Pexelizumab in ischemic heart disease: A systematic review and meta-analysis on 15,196 patients

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Object: Pexelizumab is a humanized monoclonal antibody inhibiting C5 complement. It has been postulated to improve outcomes in patients undergoing coronary artery bypass surgery and urgent reperfusion therapy for ST elevation myocardial infarction. We aimed at evaluating the risk/benefit profile of pexelizumab (bolus + infusion) versus placebo on top of current approaches in the management of patients with ST elevation myocardial infarction or undergoing coronary artery bypass.

Methods: We conducted a search of BioMedCentral, CENTRAL, mRCT, and PubMed without language restrictions (updated October 2007) for randomized controlled trials. Outcomes of interest were the risk of major adverse events (the composite of all-cause death, myocardial infarction, and thromboembolic stroke), the risk of single end points, and heart failure.

Results: Seven trials were included (15,196 patients: 7019 patients with ST elevation myocardial infarction and 8177 undergoing coronary bypass surgery). No benefit of adding pexelizumab was found in the overall analysis for major adverse events (OR 0.91 [0.76–1.09]; $P = .29$], death (OR 0.79 [0.61–1.03], $P = .11$], myocardial infarction (OR 1.04 [0.89–1.22]; $P = .14$), stroke (OR 0.95 [0.66–1.38]; $P = .8$), heart failure (OR1.0 [0.82–1.22]; $P = .99$), nor in the settings of patients with ST elevation myocardial infarction treated with mechanical or pharmacologic reperfusion therapy. Pexelizumab was associated with a 26% reduction of the risk of death in the setting of coronary artery bypass (OR 0.74 [0.58–0.94]; $P = .01$). The number needed to treat was 100.

Conclusion: Our data ruled out the hypothesis of any benefit of adding pexelizumab on top of currently available therapies for ST elevation myocardial infarction. However, pexelizumab reduces the risk of death in patients undergoing coronary artery bypass grafting.

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Ischemic heart disease is a major public health problem both in Western and in developing countries, with 7 million persons in the United States currently affected.[1] Despite improvements in diagnosis, pharmacologic therapy, and surgical therapy, ischemic heart disease remains one of the leading causes of mortality.[1] In the past few years, therapeutic strategies aimed at modifying the role of complement in ischemic heart disease have received increasing attention. Not only is the complement system activated by inflammation, but it also plays an integral role in the propagation of inflammation, the coagulation cascade, and apoptosis. Once the terminal components of complement have been activated, they drive the cleavage of C5 into C5a, a powerful anaphylatoxin and proinflammatory mediator, and C5b, which leads to formation of C5b-9, the terminal membrane attack complex (MAC). MAC is a transmembrane channel involved in thrombosis and inflammation, which also causes direct tissue injury through osmotic lysis.[2] Pexelizumab is a recombinant humanized single-chain monoclonal antibody to C5 that blocks the conversion of C5 to C5a and C5b-9, thus preventing the formation of MAC. It has been studied in a randomized fashion, in multiple studies and settings, primarily ST elevation myocardial infarction (STEMI)

Abbreviations and Acronyms

AMI = acute myocardial infarction
CABG = coronary artery bypass grafting
CHF = congestive heart failure
CI = confidence interval
MAC = membrane attack complex
MAE = major adverse event
MI = myocardial infarction
OR = odds ratio
QUOROM = Quality of Reporting of Meta-analyses
STEMI = ST elevation myocardial infarction

and on-pump coronary artery bypass grafting (CABG). Our aim was to provide, by means of systematic review and meta-analysis, an objective and quantitative evaluation of the risk/benefit profile of adding pexelizumab to currently available therapies for patients undergoing urgent reperfusion for STEMI or CABG.

Methods

Study Selection

BioMedCentral, CENTRAL, mRCT, and PubMed were searched without language restrictions (updated to October 2007), according to an established method (see appendix for the electronic search algorithm).[3] Pertinent trials were also searched in major recent international cardiology meetings. References of original and review articles were cross-checked.

Inclusion/Exclusion Criteria

Specifically, inclusion criteria were (1) randomized allocation, (2) controlled comparison of pexelizumab (2 mg/kg bolus plus 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$ 20–24-hour infusion) versus placebo in the setting of ischemic heart disease, and (3) intention-to-treat analysis. Exclusion criteria were (1) an equivocal treatment allocation process, (2) significant imbalances in major baseline characteristics among study groups, and (3) incomplete (<80%) follow-up.

Data Extraction and End Points of Interest

Four trained and independent reviewers (L.T., W.J.V.G., G.B.Z., and P.A.) performed data abstraction blindly. Divergences were resolved by consensus. The end point of interest was the combined rate of major adverse events (MAEs), defined as all-cause death, nonfatal acute myocardial infarction (AMI), or nonfatal thromboembolic stroke. Additional analyses were carried out according to clinical settings, single end points, and the rate of congestive heart failure (CHF). All data referred to the longest follow-up available in each trial.

Data Synthesis and Analysis

Review Manager 4.2.5[4] and SPSS 11.0 (SPSS, Inc, Chicago, Ill) were used. Review Manager is a comprehensive statistical and reviewing program, developed and maintained by the Cochrane Collaboration, which includes ad hoc statistical tools for pooled estimate calculations, according to several methods.

