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Effect of smoking on comparative efficacy of antiplatelet agents: systematic review, meta-analysis, and indirect comparison

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● EDITORIAL by Hirschl

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STUDY QUESTION

Does smoking status affect the efficacy of antiplatelet drugs?

SUMMARY ANSWER

The clinical benefit of clopidogrel in reducing cardiovascular death, myocardial infarction, and stroke occurs primarily in smokers; little benefit was seen in nonsmokers.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Randomized trials report a 15% reduction in death, myocardial infarction, and stroke in patients with acute coronary syndromes. This study found that clopidogrel produces larger clinical benefits in smokers than in nonsmokers.

Selection criteria for studies

We searched Medline (1966 to present) and Embase (1974 to present), with supplementary searches in major cardiology conference abstract databases, the Cumulative Index to Nursing and Allied Health (CINAHL) and the CAB Abstracts databases, and Google Scholar to identify randomized trials of clopidogrel, prasugrel, or ticagrelor that examined clinical outcomes among subgroups of smokers and nonsmokers.

Primary outcome

The primary outcome was a composite clinical outcome comprising cardiovascular death, myocardial infarction, and stroke.

Main results and role of chance

Among smokers, patients randomized to clopidogrel experienced a 25% reduction in the primary composite clinical outcome of cardiovascular death, myocardial infarction, and stroke compared with patients in the control arms (relative risk 0.75, 95% confidence interval 0.67 to 0.83). In nonsmokers, however, clopidogrel produced just an 8% reduction in the composite outcome (0.92, 0.87 to 0.98). Two studies looked at prasugrel plus aspirin compared with clopidogrel plus aspirin, and one study looked at ticagrelor plus aspirin compared with clopidogrel plus aspirin. In smokers, the relative risk was 0.71 (0.61 to 0.82) for prasugrel compared with clopidogrel and 0.83 (0.68 to 1.00) for ticagrelor compared with clopidogrel. Corresponding relative risks were 0.92 (0.83 to 1.01) and 0.89 (0.79 to 1.00) among nonsmokers.

Bias, confounding, and other reasons for caution

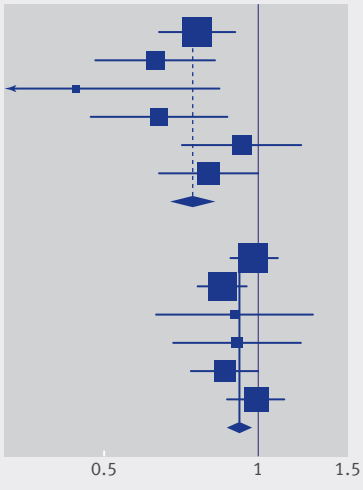
Little information was available from existing trials to assess whether smoking status affects the risks of bleeding with antiplatelet drugs. Also, the indirect comparison methods require that the included trials be similar with respect to potential modifiers of treatment effect within smoking subgroups.

Study funding/potential competing interests

This study was supported by internal funds within the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School.

Efficacy of clopidogrel stratified by baseline smoking status

Study	Cumulative incidence: Clopidogrel	Cumulative incidence: Control	Relative risk (95% CI)
Smokers			
CAPRIE	8.3	10.8	0.76 (0.64 to 0.90)
CURE	6.1	9.4	0.63 (0.48 to 0.83)
CREDO	6.3	13.8	0.44 (0.23 to 0.83)
CLARITY-TIMI 28	9.2	13.9	0.64 (0.47 to 0.89)
CHARISMA	NA	NA	0.93 (0.71 to 1.22)
CURRENT-OASIS 7	2.9	3.6	0.80 (0.64 to 1.02)
Combined			0.75 (0.67 to 0.83)
Nonsmokers			
CAPRIE	10.4	10.6	0.98 (0.88 to 1.09)
CURE	10.2†	10.9†	0.85 (0.76 to 0.96)
CREDO	9.8	10.7	0.90 (0.63 to 1.29)
CLARITY-TIMI 28	13.8	14.1	0.91 (0.68 to 1.20)
CHARISMA	NA	NA	0.86 (0.74 to 1.00)
CURRENT-OASIS 7	4.8	4.8	0.99 (0.87 to 1.15)
Combined			0.92 (0.87 to 0.98)



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Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium

On behalf of the Asia Cohort Consortium[1]

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STUDY QUESTION

Is body mass index associated with death from overall cardiovascular disease (CVD) and specific subtypes of CVD in east and south Asians?

