



# Facts Addressing Migraine Market Misperceptions

January 2016

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# 1. Executive Summary

IMS Health, the leading global provider of health-care information and real-world evidence driven analyses in the pharmaceutical industry, has conducted a retrospective analysis of migraine patients in a proprietary closed-payer dataset. The analysis examines the overall migraine market size along with cardiovascular risk in the migraine patient population in the U.S. using health care claims data. The Framingham Heart Study, a longitudinal patient study that is the widely-accepted industry standard for defining and assessing cardiovascular (CV) risk factors in a United States population, has been used to determine risk factors for Coronary Artery Disease (CAD). Patients in the headache population as well as the more specific migraine population with diagnoses, procedures, or associated drug usage for CAD risk factors have been identified within this analysis.

Informal, qualitative discussions with physicians who treat migraine in the U.S. may provide incomplete information regarding cardiovascular risk characteristics, cardiovascular comorbidities, and treatment patterns. In some cases assumptions exist that most treated migraine patients are young women who have very low risk for cardiovascular events. Some healthcare professionals are therefore comfortable prescribing existing vasoconstrictive therapies to a portion of their patients with cardiovascular risk factors, despite the known contraindications, precautions and warnings against such prescribing activity.

This analysis conducted by IMS Health specifically focuses on commonly held misperceptions regarding: 1) the market size and patient demographics for the acute treatment of migraine in the U.S.; 2) the proportion of migraine patients who have risk factors for cardiovascular disease or known cardiovascular conditions; and 3) current acute treatment patterns of migraine, specifically in migraine patients with cardiovascular risk factors or conditions. Results from this analysis can inform the potential market opportunity for new therapies in the migraine space.

The data source for this research is the IMS PharMetrics Plus database, which is comprised of adjudicated claims for health plan enrollees across the United States. PharMetrics Plus includes enrollees with both medical and pharmacy coverage, representing more than 42 million unique lives. The data include a range of geographies and plan types in the U.S. Attributes of the data include medications prescribed (date, product form, strength), diagnoses and procedures, patient demographics, payer type and provider information. The PharMetrics Plus sample is sufficiently robust so that it can be projected to the U.S. insured population of 274 million.

Three common misperceptions are addressed by this research:

***Misperception 1: Migraine is a Disease of Young Women***

Fact: 3.7 million adult patients in the insured health care system are diagnosed with migraine.

Fact: Females comprise 82% of the adult migraine *diagnosed* population in this study and 85% of the *treated* population.

Fact: Fifty-four percent (2.2 million) of *diagnosed* migraine patients are 40 years and older; 57% (1.1 million) of *treated* migraine patients are 40 years and older.

Fact: Women between the ages of 40 and 49 constitute the largest age cohort for patients *diagnosed and treated* for migraine (21%, 403k of all diagnosed and treated migraine patients).

Fact: Men comprise roughly one out of five diagnosed migraine patients (20%) but are less likely to receive a prescription treatment compared to women (41% treated compared to 51%).

***Misperception 2: The Migraine Population with CAD Risk Factors is Small***

Fact: 2.8 million adult migraine patients (76%) carry cardiovascular conditions or risk factors that contraindicate or warn against triptan use during the study period.

Fact: 1.3 million (35%) adult diagnosed migraine patients have a contraindication that limits the use of triptans.

Fact: Migraine patients have a substantially increased rate of CAD events compared to the general population (9.9% compared to 6.4%).

Fact: Having a migraine diagnosis, even among younger patients, increases the likelihood of a future CAD event as compared to patients without a migraine diagnosis (4.5 times for female patients 18-29 years of age; 5.1 times for males in same age range).

***Misperception 3: Healthcare Professionals have No Concerns Regarding Triptan Use in Patients at Risk for CAD (CV Risk); View Patients as Well-Served by Triptans***

Fact: Triptan use is lower in patients with a history of CAD event or at CV risk compared to use in the general adult migraine treated population--56% compared to 75%.

Fact: Off-label use of opioids is more likely in CV risk patients than in the general adult treated migraine population. The proportion of patients having high CV risk or a known CAD event who are prescribed opioids for treating migraine is higher than the proportion having high CV risk or a known CAD event who are prescribed triptans (74% compared to 56%).

Fact: Of the 2.3 million adult migraine patients with a CAD event or high CV risk, 1.2 million (53%) are untreated.

Fact: The relatively large size of the diagnosed migraine population with a history of CAD event or at CV risk not treated with prescription medication or choosing alternative therapies such as opioids suggests that this population is under-served.

## 1.1. Disclosures

IMS Health is a leading global information and technology services company providing clients in the healthcare industry with end-to-end solutions to measure and improve their performance. IMS Health's 7500 services experts connect configurable SaaS applications to 10+ petabytes of complex healthcare data in the IMS One™ cloud platform, delivering unique insights into diseases, treatments, costs and outcomes. The company's 15,000 employees blend global consistency and local market knowledge across 100 countries to help clients run their operations more efficiently. Customers include pharmaceutical, consumer health and medical device manufacturers and distributors, providers, payers, government agencies, policymakers, researchers and the financial community.

CoLucid was founded in 2005 and is developing oral lasmiditan for the acute treatment of migraine headaches in adults and intravenous lasmiditan for the acute treatment of unspecified headache pain in adults in emergency room and other urgent care settings. Lasmiditan has been designed to deliver efficacy for the acute treatment of migraine headaches in adults without the vasoconstrictor activity associated with previous generations of migraine therapies. It selectively targets 5-HT<sub>1F</sub> receptors expressed in the trigeminal pathway. Lasmiditan has been given the generic stem name "ditan," which distinguishes it from other drug classes, including triptans, the current standard of care for migraine.

This report was produced by IMS Health and CoLucid Pharmaceuticals. For additional information or questions regarding the contents of this report, please contact IMS Health, <http://imshealth.com/>, and submit a query on the Contact page.

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## 2. Common Misperceptions about Migraine

Large scale epidemiologic studies demonstrate that migraine afflicts 36 million Americans and accounts for more than 112 million days of lost work annually. Individuals differ widely in the frequency, severity and associated symptom profiles of their attacks as well as their comorbidities. As a consequence, individualized treatment is of crucial importance for this heterogeneous disorder making it prone to misunderstanding, under diagnosis and under treatment. The launch of triptans (5-HT<sub>1B/1D</sub> agonists) in the early 1990s dramatically improved the acute treatment of migraine. Use of triptans is limited by the known coronary vasoconstrictor effects of these drugs as well as the adverse event profile which includes non-cardiac chest pain and angina as well as myocardial infarction. As a consequence, the development of an acute migraine therapy with triptan-like efficacy, free of cardiovascular risk, has long been a goal of the field.

This analysis highlights facts surrounding several pervasive misconceptions which have an adverse impact on the delivery of optimal treatment. The analysis and data are a tool to facilitate a real-world evidence discussion of the treatment of migraine and illuminate the potential role of new therapies, such as lasmiditan, in treatment of the migraine population.

### 2.1. Misperception: Migraine is a Disease of Young Women

Healthcare professionals and lay-people commonly believe that migraine is a disease predominantly affecting young women, and that the population of patients with migraine decreases after age 40. IMS Health's analysis confirms that although there are a number of younger female patients with a migraine diagnosis, the majority of the diagnosed population (55%) is 40+ (Exhibit 1). The total adult (over 18) migraine diagnosed population is 3.7 million, of which 82% (3 million) are female and 18% (668k) are male.