Statistical Analyses

Odds ratios with 95% confidence intervals (95% CI) were used as summary statistics. Binary outcomes from individual studies were combined with both DerSimonian and Laird[5] random-effect model and fixed-effect model, according to an intention-to-treat analysis. We also carried out the z test where z = estimated effect size/standard error of the estimated effect size, and the odds ratio (OR) considered on the log scale. Inasmuch as log(OR) has a unimodal distribution, the reported z values were analyzed to obtain a 2-tailed ''*P*,'' and hypothesis testing results were considered statistically significant at the .05 level.[6] As per protocol, we calculated the number needed to treat to prevent an MAE as the inverse of random effect ORs.

We computed Cochrane Q heterogeneity test (H) by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner. Heterogeneity was considered significant at ''*P* for H'' $< .10$.[6] According to Higgins and associates,[7] we used the Q together with the resulting degrees of freedom *(df)* to calculate the proportion of variation resulting from heterogeneity: (Inconsistency: $[I^2] = [Q - df]/Q$). The degree of inconsistency among studies (I^2) was estimated with scores of less than 25%, between 25% and 75%, and more than 75%, representing, respectively, low, moderate, or high inconsistency.[7] The internal validity of the included trials was appraised according to the Cochrane Collaboration criteria, that is, judging the risk of selection, performance, attrition, and adjudication biases; the risk of bias was expressed as low (A), moderate (B), or high (C); incomplete reporting leading to inability to ascertain the underlying risk of bias was scored as D. Allocation concealment was distinguished as adequate (A), unclear (B), inadequate (C), or not used (D).[6] Sensitivity analysis was performed by excluding trials one at a time, from those with the lowest to those with the highest quality score, to assess the contribution of each study to the pooled estimates.[6] The likelihood of publication bias was assessed graphically by generating a funnel plot for the combined end point of MAEs and mathematically by means of the test derived by Egger and associates[8] (*P* for significant asymmetry < 0.1).

This study is inspired by good practice guidelines,[9] including those from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUOROM) statement.[10]

Results

Search Results

From 44 potentially relevant citations, our search identified 6 studies that randomized a total of 15,196 patients.[11-17] Two trials investigated the efficacy of pexelizumab as adjunctive therapy to primary percutaneous intervention in AMI (STEMI),[11,12] 3 in the setting of CABG surgery,[13-15] 1 in the setting of CABG surgery combined with aortic valve replacement,[16] and 1 in the setting of patients with AMI treated with fibrinolysis[17] (Figure 1). Four trials[11,13,14] randomized patients to placebo or pexelizumab bolus plus 24-hour infusion and 3 trials[12,15-17] to placebo, pexelizumab bolus only, and pexelizumab bolus plus 24-hour infusion, but we excluded the bolus-only arms, as per protocol, to avoid further heterogeneity.

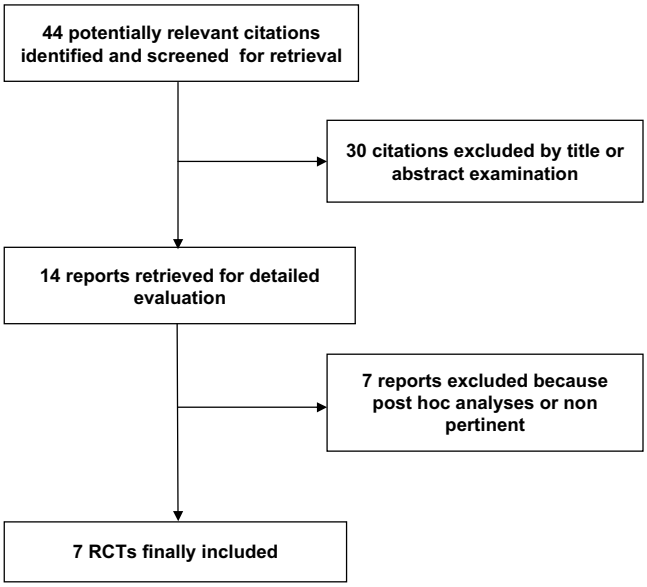

Figure 1. Flow diagram according to the QUOROM statement. *RCT,* Randomized clinical trial.

Study Characteristics and Quality Assessment

The main characteristics of the 6 trials are listed in Table 1. Generally, all studies were of good quality, that is, at low risk of bias with adequate allocation concealment. One study has been published only as an abstract presentation.[15]

Overall Quantitative Findings

The pooled estimates by the random effect model did not differ significantly from those obtained by the fixed effect model. The presented results are according to the former. In the overall analysis, no differences were found between pexelizumab and placebo for the risk of MAE (OR 0.93 [0.78–1.11], $P = .29$), death (OR 0.79 [0.61–1.03], $P = .11$), myocardial infarction (MI) (OR 1.04 [0.89–1.22], $P = .14$), stroke (OR 0.95 [0.66–1.38], $P = .8$), or CHF (OR 1.0 [0.82–1.22], $P = .98$) (Figure 2, Table 2).

