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Age Does Not Affect Metoprolol's Effect on Perioperative Outcomes (From the POISE Database)

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BACKGROUND: Perioperative β-blockade reduces the incidence of myocardial infarction but increases that of death, stroke, and hypotension. The elderly may experience few benefits but more harms associated with β-blockade due to a normal effect of aging, that of a reduced resting heart rate. The tested hypothesis was that the effect of perioperative β-blockade is more significant with increasing age.

METHODS: To determine whether the effect of perioperative β-blockade on the primary composite event, clinically significant hypotension, myocardial infarction, stroke, and death varies with age, we interrogated data from the perioperative ischemia evaluation (POISE) study. The POISE study randomly assigned 8351 patients, aged ≥45 years, in 23 countries, undergoing major noncardiac surgery to either 200 mg metoprolol CR daily or placebo for 30 days. Odds ratios or hazard ratios for time to events, when available, for each of the adverse effects were measured according to decile of age, and interaction term between age and treatment was calculated. No adjustment was made for multiple outcomes.

RESULTS: Age was associated with higher incidences of the major outcomes of clinically significant hypotension, myocardial infarction, and death. Age was associated with a minimal reduction in resting heart rate from 84.2 (standard error, 0.63; ages 45–54 years) to 80.9 (standard error, 0.70; ages >85 years; $P < .0001$). We found no evidence of any interaction between age and study group regarding any of the major outcomes, although the limited sample size does not exclude any but large interactions.

CONCLUSIONS: The effect of perioperative β-blockade on the major outcomes studied did not vary with age. Resting heart rate decreases slightly with age. Our data do not support a recommendation for the use of perioperative β-blockade in any age subgroup to achieve benefits but avoid harms. Therefore, current recommendations against the use of β-blockers in high-risk patients undergoing noncardiac surgery apply across all age groups. (Anesth Analg 2018;126:1150–7)

KEY POINTS

- **Question:** Does the impact of perioperative metoprolol on perioperative outcomes of mortality, myocardial infarction, and stroke vary according to age?
- **Findings:** In reviewing the results of the POISE trial (8351 patients, metoprolol continuous release 200 mg daily for 30 days versus placebo), we found no differences in effect between older and younger individuals for any outcome.
- **Meaning:** The effect of perioperative metoprolol on reducing myocardial infarction, and likely increasing stroke and death, is probably similar in older and younger individuals.

As the population ages, surgery is required more frequently to treat common elective (eg, joint replacement due to osteoarthritis) and emergent (eg, repair of colonic perforation due to diverticular disease) conditions associated with age.[1–20] The risk of perioperative adverse events is higher among patients with known coronary artery

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disease (CAD) or with CAD risk factors, of which age is the most significant.[1,11–20] Approximately 200 million noncardiac surgeries occur worldwide each year, with millions associated with complications, particularly among the elderly.[1,21] Consequently, the appropriate perioperative management of elderly patients is an important public health issue.[1,21]

A dominant theory regarding how perioperative β-blockade reduces myocardial infarction (MI) is through both reduction of resting heart rate and blunting of increases when stressed, with consequent decreases in myocardial oxygen demand.[3–10] However, the effect of aging on resting heart rate has not been clearly described other than the observation that the older heart has a lower maximal heart rate than the younger heart,[22–24] potentially limiting the capacity of β-blockade to achieve heart rate reductions or reduce accelerations during surgery and recovery. If this is so, the reduction in perioperative MI with β-blockade may be diminished in the elderly.

Although the elderly may manifest smaller reductions in the incidence of MI with β-blockade, they may also be more vulnerable to the adverse effects. The altered structure and function of the aging heart result in performance decline in the stressed state (ie, surgery and the perioperative period) and in diminished autoregulation. These may make the aging heart more prone to hypotension, which has been associated with negative perioperative outcomes.[25,26] For example, postural hypotension is positively associated with age and independently associated with adverse events (eg, death).[25,26] In POISE, hypotension was defined as a systolic pressure <90 mm Hg and requiring intervention with fluid resuscitation, vasopressor, intraaortic balloon pump, or study drug discontinuation. Clinically significant hypotension was strongly associated with death (odds ratio [OR], 4.97; 95% confidence interval [CI], 3.62–6.81) and stroke (OR, 2.14; 95% CI, 1.15–3.96).[21] If the elderly are more prone to hypotension—as is plausible—then they may demonstrate a greater susceptibility to the adverse effects of perioperative β-blockade.

