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ORIGINAL INVESTIGATIONS

Compliance With Guideline-Directed Medical Therapy in Contemporary Coronary Revascularization Trials

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ABSTRACT

BACKGROUND Despite the well-established benefits of secondary cardiovascular prevention, the importance of concurrent medical therapy in clinical trials of coronary revascularization is often overlooked.

OBJECTIVES The goal of this study was to assess compliance with guideline-directed medical therapy (GDMT) in clinical trials and its potential impact on the comparison between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

METHODS The Cochrane Central Register of Controlled Trials and MEDLINE were searched from 2005 to August 2017. Clinical trial registries and reference lists of relevant studies were also searched. Randomized controlled trials comparing PCI with drug-eluting stents versus CABG and reporting medical therapy after revascularization were included. The study outcome was compliance with GDMT, defined as the following: 1) any antiplatelet agent plus beta-blocker plus statin (GDMT1); and 2) any antiplatelet agent plus beta-blocker plus statin plus angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (GDMT2). Data collection and analysis were performed according to the methodological recommendations of The Cochrane Collaboration.

RESULTS From a total of 439 references, 5 trials were included based on our inclusion and exclusion criteria. Overall, compliance with GDMT1 was low and decreased over time from 67% at 1 year to 53% at 5 years. Compliance with GDMT2 was even lower and decreased from 40% at 1 year to 38% at 5 years. Compliance with both GDMT1 and GDMT2 was higher in PCI than in CABG at all time points. Meta-regression suggested an association between lower use of GDMT1 and adverse clinical outcomes in PCI versus CABG at 5 years.

CONCLUSIONS Compliance with GDMT in contemporary clinical trials remains suboptimal and is significantly lower after CABG than after PCI, which may influence the comparison of clinical trial endpoints between those study groups. (J Am Coll Cardiol 2018;71:591–602) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin-receptor blocker

CABG = coronary artery bypass grafting

CAD = coronary artery disease

GDMT = guideline-directed medical therapy

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

Guideline-directed medical therapy (GDMT) is recommended by evidence-based guidelines for all patients with coronary artery disease (CAD). In addition to being considered the first line of treatment for patients with stable CAD, GDMT as secondary prevention after coronary revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (1,2) is associated with a significant reduction in mortality and myocardial infarction (MI) risk (3). Moreover, GDMT alone may achieve a greater reduction in mortality than the choice of revascularization strategy (4).

However, currently available evidence suggests that compliance with GDMT remains poor after coronary revascularization, particularly after CABG (5–8) and in patients with comorbidities such as chronic renal disease. This poor compliance further increases patients' already higher risk of adverse outcomes (9). Moreover, randomized controlled trials (RCTs) of coronary revascularization, which are the primary source of evidence to guide contemporary clinical practice, often provide scant information regarding concurrent medical treatment (10). Therefore, whether the poor compliance with GDMT reported in population-based studies is also reflected in clinical trials and to what extent different compliance rates influence clinical outcomes between PCI and CABG remain unknown.

The aims of the present study were as follows: 1) to analyze compliance with GDMT in landmark clinical trials of coronary revascularization; 2) to compare compliance with GDMT in PCI versus CABG; and 3) to assess its potential association with clinical trial outcomes.

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METHODS

STUDY DESIGN. We performed a systematic review and meta-analysis according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (11) and The Cochrane Collaboration (12).

SEARCH STRATEGY. The Cochrane Central Register of Controlled Trials in the Cochrane Library and MEDLINE in PubMed were searched from 2005 to August 2017. This search was complemented by handsearching reference lists of relevant studies and clinical trial registries (August 2017). We did not apply limits by publication language, status, or date. Further details on search strategies are described in the protocol and the Online Appendix.

SELECTION CRITERIA. RCTs comparing PCI with drug-eluting stents versus CABG in patients with CAD were included in the study. (Inclusion and exclusion criteria are specified in the Online Appendix.)

DEFINITION OF OUTCOMES. GDMT was defined in 2 different categories: 1) GDMT1, a combination of any antiplatelet agent, beta-blocker, and statin; and 2) GDMT2, a combination of any antiplatelet agent, beta-blocker, statin, and angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker (ARB).

STUDY SELECTION AND DATA COLLECTION. Two review authors independently screened all identified references according to pre-defined inclusion criteria. Full-text articles of those references were retrieved and reviewed for final inclusion according to prespecified inclusion and exclusion criteria. Disagreements were resolved by consensus.

Authors of the included trials were invited to provide individual patient data for the main classes of GDMT: aspirin, adenosine diphosphate $P2Y_{12}$-receptor inhibitor, beta-blocker, statin, and ACE inhibitor and/or ARB. Data regarding clinical outcomes were obtained from published trial reports. One author collated outcome data into a master database and performed quality assessment, with a second author verifying its accuracy.

Compliance rates were calculated for individual drug classes and GDMT1 and GDMT2 as the number of patients prescribed each drug divided by the total number of patients with follow-up at each specific time point. Analysis was performed for patients undergoing PCI and CABG by computing compliance rates for each group. We used the absolute risk reduction as the effect measure, and differences in compliance rates and clinical outcomes were calculated by subtracting those of CABG from those of PCI. The time points selected for analysis were as follows: discharge, 1 year, 3 years, and 5 years.