Analyses According to Clinical Settings

STEMI. No differences were found between pexelizumab and placebo in the setting of emergency management of STEMI. Three trials[11,12,17] totaling 7019 patients demonstrated no benefit with respect to the risk of MAE (OR 0.90 [0.59–1.36], $P = .62$), death (OR 0.89 [0.57–1.39], $P = .6$), MI (OR 1.22 [0.9–1.65], $P = .2$), stroke (OR 1.06 [0.69–1.62], $P = .79\%$) or CHF (OR 1.03 [0.83–1.27], $P = .8$) (Figure 3, Table 2). Similar results were found in the analysis restricted to trials enrolling patients undergoing primary percutaneous coronary intervention (6388 patients). Again, no benefits were demonstrated with respect to the risks of MAE (OR 0.82 [0.35–1.91], $P = .64$), death (OR 0.73 [0.29–1.87], $P = .51$), MI (OR 1.28 [0.93–1.76], $P = .13$), stroke (OR 1.18 [0.75–1.86], $P = .47$), or CHF (OR 0.98 [0.78–1.24], $P = .89$) (Table 2).

CABG surgery. In 4 trials including a total of 8177 patients,[13-16] pexelizumab significantly reduced the relative risk of all-cause death in patients undergoing CABG surgery by 26%: (OR 0.74 [0.58–0.94], $P = .01$) with a number needed to treat of 100 (95% CI 33–167). No differences were found in the risk of MAE (OR 0.91 [0.74–1.11], $P = .25$), MI (OR 0.98 [0.83–1.15], $P = .45$), stroke (OR 0.75 [0.33–1.70], $P = .49$), or CHF (OR 0.87 [0.53–1.44], $P = .6$) (Figure 4, Table 2).

TABLE 1. Main study characteristics

Trial	No.*	Clinical Setting	Bolus dosing (mg/kg)	Infusion dosing ($mg \cdot kg^{-1} \cdot h^{-1}$)	Follow-up (mo)	Primary end point
APEX AMI[11]	5745	Primary PCI	2	0.05	3	All-cause mortality
COMMA[12]	552	Primary PCI	2	0.05	6	Infarct size#
PRIMO-CABG[13]	3099	CABG with or without valve surgery	2	0.05	3	All-cause mortality or AMI
Shernan et al[14]	606	CABG with or without valve surgery	2	0.05	1	Composite of death, AMI, severe LVDys, new CNS deficit
PRIMO-CABG II[15]	4254	CABG with or without valve surgery	2	0.05	3	All-cause mortality or AMI
Carrier et al[16]	218	CABG with AVR	2	0.05	6	Composite of death and AMI
COMPLY[17]	616	Thrombolysis in AMI	2	0.05	6	Infarct size#

*For trial designed with 3 arms (ie, placebo, pexelizumab bolus, and pexelizumab bolus + 24-hour infusion); patients randomized to bolus only were excluded; #measured by creatine kinase MB area under the curve and peak creatine kinase MB through 72 hours. *AMI,* Acute myocardial infarction; *AVR,* aortic valve replacement; *CABG,* coronary artery bypass surgery; *CNS,* central nervous system: *LVDys,* left ventricular dysfunction; *PCI,* percutaneous coronary intervention.