Thus, a rationale exists to suspect that the effect of perioperative β-blockade among the elderly may differ from that in younger patients, and the elderly may achieve fewer of the benefits but suffer more of the harms.

In this investigation, we addressed the following hypotheses: (1) older age is independently associated with clinically significant hypotension (requiring physiologic, pharmacologic, or mechanical treatment, eg, intraaortic balloon pump), all-cause mortality, MI, stroke, and a reduced resting heart rate; (2) there is an interaction such that the reduction in the risk of MI with a perioperative β-blocker is reduced in the elderly relative to younger individuals; and (3) the increase in the risk of hypotension, stroke, and all-cause mortality with a β-blocker is greater in the elderly than in younger patients.

METHODS

The details of the design, conduct, and analysis of the POISE trial have been reported.[21] The POISE trial randomized 8351 patients to receive either placebo or metoprolol succinate sustained-release 200 mg orally daily for 30 days.[21] The POISE trial recorded all pertinent hemodynamic data in the perioperative period and until hospital discharge or 30 days, as well as medications administered during this period. In the design of POISE, the population estimates based on observational and investigational data suggested a plausible event rate of 6% for the composite primary outcome of 30-day cardiovascular death, nonfatal MI, and cardiac arrest. Assuming a clinically relevant risk reduction of 25% between the study and control groups, POISE had 85% power when designed to detect this difference in primary outcome with a population of 8000. A population of 10,000 was selected in the initial design to ensure higher power. The power to detect a change in the log OR (effect size) of 0.14 of a possible interaction between age and treatment for the primary outcome, with a significance level of 0.05 using a 2-sided test, was calculated from this population to be 41%, using 2-sample, ordered categorical test.

Of note, the discussion of study power is most appropriate to consider in the study design phase. The most appropriate presentation of data for interpretation after a post hoc analysis such as this study includes means (from least squares) and confidence limits (±95% generally). This issue has been recently discussed in the literature.[27–30]

In this subanalysis, we addressed our hypotheses by interrogating the POISE database, which stored the nonidentifying anonymized case records in aggregate and had been locked at study completion. This subanalysis was designed after the main study began and was not part of the original protocol. The POISE trial was registered at ClinicalTrials.gov (NCT001182029), but the current analysis was not registered. Institutional research ethics board approval was obtained in each hospital in which the POISE study was conducted at the time of original application. Patients provided written informed consent before entering.

Outcomes within POISE were defined a priori and adjudicated by an independent committee of peers. The primary outcome in the POISE trial was a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest. An MI was defined as an elevation of biomarker (troponin T or I) beyond the 99th percentile of the normal range. Stroke was defined as a clinically significant and nonresolving change in neurologic function. Clinically significant hypotension was defined as hypotension that required intervention (systolic blood pressure <90 mm Hg requiring fluid or vasopressor administration, intraaortic balloon counterpulsation, or study drug discontinuation) regardless of location (eg, operating room, recovery room, or postoperative floor).

Analysis

We conducted a series of multivariable regression analyses with age as an independent categorical variable, grouped by decile, and with primary composite outcome of POISE-I, death, MI, stroke, clinically significant hypotension, length of hospital stay, and prerandomization heart rate (resting heart rate) as the dependent variables. We expressed the impact of age associated with each decade of older age compared to age ≤54 years as an odds ratio for the binary outcomes using the logistic regression model (treating age as a categorical variable). The time to discharge from hospital expressed as a hazard ratio using Cox proportional hazards model and the heart rate as least squares means are presented using the general linear model. Independent

Table 1. Outcome: Resting Heart Rate, Using General Linear Model[a]