**Exhibit 1: Diagnosed U.S. Migraine Patient Population by Age and Gender, 2013**

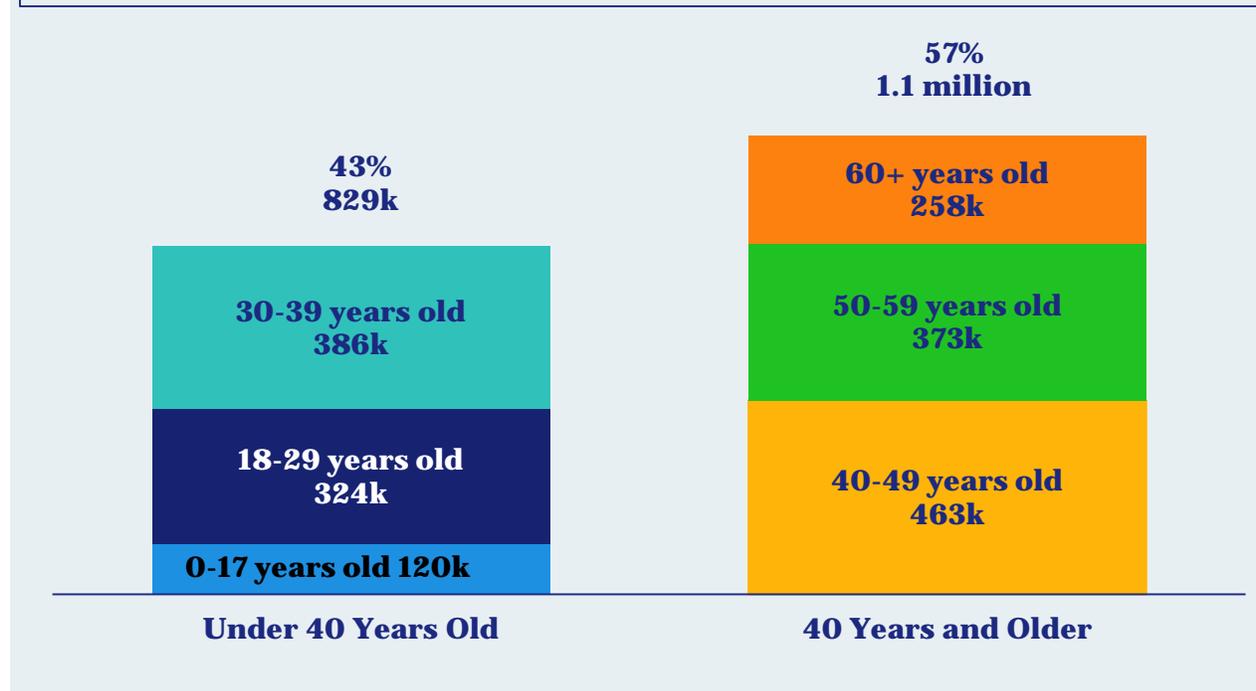
Age Group	Both Sexes		Male		Female	
	Number	Percent	Number	Percent	Number	Percent
0-17	377,963	9%	153,861	19%	224,102	7%
18-29	721,448	18%	138,000	17%	583,448	18%
30-39	749,856	18%	121,048	15%	628,809	19%
40-49	842,390	21%	133,591	16%	708,800	22%
50-59	710,513	18%	129,164	16%	581,349	18%
60+	651,771	16%	146,966	18%	504,804	16%
<b>Total</b>	<b>4,053,940</b>	<b>100%</b>	<b>822,629</b>	<b>100%</b>	<b>3,231,311</b>	<b>100%</b>

Source: IMS Health, PharMetrics Plus, January - December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

However, considering the adult *treated migraine patient population*, more than half (57%) are over the age of 40 (Exhibit 2). Within the adult diagnosed migraine population, 49%, or 1.8 million, are treated and 85% of the treated population is female.

## Exhibit 2: Diagnosed and Treated U.S. Migraine Patient Population by Age, 2013

Nearly **two-thirds** of diagnosed, **treated** migraine patients are **40 years and older**



Source: IMS Health, PharMetrics Plus, January – December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

Although men are 19% of the *diagnosed, adult* migraine patients, they are only 15% of the treated population. The number of men with migraine and the relatively smaller (in comparison to women) population should not detract from the fact that the male patient population is substantial, and potentially interesting to investigate for ways to better serve this population. The perception of migraine as exclusively a women’s disease has the result of making treatment more difficult for men and results in a substantial gap in providing them meaningful relief and care for migraine.

Thus, the IMS closed source database identifies patients over age 40, particularly female patients, as the largest addressable migraine population in the U.S.

## **2.2. Misperception: The Migraine Population with CAD Risk Factors is Small**

Triptan product labels explicitly state that triptans are contraindicated in patients with ischemic coronary artery disease, coronary artery vasospasm, angina, arrhythmias, history of stroke or transient ischemic attack (TIA), history of hemiplegic or basilar migraine, uncontrolled hypertension, myocardial ischemia, and myocardial infarction. These contraindications have been provided due to potential adverse cardiac reactions occurring following the administration of a triptan product. As a result, it is recommended that all healthcare professionals perform a full cardiovascular evaluation prior to prescribing triptans to any migraine patients.

Discussion of misperception 1 establishes that migraine is a disease that disproportionately affects women. As the discussion moves to CAD and CV risk, it is important to note that heart disease is the leading cause of mortality among women in the U.S. There is a documented lack of research examining the symptoms and risks of cardiovascular disease for women. The shortage of research often means women's risks are not assessed, they do not receive diagnostic and screening procedures and they are not aware of signs and symptoms<sup>1</sup>. Given that the majority of diagnosed and treated migraine patients are women, it is important to note CV risk for migraine patients, especially women.

Data cited in this section are based on two analyses. First, patients' observed CAD events and clinically appropriate ICD-9 codes as related to triptan labeling (contraindications and precautions and warnings) recorded in the health care claims database are flagged for analysis. Second, IMS utilizes patient cardiovascular risk factors based upon a number of attributes available in the data including ICD-9 coded comorbidities and demographic data to build a CV risk factor profile for modeling risk.

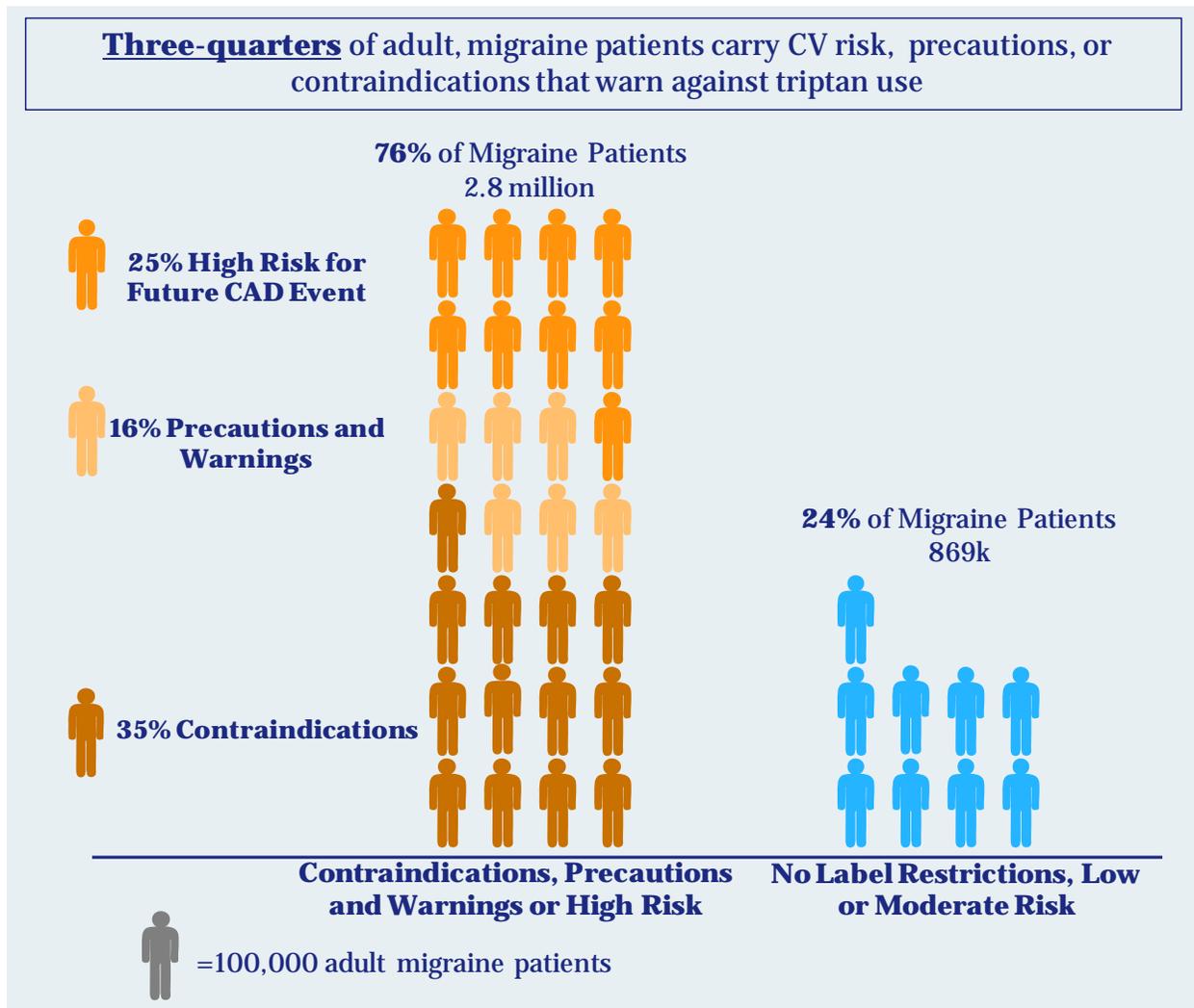
This model, using diagnoses and prescription data, predicts the likelihood of a future CAD event based upon the data available in the PharMetrics Plus database. The model for assessing risk is based upon the Framingham Heart Study, a landmark, long-term longitudinal study established to identify the common risk factors and characteristics associated with CAD events. The IMS data assess the patient risk for patients with migraine, as well as the general patient population for comparison.