Institute, New York, New York; and the [k]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain. Dr. Farkouh has received research support from Amgen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Hartzell V. Schaff, MD, served as Guest Editor for this paper.

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TABLE 1 Summary of Large, Multicenter RCTs Comparing PCI Versus CABG in Patients Undergoing Revascularization for Complex CAD

Trial (Ref. #)	Date	Site	Study Period	Population	Number of Patients	Interventions	Primary Endpoint	Follow-Up (yrs)	Outcome* PCI (%)	Outcome* CABG (%)	Outcome* p Value
SYNTAX (27)	2013	85 centers in the United States and Europe	2005–2007	3-VD or LMS	1,800	PCI with first-generation paclitaxel-eluting stent vs. CABG (1:1 ratio)	All-cause death, stroke, myocardial infarction, and repeat revascularization	1 5	17.8 37.3	12.4 26.9	0.002 <0.001
FREEDOM (28)	2012	140 international centers	2005–2010	Diabetes and multivessel coronary artery disease (3-VD or LMS)	1,900	PCI with sirolimus- or paclitaxel-eluting stents vs. CABG (1:1 ratio)	All-cause death, nonfatal myocardial infarction, or nonfatal stroke	2 5	13.0 26.6	11.9 18.7	0.005 0.005
PRECOMBAT (29)	2015	13 centers in South Korea	2005–2009	LMS	600	PCI with sirolimus-eluting stent vs. CABG (1:1 ratio)	All-cause death, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization	1 5	8.7 17.5	6.7 14.3	0.01 0.26
BEST (30)	2015	27 centers in East Asia	2008–2013	Multivessel coronary artery disease (3-VD or LMS)	880	PCI with everolimus-eluting stent vs. CABG (1:1 ratio)	All-cause death, myocardial infarction, or target-vessel revascularization	2 4.6 (median)	11.0 15.3	7.9 10.6	0.32 0.04
EXCEL (31)	2016	126 centers in 17 countries	2010–2014	LMS with low/intermediate SYNTAX scores	1,905	PCI with everolimus-eluting stent vs. CABG (1:1 ratio)	All-cause death, stroke, or myocardial infarction	3	15.4	14.7	0.98

*Outcome for primary endpoint.

3-VD = 3-vessel disease; BEST = Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial; CABG = coronary artery bypass grafting; CAD = coronary artery disease; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; LMS = left main stem disease; PCI = percutaneous coronary intervention; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; RCT = randomized controlled trial; SYNTAX = Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

RISK OF BIAS ASSESSMENT. Risk of bias of individual studies was assessed according to the recommendations of The Cochrane Collaboration (12), taking into account the following items: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data addressed (attrition bias); and 6) selective reporting (reporting bias).

STATISTICAL ANALYSIS AND EVIDENCE SYNTHESIS. Meta-analysis was conducted to assess the pooled compliance with GDMT in all the trials and to compare intervention groups (PCI vs. CABG). Outcomes and effect measures were reported as untransformed proportion and risk difference with 95% confidence intervals, respectively. The overall meta-analytical effect size was estimated by using the random effects model and the restricted maximum likelihood method. Chi-square Q statistics and I^2 statistics were used to assess heterogeneity. Meta-regression with a random effects model was performed to assess the impact of compliance with GDMT on clinical outcomes at 5 years. Overall trial data (and not individual patient data) were used, and only trials with 5-year follow-up were included in meta-regression. All statistical analyses were performed using the software Open MetaAnalyst (13). A p value <0.05 was considered statistically significant for all analyses.