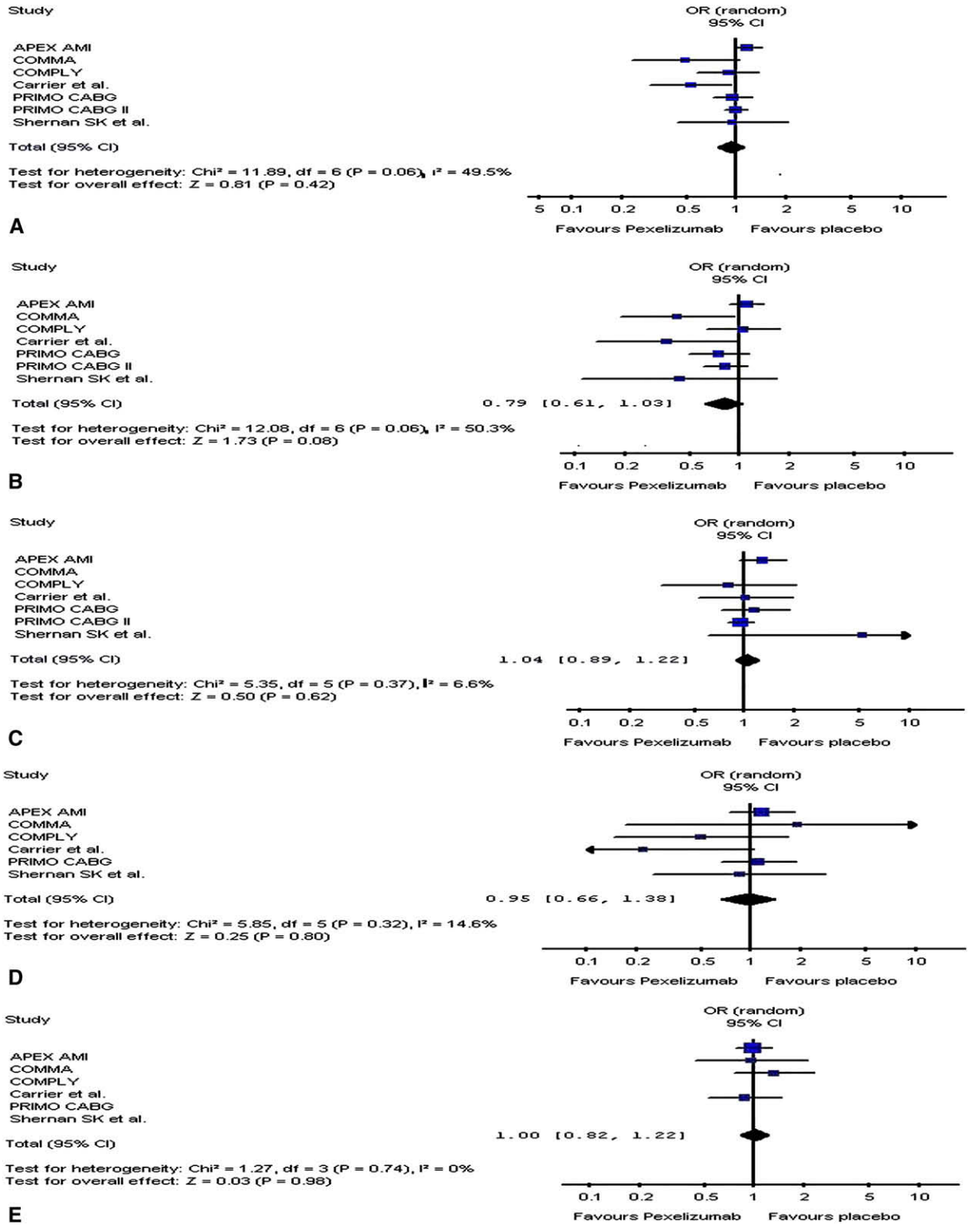

Figure 2. A, Overall analysis of the risk of major adverse events. Single study odds ratios and 95% confidence intervals are shown by *squares* and *lines.* Single study random-effect odds ratios and 95% confidence intervals are shown by *squares* and *horizontal lines.* Overall odds ratio with 95% confidence interval are shown by *diamonds.* B, Overall analysis of the risk of death. C, Overall analysis of the risk of acute myocardial infarctiion. D, Overall analysis of the risk of thromboembolic stroke. E, Overall analysis of the risk of congestive heart failure. *OR,* Odds ratio; *CI,* confidence intervals.

TABLE 2. Absolute incidence of MAE and single end points in the overall analysis and across subgroups

	MAE (%)		Death (%)		AMI (%)		Stroke (%)		CHF (%)	
	Pexelizumab	Placebo	Pexelizumab	Placebo	Pexelizumab	Placebo	Pexelizumab	Placebo	Pexelizumab	Placebo
Overall	10.7	10.7	4.1	4.6	5.6	5.5	1.9	2.1	3.8	3.8
STEMI	9.2	8.6	5.2	5.1	2.7	2.2	1.3	1.2	5.1	5.0
CABG	12.0	12.6	3.1	4.2	8.1	7.1	1.8	2.1	1.4	1.6

AMI, Acute myocardial infarction; *CABG,* coronary artery bypass graft; *CHF,* congestive heart failure; *MAE,* major adverse events; *STEMI,* ST elevation myocardial infarction.

Assessment of Heterogeneity

Significant heterogeneity with moderate/high inconsistency was found in the analyses for MAE and death both overall and in the setting of STEMI patients, but not in the setting of CABG surgery. It is conceivable that such findings reflect the disparate results of the APEX AMI[11] and COMMA[12] trials. On sensitivity analysis, the exclusion of any single trial did not substantively alter the overall results. We also performed a further sensitivity analysis adding one at a time the bolus-only arms, initially excluded as per protocol, to minimize inconsistency and heterogeneity. The results did not significantly differ from the analyses done by excluding the bolus arms.

Assessment of Possible Biases

The funnel plot for all studies according to the risk of MAE and death (Figure 5) showed an overall symmetry, further confirmed by Egger's test as ''*P* for asymmetry'' was 0.985 and 0.844, respectively, thus excluding possible publication or ''small study'' bias. Our predefined protocol was to exclude studies with a follow-up less than 80%; however, none of the retrieved citations was excluded for this reason.

Discussion

Inflammation plays a key role in atherosclerosis and plaque rupture leading to AMI, as well as in microcirculatory dysfunction after ischemia and reperfusion. Complement activation has a pivotal role in this inflammatory response. Experimental models of myocardial ischemia and reperfusion have demonstrated that inhibition of the C5 component of complement results in reduced infarct size and less apoptosis.[2]

In the PRIMO-CABG trial, pexelizumab significantly reduced the amount of myocardial damage.[13] However, these results were not reproduced.[15] The benefit of adding pexelizumab in the setting of STEMI is also controversial. In the COMMA trial, pexelizumab resulted in a statistically significant reduction in mortality but not in a reduction of infarct size assessed by creatine kinase MB.[12] The reduction of inflammatory markers, such as high-sensitivity C-reactive protein and interleukin 6, could explain this puzzling paradox.[18] However, the COMMA trial may represent the play of chance and have provided an ''optimistic'' conclusion.[12] Although probably underpowered given the low morbidity and mortality, the APEX-AMI trial was negative, suggesting no effect of pexelizumab on top of current therapies.[11] The low rate of adverse events in the APEX placebo arm was not foreseen, so it is conceivable that a treatment benefit was missed.[11]

Our systematic review and meta-analysis shows that pexelizumab does not provide any clinical benefits in patients undergoing emergency reperfusion therapy for STEMI, whereas statistically and clinically significant benefits are derived in the setting of CABG as it reduces by almost one third the relative risk of death, with an estimated number needed to treat of 100.

