disease*	206 (16%)	206 (16%)
Post coronary artery bypass graft surgery*	156 (14%)	158 (14%)
SYNTAX score†		
Baseline	17·0 (8·6)	16·8 (8·0)
Residual (post PCI)	10·6 (7·3)	10·4 (6·9)
Change from baseline to post PCI	6·5 (4·9)	6·6 (4·9)

Data are mean (SD) or n (%). There were no significant differences between groups. PCI=percutaneous coronary revascularisation. *A qualifying reason for incomplete revascularisation. †In patients without previous coronary artery bypass graft surgery.

Table 2: **Extent of coronary artery disease and the degree of incomplete revascularisation**

The composite primary efficacy endpoint occurred in 345 (26%) patients assigned to ranolazine and 364 (28%) patients assigned to placebo (figure 2, table 3). The incidence of ischaemia-driven revascularisation and ischaemia-driven hospitalisation without revascularisation did not differ significantly between groups (table 3). The treatment effect for the primary endpoint was consistent across subgroups (figure 3). Moreover, in a Cox model, the treatment effect for the primary endpoint was similar between the 886 ranolazine patients and 852 placebo patients prescribed no or one non-study anti-ischaemic drug (β blockers, calcium-channel blockers or longacting nitrates) at the time of randomisation (212 [24%] *vs* 232 [27%]; HR 0·90, 95% CI 0·75–1·09) and the 431 ranolazine patients and 435 placebo patients prescribed two to three non-study anti-ischaemic drugs (133 [31%] *vs* 132 [30%]; 1·04, 0·82–1·32; $p_{interaction}$ 0·36).

In patients undergoing ischaemia-driven revascularisation during follow-up, about half the revascularisation procedures were performed on lesions in the originally treated vessel, whereas half were performed in untreated coronary arteries (appendix). Most of the ischaemia-driven revascularisations arose at the site of a successfully treated lesion that developed restenosis or stent thrombosis (target lesion revascularisation), or were performed on a previously present baseline lesion that qualified the patient for incomplete revascularisation; fewer revascularisation events were due to new lesions that were not previously present or were non-obstructive (diameter stenosis <50%) at the time of randomisation (appendix). Ranolazine had no significant treatment effect on the need for revascularisation of each of these three types of lesions (appendix).

