major bleeds enrolled in five phase III trials comparing dabigatran with warfarin in 27,419 patients treated for 6 to 36 months. There were 627 of 16,755 patients on dabigatran who had major bleeds. These patients were older, had lower creatinine clearances, and more frequently used aspirin or nonsteroid anti-inflammatory agents than those on warfarin with major bleeds (n = 407 of 10,002). Thirty-day mortality after the first major bleed tended to be lower in the dabigatran group (9.1%) than in the warfarin group (13.0%; pooled odds ratio, 0.68; 95% confidence interval, 0.46-1.01; P = .057). With adjustments for sex, age, weight, renal function and concomitant antithrombotic therapy, the pooled odds ratio for 30-day mortality with dabigatran vs warfarin was 0.66 (95% confidence interval, 0.144-1.00; P = .051). In dabigatran patients with major bleeds, the bleeding was more frequently treated with blood transfusions (61%) than bleeds in warfarin patients (42%; P < .001). Patients with major bleeds treated with dabigatran were less frequently treated with plasma compared to warfarin patients with major bleeds (19.8% vs 30.2%; P < .001). Patients with major bleeds had shorter stays in intensive care units if they had previously received dabigatran (mean,1.6 nights) compared with those who had received warfarin (mean, 2.7 nights; P = .01).

Comment: There is obviously no ideal anticoagulant agent. Despite the fact there is no reversal agent for dabigatran, outcomes of major bleeding on this drug appear no worse and are perhaps slightly better than outcomes for patients with major bleeding on warfarin. It does not appear overall resources needed to manage major bleeding on dabigatran are greater than to manage such bleeding on warfarin. It also does not appear that the prognosis after major bleeding is worse with dabigatran than with warfarin despite the lack of a reversal agent for dabigatran. Dabigatran is an alternative to warfarin with similar or superior efficacy and overall lower risk of major bleeding. Bleeding episodes can be managed satisfactorily with relatively simple measures such as drug discontinuation and transfusion of red cells. Thus, the overall safety profile of dabigatran compared to warfarin remains favorable. Nevertheless, it is still desirable to develop a specific antidote to dabigatran.

Effect of Smoking on Comparative Efficacy of Antiplatelet Agents: Systematic Review, Meta-Analysis, and Indirect Comparison
Gagne JJ, Bykov K, Choudhry NK, et al. BMJ 2013;347:f5307.

Conclusions: In randomized clinical trials of antiplatelet drugs, the reported clinical benefit of clopidogrel to reduce cardiovascular death, myocardial infarction, and stroke is seen primarily in patients who smoke, with little demonstrated benefit in nonsmokers.

Summary: Recent subgroup analyses of randomized controlled trials evaluating clopidogrel in cardiovascular disease have raised the question if the efficacy of the drug occurs primarily or exclusively among smokers (Grubel PA et al, JAMA 2012;307:2495-6). Biochemically clopidogrel is a prodrug. It requires a two-step metabolic activation process to attain active form. Smoking induces cytochrome P450 isoenzyme 1 A2. This is a key enzyme involved in the first activation step of clopidogrel. It has therefore been postulated that smoking increases the availability of clopidogrel's active metabolite, thereby enhancing its efficacy. There are also numerous antiplatelet agents such as prasugrel, also a prodrug but requiring a less complex activation process than clopidogrel. Another new antiplatelet agent, ticagrelor, is active by itself. In this paper, the authors performed a systematic review, meta-analysis, and indirect comparisons to quantify the efficacy of clopidogrel separately in smokers and nonsmokers. They also sought to compare the efficacy of newer antiplatelet agents in these groups of patients. Data sources included Medline (1966-present) and Embase (1974-present), along with supplementary searches of databases of abstracts from major cardiology conferences. Also used were the Index to Nursing and Allied Health (CINAHL), the CAB Abstracts databases, and Google Scholar. Randomized trials of clopidogrel, prasugrel, or ticagrelor that also examined clinical outcomes among subgroups of smokers and nonsmokers were identified. Two of the current authors independently extracted all data, including information on patient populations included in the trials, treatment types and doses, definitions of clinical outcomes and duration of follow-up, definitions of smoking subgroups and number of patients in each group, and effect estimates with 95% confidence intervals for each smoking status subgroup. There were nine eligible randomized trials. One investigated clopidogrel compared with aspirin, four investigated clopidogrel plus aspirin compared with aspirin alone, and one investigated double dose clopidogrel compared with standard dose clopidogrel. These trials included 74,489 patients of whom 21,717 (29%) were smokers. Among smokers, those 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 group (relative risk [RR], 0.75;