SUMMARY ANSWER

Body mass index shows a U shaped association with death from overall CVD among east Asians, but is a weak risk factor for cardiovascular death in south Asians.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Higher body mass index has been shown to be associated with increased risk of death in east Asians but not among south Asians. In east Asians, higher body mass index is a risk factor for death from overall CVD, coronary heart disease (CHD), ischaemic stroke, and haemorrhagic stroke in east Asians, and very low body mass index is associated with increased CVD mortality; in south Asians, higher body mass index is a weak risk factor for CVD mortality.

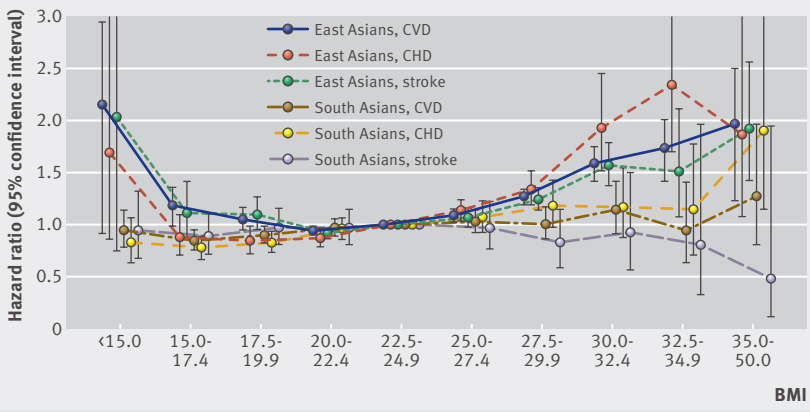
Selection criteria for studies

The Asia Cohort Consortium (ACC) includes more than 20 cohorts representing Japan, China, Korea, India, Taiwan, Bangladesh, and Singapore. Cohorts were identified through a systematic search of the literature in early 2008, followed by a survey that was sent to each cohort to assess data availability.

Primary outcome(s)

Risk of death from overall CVD, CHD, stroke, and (in east Asians only) stroke subtypes (ischaemic stroke and haemorrhagic stroke).

Adjusted hazard ratios (95% CI) for the association between body mass index and CVD mortality in east Asians and south Asians



Main results and role of chance

Of 1 124 897 men and women (mean age 53.4 years at baseline) in the analysis, we identified 49 184 deaths from CVD (40 791 in east Asians and 8393 in south Asians) during a mean follow-up of 9.7 years. East Asians with a body mass index of 25 or above had a raised risk of death from overall CVD, compared with the reference range of body mass index (22.5-24.9). The association was similar for death from CHD and ischaemic stroke. Risk of death from haemorrhagic stroke increased at body mass index 27.5 and above. Elevated risk of death from CVD was also observed at lower body mass index, compared with the reference range (hazard ratio 1.19 (95% confidence interval 1.02 to 1.39) for range 15.0-17.4; 2.16 (1.37 to 3.40) for values below 15). The increased risk associated with high body mass index (>24.9) in east Asians was stronger among those younger than 53 years, and was evident in those who never smoked, free of CVD at baseline, or those without hypertension. Adjustment for hypertension attenuated risk of death, especially from stroke. South Asians showed a weaker association between body mass index and CVD mortality than east Asians; an increased risk for CHD was observed only in individuals with a body mass index greater than 35 (hazard ratio 1.90 (95% confidence interval 1.15 to 3.12)).