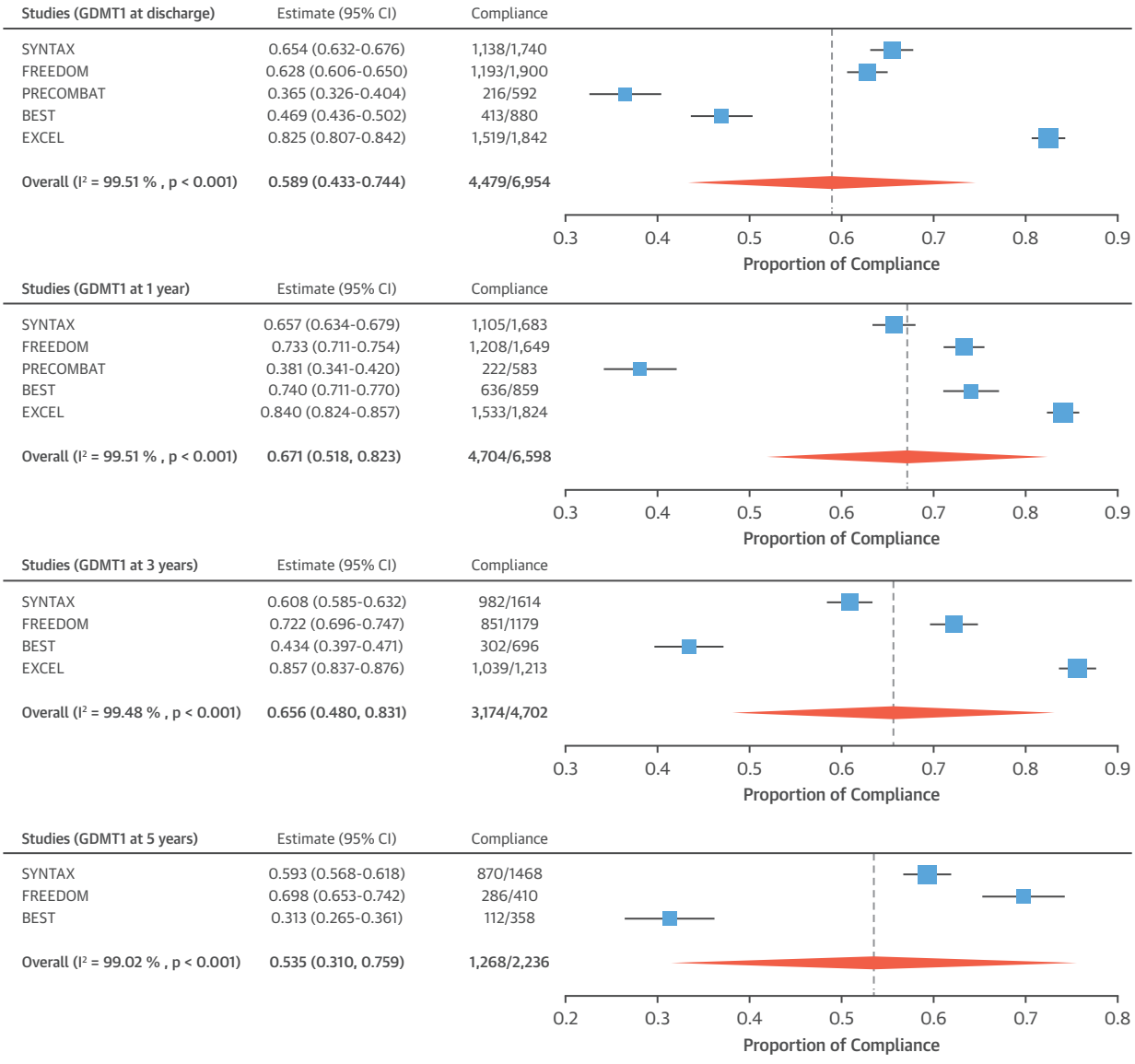
RESULTS

STUDY SELECTION. The study search strategy yielded 749 references, of which 395 were excluded after screening. A total of 46 papers were reviewed, and 18 RCTs ultimately met the inclusion criteria. However, after reviewing the full papers, only 5 were included for analysis (Online Figure 1).

Thirteen RCTs were excluded:

- MASS II (Medicine, Angioplasty, or Surgery Study) trial (14) and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial (15) compared medical therapy versus revascularization with either PCI or CABG;
- VA CARDS (Coronary Artery Revascularization in Diabetes trial) (16) had serious methodological limitations (recruitment was stopped after enrolling only 25% of the intended sample size);
- SIMA (Stenting versus Internal Mammary Artery grafting) trial (17), BARI (Bypass Angioplasty Revascularization Investigation trial) (18), LE MANS (Left Main Coronary Artery Stenting trial) (19), SoS

FIGURE 1 Compliance With GDMT1, Defined as Any Antiplatelet Agent + Beta-Blocker + Statin, in All Clinical Trials Over Time