IMS Health's analyses show that 3.7 million adult patients are diagnosed with migraine during the one year study period. By leveraging medical codes and applying the risk model derived from the Framingham Heart Study, 2.8 million diagnosed patients (76%) carry cardiovascular conditions or risk factors that contraindicate or warn against triptan use (Exhibit 3).

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<sup>1</sup> Wenger, Nannete MD; Women and Coronary Heart Disease: A Century After Herrick: Understudied, Underdiagnosed, and Undertreated; Summaries of the AHA Council Lectures 2011

**Exhibit 3: Triptan Label Restrictions and CV Risk in the Adult Diagnosed U.S. Migraine Patient Population, 2013**

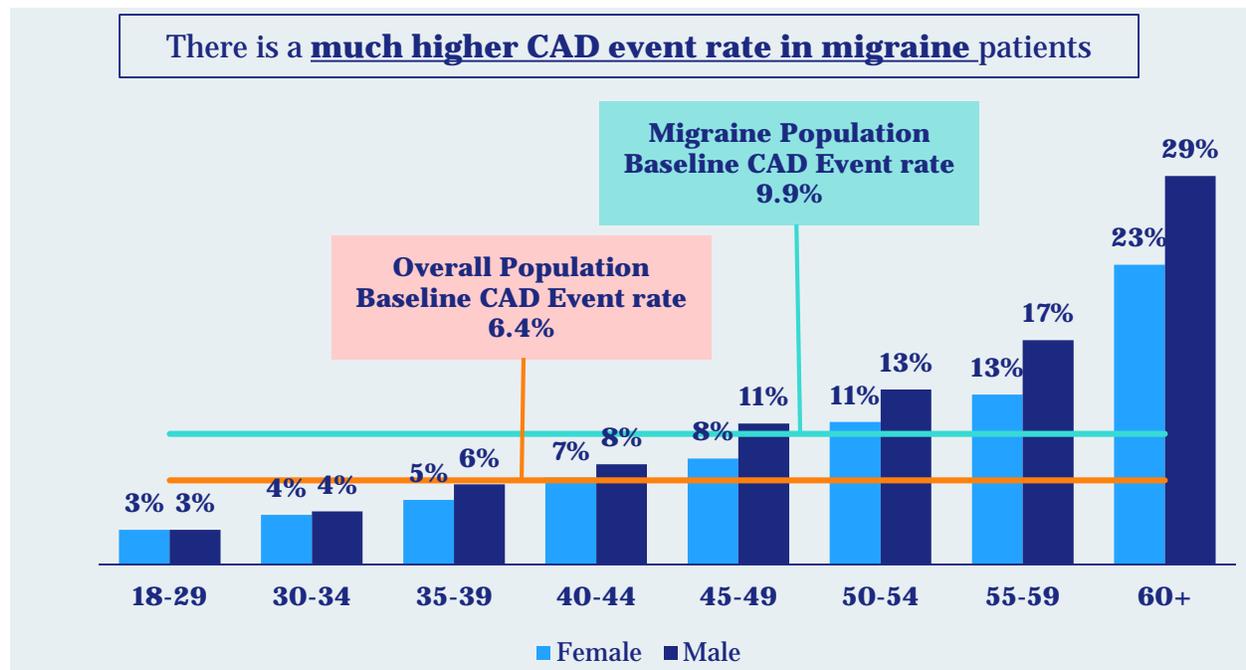


Source: IMS Health, PharMetrics Plus, January – December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

In the general insured adult patient population in the IMS PharMetrics Plus database (a population of insured patients predominantly under the age of 65), the rate of Coronary Artery Disease (CAD) events is 6.4%. As expected, the cardiovascular event rate increases with age. For example, the one year CAD event rate in the population over age 50 is 11.6% annually. The comparator for risk that will be used in this discussion will therefore be 6.4%.

Compared to the general population, diagnosed migraine patients have higher rates of CAD events-- 1.5 times the rate of the general population, 9.9% compared to 6.4% (Exhibit 4). In every age and gender cohort comparison, CAD event rates of migraine patients are higher; in patients under 40 the rates are 3 times as high as the general population rate (4.6% compared to 1.4%), and in patients 40+, CAD event rates are 1.8 times higher among migraine diagnosed patients (18.0% compared to 10.2%). This is true for both men and women across all age cohorts.