95% confidence interval [CI], 0.67-0.83). There was just an 8% decrease in nonsmokers in the composite outcome (RR, 0.92; 95% CI, 0.87-0.98). There were two studies that investigated prasugrel plus aspirin compared with clopidogrel plus aspirin, and one study investigated ticagrelor plus aspirin compared with clopidogrel plus aspirin. In smokers, the RR was 0.71 (95% CI, 0.61-0.82) for prasugrel compared with clopidogrel and 0.83 (95% CI, 0.68-1.00) for ticagrelor compared with clopidogrel. Corresponding RRs among nonsmokers were 0.92 (95% CI, 0.83-1.01) and 0.89 (95% CI, 0.79-1.00).

Comment: The data suggest that clinicians may consider potential benefits and risks of antiplatelet drugs differently for those patients that continue to smoke and those that do not. However, there is little understanding, or no understanding, of how the potential enhanced antiplatelet effect in smokers might also increase the risk of bleeding. It will be important to design future trials to determine whether different doses of clopidogrel should be used in smokers and nonsmokers to achieve clinical benefit.

Electronic Cigarettes for Smoking Cessation: A Randomised Controlled Trial
Bullen C, Howe C, Laugesen M, et al. Lancet 2013;382:1629-37.

Conclusions: Electronic cigarettes are associated with few adverse events and, with or without nicotine, are modestly effective in aiding smoking cessation. Results are similar to achievement of abstinence with nicotine patches.

Summary: Electronic cigarettes were first introduced in 2004. These devices span a range of individual devices, many of which vaporize nicotine for inhalation. Twenty-seven precent of patients making an attempt to quit cigarettes in the UK have utilized electronic cigarettes (West R, July 20, 2012; http://www.smokinginengland.info/lastest-statistics/; accessed August 9, 2013). It has been predicted that sales are increasing so rapidly they will surpass actual cigarette sales within the decade (Purkayastha D; http://www.thefreelibrary.com/;BAT Ramps-up E-cigarette Expansion as Sales Go Up in Smoke). One trial, however, of 300 smokers demonstrated low rates of cessation at 12 months for both nicotine e-cigarettes and placebo e-cigarettes (Caponnetto P et al, PloS One 2013;8:e66317). There is also controversy as to whether electronic cigarettes have the potential to produce harm (U.S. Food and Drug Administration; http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm). This trial sought to access whether electronic cigarettes with cartridges containing nicotine were more effective for smoking cessation than nicotine patches. There was also a blind comparison with electronic cigarettes containing no nicotine (placebo e-cigarette). The hypothesis was that nicotine e-cigarettes would be a more effective than patches and placebo e-cigarettes for smoking reduction, tobacco dependence, and relief of withdrawal symptoms and that there would be no greater risk of adverse events than with nicotine patches. This was a randomized, controlled superiority trial from Aukland, New Zealand conducted between September 6, 2011 and July 5, 2013. Adult smokers (≥18 years) wanting to quit were randomized and stratified by ethnicity, sex, and level of nicotine dependence in a 4:4:1 ratio of 16-mg nicotine e-cigarettes, nicotine patches (21 mg patch, one daily), or placebo e-cigarettes (no nicotine), from 1 week before until 12 weeks after quit day. There was also additional low intensity behavioral support via voluntary telephone counseling. Primary outcome was biochemically verified continuous abstinence at 6 months (exhaled breath carbon monoxide measurement <10 ppm). Primary analysis was on an intention-to-treat basis. There were 657 people randomized (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) and who were included in the intention-to-treat analysis. At 6 months, verified abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8 % (17 of 295) with patches, and 4.1% (3 of 73) with placebo e-cigarettes. The risk difference for nicotine e-cigarettes vs patches was 1.51 (95% confidence interval, −2.49 to 5.51). Risk difference for nicotine e-cigarettes vs placebo e-cigarettes was 3.16 (95% confidence interval, −2.29 to 8.61). Abstinence was substantially lower than anticipated by prestudy power calculations.

Comment: Electronic cigarettes are big business. The study, however, would not suggest anything more than a very modest effect on abstinence rates through the use of electronic cigarettes. The authors found that electronic cigarettes had higher acceptance rates among smokers than other forms of nicotine replacement therapy. Since there were no dramatic differences in adverse events between other forms of nicotine replacement therapy and electronic cigarettes, it may be possible, through the design of more adequately powered trials, to demonstrate that electronic cigarettes can indeed have some potential for improving population health. Currently, however, the data would not appear to support widespread use of these devices if the goal is to have a significant effect on smoking cessation.