Variable Age Group (y)	Metoprolol LS Means (95% CI)	Placebo LS Means (95% CI)	Adjusted Difference by Tukey LS Means (95% CI)	*P* Value
45–54	80.0 (78.8–81.2)	81.0 (79.9–82.2)	−1.0 (−3.7 to 1.6)	.22
55–64	78.6 (77.8–79.4)	78.5 (77.7–79.3)	0.1 (−1.7 to 2.0)	.84
65–74	77.3 (76.6–77.9)	77.3 (76.7–77.9)	−0.4 (−1.5 to 1.4)	.94
75–84	76.0 (75.3–76.7)	76.6 (75.9–77.3)	−0.6 (−2.2 to 1.04)	.25
≥85	77.0 (75.4–78.6)	77.6 (75.9–79.2)	−0.6 (−4.3 to 3.2)	.64

P value for the interaction term for age group and treatment group = .74. Sample size = 8351.

Abbreviations: CI, confidence interval; LS, least squares.

[a]Model adjusted by age categories, history of stroke, history of coronary artery disease, emergent surgery, chronic renal failure, history of congestive heart failure, treatment group, and interaction between age and treatment group.

variables included allocation to metoprolol or placebo and other variables chosen on the basis of their postulated biological relation to the dependent variable and performance in previous POISE analyses and included history of stroke, history of CAD, emergent/urgent surgery, preoperative creatinine >2 mg/dL (>177 mmol/L), and documented history of congestive heart failure. All variables were entered simultaneously in each regression. In each analysis, we have presented the effect estimates of the age groups for the treatment versus placebo; if the interaction term was not significant, then it was excluded from the final model, and the main effects of each independent variable and the corresponding 95% CIs were presented. The statistical analysis plan, including the variables selected for inclusion, was approved by the POISE steering committee.

Examination of residuals provided an assessment of model assumptions for each of the regression analyses. Goodness-of-fit (GoF) for the logistic models were performed using the Hosmer–Lemeshow (H–L) test.[31,32] Schoenfeld residuals were calculated for the Cox proportional hazards model to assess model fit. For the generalized linear model, plots of residuals against the predicted values were examined to check for the homogeneity of the variance of the residuals.

We performed all analyses using SAS version 9.2 for UNIX, and power calculations were done using PASS, v13.0.8 (NCSS, LLC, 1983). A 2-sided significance level of 0.05 was used for all analyses. No adjustments for multiplicity were made for multiple efficacy end points. All analyses were based on the intention-to-treat principle.

RESULTS

The POISE trial included 8351 patients from 190 centers in 23 countries of which 4174 patients were randomized to metoprolol CR and 4177 to placebo. The 30-day follow-up was complete for 99.8% of the trial participants (8 metoprolol patients and 12 placebo patients did not complete the 30-day follow-up). Vascular, orthopedic, and intraperitoneal surgery accounted for 84.2% of all surgeries. A majority of patients received a general anesthetic either as their only anesthetic agent or as a component of a combined anesthetic/analgesic (eg, general anesthetic and thoracic epidural).

We summarize below the impact of age on the variables of interest. The examination of the residuals fitted against the predicted values from model without the interaction term showed a good fit. Descriptive data are presented in the online supplemental tables.

Table 2. Outcome: CV Death/Nonfatal MI/Nonfatal Cardiac Arrest (Primary Outcome From POISE), Using Logistic Regression Model[a]

Patient Descriptor	Odds Ratio (95% Confidence Interval)	Interaction Wald χ^2 *P* Value
Metoprolol versus placebo		.24
Age 45–54 y	0.32 (0.13–0.76)	
Age 55–64 y	0.78 (0.49–1.26)	
Age 65–74 y	0.94 (0.68–1.28)	
Age 75–84 y	0.84 (0.63–1.12)	
Age ≥85 y	0.95 (0.55–1.63)	

Sample size = 8351.

Abbreviations: CV, cardiovascular; MI, myocardial infarction; POISE, perioperative ischemia evaluation.