**Exhibit 4. CAD Event Rate in the Adult Diagnosed U.S. Migraine U.S. Patient Population, 2013**

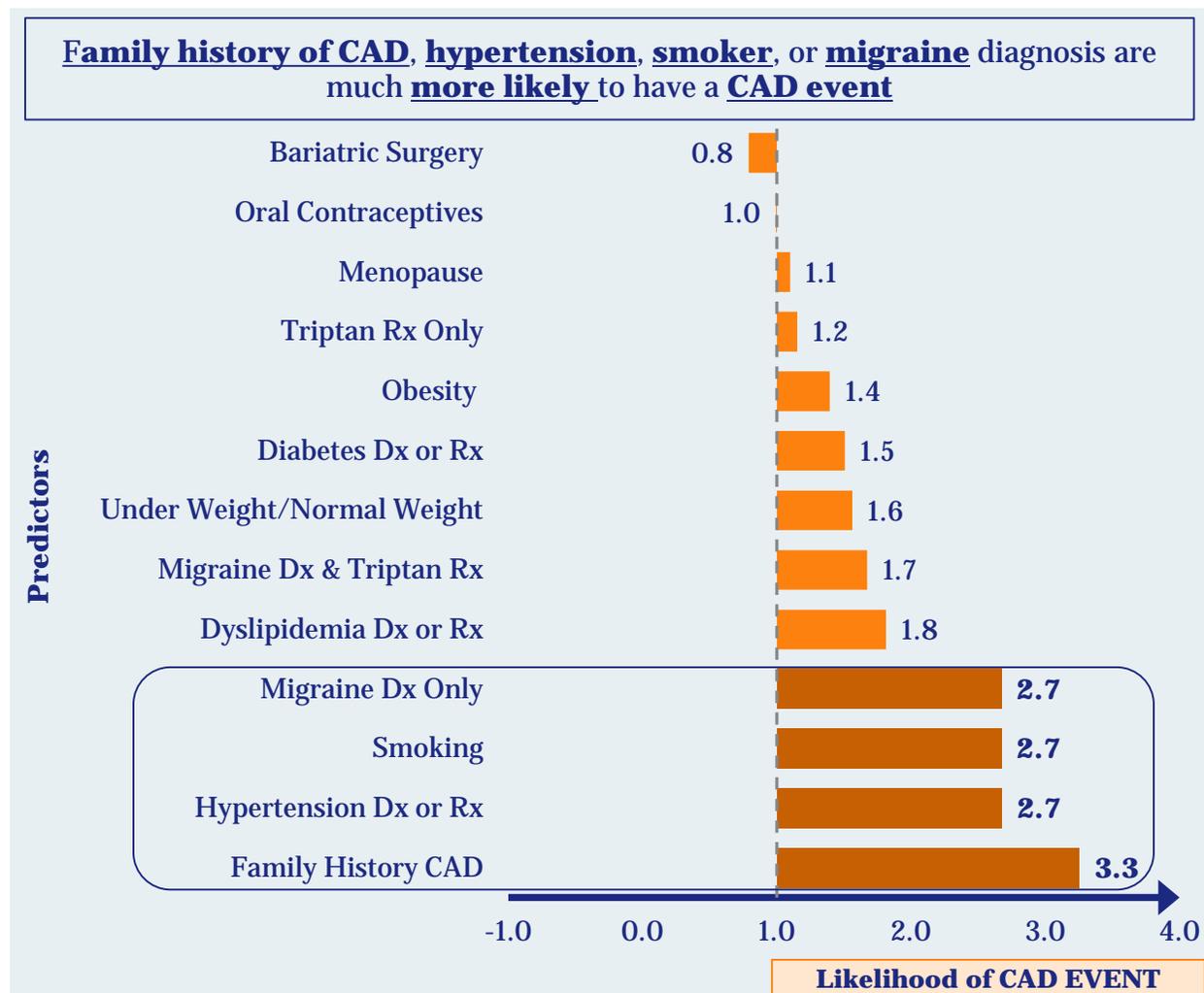


Source: IMS Health, PharMetrics Plus, January – December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

This study also compares the rate of CAD events for *diagnosed and treated migraine* patients as well as those treated with triptans or other acute therapies. Triptan treated patients have an event rate of 5.9% compared to the event rate for the overall migraine population of 9.9% during the study time period. This suggests that, as shown by prescription data, physicians avoid use of triptans in high risk populations, either not treating patients with drug therapy or choosing alternatives such as bultalbital and opioids. In other words, physicians are selective in prescribing triptans.

In addition to examining the rate of experiencing a coronary artery event, the study analyzes risk factors to determine the likelihood of predicting a future CAD event in the twelve months of the study. IMS modeled CAD risk factors based upon the Framingham Heart Study and developed a logistic regression model to provide a specific odds ratio (OR) for each patient included in the study during a 3-year period. ORs are commonly used to quantify the association of risk in a population; an OR of 1 indicates there is no association; an OR >1 indicates that the predictor favors the likelihood of the outcome. An OR does not indicate causation, but a predictive relationship. Due to the specific differences within age groups, and the varying risk factors associated with gender, the modeled risk factor ORs are unique to each age and gender cohort of interest. Exhibit 5 summarizes the OR predictor, regardless of age or gender.

**Exhibit 5: Risk Factors for Predicting a CAD Event (Odds Ratios) Among a General Adult Patient Sample (CAD Event Cohort), 2013**



Source: IMS Health, PharMetrics Plus, October 2012 – September 2013 Cohort, 2015. Note: Any predictor that falls to the right side of the dashed line ( $OR \geq 1.0$ ) favors the likelihood of an outcome (i.e. future CAD event); the further away from 1.0, the stronger the relationship between the predictor and the outcome (i.e., CAD event). For example, Family History of CAD indicates that patients are 3.3 times more likely to have a CAD event when compared to patients without a Family History of CAD coded during the study time period, all else held equal. Not all predictors are statistically significant. The table in the Methodology Section (page 21) shows ORs by age and gender as applied in the model.

Exhibit 5 shows the ORs in aggregate, while Exhibit 10 in the Methodology Section shows all ORs by age and gender in detail. Risk factors of family history of CAD, hypertension and smoking increase the likelihood of a future CAD event in both females and males for all age cohorts. For example, men and women (18-29) with a family history of CAD are about four times more likely to have an event (odds ratio of 4.1 and 3.8 respectively) than patients without a family history of CAD. Dyslipidemia, diabetes, and obesity also increase the chances of a future event; however, the increases are more variable by patient age and gender.

A migraine diagnosis is a predictor of a future CAD event. The analysis shows that among female patients ages 18-29, a migraine diagnosis carries a risk of four times more likely (OR 4.5) to have a future CAD event. Note that this is higher than the risk for women with a hypertension diagnosis or treatment. In fact, a migraine diagnosis in this age cohort of 18-29 is the highest predictor of a future CAD for women. Likewise, a migraine diagnosis in younger male patients also resulted in the highest risk (OR, 5.1 and 5.7), for those 18-29 and 30-34 respectively.

### **2.3. Misperception: Healthcare Professionals have No Concerns Regarding Triptan Use in Patients at Risk for CAD (CV Risk); View Patients as Well-Served by Triptans**

The definition of a patient who is “well served” is somewhat subjective. IMS collects data on prescription drugs; however, IMS does not include over the counter (OTC) or alternative (chiropractic, acupuncture) therapy. For this analysis, IMS did not capture medication “in hand”, i.e. medication filled prior to the study period, and IMS may not capture “off-label” use of certain drugs to treat migraine.

The exact nature of the untreated population cannot be easily assessed. Those patients may be categorized as untreated because they have medication ‘in hand’ from prior to the study period; or, they may be untreated because they have not had success with any of the available products or are concerned about the risks associated with existing products after consultation with their health care provider.

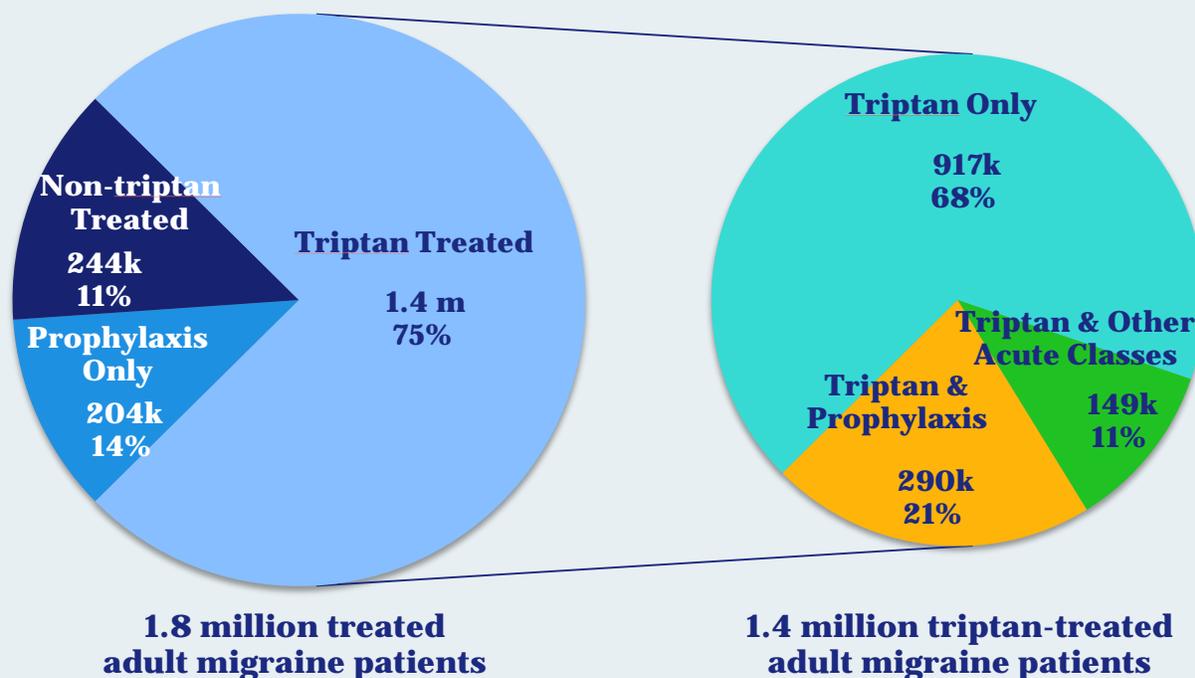
In addition, the definition for a migraine patient treated with an opioid or butalbital is conservative in this IMS analysis. Only opioid use in migraine patients that met the following criteria were included in this analysis: a diagnosis of interest within 14 days prior to the prescription, a refill of the same product class in 30 days, and no record of any surgery within 30 days prior. This is considered a conservative estimation of opioid use.

