



THIN Database Study Plan:

Initial Treatment of High Risk Hypertension Patients: ARB Monotherapy versus FDC Therapy

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January 2012

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1. Motivation

Hypertension is one of the most common diseases in the world, affecting an estimated 20% of the adult population overall. It is also one of the most significant, single, modifiable risk factors in cardiovascular disease, and appropriate treatment has the potential to reduce cardiovascular morbidity and mortality significantly. The treatment pathway for patients with hypertension varies from country to country but European guidelines stress the importance of monotherapy and fixed-dose combination (FDC) therapy (Figure 1). They suggest that most hypertensive patients can only achieve effective BP control by a combination of at least two antihypertensive drugs (Mancia 2009).

Figure 1. Monotherapy versus combination therapy strategies (ESC/ESH Guidelines; Mancia et al. 2007)

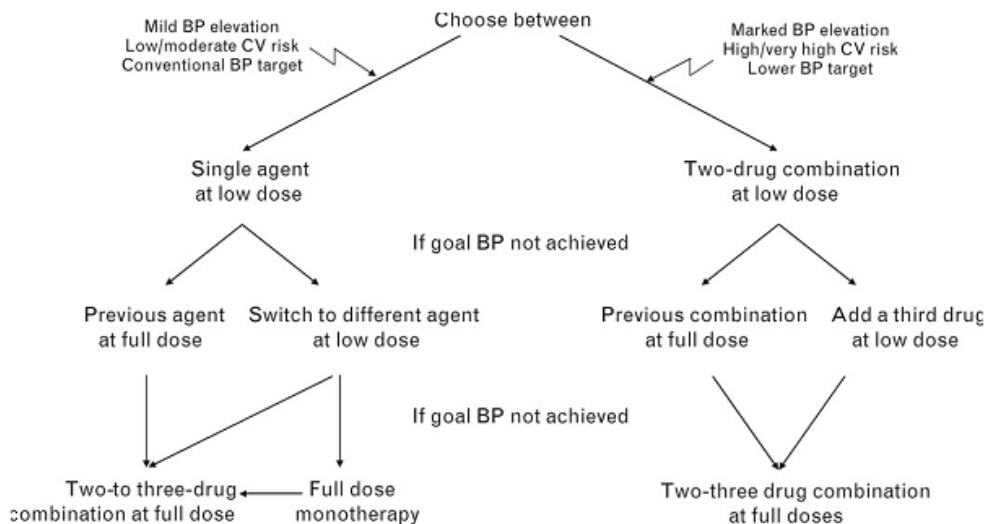


Figure 3 Monotherapy versus combination therapy strategies.

Guidelines and best practices vary for subgroups of patients. Some—such as those who present with higher grade hypertension and/or significant cardiovascular risk factors—may be good candidates for initial FDC therapy. Others—such as those who present with lower grade hypertension and fewer cardiovascular risk factors—may be able to delay movement to FDC, thereby potentially reducing their exposure to negative metabolic effects of some diuretics.

PHMR Associates has been asked by Takeda (Europe) to conduct UK healthcare database analyses to provide a better understanding of the population that may benefit from Azilsartan Medoxomil—a new angiotensin-receptor blocker (ARB)—in the treatment of Essential Hypertension. Identifying a potential initial Azilsartan Medoxomil FDC population and an Azilsartan Medoxomil monotherapy population will highlight care improvement and cost savings opportunities for subgroups of patients and permit more selective marketing to physicians and payers in charge of such patients. More generally, however, the research will provide information on how closely physicians treating high risk patients adhere to guidelines for initial treatment of hypertension and how treatment protocols affect outcomes.

2. Objectives and Specific Aims

Research Objectives

The objectives of the study are: (1) to determine which patients are good candidates for initial treatment with two-drug fixed combination therapy at low dose, rather than monotherapy (e.g., individuals with more severe hypertension), and which patients would benefit from prolonged ARB monotherapy (e.g., patients at risk of developing diabetes); (2) to examine the divergence, if any, between recommended treatment and treatment provided in practice; and (3) to consider the effect upon reaching target blood pressure goals of different treatment regimens for high risk subgroups of patients.