The lack of benefit of pexelizumab in the setting of patients with STEMI contrasts with the apparent benefit observed in patients undergoing CABG. Such data, despite promising premises from experimental studies, emphasize the challenge of translating preliminary data into clinical practice. Animal models demonstrate increased accumulation of MAC (C5b-9) in reperfusion injury but stable levels of C5a during cardiopulmonary bypass.[19,20] The latter suggests a possible pulmonary vascular sequestration of C5a-activated granulocyte resulting in the bypass-related neutropenia.[19,20]

Upstream delivery of pexelizumab before surgery may reduce the ''generalized'' inflammatory process accompanying cardiopulmonary bypass. On the other hand, once microvascular damage and myocardial death owing to necrosis, ''local'' inflammation, and apoptosis[21] have become irreversible in the setting of STEMI, complement activation is likely to have progressed to MAC formation, nullifying any benefit derived from the administration of pexelizumab (Figure 6). Furthermore, penetration of pexelizumab into myocardial tissue may be limited owing to microvascular obstruction. Metabolic and inflammatory derangements have also been observed during both reperfusion therapy for STEMI and cardiopulmonary bypass.[19,20] However, despite some similarities, the different effect of pexelizumab might reflect the presence of different activation pathways and/or magnitudes of activation of the complement cascade.

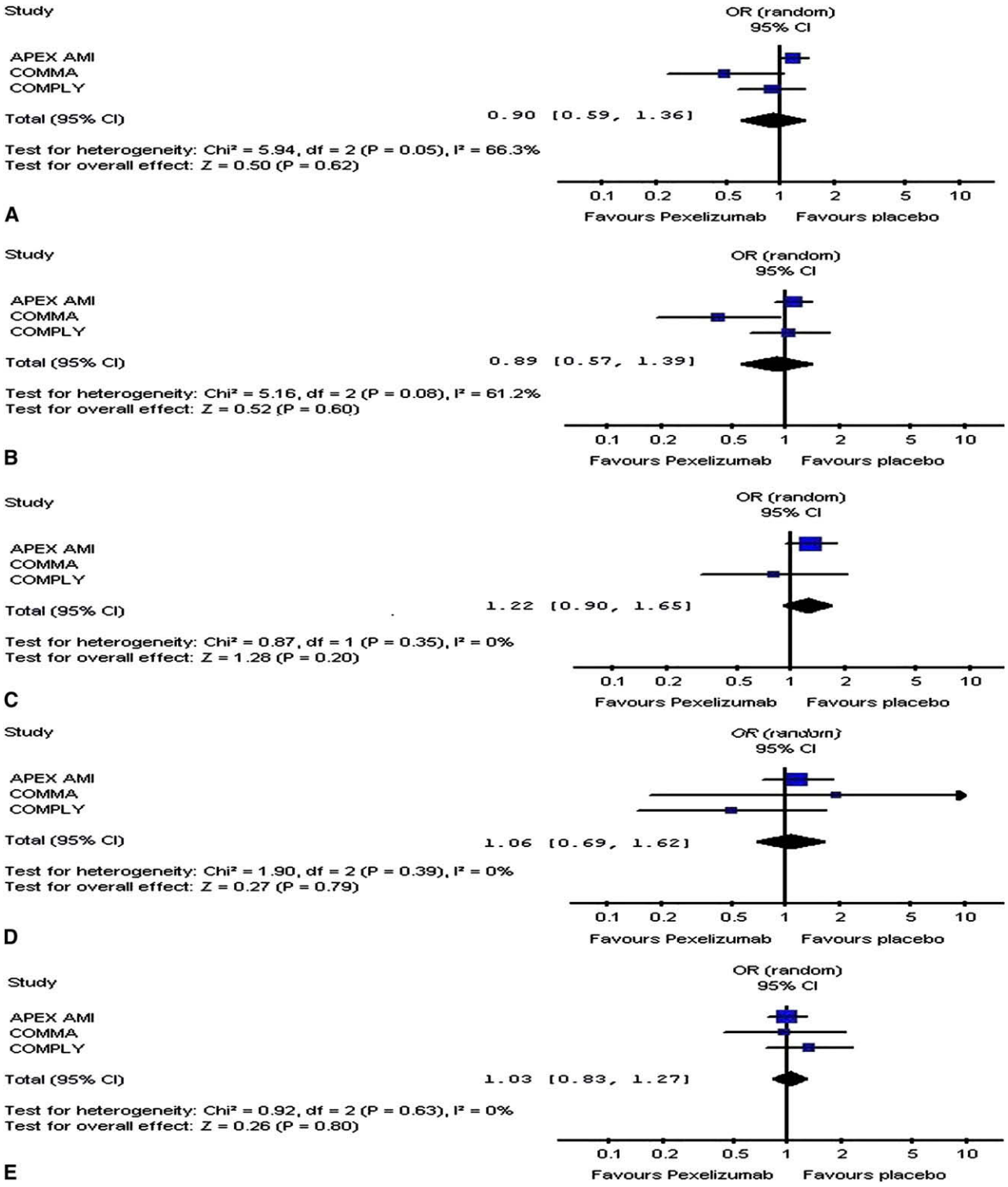

Figure 3. A, Overall analysis of the risk of major adverse events in the setting of STEMI elevation. Single study odds ratio and 95% confidence intervals are shown by *squares* and *lines.* Single study random-effect odds ratios and 95% confidence intervals are shown by *squares* and *horizontal lines.* Overall odds ratio with 95% confidence interval are shown by *diamonds.* B, Overall analysis of the risk of death. C, Overall analysis of the risk of acute myocardial infarction. D, Overall analysis of the risk of thromboembolic stroke. E, Overall analysis of the risk of congestive heart failure. *OR,* Odds ratio; *CI,* confidence intervals.