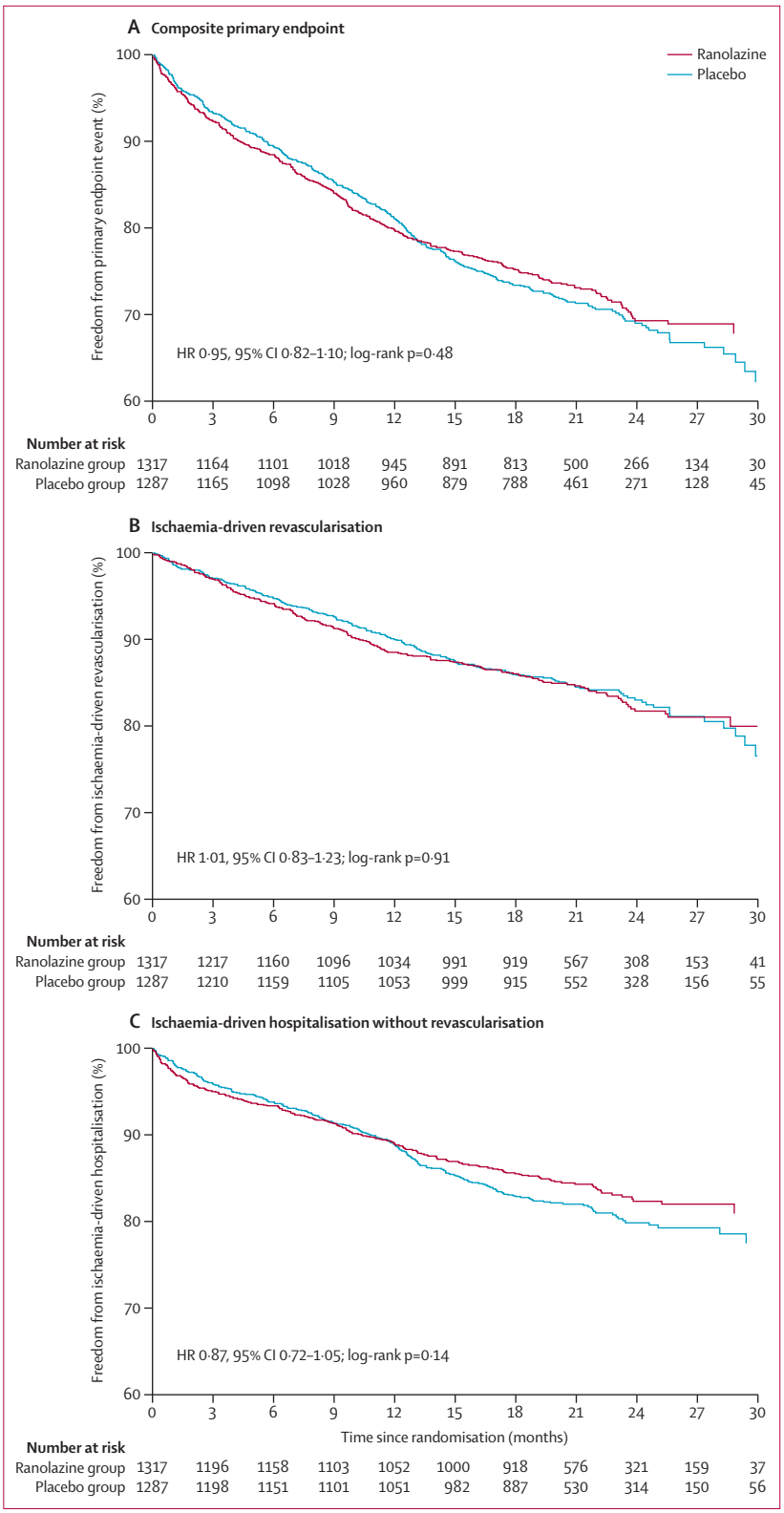

Figure 2: **Kaplan-Meier time-to-event curves for the primary efficacy endpoint**
(A) Composite primary endpoint of the time to first occurrence of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation. (B) Time to first occurrence of ischaemia-driven revascularisation. (C) Time to first occurrence of ischaemia-driven hospitalisation without revascularisation. HR=hazard ratio.

	Ranolazine group (n=1317)	Placebo group (n=1287)	HR (95% CI)	p value
Primary efficacy endpoint	345 (26%)	364 (28%)	0·95 (0·82–1·10)	0·48
Ischaemia-driven revascularisation	201 (15%)	200 (16%)	1·01 (0·83–1·23)	0·91
Ischaemia-driven hospitalisation*	201 (15%)	230 (18%)	0·87 (0·72–1·05)	0·14
Secondary efficacy endpoints				
Sudden cardiac death	7 (<1%)	11 (1%)	0·67 (0·24–1·69)	0·40
Cardiovascular death	21 (2%)	20 (2%)	1·07 (0·58–1·99)	0·82
Myocardial infarction	111 (8%)	116 (9%)	0·97 (0·75–1·26)	0·81
Q wave	7 (<1%)	7 (<1%)	1·05 (0·36–3·07)	0·93
Non-Q-wave	104 (8%)	109 (8%)	0·96 (0·74–1·27)	0·81
Spontaneous	101 (8%)	103 (8%)	0·99 (0·76–1·31)	0·97
Periprocedural	11 (1%)	15 (1%)	0·72 (0·32–1·56)	0·41
Safety events†				
Major adverse cardiovascular events	142 (11%)	144 (11%)	1·00 (0·79–1·26)	0·99
All-cause mortality	42 (3%)	36 (3%)	1·17 (0·75–1·83)	0·49
Stroke	22 (2%)	20 (2%)	1·10 (0·60–2·04)	0·75
Transient ischaemic attack	13 (1%)	3 (<1%)	4·36 (1·40–19·02)	0·02
Heart failure hospitalisation	38 (3%)	25 (2%)	1·55 (0·94–2·60)	0·09
Ischaemia-related	18 (1%)	19 (2%)	0·95 (0·49–1·81)	0·87
Non-ischaemia-related	22 (2%)	13 (1%)	1·72 (0·88–3·51)	0·12

Data are n (%), unless otherwise indicated. HR=hazard ratio. *Without revascularisation. †n=1322 in the ranolazine group, n=1297 in the placebo group (safety analysis set).