[a]Model adjusted by treatment allocation, age groups, history of stroke, history of coronary artery disease, emergency surgery, chronic renal failure, history of congestive heart failure, and interaction between age and treatment.

Heart Rate

The mean resting heart rate of the study population at randomization was 79.6 beats per minute and did not differ significantly between the metoprolol and placebo groups at randomization (Table 1; Supplemental Digital Content 1, Table 1S, http://links.lww.com/AA/C227). Heart rate decreased significantly over the deciles of age ≤84 years to a mean of 79.9 (95% CI, 79.0–80.9) beats per minute and then to 80.9 (95% CI, 79.6–82.3) beats per minute in those >age 85 years. The mean resting heart rate was also significantly higher among patients with renal failure (82.9 [95% CI, 81.5–84.3]) and those undergoing emergency surgery (84.4 [95% CI, 83.3–85.5]).

Primary Outcome

The primary outcome (composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest) occurred significantly less commonly in the metoprolol group than in the placebo group (OR [95% CI], 0.83 [0.70–0.99]; *P* = .04) (Table 2; Supplemental Digital Content 2, Table 2S, http://links.lww.com/AA/C228). There was no evidence of any interaction effect between age and study group (*P* = .24). Although point estimates suggested a decrease in the composite end point with metoprolol across all age groups, CIs in individual categories included increases of ≤63% (Table 2).

Clinically Significant Hypotension

Hypotension increased with age in all older patient age groups (age ≥55, OR >1.29) compared to the youngest age group (age ≤54 years) (Table 3; Supplemental Digital Content

Table 3. Outcome: Clinically Significant Hypotension, Using Logistic Regression Model[a]

Patient Descriptor	Odds Ratio (95% Confidence Interval)	Interaction Wald χ^2 *P* Value
Metoprolol versus placebo		.74
Age 45–54 y	2.11 (1.28–3.48)	
Age 55–64 y	1.81 (1.33–2.46)	
Age 65–74 y	1.57 (1.26–1.96)	
Age 75–84 y	1.54 (1.21–1.96)	
Age ≥85 y	1.91 (1.09–3.32)	

Sample size = 8351.

[a]Model adjusted by treatment allocation, age groups, history of stroke, history of coronary artery disease, emergency surgery, chronic renal failure, history of congestive heart failure, and interaction between age and treatment.

Table 4. Outcome: Death, Using Logistic Regression Model[a]

Patient Descriptor	Odds Ratio (95% Confidence Interval)	Interaction Wald χ^2 *P* Value
Metoprolol versus placebo		.22
Age 45–54 y	0.66 (0.18–2.35)	
Age 55–64 y	2.92 (1.15–7.42)	
Age 65–74 y	1.0 (0.61–1.62)	
Age 75–84 y	1.55 (1.01–2.40)	
Age ≥85 y	1.36 (0.66–2.82)	

Sample size = 8351.

[a]Model adjusted by treatment allocation, age groups, history of stroke, history of coronary artery disease, emergency surgery, chronic renal failure, history of congestive heart failure, and interaction between age and treatment.

3, Table 3S, http://links.lww.com/AA/C229). The odds of developing hypotension were 66% more in the metoprolol group compared to the placebo group (OR, 1.66; 95% CI, 1.45–1.90). The *P* value from H–L GoF for the model without the interaction term was 0.150. The effect of metoprolol was apparent in each age subgroup—no CI crossed 1.0 (Table 3).

Death

The point estimate of the OR of death was <2 in all groups up to age 74 years, but it was much higher in those ages 75–84 years (OR, 2.85; 95% CI, 1.47–5.54) and markedly increased in those ≥85 years (OR, 4.27; 95% CI, 2.05–8.89) (Table 4; Supplemental Digital Content 4 and 5, Tables 4S, 5S, http://links.lww.com/AA/C230, http://links.lww.com/AA/C231). The odds of death were significantly more common among patients in the metoprolol group (OR, 1.36; 95% CI, 1.03–1.78; *P* = .03). Although point estimates suggested a decrease in death with metoprolol across all age groups, CIs in individual categories included increases of ≤63% (Table 4). The *P* value from the H–L GoF test was .51.