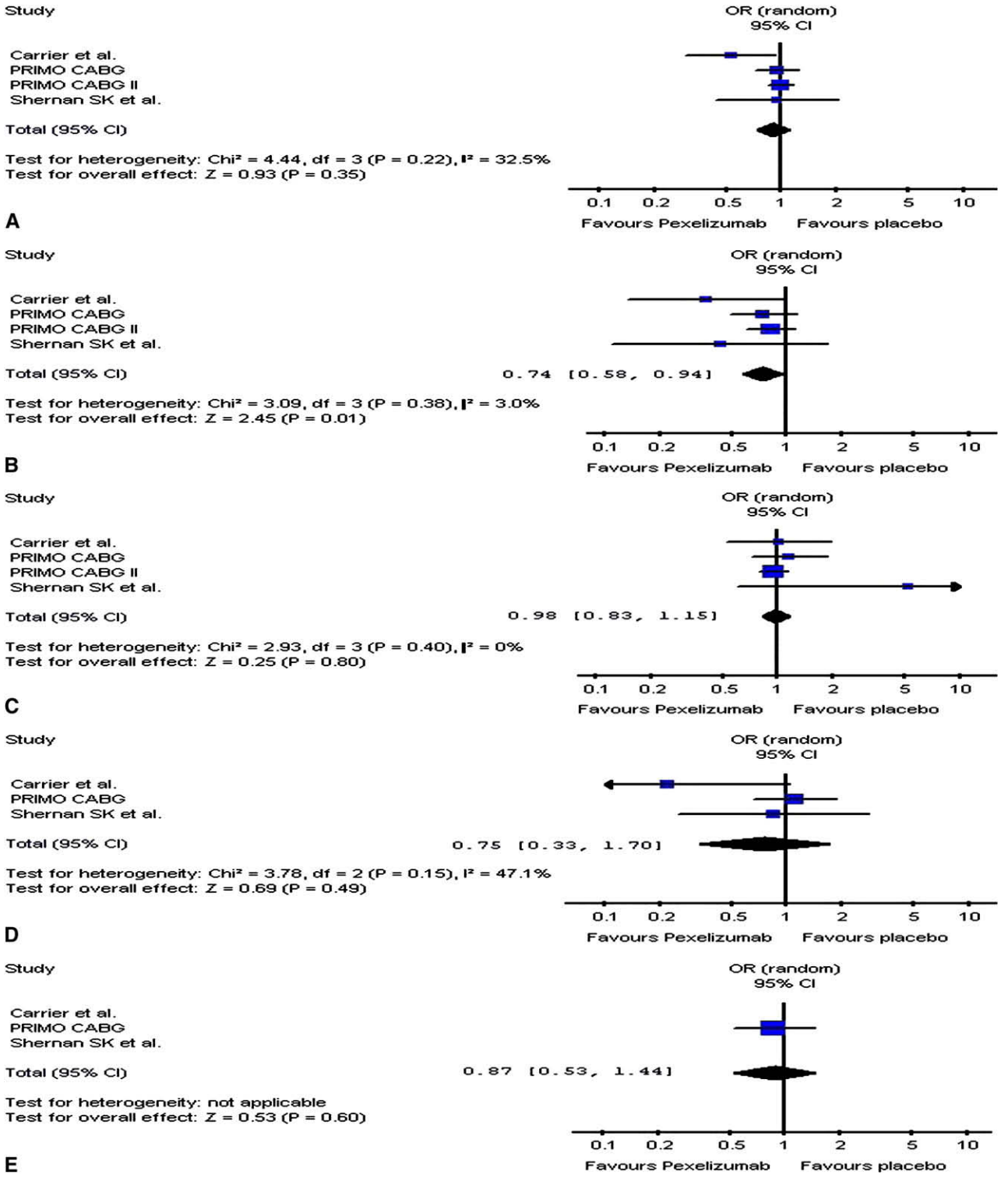

Figure 4. A, Overall analysis of the risk of major adverse events in the setting of CABG surgery. Single study odds ratio and 95% confidence intervals are shown by *squares* and *lines.* Single study random-effect odds ratios and 95% confidence intervals are shown by *squares* and *horizontal lines.* Overall odds ratio with 95% confidence interval are shown by *diamonds.* B, Overall analysis of the risk of death. C, Overall analysis of the risk of acute myocardial infarction. D, Overall analysis of the risk of thromboembolic stroke. E, Overall analysis of the risk of congestive heart failure. *OR,* Odds ratio; *CI,* confidence intervals.

