

Marketing Claims of Newer Drugs and the Evidence

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Marketing new drug therapies is a major focus of pharmaceutical companies, with many of the largest pharmaceutical companies spending more money on drug marketing than on research and development.¹

Thirty-four new molecular entities have been approved this year by the Food and Drug Administration (FDA).² As market competition increases, the promotion of drugs to prescribers and consumers often follows. The time it takes to evaluate the evidence to validate claims of improved efficacy, safety, and convenience of new therapies can be burdensome. With the pressure to generate sales and profits, pharmaceutical marketing messages may not be an accurate or complete reflection of the data available. This newsletter will review recent drug marketing statements and provide perspective on the evidence behind these claims.

Insulin Degludec (Tresiba) Comparative Efficacy

Marketing Angle: "Are you Tresiba ready?" Marketing promotes use of a once-daily insulin that lasts longer than 24 hours to lower hemoglobin A1C (A1C).³

Evidence Fact: Evidence has not demonstrated that insulin degludec (Tresiba) is superior to other long-acting insulin in lowering A1C and is much more expensive.⁴

Insulin degludec (Tresiba) is a long-acting insulin approved by the FDA in 2015.⁵ There is evidence that insulin degludec can be given at different times of the day without compromising efficacy due to a half-life of approximately 25 hours, other long-acting insulins, such as insulin glargine, have a half-life of 12 hours.^{5,6} The longer duration of action has not been shown to translate into improved A1C lowering. A Drug Effectiveness Review Project (DERP) report found that in an analysis of 4,434 patients there was moderate evidence of no difference between insulin degludec and insulin glargine in the number of patients with type 2 diabetes mellitus (T2DM) that were able to obtain an A1C less than 7% (pooled risk ratio 0.96; 95% CI, 0.90 to 1.03) and there was low quality evidence of no difference in A1C lowering in patients with type 1 diabetes (T1DM), based on 3 trials.⁴ The risk of nocturnal hypoglycemia, defined by most studies as a reading less than 56 mg/dL between the hours of 1 am to 6 am, has been shown to be less with insulin degludec compared to insulin glargine in patients with T1DM and T2DM.⁴ Studies lasting 52 weeks found a small absolute risk reduction (ARR) of 2.0% (number needed to harm [NNH] 50) in patients with T1DM and a mean ARR of 4.2% (NNH of 43) in studies of patients with T2DM.⁴ The risk of severe hypoglycemia was not different between insulin degludec and insulin glargine in patients with T1DM or T2DM. These results are most applicable to patients with T1DM and an average age of 44 years and a 19 year history of T1DM and to patients with T2DM with an average age of 59 years and an 11 year history of diabetes. The mean A1C was 8.5% in patients with T1DM and T2DM. Patients with diabetes complications were excluded from most studies. The cost of insulin degludec is approximately \$5 more per mL based on the national average actual acquisition cost (AAAC).⁷

OHP FFS policy allows for insulin glargine (Lantus) vials and pens without prior authorization. Insulin degludec requires prior authorization approval.

Empagliflozin (Jardiance) and Cardiovascular Effects

Marketing Angle: "For adults with type 2 diabetes and heart disease Jardiance is the only type 2 diabetes pill with a lifesaving cardiovascular benefit."⁸

Evidence Fact: In a subgroup analysis of the trial described below, there was no reduction in cardiovascular (CV) deaths in Europe and North America (representing 61% of the global study population). This makes it uncertain if there is a benefit in the Oregon Health Plan (OHP) fee-for-service (FFS) population. In addition, the primary event rate of CV death was not measured appropriately, as 40% of the CV deaths reported in the trial were not CV in origin, but were 'non-assessable'.⁹ Baseline characteristics of patient included in the trial demonstrate that results are most applicable to patients with a diabetes diagnosis of at least 10 years, an average age of 63 years and living outside North America and Europe.¹⁰