Myocardial Infarction

The odds of MI increased progressively with age in each decade >64 years against those with age <55 years (OR, 1.73; 95% CI, 1.09–2.75) but was significantly less among patients in the metoprolol group (OR, 0.72; 95% CI, 0.59–0.88; *P* = .002) (Table 5; Supplemental Digital Content 6, Table 6S, http://links.lww.com/AA/C232). Although point estimates suggested a decrease in MI with metoprolol across all age groups, CIs in individual categories included increases of ≤63% (Table 5). The *P* value from the H–L GoF test was .94.

Table 5. Outcome: Myocardial Infarction, Using Logistic Regression Model[a]

Patient Descriptor	Odds Ratio (95% Confidence Interval)	Interaction Wald χ^2 *P* Value
Metoprolol versus placebo		.20
Age 45–54 y	0.28 (0.10–0.77)	
Age 55–64 y	0.59 (0.34–1.02)	
Age 65–74 y	0.92 (0.65–1.31)	
Age 75–84 y	0.69 (0.50–0.95)	
Age ≥85 y	0.85 (0.45–1.63)	

Sample size = 8351.

[a]Model adjusted by treatment allocation, age groups, history of stroke, history of coronary artery disease, emergency surgery, chronic renal failure, history of congestive heart failure, and interaction between age and treatment.

Table 6. Outcome: Stroke, Using Logistic Regression Model[a]

Variable	Odds Ratio (95% Confidence Interval)	Interaction Wald χ^2 *P* Value
Metoprolol versus placebo		.349
Age 45–54 y	0.98 (0.25–3.96)	
Age 55–64 y	3.36 (0.70–16.23)	
Age 65–74 y	4.08 (1.36–12.25)	
Age ≥75 y[b]	1.60 (0.69–3.71)	

Sample size = 8351.

[a]Model adjusted by treatment allocation, age groups, history of stroke, history of coronary artery disease, chronic renal failure, emergency surgery, history of congestive heart failure, and interaction between age and treatment.

[b]Age group ≥85 had only 4 outcomes and hence the last age group is grouped as age ≥75 y.

Stroke

Because there were only 60 outcomes, age stratification into 5 groups yielded unstable results (Table 6; Supplemental Digital Content 7, Table 7S, http://links.lww.com/AA/C233). Hence, we stratified age into 4 groups, with the highest age group as ≥75years and all other age groups remaining the same. The odds of stroke did not vary significantly with age. However, the OR of stroke was significantly more common among patients in the metoprolol group (OR, 2.19; 95% CI, 1.27–3.78; *P* = .005) and among those with a history of stroke (OR, 2.77; 95% CI, 1.59–4.81). Point estimates for individual age groups included both reductions and increases in stroke with metoprolol, with wide confidence intervals (Table 6). The *P* value from the H–L GoF test was .06.

Discharge From Hospital

There was no consistent pattern in the hazard ratio with the increasing age groups (Supplemental Digital Content 8 and 9, Tables 8S, 9S, http://links.lww.com/AA/C234, http://links.lww.com/AA/C235). The rate of hospital discharge in the metoprolol group did not vary significantly from the placebo group (hazard ratio, 1.01; 95% CI, 0.97–1.05). Schoenfeld residuals from the Cox proportional hazards model showed that the proportionality assumption of the Cox model was not violated.

Interaction Between Treatment Group and Age

We found no evidence of any interaction between age and treatment group, as the *P* value for each of these comparisons was nonsignificant, and the confidence limits for

each of the odds ratios on the variables of interest spanned 1.0 (Supplemental Digital Content 10, Table 10S, http://links.lww.com/AA/C236). However, the absence of any significant interaction terms fails to support the hypothesis that any age group would be more or less prone to either the beneficial or deleterious effects of the study drug (metoprolol) than any other age group.

Patient Randomization by Age Decile

Most patients were between 55 and 85 years of age, and group randomization was evenly balanced by age decile (Supplemental Digital Content 11, Table 11S, http://links.lww.com/AA/C237).