Table 3: **Efficacy and safety endpoints**

The key secondary efficacy endpoints of sudden cardiac death, cardiovascular death, and myocardial infarction occurred with similar frequency in both groups (table 3). The incidence of major adverse cardiovascular events, all-cause mortality, stroke, or hospitalisation for heart failure likewise did not differ significantly between groups; however, the incidence of adjudicated transient ischaemic attack events was higher in patients given ranolazine (table 3). Safety outcomes in the treatment groups occurred with similar frequency in several subgroups, except for major adverse cardiovascular events in very elderly patients (appendix). 401 (15%) of the 2619 patients in the safety analysis set were aged 75 years or older (n=206 in the ranolazine group and n=195 in the placebo group). In this subgroup, major adverse cardiovascular events were more frequent in patients in the ranolazine group than in those in the placebo group (HR 1·79, 95% CI 1·06–3·10; p=0·03; appendix). By contrast, the rates of major adverse cardiovascular events were similar in the 2218 (85%) patients younger than 75 years (HR 0·88, 95% CI 0·67–1·13; p=0·31). The p value for interaction between treatment group and advanced age for the outcome of major adverse cardiovascular events was 0·02. Among patients aged 75 years or older, the imbalance in major adverse cardiovascular events was driven by non-fatal events: myocardial infarction (n=26 with ranolazine *vs* n=18 with placebo; 1·53, 0·84–2·83; p=0·17) and stroke (n=8 *vs* n=4; 2·17, 0·68–8·21; p=0·21). In this subgroup, there were two cardiovascular deaths in the ranolazine group and one in the placebo group.

The median duration on study drug was slightly shorter in the ranolazine group than in the placebo group (579 days [IQR 229–674] *vs* 586 days [361–688]; p=0·004), and the number of patients discontinuing study drug during follow-up was higher in the ranolazine group (529 [40%] *vs* 463 [36%]; p=0·006). 373 (28%) patients in the ranolazine group versus 295 (23%) patients in the placebo group discontinued study drug at 12 months or earlier (p=0·01). The appendix shows detailed reasons for study drug discontinuation. We recorded discontinuation due to an adverse event in 189 (14%) of 1322 patients in the ranolazine group and 137 (11%) of 1297 patients in the placebo group (p=0·004; table 3; appendix). Dizziness, constipation, nausea, hypotension, vomiting, and vertigo were reported more often in the ranolazine group than in the placebo group (appendix).

Discussion

Our findings show that compared with placebo, ranolazine did not reduce rates of the composite primary efficacy endpoint of ischaemia-driven revascularisation or ischaemia-driven hospitalisation without revascularisation. There were also no differences between the treatment groups in the prespecified major secondary efficacy endpoints of sudden cardiac death, cardiovascular death, and myocardial infarction. Ranolazine was associated with more frequent adverse events leading to early drug discontinuation, and a higher rate of non-fatal major adverse cardiovascular events in patients aged 75 years and older, than was placebo.

Previous studies[2,3,5–16] have reported that incomplete revascularisation after percutaneous coronary intervention is associated with poor prognosis. In the ACUITY trial,[2] incomplete revascularisation, as estimated by a residual SYNTAX score of more than 8, was a powerful predictor of 30 day and 1 year mortality and major adverse cardiovascular events. In the SYNTAX trial,[26] a residual SYNTAX score of more than 8 was strongly associated with 5 year mortality. In the present study, the mean residual SYNTAX score after percutaneous coronary intervention was 10·5 (SD 7·1), and ischaemic events during follow-up occurred frequently, at a rate similar to that we predicted from previous studies.[2,26] However, despite this degree of untreated coronary atherosclerosis, ranolazine did not reduce ischaemia-driven hospitalisation or revascularisation events during a median follow-up of 1·8 years.