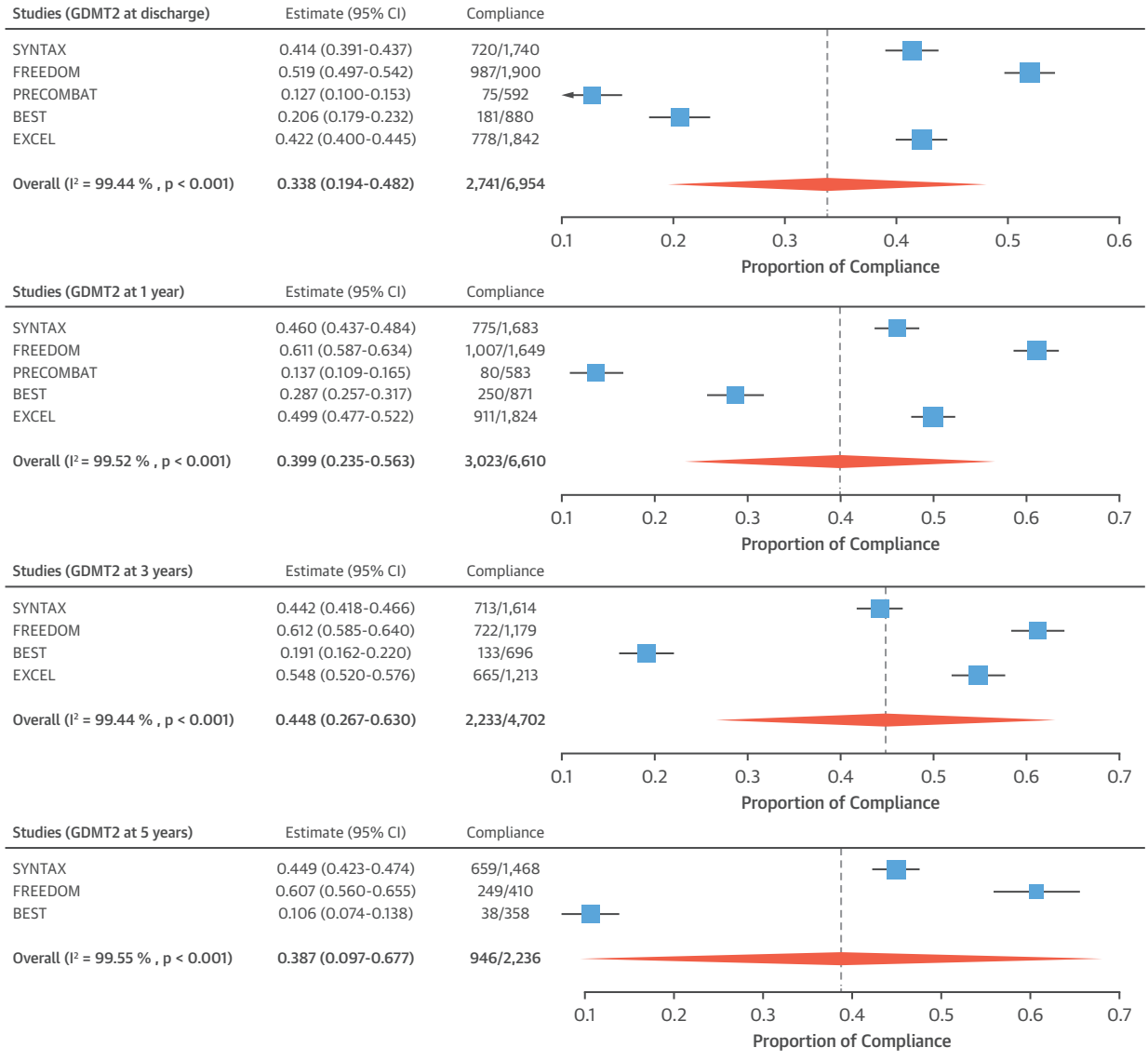


Proportion of compliance calculated as number of patients prescribed guideline-directed medical therapy (GDMT) 1 divided by the total number of patients at each time point. BEST = Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial; CI = confidence interval; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX = Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

(Stent or Surgery trial) (20), ERACI II (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery Trial) (21), and CARDia (Coronary Artery Revascularization in Diabetes) trial (22) used bare-metal stents;

- The MICASA (Myocardial Injury Following Coronary Artery Surgery Versus Angioplasty) trial (23) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) (24) did not collect data regarding medical therapy; and

FIGURE 2 **Compliance With GDMT2, Defined as Any Antiplatelet Agent + Beta-Blocker + Statin + ACE Inhibitor or ARB, in All Clinical Trials Over Time**



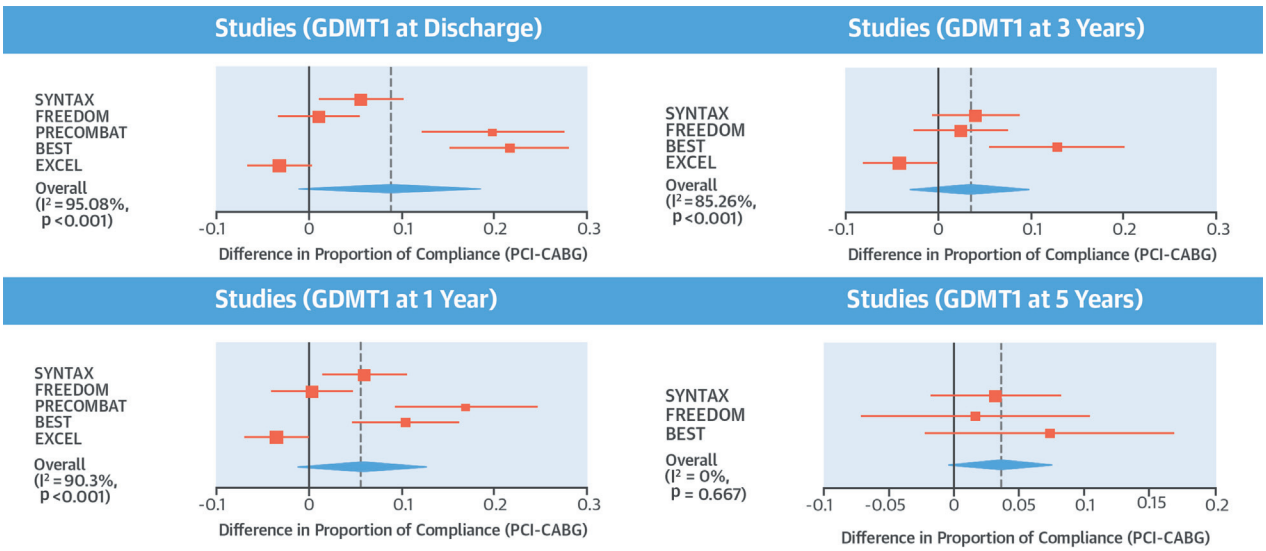
Proportion of compliance calculated as number of patients prescribed GDMT2 divided by the total number of patients at each time point. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; other abbreviations as in Figure 1.