In summary and in relation to our hypotheses, we found that older age was associated with death, MI, clinically significant hypotension, and lower heart rate but was not associated with stroke. We found no evidence of any interaction between treatment assignment and age for any outcomes studied, indicating that the effect of β-blockers on each outcome was not found to differ between older and younger patients (Supplemental Digital Content 10, Table 10S, http://links.lww.com/AA/C236).

DISCUSSION

Principal Findings

In this substudy using data from the POISE trial, we examined the effect of age on perioperative heart rate and the major outcomes (hypotension, death, MI, stroke), and we searched for the possibility of an interaction between β-blockade and age. We observed that the mean resting heart rate decreased slightly (from 79.6 to 76.4 beats per minute) as age increased (from the 45 to 54 years of age decile to the 85 years of age and older group). Age was associated with higher rates of clinically significant hypotension, death, and MI, although increases in MI were restricted to the 2 oldest age deciles (ie, patients >74 years of age). We observed, however, no association between age and frequency of stroke. The impact of a perioperative β-blocker on major outcomes (clinically significant hypotension, stroke, MI, and death) was similar in older and younger patients, reflected in tests of interaction that in no case approached statistical significance (Supplemental Digital Content 8, Table 8S, http://links.lww.com/AA/C234). We also noted associations between other patient characteristics and the outcomes of interest. In particular, a history of CAD was associated with both a lower frequency of clinically significant hypotension and a higher frequency of MI. Emergency surgery was associated with more frequent mortality. The presence of renal failure correlated with clinically significant hypotension, death, and MI. A history of stroke correlated with more strokes.

We chose to present age as deciles to facilitate clinical interpretation. Using age as a dichotomous variable may have increased the statistical power to detect interaction effect but would have created another arbitrary issue in terms of defining the age cut-point for statistical analysis, which would have also created challenges with clinical interpretation. Nonetheless, we remain confident in the results measured that illustrate absolutely no suggestion of interaction between age and study group as applied to any of the study outcomes. We do not anticipate that another group will conduct a larger trial to address the possibility of interaction.

Early observational research had shown promise with the effect of perioperative β-blockade because β-blockers affect several postulated mechanisms of injury. Although subsequent randomized trials,[33–36] dominated by results from POISE, the largest trial,[21] have demonstrated that β-blockade reduces the frequency of MI (from 6.9% to 5.8%), these also showed that β-blockade increases all-cause mortality (from 2.3% to 3.1%) and stroke (from 0.5% to 1.0%). Anatomically, age affects the heart in several structural and functional ways.[3–10,37–40] Microscopically, myocardial cells decrease in number but increase in size.[6–10,41–44] Functionally, adrenoceptors decrease in number and responsiveness with age.[4,7,8,45,46] This investigation has served to show that the competing physiologic hypotheses resulted in no significant difference of perioperative β-blockade between the aged and less aged heart.

Before the publication of the POISE trial, various medical societies had recommended consideration of β-blockade perioperatively in patients at risk of adverse cardiovascular outcomes. In practice, "recommended consideration" had transformed into "recommended," not simply for "patients at risk" but for "patients" in general. Both of these phenomena represented inappropriately broad generalizations of limited evidence from small trials. POISE was startling in that its results demonstrated actual harmful effects (death and stroke) with broad application of perioperative β-blockade that outweighed the benefits of reduction in MI. These unexpected findings led to close examination of POISE to find possible caveats, 1 of which was the possibility that β-blockade might have had differential effects according to age. This was suggested partly on the basis of a widely held but never proven hypothesis that the resting heart rate decreased significantly with age, which would have made the elderly prone to the adverse effects of β-blockade and unable to receive the benefits. While this study did find a statistically significant reduction in resting heart rate associated with age, the reduction from a mean of 80 at 45–54 years of age to a mean of 76 when >85 years of age was not clinically significant and was not sufficient to produce any interaction effect with age. Consequently, we can be definitive in concluding that no interaction between age and the effect of perioperative β-blockade exists, and that perioperative β-blockade cannot be systematically recommended for any patients. However, room remains for clinician discretion in implementing this recommendation.