Within just the *diagnosed, adult migraine* population, the overall *treated migraine market* size is 1.8 million (49% of diagnosed) patients, with 1.6 million (42% of diagnosed) patients receiving acute treatments for migraine and 653k (18% of diagnosed) patients receiving migraine prophylaxis. There is overlap among these patients, whereby, 410k patients receive both an acute and prophylaxis therapy.

Among the *treated, adult migraine* patients, 75% (1.4 million) receive a triptan treatment during that year. Of the 1.4 million triptan patients, nearly a third (32%) is filling multiple classes of acute and prophylaxis prescription medications during a 12-month period (Exhibit 6).

## Exhibit 6: Acute Treated Adult U.S. Migraine Patient Population, 2013

**Two-thirds** of adult, migraine patients are **treated with triptans**; **32%** of them also receive **multiple medication classes**

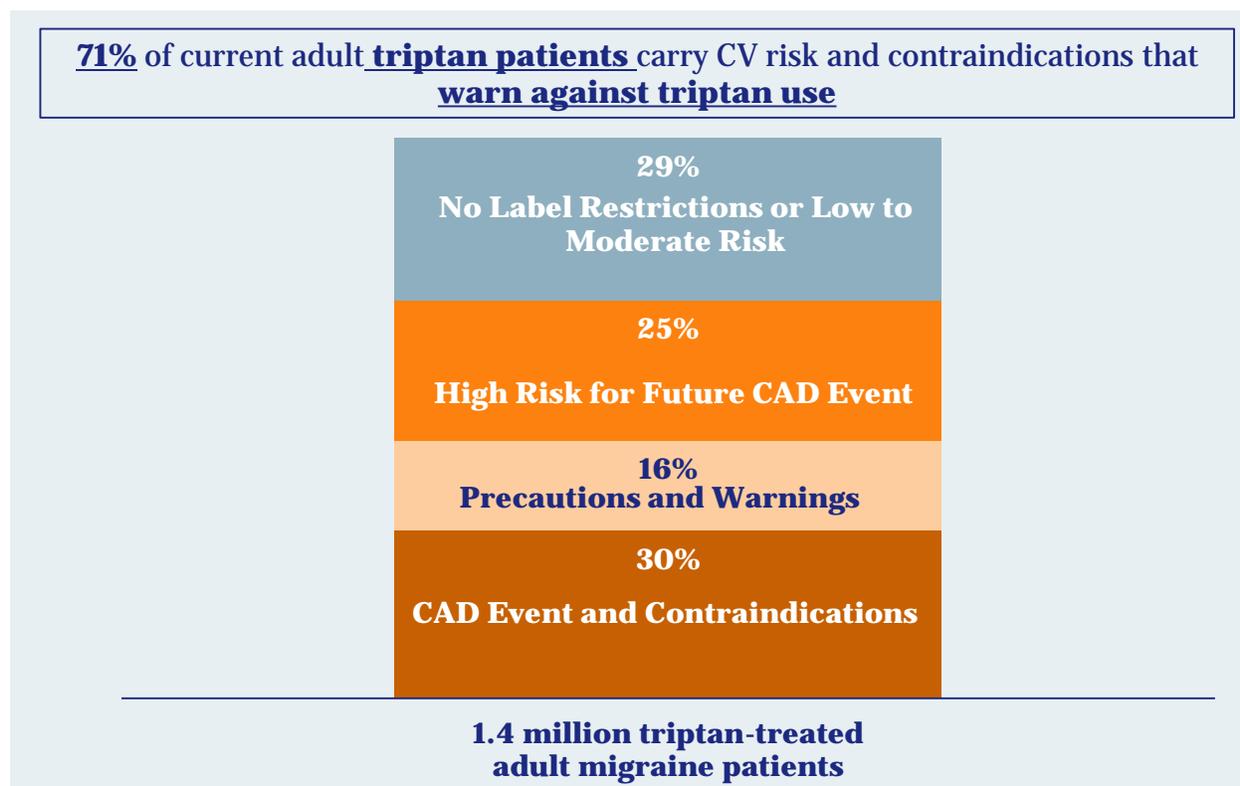


Source: IMS Health, PharMetrics Plus, January – December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

There are a number of patients treated with other classes of currently available therapies, specifically the butalbital and opioids (17%). The quantification of treatment patterns with opioids in this analysis is conservative, and it is likely that the use of opioids in the acute treatment of migraine is underreported. If medication in hand and all therapies are considered, the overall percentage of patients filling prescriptions would likely be higher. Therefore a substantial majority of diagnosed migraine patients are treated, and are treated with multiple therapy classes.

Seventy one percent (962k) of all adult patients prescribed a triptan have CV conditions or risk factors for CAD (Exhibit 7), suggesting that triptans are being used ‘inappropriately’, or contrary to triptan product labeling for contraindications, precautions and warnings. Thirty percent (405k) of adult, migraine patients receiving triptan treatment have had a recent CAD event or are taking a triptan with a defined contraindication, 25% (338k) are in a high-CV risk category, while an additional 16% (218k) are receiving a triptan with defined precautions and warnings.

## Exhibit 7: Risk Assessment of Triptan Treated Adult U.S. Migraine Patient Population, 2013



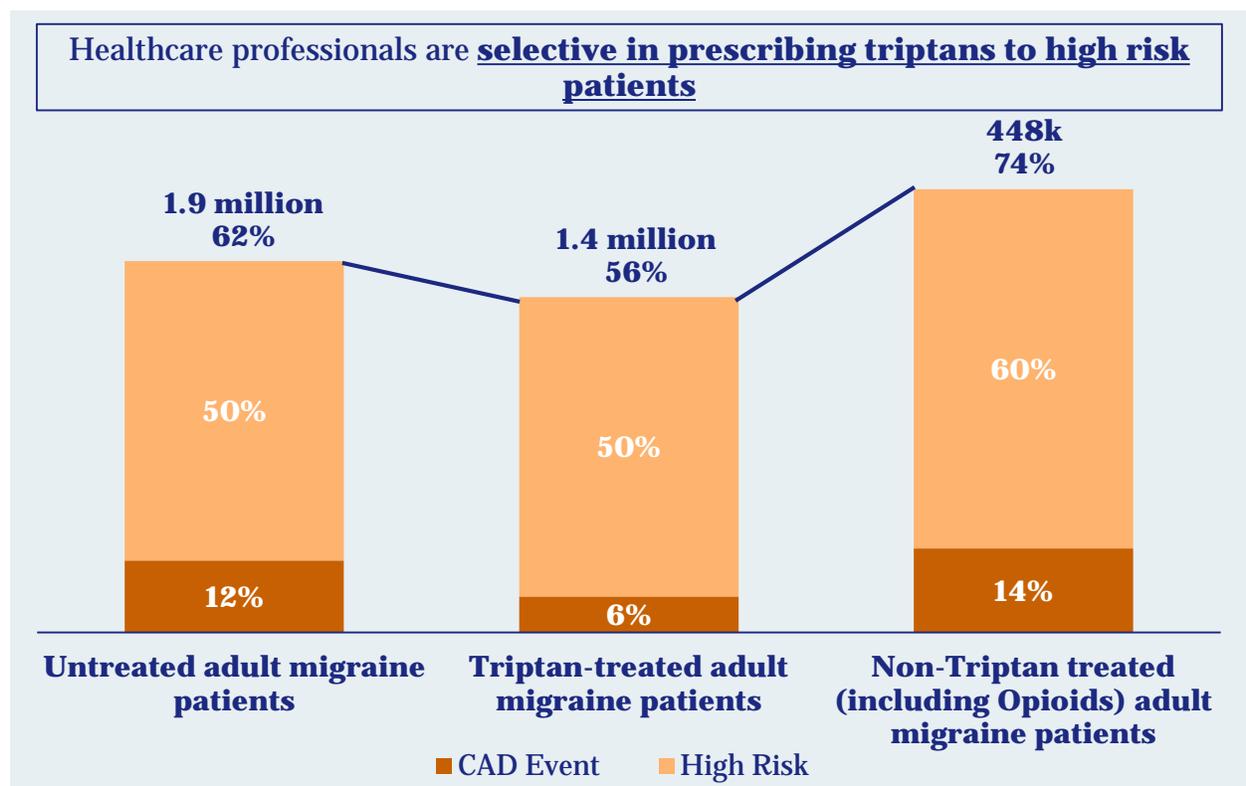
Source: IMS Health, PharMetrics Plus, January – December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