Bias, confounding, and other reasons for caution

The use of death certificates could have involved some misclassification in causes of death. Non-fatal CVD events remained unidentified and were therefore misclassified as non-cases. History of diabetes or hypertension was measured at baseline only and was based on self reported data in some cohorts, which could have underestimated the mediating effects of hypertension and diabetes. We cannot exclude the possibility of unmeasured or residual confounding—specifically, higher body mass index is related to higher educational status, better living conditions, and better nutrition in south Asians.

Study funding/potential competing interests

The full list of funding sources is available in the main paper on bmj.com. Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the US National Cancer Institute at the National Institutes of Health and the Fred Hutchinson Cancer Research Center for the submitted work; no other interests.

Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study

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STUDY QUESTION

Does an association exist between the type of stress ulcer prophylaxis administered and the risk of postoperative pneumonia in patients having coronary artery bypass graft (CABG) surgery?

SUMMARY ANSWER

CABG patients treated with proton pump inhibitors for stress ulcer prophylaxis had a small increase in the risk of postoperative pneumonia compared with patients treated with H_2 receptor antagonists; this risk remained after multiple analytic approaches were used to account for confounding.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Proton pump inhibitors and H_2 receptor antagonists are frequently administered after CABG for stress ulcer prophylaxis. Treatment with proton pump inhibitors may result in a small elevation in the risk of pneumonia compared with H_2 receptor antagonists.

Participants and setting

We included 21 214 patients having CABG surgery between 2004 and 2010 from the Premier Research Database. The primary analysis included only those patients who underwent CABG on the third day of hospital admission or thereafter. We did this to obtain a preoperative period in which to measure patients' baseline comorbidities and other risk factors.

Design, size, and duration

This was a retrospective cohort study. The primary outcome was the occurrence of postoperative pneumonia during the index hospital admission. We minimized confounding by using stratification by tenths of propensity score and propensity score matching. We also did an instrumental variable analysis among those patients treated at hospitals with a strong preference for either of the two drug classes.

Main results and the role of chance

Overall, 492 (5.0%) of the 9830 patients who received a proton pump inhibitor and 487 (4.3%) of the 11 384 patients who received an H_2 receptor antagonist developed postoperative pneumonia during the index hospital admission. After propensity score adjustment, an elevated risk of pneumonia associated with treatment with proton pump inhibitors compared with H_2 receptor antagonists remained (relative risk 1.19, 95% confidence interval 1.03 to 1.38). In the instrumental variable analysis, use of proton pump inhibitors (compared with H_2 receptor antagonists) was associated with an increased risk of pneumonia of 8.2 (95% confidence interval 0.5 to 15.9) cases per 1000 patients.

Bias, confounding, and other reasons for caution

The increase in risk of pneumonia was present across a range of analytic techniques and sensitivity analyses. However, the observed increase in risk of pneumonia associated with proton pump inhibitors was small, with confidence intervals that were significant but were close to including the null. This should be considered when interpreting these results.

Generalizability to other populations

Future studies will need to determine whether these findings apply to other high risk patient populations.

Study funding/potential competing interests

SS is principal investigator of the Brigham and Women's Hospital DEcIDE Center on Comparative Effectiveness Research and the DEcIDE Methods Center, both funded by the Agency for Healthcare Research and Quality (AHRQ), and of the Harvard-Brigham Drug Safety and Risk Management Research Center funded by the Food and Drug Administration. SS is a paid consultant to WHISCON LLC and Booz and Co, and he is principal investigator of investigator initiated grants to the Brigham and Women's Hospital from Pfizer, Novartis, and Boehringer-Ingelheim unrelated to the topic of this study. JAR is a paid consultant to WHISCON LLC and is a recipient of a career development award from the AHRQ (K01 HS018088).