- Two other trials were excluded because they did not collect data regarding medical therapy during follow-up (25,26).

Therefore, the following trials were included in the final analysis:

- SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial (27);
- FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (28);
- PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial (29);
- BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent

CENTRAL ILLUSTRATION **Compliance With GDMT1, Defined as Any Antiplatelet Agent + Beta-Blocker + Statin, for PCI and CABG**



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Difference in compliance calculated by subtracting proportion of compliance in coronary artery bypass grafting (CABG) from proportion of compliance in percutaneous coronary intervention (PCI). BEST = Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease trial; EXCEL = Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial; GDMT1 = guideline-directed medical therapy 1; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX = Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery trial.

Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial (30); and

- EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (31).

An additional 2 surgical trials (CORONARY [CABG Off or On Pump Revascularization Study] [32] and ART [Arterial Revascularisation Trial] [33]) were added due to their relevance in the field of coronary revascularization and the availability of data on medical therapy. These trials were analyzed separately because they did not compare PCI versus CABG (Online Figures 2 and 3, Online Table 1).

STUDY CHARACTERISTICS. The 6 studies included in this review were all large, multicenter RCTs that compared PCI versus CABG in patients undergoing revascularization for complex CAD (**Table 1**). All those studies were considered landmark trials that provide the evidence basis for contemporary practice of coronary revascularization.

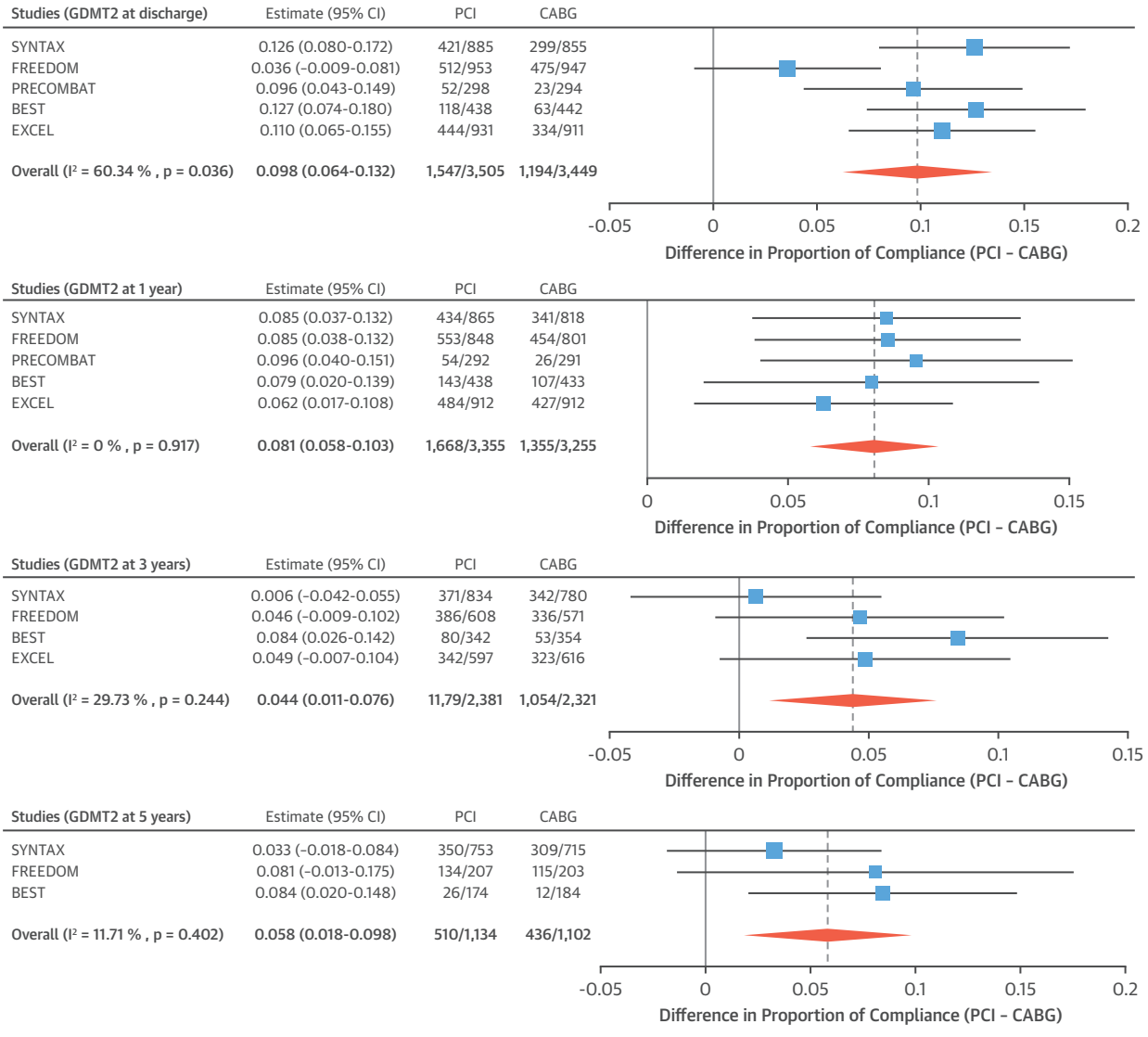
RISK OF BIAS WITHIN STUDIES. All the studies included in this review were RCTs of high methodological quality (Online Table 2).