However, the data suggest that healthcare professionals, as a whole, alter their treatment patterns for migraine patients with CV conditions or risk factors for CAD, frequently choosing to forego treatment or choosing a non-triptan, non-vasoconstrictive therapy.

Treatment rates are also lower among migraine patients with a CAD event or high CV risk (47% compared to 53%). Only 69% of patients at high-risk or with a CAD event are triptan-treated compared to triptan-treated rates of 75% among all migraine patients.

The IMS data show that adult, migraine patients with CAD events and high CV risk have a higher treatment rate with butalbital and opioids. Opioids are not indicated for the treatment of migraine and have been associated with abuse and medication overuse headache. Off-label use of opioids is more likely in CV risk patients than in the general adult treated migraine population. The proportion of patients having high CV risk or a known CAD event who are prescribed opioids for treating migraine is higher than the proportion having high CV risk or a known CAD event who are prescribed triptans (74% compared to 56%) (Exhibit 8). Thus, these patients are likely not currently well served by available therapies.

## Exhibit 8: CAD Event Rate and High CV Risk among Diagnosed Adult U.S. Migraine Patient Population by Type of Treatment, 2013



Source: IMS Health, PharMetrics Plus, January – December 2013 Cohort Projected to U.S. Insured Patient Population, 2015

The fact that there is such a substantial diagnosed population that is not treated indicates that at least some portion of this nearly 1.9 million untreated patients are not well served by current therapies. In addition, these data indicate that currently diagnosed migraine patients may not be well served by triptans, since in a third-party covered population these widely available medications are used by less than half of all adult, diagnosed migraine patients (37%).

Although the focus of this analysis is on the migraine population, IMS has also examined the treatment patterns in the overall primary headache population for two reasons: 1) many patients diagnosed with primary, non-traumatic headaches are thought to actually suffer from migraines and receive treatment; and 2) to understand the overall incidence of CV conditions or high risk of CAD in primary headache patients who could also benefit from a non-vasoconstrictive drug therapy.

Results of our study indicate that primary headache patients and migraine patients share many similarities and needs. Of particular interest:

- The diagnosed adult, primary headache patient population (10.8 million) is substantially larger than the migraine population (3.7 million).

- The overall CAD event rate is higher among adult diagnosed primary headache patients (12.2% vs. 6.4%) than the general population.
- Triptans are frequently prescribed for adult diagnosed and treated primary headache—27% of all triptan use is for patients with a diagnosis of primary headache.
- Frequency of triptan use decreases in patients with CAD events and CV risk factors—66% for adult diagnosed and treated primary headache patients compared to 60% for adult diagnosed and treated headache patients with a CAD event or who are at high CV risk.

### **3. Opportunity for New Therapies for Migraine Patients with CV Conditions or Risk Factors**

As shown by IMS data, physicians tend to alter their use of triptans in high risk patients, either by not treating patients with drug therapy or choosing alternatives such as butalbital and opioids. In other words, physicians are selective in prescribing triptans. Thus there is a significant market opportunity for new therapies that can be prescribed to the 2.8 million U.S. adult migraine patients who have had either a CAD event, are at high CV risk, or are otherwise contraindicated for triptan use. These data infer that new therapies for the acute treatment of migraine, specifically those absent the contraindications, precautions and warnings associated with vasoconstrictive properties of triptans, may expand the number of treated migraine patients who receive therapy.

The IMS study identifies that half of the diagnosed adult migraine population are not treated (1.9 million). This study does not answer the 'why's' behind this finding; however, in a diagnosed population, this finding can be safely identified as an opportunity in half the diagnose migraine population. If some of these patients are not being treated because of concern about contraindications, or warnings and precautions per triptan product labeling, there is a substantial unmet need that can be immediately addressed with a new therapy without vasoconstrictive properties.

There is also use of opioids and butalbital within the migraine population, which may be reduced with the introduction of a new therapeutic option. These products are disproportionately prescribed for patients who have had a CAD event or are at high CV risk; indicating that they are prescribed due to lower cardiovascular risk. Introduction of a product specifically indicated for the treatment of migraine without the triptan-associated CV issues is likely to 1) appeal to patients, providers, and payers or 2) provide an attractive therapeutic option to patients, providers, and payers.

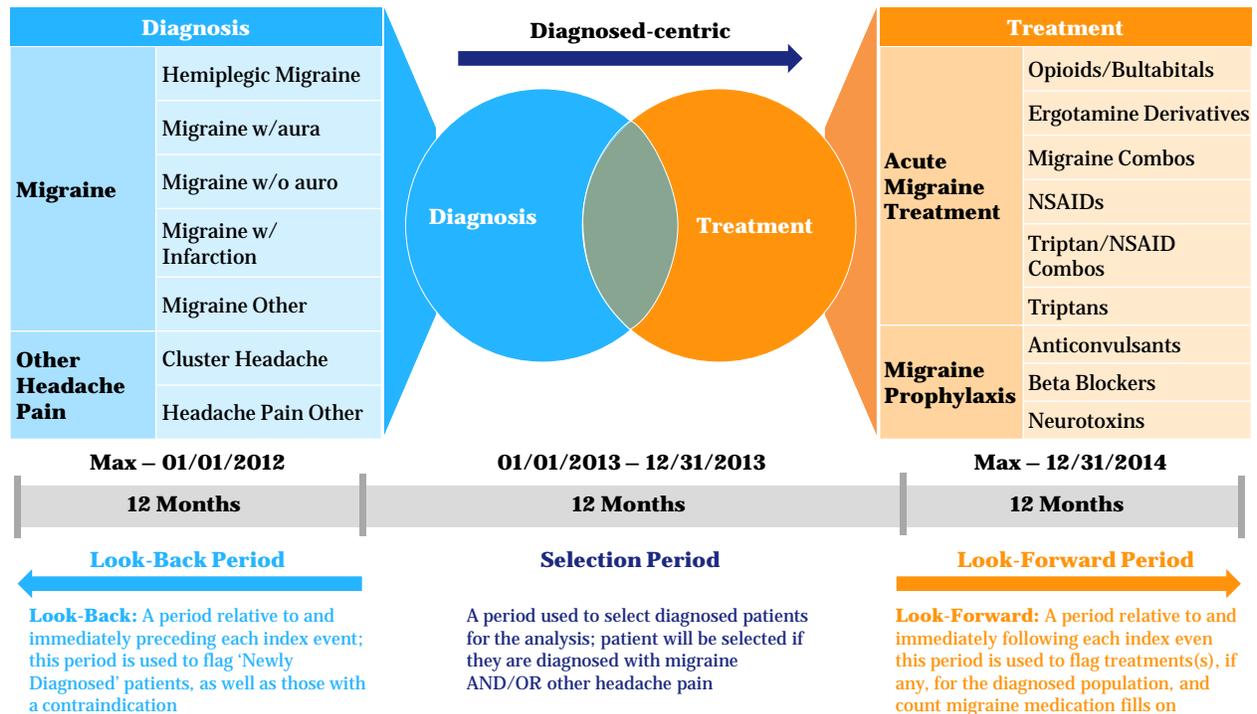
## 4. Methodology

### 4.1. Overview

IMS Health's PharMetrics Plus database is comprised of adjudicated claims for health plan enrollees across the United States. PharMetrics Plus includes enrollees with both medical and pharmacy coverage, representing more than 50 million unique lives. The data includes a range of geographies and plan types in the U.S. Attributes of the data include medications prescribed (date, product form, strength), diagnoses and procedures, patient demographics, payer type and provider information.