Relative risk of postoperative pneumonia in patients undergoing coronary artery bypass graft surgery treated with proton pump inhibitors (PPI) compared with H_2 receptor antagonists (H2RA)

	No of outcomes/No of patients			
Analysis	PPI	H2RA	Risk ratio (95% CI)	Risk difference (95% CI) per 1000 patients
Unadjusted	492/9830	487/11 384	1.17 (1.04 to 1.32)	7.3 (1.6 to 13.0)
Age, sex, race, calendar year adjusted	492/9830	487/11 384	1.19 (1.04 to 1.36)	—
Propensity score tenths stratified	411/8514	421/10 059	1.19 (1.03 to 1.38)	—
Propensity score matched	369/7537	323/7537	1.14 (0.99 to 1.32)	6.1 (−0.6 to 12.8)

Quantification of harms in cancer screening trials: literature review

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STUDY QUESTION

Do cancer screening trials quantify the expected harms of screening?

SUMMARY ANSWER

Cancer screening trials seldom report the information necessary to weigh benefits against harms. Overdiagnosis was reported in 7% of 57 cancer screening trials, and false positive findings in 4%.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Screening of healthy individuals should be offered only when strong evidence from randomised trials show that benefits outweigh harms. For this assessment to be possible, both benefits and harms should be well documented. We found that in the randomised trials of cancer screening, harms were reported far less consistently than benefits—that is, the reduction in cancer specific mortality.

Selection criteria for studies

We included randomised trials that assessed the efficacy of cancer screening for reducing incidence of cancer, cancer specific mortality, and/or all cause mortality from the reference lists of relevant Cochrane Systematic Reviews. We also searched CENTRAL, Medline, and Embase.

Primary outcome

The proportion of trials that reported one or more of seven predefined harms (withdrawals because of adverse events, overdiagnosis, false positive findings, psychosocial consequences, somatic complications, and invasive procedures).

Main results and role of chance

We found 57 trials reported in 198 articles that met our eligibility criteria. The trials assessed 10 cancer screening interventions: breast cancer screening with mammography, self examination, or clinical examination; colorectal cancer screening with sigmoidoscopy or colonoscopy, faecal occult blood testing, or virtual colonoscopy; liver cancer screening with ultrasonography, α fetoprotein, or a combination; lung cancer screening with chest radiography or low dose spiral computed tomography of chest; ovarian cancer screening with ultrasonography, serological markers, or a combination; oral cancer screening with visual inspection; prostate cancer screening with prostate specific antigen, digital rectal examination, or a combination; and testicular cancer screening with self examination or clinical examination. The proportion of trials reporting each outcome related to harm in at least one of the eligible articles describing that trial is summarised in the table. The median proportion of space in the results section that was used to report harms was 12% (interquartile range 2-19%).

Bias, confounding, and other reasons for caution

We considered that a screening harm was reported only when the absolute number of events or the absolute rate were was provided for the screened and unscreened groups. Harms were described in some additional trial publications that focused only on the screened groups, but in our sensitivity analyses with less stringent criteria most harms were still reported in less than half of the trials.

Study funding/potential competing interests

BH is supported by Fundação para a Ciência e Tecnologia (Portuguese Governmental agency). The funder had no role in study design or data collection, analysis, or interpretation.

Number of cancer screening trials that quantified cancer mortality, incidence, and harms for screened and control groups

	Absolute number	Percentage of trials (95% CI)
General outcomes		
Cancer specific mortality	47/57	82 (70 to 91)
Cancer specific incidence	51/57	89 (78 to 96)
Harm outcomes		
Withdrawals because of adverse events	1/57	2 (0 to 9)
Numerical estimate for overdiagnosis	4/57	7 (2 to 17)
Numerical estimate for false positive findings	2/57	4 (0 to 12)
Numerical estimate for negative psychosocial consequences	5/57	9 (3 to 19)
Numerical estimate for somatic complications	11/57	19 (10 to 32)
Numerical estimate for invasive procedures	27/57	47 (34 to 61)
All cause mortality	34/57	60 (46 to 72)