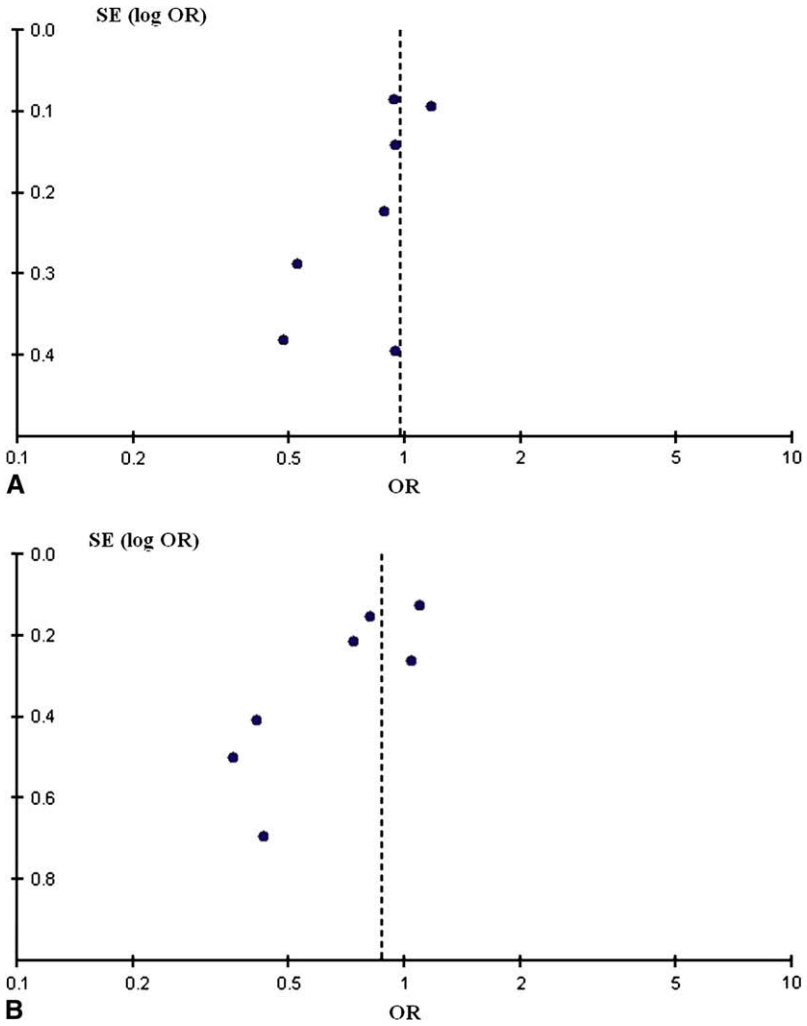

Figure 5. Funnel plot analyses according to major adverse event (A) and death (B). *SE,* Standard error; *OR,* odds ratio.

A previous meta-analysis[22] suggested a beneficial effect on 30-day mortality in both clinical settings. Our independent, unfunded, and updated analysis differs significantly from the previous study in several ways. First, we did not include the bolus-only arms in the primary analysis, inasmuch as our sensitivity analysis demonstrated both increased heterogeneity and inconsistency by including this group. We included all the available data on the topic, assessing not only the risk of overall death but also that of other MAEs, including stroke and congestive heart failure. We performed a pre-specified analysis according to different clinical settings, showing an unexpected discrepancy in the usefulness of pexelizumab in patients with STEMI compared with those undergoing CABG. The reason that our findings differ from those of the previous study might be due to the addition of two large recent trials not included in the previous analysis.[11,15]

A limitation inherent to all meta-analyses is the potential heterogeneity among studies, in terms of protocols (eg, control treatments and length of follow-up), patients, and/or sample sizes. Such diversity may lead to inaccurate conclusions. However, both the Cochrane Q heterogeneity test (which assesses heterogeneity among ORs and the validity of pooling the results) and the test of inconsistency (I^2) indicated significant heterogeneity and inconsistency only for the overall analyses of MAE and death, possibly consistent with the diversity between trials evaluating pexelizumab in the STEMI or CABG setting. Moreover, the overall quality of included trials was good, thus confirming the robustness of the present meta-analysis.

Conclusion

The rationale and potential benefits of adding a C5 complement inhibitor to currently available therapy for STEMI and CABG surgery are attractive. Unfortunately, there appears to be no improvement in outcomes for patients undergoing reperfusion for STEMI. Alternatively, the benefit in patients undergoing on-pump CABG appears real and impressive, with a significant reduction in death.

