According to one commentator (239), case reports suggest that anticoagulants might play a role in migraine prophylaxis. The question that arises is, should a physician consider prescribing warfarin for migraine prophylaxis? There are no randomized controlled trials and there is little published literature on this indication, and the mechanism of warfarin's effect on migraines is not well understood. As further opined by this commentator, most physicians would not prescribe warfarin for migraine prophylaxis. However, for an individual patient, this treatment would be reasonable, if a patient has already tolerated warfarin that had earlier been used for a different indication (for reducing risk for stroke), or has reported a decreased incidence of migraines while taking it, or cannot tolerate other prophylaxis medications.

c. Off-Label Uses and Genetic Biomarkers

Biomarkers that identify genetic mutations or chromosomal rearrangement are sometimes used as part of the inclusion criteria or exclusion criteria. For some drugs, evidence demonstrates that the drug is effective only for patients who possess the genetic biomarker in question, and that the drug does not work in other patients. Because of the natural urge of patients with a certain disease, such as breast cancer or cystic fibrosis, to seek and receive treatment, patients are likely to overlook the fact that the drug works only in the subset that is carved out by the biomarker. This illustrates the situation where the genetic biomarker found its way into the package insert. The take-home lesson is applicable to all drugs, where efficacy is found only in a subset that possesses the biomarker and where the drug has been shown not to work in other patients having a disease with the same name (but not with the same biomarker expression).

Cystic fibrosis is caused by mutations in *Cystic Fibrosis Transmembrane Conductance Regulator* (CFTR) protein activity. The most common mutation in CFTR is a deletion of phenylalanine-508 (240). This mutation can be abbreviated as "delta508." FDA's *Medical Review* pointed out that the study drug (ivacaftor (Kalydeco)) is *not effective* in cystic fibrosis patients where the delta508 mutation occurs in both copies of the CFTR gene, writing that the study (241), "demonstrates the **lack of efficacy** in the CF population who are **homozygous** for the deltaF508 deletion in CFTR."

In the *Medical Review* for a cystic fibrosis drug (ivacaftor), the FDA reviewer commented about off-label uses of this drug (242). The FDA reviewer pointed out that the study drug (ivacaftor alone) was not effective for patients homozygous for the deltaF508 mutation, writing that:

> [l]ack of efficacy in this deltaF508/deltaF508 CF population is important to note, because [ivacaftor] represents the first entity that appears to treat one underlying defect of CFTR function that causes the disease. **It is therefore important to state that [ivacaftor] demonstrated no clinical benefit in patients homogeneous for the deltaF508-CFTR mutation**.

[239]Fitzgerald AS, O'Malley PG. Staying on track when prescribing off-label. Family Physician. 2014;89:4–5.

[240]Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cysticfibrosis homozygous for Phe508del CFTR. New Engl. J. Med. 2015;May 17 [Epub ahead of print].

[241]Medical Review for NDA 203,188.Ivacaftor (Kalydeco®) FDA's website at March 2015.

[242]Medical Review for NDA 203,188.Ivacaftor (Kalydeco®) FDA's website at March 2015.