OVERALL COMPLIANCE WITH GDMT. **Figures 1 and 2** illustrate compliance to GDMT1 and GDMT2, respectively, over time in all the trials. Data regarding individual drug classes are available in Online Table 3. There was substantial variability between studies in both GDMT1 and GDMT2, as noted by the high I^2 values at each time point.

COMPLIANCE WITH GDMT IN PCI VERSUS CABG GROUPS. The **Central Illustration and Figure 3** illustrate the difference between PCI and CABG in the proportion of compliance with GDMT1 and GDMT2, respectively, over time. For all studies except EXCEL with GDMT1, compliance was higher with PCI than with CABG. Data regarding individual drug classes are provided in Online Table 4.

COMPLIANCE WITH GDMT AND CLINICAL OUTCOMES. **Figure 4** illustrates the inverse association between the difference in compliance with

FIGURE 3 Compliance With GDMT2, Defined as Any Antiplatelet Agent + Beta-Blocker + Statin + ACE Inhibitor or ARB, for PCI and CABG



Difference in compliance calculated by subtracting proportion of compliance in coronary artery bypass grafting (CABG) from proportion of compliance in percutaneous coronary intervention (PCI). Abbreviations as in Figures 1 and 2.

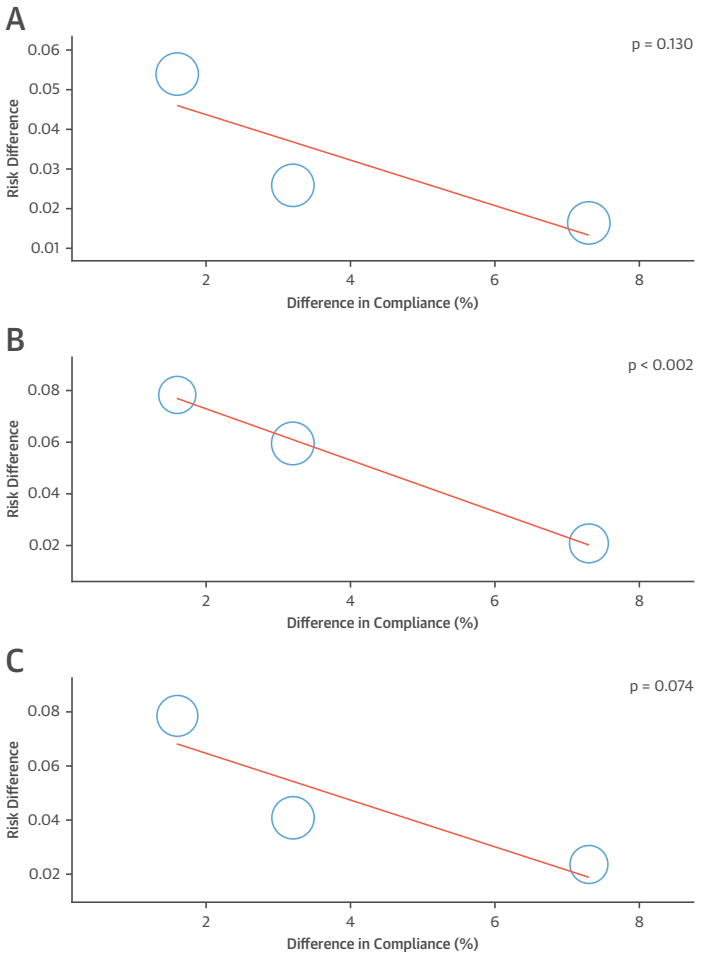
GDMT1 at 5 years and the difference in clinical outcomes (all-cause mortality, MI, and a composite endpoint of all-cause mortality, MI, and stroke) for clinical trials with 5-year follow-up. As compliance with GDMT increased in the PCI group relative to the CABG group, the better outcomes of CABG became less evident. There was no difference in clinical outcomes when compliance for PCI exceeded that of CABG by approximately 8%.

Data for all other trials and time points are available in Online Table 5. There was no apparent association between compliance with GDMT2 and clinical outcomes.

