Table. Estimated Hazard Ratios for Time to Death or Heart Failure Rehospitalization Through 180 Days

Subgroup	Value, Mean (SD)	No. of Patients		HR (95% CI)[a]	*P* Value	*P* Value for Interaction
		Liraglutide	Placebo			
LVEF, %						
≤Median	16.5 (4.4)	79	73	0.97 (0.59-1.60)	.92	.11
>Median	28.7 (4.8)	75	73	1.73 (1.06-2.84)	.03	
BMI[b]						
<Median	25.9 (3.5)	80	69	1.11 (0.68-1.82)	.67	.17
≥Median	39.1 (6.7)	73	76	1.53 (0.94-2.50)	.09	

Abbreviations: BMI, body mass index; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[a] Hazard ratios <1.0 favor liraglutide.

[b] Calculated as weight in kilograms divided by height in meters squared.

Within the FIGHT study population, Carbone and colleagues inquire about how quantitative differences in LVEF affected responses to liraglutide within the larger population of patients with advanced heart failure and reduced LVEF. In the requested subgroup analysis (**Table**), liraglutide treatment was associated with signals of worse outcomes among patients with an LVEF above the median (25%), but responses were not significantly different from placebo among those with an LVEF at or below the median. Owing to the entry criteria of the FIGHT trial, even the group with LVEF above the median had severely reduced systolic function and other factors indicating increased risk. Nevertheless, a greater severity of LVEF reduction does not appear to be driving adverse effects of liraglutide within a population composed of patients with advanced heart failure.

Carbone and colleagues also consider the possible effect of body composition on responses to GLP-1 agonists and inquire whether patients' BMI or weight loss during the trial affected their responses to liraglutide. Specifically, there is concern that further weight loss among already cachectic patients may have contributed to adverse outcomes. In this context, it is important to highlight that in the FIGHT cohort, the median (interquartile range) BMI was 32 (26-37). The requested subgroup analysis (Table) indicates that liraglutide treatment was not associated with worse outcomes among patients with BMI at or above or below the median. Unlike baseline BMI, the magnitude of weight loss cannot be predicted at onset of treatment and thus cannot influence the decision to prescribe liraglutide in patients with advanced heart failure.

Overall, it appears that the safety concerns about liraglutide among patients with advanced heart failure arise specifically regarding patients with type 2 diabetes. These findings underscore our suggestion for caution when initiating liraglutide for the sake of diabetes management among patients with advanced heart failure.

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Factors Influencing Prescription Drug Costs in the United States

To the Editor Dr Kesselheim and colleagues stated that the United States spends more on prescription medicines than other countries.[1] However, the solutions they proposed are unlikely to fix the problem, but may stymie US-based innovation instead.

First, the authors suggested the US Patent and Trademark Office should play a greater role in lowering health care costs. The current mission of this office is to assess novelty of an invention, not superiority over previous inventions. The Patent and Trademark Office is understaffed, leading to long delays in assessing inventions.[2] The criterion of assessing superiority is unclear and difficult to implement. For example, a compound might be a potent inhibitor of an enzyme involved in cancer but a poor drug for other reasons. This type of information is not present in patent applications and often is discovered long after a patent is granted. Patenting minor improvements does not mean higher prices. The value of a patent is assigned by the market, not by the existence of the patent per se. If a minor improvement is patented, a company still must invest in developing the improvement and bringing it to market. The market decides whether the minor improvement is worth paying for.

Second, Kesselheim and colleagues did not discuss the unique role of the United States in drug development. The United States has traditionally been the primary driver of drug development. However, US culture is more risk averse to adverse effects of drugs compared with other countries. This is not

entirely bad, as it prevented approval of thalidomide in the United States, which was approved by European countries and resulted in severe birth defects.[3] Nevertheless, the expenses of entering the US market are higher than entering other markets,[4] and companies need to recoup the money invested. This is a prime driver of prescription drug costs. Also, the authors noted that many drugs are developed based on research funded by the National Institutes of Health and conducted at nonprofit academic centers. However, many steps occur between a laboratory discovery and a drug, such as patenting, pharmacokinetic and toxicology studies, large-scale preparation, and clinical trials. These costs dwarf the costs of the initial discovery.[5]

The high cost of drugs in the United States is a major problem. My concern is that the solutions offered in the article will result in a dampening on innovation in the United States rather than reducing prescription drug costs.

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To the Editor In their Special Communication, Dr Kesselheim and colleagues[1] challenged an industry claim by finding that "there is little evidence of an association between research and development costs and drug prices," with drugs instead priced in the United States based on what health systems and society can bear. Several interrelated trends in corporate governance and the financial sector can further explain this phenomenon of high and often escalating prices despite large companies investing only 10% to 20% of their revenue on research and development.