The evidence from an industry sponsored study demonstrated that empagliflozin reduced the composite endpoint of death from CV causes, nonfatal myocardial infarction (MI) and nonfatal stroke when compared to placebo (ARR 1.6%/number needed to treat [NNT] 63) over 3.1 years in patients with underlying CV disease, when all study sites were included.¹⁰ There was no statistically significant differences between empagliflozin and placebo in incidence of non-fatal MI or non-fatal stroke.¹ The reduction in CV events was driven by a decreased risk of death related to CV causes with empagliflozin compared to placebo, 5.9% vs. 3.7%, respectively (HR 0.62; 95% CI, 0.49 to 0.77; P<0.001).¹ This translates to a relative risk reduction of 38% in death from CV causes, which is only a 2.2% absolute difference between empagliflozin and placebo.¹⁰ Absolute risk reduction is often a better way to evaluate the clinical difference between treatment groups as it reflects the actual magnitude of change. Statistically significant reductions due to death from any cause favored empagliflozin over placebo, 8.3% vs. 5.7%, respectively (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001).¹⁰

It is unknown if the risk reduction in CV endpoints seen with empagliflozin would be seen in T2DM patients *without* preexisting CV disease. This is important because currently we only have evidence of CV benefits in older patients with CV disease and a multi-drug approach to managing their diabetes and other comorbidities. Lastly, the risk of ketoacidosis and serious urinary tract infections seen with empagliflozin need to be balanced with its benefits.¹¹

OHP FFS policy requires prior authorization approval for empagliflozin and other SGLT-2 inhibitors.

Non-vitamin K Oral Anticoagulants Comparative Efficacy

Marketing Angle: Consumer commercials advertise "Pradaxa is proven better than warfarin at reducing stroke."¹² Other marketing focuses on non-vitamin K oral anticoagulants (NOAC) being more convenient than warfarin due to lack of dietary interactions and lack of blood monitoring.^{13,14}

Evidence Fact: Subgroup analysis of patients with atrial fibrillation (AF) demonstrate that superior efficacy of NOACs over warfarin is valid only for those patients who are consistently unable to maintain a therapeutic international normalized ratio (INR).¹⁴ Appropriate patient selection for NOAC treatment warrants consideration. NOACs have a potential for significant drug interactions with combinations of P-glycoprotein and CYP 3A4 inhibitors and inducers. Dosing adjustments based on renal function is required for all NOACs.

Advertising promotes the use of NOACs, such as dabigatran and apixaban, at being superior to warfarin at reducing the risk of stroke in patients with AF. Numerically, both these treatments were superior to warfarin for the overall findings. However, a DERP report found that the efficacy of NOACs was not superior to warfarin in patients who were taking warfarin with an INR in the therapeutic range at least 66% of the time.¹⁵ This finding was illustrated in the open-label study comparing dabigatran (Pradaxa) to warfarin. Results found an ARR for the primary endpoint of stroke or systemic embolism to be 0.60% and a number needed to treat of 167 with dabigatran compared to warfarin.¹⁶ However only 64% of patients taking warfarin were in the therapeutic range, suggesting sub-optimal warfarin management. The open-label study design imparts a high risk of performance bias with the potential to influence the results.

A reduction in risk of hemorrhagic stroke, lack of laboratory monitoring and less food and drug interactions compared to warfarin have been cited as some of the benefits of NOACs. A less emphasized risk of NOAC therapy is the potential for increased risk of bleeding when combined with other drugs that share the same metabolic pathways (CYP3A4 and P-glycoprotein). Apixaban and rivaroxaban have warnings against concomitant use with other drugs that are metabolized by the CYP3A4 metabolic pathway and apixaban, dabigatran and rivaroxaban have warnings against use with P-glycoprotein inducers/competitors. Edoxaban should not be used with the P-glycoprotein inducer, rifampin, but does not undergo metabolism via the other shared metabolic pathways. NOAC efficacy and safety studies often exclude patients who take drugs that may alter the plasma concentrations of NOACs. Evidence regarding concomitant use of NOACs with drugs with similar metabolic pathways often comes from animal models with limited evidence available from human studies. A retrospective cohort study in 91,330 patients taking either apixaban, dabigatran, or rivaroxaban for atrial fibrillation (AF) found an increased adjusted risk of major bleeding (hospitalization or emergency room visit with primary diagnosis of intracranial hemorrhage or gastrointestinal, urogenital, or other bleeding) when NOACs were used in combination with amiodarone, fluconazole, rifampin or phenytoin (Table 1).¹⁷ Diltiazem and amiodarone were prescribed in 22.7% and 21.1%, respectively, of patients taking NOACs despite warnings against these combinations.¹⁷

In addition to drug interactions, renal function should be considered. All NOACs have recommendations for dosing adjustments based on

reduced renal function. Warfarin is recommended for patients with severe renal impairment (CrCl <15 mL/min). NOAC trials also excluded patients with chronic kidney disease, who are at increased risk of stroke, preventing efficacy conclusions in this population.^{16,18-20} Additionally, edoxaban use in patients with CrCl greater than 95 mL/min is not recommended.