There are several possible explanations why ranolazine might have been ineffective. First, despite contributing to a high residual SYNTAX score, many of the lesions left untreated after percutaneous coronary intervention might have been of little clinical consequence, consisting of relatively small vessels supplying limited myocardium. However, the ischaemic event rate was high, and nearly

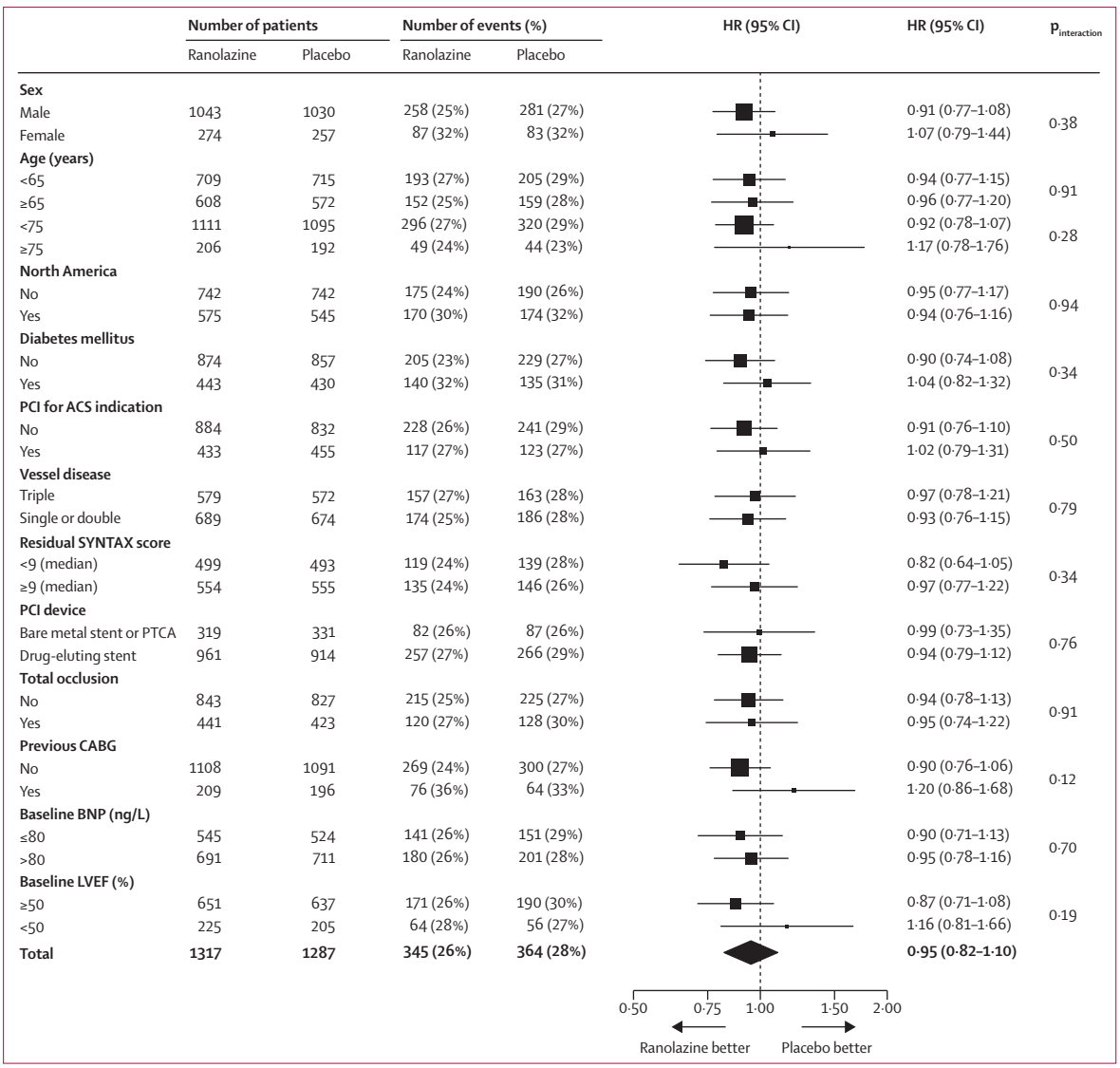

Figure 3: **Subgroup analysis of the primary efficacy endpoint**

PCI=percutaneous coronary revascularisation. ACS=acute coronary syndrome. PTCA=percutaneous transluminal coronary angioplasty. CABG=coronary artery bypass graft surgery. BNP=B-type natriuretic protein. LVEF=left ventricular ejection fraction.