First, large, publicly traded companies are valued by shareholders and investment analysts based on expectations of growth of approximately 10% on a year-to-year basis. This near-term growth expectation partially explains why companies are averse to risky long-term in-house research and instead rely on acquisitions of compounds often developed with public and venture capital. Gilead's approach to hepatitis C drugs has demonstrated the possibilities of financial success by specializing in late-stage acquisition and regulatory approval.[2]

Second, these acquisitions are typically financed with debt as well as stockpiled cash accrued via high prices on prior sales. Price increases on medicines, which in turn can raise a company's share price based on the promise of future growth, are also a form of leverage used to borrow from investors for acquisitions. The EpiPen case demonstrates this strategy. Mylan's successive price increases facilitated the raising of more than $6 billion via stock issuances and debt between 2015 and 2016.[3] These moves positioned Mylan for their $7.2 billion acquisition of Swedish biotech company Meda.[4]

Third, large companies have directed inordinate flows of revenue toward a financial maneuver known as share buybacks, in which companies buy their own shares to increase the value of the remaining ones. From 2005 to 2014, the 19 pharmaceutical companies in the S&P 500 Index spent $226 billion repurchasing their own shares, equivalent to 51% of their combined research and development expenditures over this period. Composing 4.14% of the sample, these companies contributed 7.38% of returns to shareholders.[5] Thus, companies could increase access and affordability of medicines in the form of lower prices or reinvest more of their revenue into research for areas of unmet medical needs and still amply reward shareholders.

All 3 trends have been encouraged by tying executive compensation to share price via stock options. Any reform proposals should consider these features of corporate governance and the ways that the financial sector influences the pharmaceutical industry.

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In Reply Dr Arbiser's description of patent law is problematic. The Patent Act requires that a patentable product be not only novel but also "nonobvious" compared with existing products. However, the US Patent and Trademark Office has traditionally applied a low bar for this requirement for drugs,

permitting patents on new crystalline structures, formulations, and single-isomer isolations of mixed enantiomer products, even though many of these alterations to existing molecules would be obvious to skilled chemists and offer no therapeutic novelty. This determination does not require an assessment of clinical superiority.

A low nonobvious threshold increases prices because pharmaceutical manufacturers can claim exclusivity over, extensively market, and charge more for products that have patent-protected minor changes than for the older products they replace, which are often on the cusp of generic competition. In 2011, Congress created a streamlined administrative process for reexamining patents (inter partes review) that is helping to address some of these issues. Additional progress could be achieved by mandating review of pharmaceutical patents when they are registered with the US Food and Drug Administration (FDA), with a government or public interest lawyer tasked with challenging the patent's validity.[1] The solution for problems caused by understaffing of the Patent and Trademark Office is obvious.

Second, Arbiser inappropriately downplays the role that scientists outside the United States have played in innovation, particularly transformative drug development. One review of research productivity from 1982 through 2003 found greater output per dollar invested in Europe than the United States.[2] There is no evidence that drug registration costs in the United States are substantially higher than elsewhere or that the United States requires more data for drug approvals than other countries; experience over the last decade shows that the FDA is the fastest drug regulatory agency in the world.[3] Although drug development is unarguably expensive, the 24% profit margin forecast for brand-name drug manufacturers in 2016 is again among the highest of all global industries,[4] suggesting there is room to advance affordability and access for US patients and preserve robust incentives for private investment in innovation. The claim that companies' costs in commercializing a drug "dwarf" the costs of achieving the (often publicly funded) discoveries on which the drug is based is unsubstantiated and almost certainly incorrect.

We agree with Mr Roy and colleagues that corporate governance structures and other financial pressures affect corporate behavior. High annual growth targets can also contribute to companies heavily marketing their products for off-label uses in violation of FDA rules, with the hope that gains in profits will far exceed any fines.[5] Though many off-label uses are not evidence-based and can pose substantial risks to patients, this practice is likely to grow with the protection of off-label promotion under the First Amendment, leading to increased spending on prescription drugs without clear accompanying patient benefit.[6] The data Roy and colleagues present on the enormous sums spent by drug makers merely to buy back their own shares, thus increasing their market price, makes a telling point about the misdirection of the industry's enormous profits toward goals other than research and development.

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Expectations for Physicians Prescribing Marijuana

To the Editor The Viewpoint on medical board expectations for physicians recommending marijuana[1] summarized model guidelines proposed by the Federation of State Medical Boards (FSMB) for its members.[2]

We have 2 principal concerns. Regarding conflicts of interest, Dr Chaudhry and colleagues stated, "the physician should not be associated in any way with a dispensary or cultivation center." This wording is more restrictive than the actual policy ratified by the FSMB. It would impede physicians who wish to collaborate with dispensaries and cultivators in studying which specific cannabinoid:terpenoid ratios patients find effective. Such data collection, in the absence of desperately needed clinical trials, can help unravel the diverse efficacy of various cannabinoids. Such an association for research purposes should not exclude physicians who recommend medicinal cannabis.

Also worrisome is the recommendation by Chaudhry and colleagues that "state medical and osteopathic boards advise their licensees to abstain from the use of marijuana for medical or recreational purposes while actively engaged in the practice of medicine." This provision does not appear in the model guidelines developed by the FSMB Workgroup, adopted as policy by the FSMB House of Delegates in April 2016.[2]

Although most physicians enter rehabilitation programs because of dependence on alcohol, opioids, or both, the FSMB does not advise that users of recreational alcohol or prescribed opiates suspend their practice. Using medicinal cannabis is not prima facie evidence of impairment or abuse. Advising those physicians to suspend practice would be an unwarranted intrusion into a private physician-patient relationship and a stigmatization of clinicians making a rational