In order to understand the overall headache and migraine diagnosed and treated patient population, patients with a headache diagnosis of interest during January 1, 2013 through December 31, 2013 are included in the study from their first claim of interest. Patients must have continuous healthcare enrollment during the entire period (3 years), which ensures a more complete view of the patient's relevant healthcare claims. From that first diagnosis claim in 2013, patients are followed forward for 12-months (1-year) to track relevant treatment patterns. Patient history and events (up to a 12-month look back and 12-month look forward) are examined to determine presence of contraindications, precautions and warnings as indicated by triptan labels and as coded in the healthcare billing system. In addition, patients' historic information is used to determine cardiovascular risk and CAD event rates among the diagnosed headache and migraine patients (Exhibit 9). The sample data is projected to the U.S. insured population in 2013 of 274 million.

**Exhibit 9: PMTX Plus Sample Selection for Market Sizing Cohort**



This study recreates elements of the model from the Framingham Study using the IMS PharMetrics Plus data. The PharMetrics Plus data does not capture all the Framingham variables, but enough that it is sufficient for modeling purposes. The identified cardiovascular risk factors (see dependent variables below) are used to determine the likelihood (expressed as an odds ratio) of having a CAD event.

The data used for modeling consist of one row of variables per patient. The response variable is the naïve CAD event during the study period (between October 1, 2013 and September 30, 2014). Patients with a naïve CAD event are included in the model data set. IMS has selected a control set of patients without a CAD event during the entire study period from a random sample of 10% of the PharMetrics Plus patient population. Any patient with a CAD event in the index or look back period has been dropped.

Dependent variables are based on the two year look-back from the naïve CAD event date for CAD patients or a randomly assigned index date during the index period for the non-CAD event patients. The dependent variables for modeling the CAD event are:

- 1) Hypertension diagnosis or treatment
- 2) Diabetes diagnosis or treatment
- 3) Dyslipidemia diagnosis or treatment
- 4) Menopause diagnosis
- 5) Obesity (direct ICD-9 code or BMI coding of 30 or more)
- 6) Underweight/Normal weight diagnosis
- 7) Smoking diagnosis or cessation treatment
- 8) Family history of CAD
- 9) Oral Contraceptives
- 10) Bariatric Surgery
- 11) Migraine diagnosis
- 12) Triptan Treatment
- 13) Age group
- 14) Gender

IMS uses the empiric baseline rates of CAD events by age and gender and then uses a logistic regression model to compute the relative risks as odds ratios. Results are displayed in Table 1.

Once odds ratios of the cardiovascular risk factors are determined from the sample data (Exhibit 10), headache patients are assigned to one of four CAD risk groups, based on individual CV history: CAD Event (Observed during study period), High (Top 25%), Moderate (Middle 50%) and Low (Bottom 25%).

## Exhibit 10: Odds Ratios by Age and Gender among PMTX+ Adult Patient Sample

Females	18-29 (n=96,390)	30-34 (n=38,186)	35-39 (n=45,708)	40-44 (n=55,449)	45-49 (n=64,720)	50-54 (n=78,413)	55-59 (n=81,454)	60-64 (n=73,566)	65+ (n=59,277)
Diabetes Dx or Rx	1.2	1.5*	1.6*	1.6*	1.6*	1.7*	1.7*	1.7*	1.4*
Dyslipidemia Dx or Rx	2.3*	2.0*	1.7*	1.8*	1.7*	1.7*	1.7*	1.7*	1.7*
Family History CAD	3.8*	3.1*	3.0*	3.7*	3.3*	3.0*	3.1*	2.9*	1.9*
Hypertension Dx or Rx	2.6*	2.0*	2.4*	2.4*	2.3*	2.4*	2.3*	2.3*	3.3*
Menopause	1.1	2.2*	1.6*	1.4*	1.4*	1.2*	1.1*	1.1*	1.0
Obesity	1.6*	1.4*	1.5*	1.5*	1.5*	1.4*	1.3*	1.3*	1.2*
Smoking	2.3*	1.9*	1.9*	2.2*	2.4*	2.4*	2.6*	2.4*	2.0*
Under/Normal Weight	2.1*	1.7*	1.7*	1.7*	1.7*	1.6*	1.6*	1.6*	1.6*
Oral Contraceptives	1.0	0.8	0.9*	0.8*	0.8*	0.7*	0.9	1.2	1.3
Bariatric Surgery	1.0	0.6	0.8	0.7*	0.9	0.7*	0.7*	0.7*	0.7
Migraine Dx and Triptan Rx	2.8*	2.6*	2.3*	2.0*	1.6*	1.5*	1.5*	1.5*	1.2
Migraine Dx Only	4.5*	3.6*	3.1*	2.5*	2.6*	2.4*	2.3*	2.2*	1.9*
Triptan Rx Only	2.0*	1.3	1.2	1.2	1.1	1.1	1.1	1.1	0.8*
Males	18-29 (n=99,841)	30-34 (n=36,823)	35-39 (n=43,317)	40-44 (n=52,254)	45-49 (n=61,201)	50-54 (n=74,557)	55-59 (n=79,119)	60-64 (n=72,213)	65+ (n=58,371)
Diabetes Dx or Rx	2.0*	1.6*	1.6*	1.5*	1.6*	1.5*	1.5*	1.4*	1.3*
Dyslipidemia Dx or Rx	1.8*	2.1*	1.9*	2.0*	2.0*	1.9*	1.9*	1.9*	1.9*
Family History CAD	4.1*	4.3*	4.7*	4.6*	3.9*	3.8*	3.8*	2.9*	2.0*
Hypertension Dx or Rx	4.0*	3.5*	3.0*	2.8*	2.7*	2.7*	2.7*	2.6*	3.1*
Menopause									
Obesity	1.6*	1.3	1.6*	1.6*	1.5*	1.5*	1.4*	1.4*	1.3*
Smoking	3.4*	2.6*	2.9*	3.2*	3.2*	3.3*	3.1*	2.9*	2.3*
Under/Normal Weight	2.4*	2.6*	2.1*	1.5*	1.4*	1.5*	1.2*	1.3*	1.5*
Oral Contraceptives									
Bariatric Surgery	2.7	0.7*	0.6	0.6	0.8	0.9	0.9	1.2	1.5
Migraine Dx and Triptan Rx	1.7*	1.4*	2.0*	1.7*	2.0*	1.3*	1.2	1.1	1.4
Migraine Dx Only	5.1*	5.7*	3.9*	3.1*	3.1*	2.5*	2.3*	2.1*	2.3*
Triptan Rx Only	1.3	1.7	1.7*	2.1*	1.1	1.3	1.2	1.2	0.8

Dx=Diagnosed; Rx = Prescription Treated

\*Statistically significant at 95% confidence interval

Source: IMS Health, PharMetrics Plus, October 2012 – September 2014 Cohort, 2015

## 4.2. Patient Cohorts

1. The analysis uses two patient cohorts within the IMS LifeLink PharMetrics Plus Claims Database:
  - a. Market Sizing Cohort
    - i. Purpose: Headache and Migraine Diagnosed Sample
    - ii. Data Time Frame: January 1, 2012 – December 31, 2014
    - iii. Selection Period: January 1, 2014 – December 31, 2014
    - iv. Look-Back Period: 24 months prior to first event of interest date during the index period.
  - b. Modeling Cohorts
    - i. 10% PharMetrics Plus random sample
      1. Purpose: Baseline CAD Event Rates
      2. Data Time Frame: October 1, 2011-September 30, 2014
    - ii. CAD Event Cohort
      1. Purpose: Cardiovascular Risk Factor Odds Ratios
      2. Data Time Frame: October 1, 2011 – September 30, 2014
      3. Selection Period: October 1, 2013 – September 30, 2014
      4. Look-Back Period: 2 years from the CAD event

### 4.2.1. CAD Event Definition

A CAD event corresponds to the ICD-9, CPT and ICD-9 procedure codes of interest. For the event to be defined as naïve there cannot be another CAD event in the look back period. IMS Health clinical team has provided the codes for a CAD event.