Strengths of this evaluation include the large sample size, minimal loss to follow-up, simplicity of design, geographic breadth, and the detailed analysis. With >8000 patients, the POISE trial was the largest trial of a perioperative therapy. Patients were recruited from centers on 5 continents and underwent a broad range of surgeries. To reiterate, we were able to conclusively refute the hypothesis that age had any impact on either the deleterious or beneficial effects of β-blockade seen in the POISE trial.

Limitations of this trial and substudy included a worldwide trial requiring a relatively simple design with a single daily dose of drug without initial titration. The results may not apply to other doses, drugs, or durations of administration.[47]

The POISE trial was conducted between 2003 and 2007 and drew attention to the impact of clinically significant hypotension on outcome, possibly resulting in a relatively higher frequency of detection of the same in the more recent POISE II trial. However, we have no reason to suspect that this later finding should have selectively modified the incidence of clinically significant hypotension in our analysis. Any post hoc subgroup analysis carries the risk of capitalizing on the play of chance; our failure to find any subgroup effect related to age makes this issue moot for the current investigation.

Although we did not detect any modification of effect of metoprolol as a result of age within the limits of this study, this does not absolutely mean that no age modification exists. The trial was not powered to detect small but important subgroup effects. In general, 4 times as many patients are required to achieve the same power to detect an interaction of the same magnitude as a main effects study. Indeed, the CIs around the point estimates for the key outcomes of death, MI, and stroke for individual age strata were wide. One could therefore argue for a threshold *P* value as high as .2 for the credibility of a subgroup effect. However, even setting such a high threshold would, in this case, not raise the suspicion of a subgroup effect: *P* values for all tests of interaction were ≥.2 (Supplemental Digital Content 10, Table 10S, http://links.lww.com/AA/C236).

It should also be acknowledged that the observed statistically significant decline in heart rate associated with age is unlikely to represent major, if any, clinical significance. Moreover, because the POISE trial was not designed to measure the fitness levels of study participants, it is plausible that fit older patients may have had lower resting heart rates than less fit younger patients. Nonetheless, the study findings remain robust in that no discernible difference in study drug effect could be detected between younger and older participants.

Interpretation

Although the finding of lower resting heart rate with increasing age was expected based on physiologic rationale, extensive literature investigation before beginning this review did not uncover prior proof of this association. Exercise physiology studies have shown that maximal heart rate per minute decreases approximately 1 beat per minute for each year of age after 40 years of age, and that this decrease can be blunted by ≥50% by regular physical exercise.[22–24] This review also indicates that resting heart rate decreases on average by approximately one tenth of 1 beat per minute for each year of life after 40–45 years of age. This minor change in resting heart rate with age lends support to our findings indicating the absence of any interaction between age and treatment group.

We found anticipated associations between age and the major adverse outcomes of MI and death, with no increase until 55 years of age relative to those 45–54 years of age, borderline significance in those 55–64 years of age, and strong association in those >65 years of age. The failure to detect an association between age and the occurrence of stroke was surprising but may well be explained by the small number of strokes that occurred (60 events). Consequently, the CIs around the ORs associated with each age decile and stroke were wide.

In none of our analyses was an interaction detected between age and metoprolol use with regard to any of the adverse outcomes of death, MI, hypotension, or discharge from hospital. We found no evidence that the decreased resting heart rate in the elderly prevented any beneficial effect on MI, and it did not increase any adverse impact on stroke or death. Thus, we can provide no support for any postulated age subgroup that would see the benefits, but not the harms, associated with perioperative β-blocker usage. We have, however, not absolutely excluded age as an effect modifier: the trial was not powered to do so, and CIs around individual age strata are wide. Nevertheless, in the absence of any evidence in support of age modifying the effects of metoprolol in patients undergoing noncardiac surgery, current recommendations against the use of β-blockers in higher risk patients undergoing noncardiac surgery apply across all age groups.[48-53]

DISCLOSURES

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