half of all revascularisation procedures during follow-up were performed on these untreated lesions. Moreover, there was no significant interaction between the residual SYNTAX score (the calculation of which incorporates lesion location and myocardium at risk) and treatment on the primary endpoint. Second, the correlation between severity of angiographic stenosis and ischaemia is known to be modest,[27] and the incidence and severity of residual ischaemia in the present patient population is unknown. In the FAME 2 trial,[28] the presence of untreated epicardial stenoses with a fractional flow reserve of 0·80 or less was strongly associated with the need for hospitalisation and ischaemia-driven revascularisation within 2 years. FAME 2 differs from the present study in that the untreated lesions were readily amenable to percutaneous coronary intervention, and some events in the control group could have been driven by the unmasked nature of that study. Nonetheless, the requirement for substantial myocardial ischaemia in our study might have identified patients more likely to benefit from ranolazine. However, assessment for residual ischaemia after percutaneous coronary intervention is not routine (with either fractional flow reserve or non-invasive testing). Thus, we used an anatomical definition of incomplete revascularisation based on previous studies showing that the presence of one or more lesions with stenoses of 50% or more in diameter and reference vessel diameter 2 mm or more maximised the sensitivity and specificity for subsequent ischaemic major adverse cardiovascular events.[2] Third, anatomic incomplete revascularisation

could represent a surrogate for atherosclerosis burden and future events attributable to vulnerable plaque rather than ischaemia,[24] which ranolazine would not be expected to suppress. However, few adjudicated ischaemia-driven revascularisation events were attributable to new rapidly progressing lesions. In this regard, our findings differ from those of the PROSPECT study,[24] in which nearly half the follow-up events after percutaneous coronary intervention arose from angiographically mild lesions that rapidly progressed. This difference might be because PROSPECT included only patients with acute coronary sundromes (in whom the incidence of untreated vulnerable plaques is higher than in patients with stable coronary artery disease), and fewer patients had incomplete revascularisation.[24] Additionally, a high proportion of patients in the present study were treated with statins, dual antiplatelet treatment, and other guideline-directed medical treatments, which could have mitigated the effect of untreated atherosclerosis on future events. However, neither these drugs nor ranolazine would be likely to reduce ischaemia-driven target lesion revascularisation due to restenosis or stent thrombosis, which contributed to about 40% of ischaemia-driven revascularisation events. Finally, ranolazine has a unique anti-ischaemic mechanism that distinguishes it from other drugs. Ischaemia increases intracellular sodium concentrations, which, by increasing ion flux through the membrane-based sodium–calcium exchanger, leads to intracellular calcium overload, with resultant abnormalities in ventricular repolarisation and relaxation. Ranolazine selectively inhibits the late sodium current,[29] thereby reducing intracellular calcium overload during ischaemia.[17] Unlike other drugs, the anti-ischaemic effects of ranolazine are not dependent on reductions in heart rate or blood pressure, and ranolazine does not affect the rate-pressure product at maximum exercise—a measure of myocardial work. Thus, ranolazine does not prevent the development of ischaemia, but rather diminishes its severity. A different anti-ischaemic drug might have been more effective for the application tested.

Additional insights from the present study results can be gained by considering the findings of the MERLIN-TIMI 36 trial,[21] in which the rates of ischaemia-related hospitalisation and revascularisation were also similar in patients with acute coronary syndrome given ranolazine or placebo. However, in a modest-sized (n=914) subgroup of patients from MERLIN with previous angina who were treated with percutaneous coronary intervention, ranolazine reduced the risk of recurrent ischaemia (HR 0·69, 95% CI 0·51–0·92; p=0·01) and cardiovascular death (0·39, 95% CI 0·55–0·91; p=0·01), a finding that partly prompted the present study.[22] These hypothesis-generating results were not validated in the present larger, adequately powered trial, emphasising once again the caution needed in interpretation of post-hoc, underpowered subgroups.[30]

Use of ranolazine in patients who had undergone percutaneous coronary intervention in our study was not associated with major safety concerns. The rates of all-cause mortality, myocardial infarction, stroke, hospitalisation due to heart failure, and major adverse cardiovascular events (the composite of cardiovascular mortality, myocardial infarction, or stroke) were similar between the ranolazine and placebo groups. We recorded an excess in adjudicated transient ischaemic attack events in patients given ranolazine, but the number of such events was small, and the absence of an increase in stroke argues against a major thromboembolic mechanism. The incidence of stroke and transient ischaemic attack has not been reported in previous ranolazine trials. In patients aged 75 years or older in the present study, the rate of major adverse cardiovascular events during follow-up was increased in patients in the ranolazine group compared with those in the placebo group. Statistical adjustment for testing of multiple subgroups was not done, and this finding might represent type I error. However, in previous chronic angina studies, in patients aged 75 years or older treated with ranolazine (n=114), a higher incidence of adverse events, serious adverse events, and drug discontinuations because of adverse events were noted in patients given ranolazine than in those given placebo.[31]