Coronary Artery Disease Events are used as end-point predictors in modeling. They include:

- Myocardial Infarction (Myocardial infarction acute/old, Acute coronary insufficiency, Impending MI)
- TIA (Transient ischemic attack)
- Stroke (Cerebral infarction / occlusion / thrombosis / embolism - acute and old)
- Claudication
- Angina
- Coronary Bypass Surgery
- Coronary Angioplasty/Stenting
- Carotid Artery Surgery/Stenting
- Peripheral Vascular Bypass Surgery

### **4.2.2. Risk Factor Aggregation**

The diagnosis codes, NDC and procedure codes are mapped to their corresponding predictive variable. All predictor variables are “yes” and “no” variables except age and gender. If a patient has any condition during the 2 year look back, that patient is coded with the condition. IMS Health clinical team has provided the codes for the risk factors.

Risk Factors include diagnoses, procedures, and prescription products associated with:

- Diabetes
- Dyslipidemia
- Hypertension
- Weight/Obesity Concerns (includes codes for Bariatric Surgery, Normal/Under Weight)
- Smoking
- Migraine
- Triptan Use
- Menopause
- Oral Contraceptive Use
- Family History of CAD

### **4.3. Modeling Approach**

IMS has analyzed two cohorts of patients separately:

1. The CAD risk data. Data sets 1 and 2.
2. The Migraine cohort.

This produced two models:

#### **1. Average CAD risk**

The first step of the average CAD risk model is to calculate the base rate of CAD events in males and females for the following age groups:

- 1) 18 – 29
- 2) 30 – 34
- 3) 35 – 39
- 4) 40 – 44
- 5) 45 – 49
- 6) 50 – 54
- 7) 55 – 59
- 8) 60 – 64
- 9) 65+

From the 10% sample (Data set 1) IMS has computed the number of patients in each group that had a CAD event during the data time frame and has divided the number of patients that had a CAD event by the number of patients in each group. This forms the base rate of a CAD event.

The patients in data set 2, the CAD event data set, are used to enrich the 10% sample for the calculation of relative risk. Data sets 1 and 2 are combined and a logistic model has been fit to each of the 20 age and gender segments.

#### *Coding the Variables for Relative Risk*

The outcome variable for the model is the presence of a CAD event from October 2013 to September 2014. The event is naïve because IMS removed patients who had a CAD event in the two year look back period from the first CAD event in the index period. The predictive variables used in the model are identical to those used in the CAD event model.

### **2. Migraine cohort**

The same two models have been applied to migraine cohort, data set 3. The average risks for the age and gender segments are estimated. The data set is not enriched and a logistic regression has been fit to each age and gender cohort. These logistic regressions have been used to compute the odds ratios.

### **4.3.1. Scoring of the Patients for CAD Risk**

Finally the average rates and the odds ratios of the risk factors from the logistic model have been applied to the diagnosed headache and migraine patient cohort.

First, diagnosed patients, who had a CAD event in the pre-or post-index period are assigned to the CAD Event group. Next, the remaining patients are assigned to 1 of 3 groups, based on scoring of cardiovascular risk factors in their history:

- 1) CAD Event
- 2) High: meaning the patient has a score in the top 25%. This is usually called the top quartile.
- 3) Medium: meaning the patient has a score between the 25% and 75% percentile.
- 4) Low: meaning the patient has a score in the bottom 25%. This is usually called the bottom quartile.

## **4.4. Methodology Appendix**

### **4.4.1. Logistic Regression**

In traditional regression, one has a dependent variable  $Y$  that they wish to model on a set of independent variables  $X_1, \dots, X_n$ . The dependent variable is continuous, taking any value. There is an extension called logistic regression where the dependent variable takes one of two values. The values are canonically labeled success or failure, but they can refer to anything, such as “CAD event” and “No CAD event.” One uses logistic regression to analyze the case when the dependent variable has two values.

One models the dependent variable as  $Y = \beta_0 + \beta_1 X_1 + \dots + \beta_n X_n + \varepsilon$  in traditional regression.  $\varepsilon$  stands for the error that is usually Normal with mean 0 and unknown variance. One needs a function that returns a value between 0 and 1 for logistic regression. The logistic function is typically used and it has the form:

$$L(x) = \frac{e^x}{1 + e^x}$$

For logistic regression, the model is  $Y = L(\beta_0 + \beta_1 X_1 + \dots + \beta_n X_n)$ . The error term  $\varepsilon$  has been eliminated because the probability model is: Y is a success with probability  $L(\beta_0 + \beta_1 X_1 + \dots + \beta_n X_n)$  and a failure with probability  $1 - L(\beta_0 + \beta_1 X_1 + \dots + \beta_n X_n)$ . A computer maximization program is used to find coefficients that maximize the probabilities of seeing the success and failures.

## 5. Authors



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Jenn Millard is a Principal in the Real World Evidence Solutions group and has served as a consultant, performing both quantitative and qualitative analyses to understand market dynamics. Jenn is highly experienced at delivering and implementing recommendations covering a variety of strategic sales and marketing issues, with significant focus on product launch, performance management and market insight development. Jenn is an accomplished researcher with over 15 years of research experience, which encompasses many therapeutic areas, including multiple sclerosis, diabetes, vaccines, mental health, pain, respiratory, rare diseases, and migraine. Before joining IMS Health, Jenn worked for Fox Chase Cancer Center and the University of Pittsburgh Cancer Institute, where she designed primary market research studies; moderated qualitative research sessions; prepared research protocols; and coordinated grant submissions. Jenn has earned her B.S. degree from Pennsylvania State University with a dual major in Marketing and Psychology and earned her M.B.A. in Marketing from Temple University's Fox School of Business.



### **Donna DiStefano**

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Donna is an Engagement Manager with the Commercial Services group within IMS Health. Donna is focused on developing customized opportunities for market access, product development, market sizing, and product strategy. Donna has extensive experience in several therapeutic areas including ophthalmology, diabetes, chronic kidney disease, cardiovascular disease. She has held several positions in both Commercial Analysis and Product marketing. She is particularly skilled at building collaboration with sales, marketing and commercial analysis teams by integrating market research, competitive intelligence, secondary data and market analytics to address key business objectives. Before joining IMS, Donna was with Reata Pharmaceuticals in Irving Texas; prior to that she spent nearly five years at Alcon Laboratories in various positions in Marketing and commercial analysis in the pharmaceutical and surgical franchises. Donna holds a BS in Biology from Loyola University in Maryland, and an MPH from Rutgers University.



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Kelly leads the Commercial Services team that focuses on providing pre-launch and in-market operational guidance to specialized pharmaceutical companies, the creative agencies that support the healthcare industry, and advocacy organizations that seek to incorporate Real World Evidence into their healthcare initiatives. Kelly is highly experienced in providing evidence-based operational guidance to marketing, sales, and business development client teams. She has hands-on experience in the assessment of product potential, development of multi-channel operational plans tied to reaching that potential, and creation of diagnostic solutions across several therapeutic markets (spanning orphan drug categories through mainstream conditions that impact a broad base of patients). Kelly holds a B.S. degree in Marketing from the Pennsylvania State University.



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