DISCUSSION

Despite the compelling benefits demonstrated by GDMT as secondary prevention after coronary revascularization, compliance remains low even in the tightly controlled environment of clinical trials. Furthermore, in our study, compliance with GDMT was higher in patients undergoing PCI compared with

FIGURE 4 Meta-Regression Relating Compliance With GDMT1 (Any Antiplatelet Agent + Beta-Blocker + Statin) at 5 Years and Clinical Trial Outcomes at 5 Years



(A) Mortality, **(B)** myocardial infarction (MI), and **(C)** a composite of death, MI, and stroke. Only 3 trials were included (SYNTAX, FREEDOM, and BEST) because the others did not report 5-year outcomes. The x-axis represents the difference in compliance with GDMT1 between PCI and CABG; the y-axis represents the difference in clinical outcomes between PCI and CABG. As the difference in compliance favoring PCI widens, the superiority of CABG in terms of clinical outcomes decreases. The p value is for comparison between PCI and CABG. The **size of the circles** reflects the weight of the study. Abbreviations as in Figures 1 and 3.

patients undergoing CABG, which may skew the comparison of clinical endpoints between those revascularization strategies.

OVERALL COMPLIANCE WITH GDMT. Overall compliance with aspirin and statins was high and reasonably stable over time, but there was some variation among trials, with compliance rates ranging from 75% to 95%. Some of the lack of compliance with aspirin may be related to intolerance to aspirin and/or concurrent use of anticoagulation therapy. Nonetheless, compliance with at least 1 antiplatelet agent was close to 100% in most trials throughout follow-up. Although aspirin intolerance or hypersensitivity can affect up to 10% of the population, there are currently rapid desensitization protocols that can be used in patients requiring dual antiplatelet therapy (34). Conversely, prevention of aspirin resistance has justified consideration of high-dose aspirin (325 mg daily) instead of low-dose aspirin (81 mg daily), but its benefits remain uncertain (35).

The differences in the use of adenosine diphosphate $P2Y_{12}$-receptor inhibitors may be related to whether dual antiplatelet therapy was used and for how long after revascularization. Considering the controversy regarding dual antiplatelet therapy after coronary revascularization (36–38), the significant differences between trials are not unexpected, particularly when considering surgical trials (CORONARY and ART). Although dual antiplatelet therapy is recommended after PCI, its benefit after CABG remains uncertain and is only recommended in specific circumstances (e.g., off-pump surgery) (35).

Compliance with beta-blockers and ACE inhibitors/ARBs was lower and more variable, ranging from 43% to 80% and 28% to 79%, respectively. These findings are in keeping with previous reports from real-world registries (3). One possible explanation is the fact that although the efficacy of antiplatelet agents and statins in reducing cardiovascular events after coronary revascularization has long been recognized (1,39,40), the advantages of other drug classes have been established more recently (41) and may vary according to comorbidities and risk factors. Indeed, ACE inhibitors/ARBs are not routinely recommended after CABG unless in the presence of hypertension, diabetes, left ventricular systolic dysfunction, and chronic kidney disease (35,41), due to a potential increase in postoperative complications (42). In addition, controversies regarding the adverse effects of beta-blockers and statins may influence prescribing decisions (43–45).

Variability between trials was also found regarding compliance with GDMT1 and GDMT2. Although there was significant heterogeneity, even the highest compliance rates were unsatisfactory, as <40% of the patients were taking all the guideline-recommended drugs at 1 year. Furthermore, there was a modest decline in compliance over time. Although this outcome has been documented in the real world, more stable compliance was expected in this study due to the stricter follow-up required by clinical trial protocols (46).

The underuse of GDMT, particularly after CABG (8), is likely multifactorial. It may be related to underestimation of the importance of GDMT and the misconception that the value of maintaining GDMT is reduced once diseased coronary arteries have been mechanically revascularized with either PCI or CABG (47–49). In keeping with this, medical therapy is often neglected in coronary revascularization trials and hence poorly reported or not even collected at all, as happened in the recent NOBLE trial (24). On the contrary, GDMT compliance seemed higher in patients undergoing PCI than in those treated without revascularization (50,51), likely because hospital admission, often precipitated by an acute coronary event, provided an opportunity to reconsider prescription of cardioprotective medication. The conflicting evidence currently available calls for further studies to elucidate the factors related to GDMT noncompliance.

Irrespective of the underlying reasons, poor compliance with medical therapy that has demonstrated compelling benefits for secondary prevention in landmark clinical trials is a matter of concern. Considering that clinical trials operate within a strictly controlled environment and include a highly selected population of patients, drug compliance would be expected to be optimal. Furthermore, clinical trials provide the evidence to support current clinical practice and emphasize ideal standards. Therefore, optimizing compliance to GDMT is paramount to improve compliance and outcomes in everyday practice.

COMPARISON OF COMPLIANCE BETWEEN PCI AND CABG. Compliance with GDMT was consistently lower for patients undergoing CABG compared with PCI. The difference was particularly marked for $P2Y_{12}$-receptor inhibitors, as dual antiplatelet therapy is formally recommended in the guidelines after PCI (41). In contrast, aspirin and statins were identically used in both groups, and beta-blockers were more common in the CABG group in the EXCEL trial, perhaps due to their potential utility in preventing or treating post-operative atrial fibrillation (52).