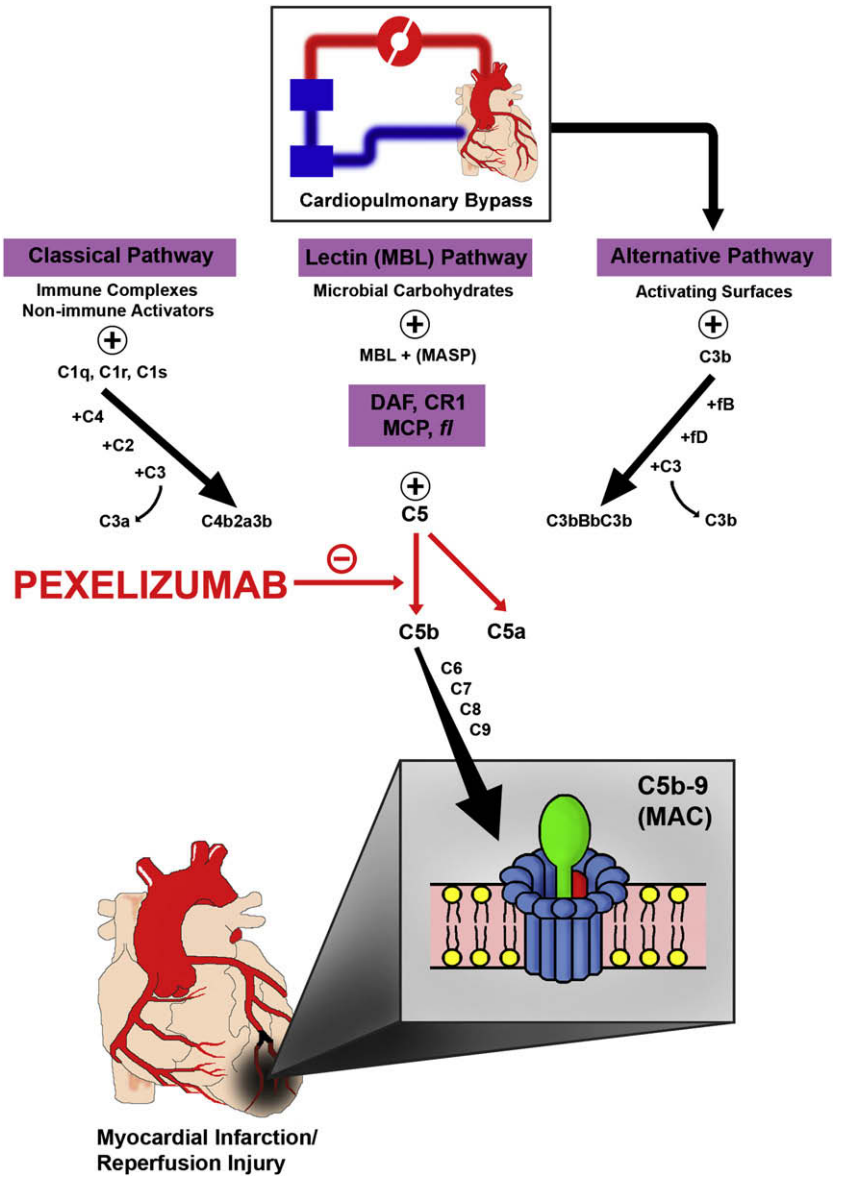

Figure 6. Complement is a highly conserved innate immune cascade of several proteins interacting to recognize and destroy pathogens. According to the nature of the pathogen and/or the activating surface, three different activation pathways are known: classical, alternative, and lectin. The classical pathway is activated by the interaction of C1q with antibody–antigen complexes, but also with nonimmune molecules. The alternative pathway is activated by activating surfaces in the absence of immune complexes and leads to the deposition of C3 fragments on the target cells. The lectin pathway is activated by binding of mannan-binding lectin to carbohydrates expressed on pathogens but not on "self" cells. The common end result of these pathways is either the opsonization or the destruction (through formation of the lytic molecule C5b-9, the membrane attack complex) of the target pathogen. The system is regulated by proteins such as fI, DAF, CR1, MCP. During cardiopulmonary bypass, the complement system is mainly activated by the alternative pathways. This leads to the generalized inflammatory process accompanying the bypass. Upstream delivery of pexelizumab might be efficacious as it inhibits the formation of MAC at an early stage, and also of C5a, a potent anaphylotoxin. In the STEMI setting the late delivery of pexelizumab, once the microvascular damage and myocardial death have become irreversible, might be ineffective as the MAC and C5a formation have been completed. Moreover, the microvascular disfunction can also limit the penetration of pexelizumab into the perinfarct area, where a localized inflammatory/apoptotic process is present. *C,* Complement component; *DAF,* decay accelerating factor; *MAC,* membrane attack complex; *MASP,* MBL-associated serine proteinase; *MBL,* mannan-binding lectin; *MCP,* membrane cofactor protein; *STEMI,* ST elevation myocardial infarction.

Dr Testa[a] (MD, PhD, FEAPCI) designed the study and was involved in data acquisition, statistical analysis, interpretation, and drafting of the manuscript. Drs. van Gaal[a] (MD, PhD), Biondi Zoccai[b] (MD), and Agostoni[c] (MD) were involved in data acquisition and drafting of the manuscript. Drs Abbate[d] (MD), Porto[e] (MD), and Bhindi[a] (MD, PhD, FESC) provided critical revisions of the manuscript. Drs Andreotti[e] (MD, FESC) and Banning[a] (MD, FESC), and Prof Crea[e] (MD, FESC, FACC) provided expert critical revisions of the manuscript. All the authors had full access to data. (Institute of Cardiology, John Radcliffe Hospital, Oxford, United Kingdom[a]; Division of Cardiology, University of Turin, Turin, Italy[b]; Antwerp Cardiovascular Institute Middelheim, AZ Middelheim, Antwerp, Belgium[c]; Department of Medicine, Virginia Commonwealth University, Richmond, Va[d]; and Institute of Cardiology, Catholic University, Rome, Italy.[e]

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Appendix

Algorithm for PubMed Search

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (clinical trial [tw] OR ((singl*[tw] OR doubl*[tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind [tw])) OR (latin square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) NOT (comment [pt] OR editorial [pt] OR meta-analysis [pt] OR practice-guideline [pt] OR review[pt])) AND pexelizumab.