Our study has several limitations. First, hypertension was slightly more prevalent in the placebo group and previous percutaneous coronary intervention was slightly more prevalent in the ranolazine group. These differences were small and probably did not affect the results. Second, background antianginal drug use (other than ranolazine) was left to local standards, and most patients were receiving one or two additional anti-ischaemia drugs (β blockers, calcium-channel blockers, or nitrates). Whether the results would have been different had control patients been naive to antianginal drugs is unknown. However, no interaction was shown between the number of prescribed non-study anti-ischaemic drugs and treatment effect on the recurrent ischaemia-related primary endpoint. Third, detailed data for the number and configuration of stents were not collected, although they were likely to be balanced by randomisation. Moreover, baseline and residual data for SYNTAX score were similar between the groups, and ranolazine did not affect recurrent ischaemic events arising either from treated or untreated coronary segments. Fourth, 40% of the ranolazine patients and 36% of the placebo patients discontinued study drug before the end of the follow-up duration, and the median duration of ranolazine use was shorter, which could have biased the results toward the null. However, the median duration of treatment with ranolazine was 579 days (1·6 years), and it is unlikely that absence of treatment is entirely responsible for the nearly identical course of recurrent events

recorded, especially in the first year of follow-up. Fifth, we chose the primary endpoint of time to first occurrence of ischaemia-driven revascularisation or hospitalisation because ranolazine was not expected to have an effect on the hard endpoints of death or myocardial infarction. These relatively soft endpoints are subjective and might vary on the basis of patient and physician tolerance for angina, symptom presentation, and interpretation. Nonetheless, the chosen endpoints were robust, because the criteria for their diagnosis were detailed and prespecified, and required masked adjudication by a clinical events committee based on review of original source documents. That the trial was placebo-controlled also denotes that any uncertainty or bias in event adjudication would be applied equally to both study groups.

In summary, routine treatment with ranolazine did not reduce the rate of ischemia-driven revascularisation or hospitalisation in patients with a history of chronic angina who had incomplete revascularisation after percutaneous coronary intervention.

Contributors

GW, GWS, and OB-Y designed the study. RF-F, KPA, SJ, and EMO were members of the steering committee and contributed to the implementation of the study. OD and AO did the statistical design and analysis. PG did the angiographic analysis. KPA, PG, SJ, AI, AZ, MS, and EMO participated in patient enrollment and follow-up. GW and GWS had full access to the data, wrote the manuscript, and accept responsibility for the integrity of the study. All other authors critically reviewed the manuscript for revision. All authors have approved the final manuscript and agree with its content and conclusions.

Declaration of interests

GW serves on the medical advisory boards of AngioSlide, AstraZeneca, Calore, Corindus, Medtronic, Medivisor, and MI Medical Incentives, and receives institutional research grants from AngioSlide and Corindus. PG has received consulting fees from Abbott Vascular, Cardiovascular Systems, and Edwards Lifesciences; an institutional research grant from Boston Scientific; and is an employee of Cardiovascular Research Foundation, which received a grant from Gilead Sciences for study management. OB-Y is a former employee of Gilead Sciences and is a currently employee of the Cardiovascular Research Foundation, which received a grant from Gilead Sciences for study management. KPA has received consulting fees and research grants from Gilead Sciences, research grants from Sanofi Aventis and Regeneron, and consulting fees from CytRx. EMO has received research grants from Gilead Sciences and Jansen Pharmaceuticals, and consulting fees from Astra-Zeneca, Merck, Eli-Lilly–Daiichi Sankyo, and Boeringer Ingelheim. AO is an employee of Gilead Sciences. OB-Y and RF-F are former employees of Gilead Sciences. SJ has received institutional research grants from Gilead Sciences. GWS has served as a consultant for Reva, Boston Scientific, Astra Zeneca, Eli Lilly–Daiichi Sankyo, InspireMD, Volcano, InfraReDx, Cardiovascular Systems, and Matrizyme. All other declare no competing interests.