Compliance with GDMT1 and GDMT2 was also better in the PCI group compared with the CABG group, with a difference close to 10% at 1 year for GDMT2. The underlying reasons are difficult to identify. The common although erroneous assumption that more complete revascularization after CABG obviates the need for further medical therapy cannot be overlooked. Medical therapy, particularly antiplatelet agents (53) and statins (54), reduces platelet activation, endothelial dysfunction, oxidative stress, and inflammation, which have all been associated with the development and progression of atherosclerosis (55–57), which is itself the primary mechanism leading to graft failure, particularly in venous grafts (58). Conversely, the lower compliance with ACE inhibitors/ARBs may be based on evidence suggesting that these drugs have no impact on midterm mortality or recurrent ischemia after CABG (59). Concerns about the detrimental effect of ACE inhibitors/ARBs on renal function and hyperkalemia in the post-operative period further compound the lower compliance with these drugs. However, this theory remains highly controversial (42,60,61), and the benefit of these drugs after the first 3 months has been compellingly demonstrated (62–64).

Another potential explanation for the low overall compliance with GDMT and the variability observed between individual trials is the high cost of medicines. Cost-effectiveness analyses support this possibility and imply that providing full coverage for secondary prevention therapy may save lives and decrease consumption of health care resources (65,66). Cardiovascular drugs are not easily affordable in many countries, particularly in South America and Southeast Asia. Therefore, in trials in which standard medication was not provided by the study team, the low compliance rates may reflect patients' inability to access expensive drugs. Although we could not analyze compliance rates stratified according to country, the hypothesis that the high price of cardiovascular medication significantly limits compliance in clinical trials deserves further investigation.

INFLUENCE OF GDMT ON CLINICAL TRIAL OUTCOMES. Our data suggest that there is a correlation between the difference in compliance rates and clinical outcomes when comparing PCI and CABG at 5 years. The better outcomes achieved with CABG versus PCI became less obvious as the compliance with GDMT increased in PCI versus CABG. Therefore, if compliance rates were identical in both groups, the superiority of CABG for major clinical endpoints might have been even more marked, as part of the benefit of PCI might be explained by better compliance with GDMT. However, because the population of patients included in each trial was different, the influence of confounding factors cannot be excluded. In addition, the correlation between GDMT1 and clinical outcomes was not corroborated by a similar correlation with GDMT2. Nevertheless, the importance of this hypothesis deserves consideration. Although some

might argue that the varying profiles of medical therapy in PCI and CABG is part of the difference in the "strategies" of PCI and CABG, a fair and accurate comparison between PCI and CABG cannot be appreciated unless medical therapies are equalized with both approaches. Other than for dual antiplatelet therapy, single antiplatelet treatment, beta-blockers, and statins seem advantageous irrespective of the revascularization strategy.

STUDY LIMITATIONS. In this study, medication prescription was considered as a surrogate for medication adherence, which may have resulted in overestimating true compliance rates. Medication nonadherence is a well-recognized issue in cardiovascular disease and may be responsible for approximately 125,000 preventable deaths every year as only about one-half of the patients consistently take prescribed medications (67). In addition, in this study, it was impossible to assess whether treatment doses were appropriate and to ascertain the reasons for noncompliance because this factor was not tracked in any of the randomized trials. Finally, the meta-regression relating compliance to subsequent outcomes was based on only 3 studies and compliance data at one point in time, adding imprecision to the results. We did not have access to individual patient-level data in the present analysis, which would have been superior to meta-regression in linking compliance with outcomes.

CONCLUSIONS

Although GDMT is crucial for patients to derive the most benefit from coronary revascularization, compliance was low even in landmark randomized clinical trials. Moreover, drug compliance was consistently lower in the CABG group compared with the PCI group, and this difference may have influenced the differences in major clinical outcomes between groups. Further research is warranted to delineate the extent to which different rates of compliance with GDMT after PCI compared with CABG influence the relative short- and long-term outcomes with these revascularization modalities.

The potential consequences of poor compliance with GDMT on long-term clinical outcomes are substantial. Therefore, a pressing need exists to develop effective strategies to improve compliance with life-saving drugs. Clinical trials have an important role to play by serving as an example of ensuring outstanding compliance with GDMT.

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PERSPECTIVES

COMPETENCY IN PRACTICE-BASED LEARNING AND IMPROVEMENT: Compliance with GDMT in contemporary clinical trials is suboptimal and lower in trials of patients undergoing CABG than in those investigating PCI.

TRANSLATIONAL OUTLOOK: More concerted efforts are needed to improve compliance with GDMT among patients participating in clinical trials of coronary revascularization and to understand the impact of compliance on the comparative outcomes of patients undergoing percutaneous or surgical coronary revascularization.

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KEY WORDS coronary artery bypass surgery, drug compliance, guideline-directed medical therapy, percutaneous coronary intervention, secondary cardiovascular prevention

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this article.