Tolerability, based on withdrawal rates, was higher in clinical trials with some NOACs compared to warfarin. Twice-daily dosing may pose adherence concerns in some patients and the shorter half-lives of NOACs compared to warfarin, putting patients at a higher risk of thrombosis if a dose is missed.

Table 1. Adjusted incidence Rates of Major Bleeding per 1000 person-years^{17*}

Combinations	Increased Risk with Combination Therapy
NOAC + Amiodarone	13.94 (99% CI, 9.76 to 18.13)
NOAC + Fluconazole	138.46 (99% CI, 80.96 to 195.97)
NOAC + Rifampin	36.90 (99% CI, 1.59 to 72.22)
NOAC + Phenytoin	52.31 (99% CI, 32.18 to 72.44)

* Apixaban, edoxaban and rivaroxaban included

OHP FFS policy allows coverage of warfarin, apixaban, dabigatran, edoxaban and rivaroxaban without a PA

Hepatitis C Treatment Candidates

Marketing Angle: Marketing claims imply new hepatitis C direct-acting antivirals (DAA) cure 99% of hepatitis C cases and treatment is appropriate for all patients that "are ready".¹⁷

Evidence Fact: There are limitations to the evidence demonstrating sustained viral response (SVR) rates of up to 99% with DAA therapy. Important safety concerns and lack of evidence for important health outcomes requires diligent prescribing of DAAs to the most appropriate patients.

There is widespread marketing promoting the use of DAAs for the treatment and potential cure of hepatitis C. While these new treatments offer significant improvements in SVR over control (ARR 30.3%; NNT 4), limitations to the evidence remain. Chronic hepatitis C is a slowly progressing disease over decades and it is unknown if delaying treatment in those with mild disease (F0-F2 fibrosis) results in poorer outcomes.¹⁸ Additionally, SVR is a non-validated surrogate outcome. There is recent data suggesting that treatment with DAAs improves patient reported outcomes compared to placebo²¹ and evolving evidence on other clinically significant long term outcomes. However, due to the time to progress to complications, there is insufficient direct evidence that treatment of hepatitis C with DAAs improves complications including ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, or liver transplantation with long-term use.¹⁸ Additionally, there is evidence of up to a 30% incidence of spontaneous viral clearance within the first 6 to 12 months of acute hepatitis C infection.^{22,23}

Patient exclusion criteria and reliance on short-term data are also limitations to understanding the full treatment effect of DAAs. Trials excluded patients with hepatitis B infection, which have led to post-

marketing reports of reactivation of latent hepatitis B infection in patients receiving DAAs in the general population.¹⁹ In response, the FDA has issued a Boxed Warning to be added to all DAAs to inform practitioners of this risk. Additional safety concerns regarding serious and life-threatening symptomatic bradycardia in patients taking sofosbuvir (Sovaldi) or ledipasvir/sofosbuvir (Harvoni) who were also taking other DAAs and amiodarone have been reported.²⁰ The FDA recommends that patients avoid sofosbuvir or ledipasvir/sofosbuvir in combination with DAAs and amiodarone. Successful evaluation of the most appropriate candidates for hepatitis C treatment will increase the chance of a successful outcome and minimize the risk of inappropriate prescribing.

Conclusion

While newer therapies may present an advantage in certain populations, the evidence needs to be carefully considered before universally applying these benefits to all patients. While numeric superiority may exist, it is also important to consider the number of patients that need to be treated and for what duration of time to receive treatment benefits. An additional concern is that most new drug studies are conducted by the manufacturer, which presents an inherent risk of bias due to conflicts of interest. Most importantly, treatment selection needs to represent a clinically meaningful benefit to the patient.

Complete evidence reviews are available at www.orpd.org/drugs/.

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