Acknowledgments

The study was sponsored and funded by Gilead Sciences and the Menarini Group.

References

1 Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015; **131:** e29–322.

2 Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circulation* 2012; **125:** 2613–20.

3 Genereux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol* 2012; **59:** 2165–74.

4 Gossl M, Faxon DP, Bell MR, Holmes DR, Gersh BJ. Complete versus incomplete revascularization with coronary artery bypass graft or percutaneous intervention in stable coronary artery disease. *Circ Cardiovasc Interv* 2012; **5:** 597–604.

5 Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 2006; **113:** 2406–12.

6 Hannan EL, Wu C, Walford G, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interven* 2009; **2:** 17–25.

7 Wu C, Dyer AM, King SB 3rd, et al. Impact of incomplete revascularization on long-term mortality after coronary stenting. *Circ Cardiovasc Interven* 2011; **4:** 413–21.

8 van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. *J Am Coll Cardiol* 2002; **39:** 559–64.

9 Mancini GB, Bates ER, Maron DJ, et al. Quantitative results of baseline angiography and percutaneous coronary intervention in the COURAGE trial. *Circ Cardiovasc Qual Outcomes* 2009; **2:** 320–27.

10 Vieira RD, Hueb W, Gersh BJ, et al. Effect of complete revascularization on 10-year survival of patients with stable multivessel coronary artery disease: MASS II trial. *Circulation* 2012; **126:** S158–63.

11 Nikolsky E, Gruberg L, Patil CV, et al. Percutaneous coronary interventions in diabetic patients: is complete revascularization important? *J Invasive Cardiol* 2004; **16:** 102–06.

12 Hussain F, Philipp RK, Ducas RA, et al. The ability to achieve complete revascularization is associated with improved in-hospital survival in cardiogenic shock due to myocardial infarction: Manitoba cardiogenic SHOCK Registry investigators. *Catheter Cardiovasc Interv* 2011; **78:** 540–48.

13 Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015; **65:** 963–72.

14 Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013; **369:** 1115–23.

15 McPherson JA, Maehara A, Weisz G, et al. Residual plaque burden in patients with acute coronary syndromes after successful percutaneous coronary intervention. *JACC Cardiovasc Imaging* 2012; **5:** S76–85.

16 Head SJ, Mack MJ, Holmes DR, Jr, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg* 2012; **41:** 535–41.

17 Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. *Heart* 2006; **92:** iv6–14.

18 Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol* 2004; **43:** 1375–82.

19 Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA* 2004; **291:** 309–16.

20 Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L, ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol* 2006; **48:** 566–75.

21 Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007; **297:** 1775–83.

22 Gutierrez JA, Karwatowska-Prokopczuk E, Murphy SA, et al. Effects of ranolazine in patients with chronic angina in patients with and without percutaneous coronary intervention for acute coronary syndrome: observations from the MERLIN-TIMI 36 trial. *Clin Cardiology* 2015; **38:** 469–75.

23 Zellweger MJ, Fahrni G, Ritter M, et al. Prognostic value of "routine" cardiac stress imaging 5 years after percutaneous coronary intervention: the prospective long-term observational BASKET (Basel Stent Kosteneffektivitats Trial) LATE IMAGING study. *JACC Cardiovasc Interv* 2014; **7:** 615–21.

24 Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364:** 226–35.

25 Weisz G, Farzaneh-Far R, Ben-Yehuda O, et al. Use of ranolazine in patients with incomplete revascularization after percutaneous coronary intervention: design and rationale of the Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial. *Am Heart J* 2013; **166:** 953–59, e3.

26 Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013; **128:** 141–51.

27 Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360:** 213–24.

28 De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; **371:** 1208–17.

29 Fraser H, Belardinelli L, Wang L, Light PE, McVeigh JJ, Clanachan AS. Ranolazine decreases diastolic calcium accumulation caused by ATX-II or ischemia in rat hearts. *J Mol Cell Cardiol* 2006; **41:** 1031–38.

30 Wittes J. On looking at subgroups. *Circulation* 2009; **119:** 912–15.

31 Gilead. Ranolazine prescribing information: 8.5 geriatric use. 2013. http://www.gilead.com/~/media/Files/pdfs/medicines/cardiovascular/ranexa/ranexa_pi.ashx (accessed Sept 1, 2015).