Specific Aims

Specific research questions (D=descriptive analysis; R=regression analysis) include:

- a) What percentage of newly diagnosed patients meet guideline-derived criteria for initial treatment with FDC (e.g., patients with high index BP and/or CV risk factors)? What percentage of such patients are treated with initial FDC therapy? (D)
- b) What percentage of newly diagnosed patients meet guideline-derived criteria for avoidance of FDC therapy (e.g., patients at risk of diabetes, metabolic syndrome, etc.)? What percentage of such patients are treated with initial ARB/other monotherapy? (D)
- c) Among newly diagnosed patients, what percentage change therapy within the first year post-diagnosis? What percentage switch from an ARB to another ARB? What percentage switch from ARB monotherapy directly to FDC therapy? What is the difference in mean time-to-switch between those who try more than one ARB treatment regime and those who switch from ARB monotherapy to FDC treatment? (D)
- d) Which observable patient characteristics (e.g., age, sex, baseline BP range, clinical conditions, BMI, etc.) are associated with initial FDC treatment (versus initial monotherapy treatment) in practice? (R)
- e) How are different treatment regimes (e.g., ARB monotherapy, FDC, etc.) associated with achieving blood pressure target levels in practice, controlling for patient characteristics? (R)

3. Disease Background

The International Society of Hypertension and World Health Organization define hypertension as a sustained blood pressure (BP) of $\geq 140/90$ mmHg for most patients (but lower for diabetic patients at $\geq 130/80$ mmHg). Hypertension is graded according to blood pressure ranges. Treatment recommendations vary with grade (Table 1).

Table 1. Grades of hypertension and associated treatment recommendations

Blood pressure (BP) category	Systolic BP mm Hg	Diastolic BP mm Hg	Lifestyle intervention	Drug therapy
Normal	<120	<80	–	–
High-normal	135–139	85–89	Yes	Consider*
Mild hypertension (grade 1)	140–159	90–99	Yes	Consider†
Moderate hypertension (grade 2)	160–179	100–109	Yes	Yes
Severe hypertension (grade 3)	≥180	≥110	Yes	Yes

*Drug therapy may be indicated for people with established cardiovascular disease, chronic renal disease, or diabetes with complications at BP levels > 130/80 mm Hg.
†Drug therapy is recommended for people with established cardiovascular disease or diabetes or evidence of target organ damage or a 10 year cardiovascular risk ≥ 20%.

Source: Joint British Societies (2005).

Essential (primary) hypertension is diagnosed when no identifiable cause can be found and accounts for 95% of all cases of hypertension. Secondary hypertension, where a cause can be identified, accounts for less than 5% of cases. In classic essential hypertension both the systolic and diastolic blood pressures are high, but isolated systolic and isolated diastolic hypertension are also seen. Malignant or accelerated hypertension is associated with a rapid rise in arterial pressure and, if untreated, results in rapid end-organ damage and death. The term “benign” essential hypertension has been used to describe a less aggressive form of hypertension but this term is not widely accepted because the condition is not benign. It is associated with significant morbidity and mortality. Resistant hypertension is used to describe cases of hypertension that are refractory to standard medical therapy (three different classes of anti-hypertensive drugs) (Forbes et al. 2010).

Hypertension can be broadly classified as “high renin” or “low renin”. Correspondingly, there are two categories of antihypertensive drug, those which inhibit (ACE inhibitors, ARBs and beta-blockers) and those which do not inhibit (calcium channel blockers (CCBs) and diuretics) the renin-angiotensin system. Renin-profiling studies have demonstrated that younger people of <55 years and Caucasians tend to have higher renin levels relative to older people (≥55years) or the black population (of African descent). Thus, drugs which reduce BP at least in part by suppressing the renin–angiotensin system at one point or another are generally more effective as initial BP-lowering therapy in younger Caucasian patients. In contrast, CCBs and diuretics are less effective as initial BP-lowering therapy in these patients, and are better used first-line in older Caucasians or the black population of any age. ARBs remain 2nd/3rd line therapies, mainly due to the availability of cheaper alternatives such as ACE inhibitors. However this may change to 1st/2nd line when ARBs become generic (Forbes et al. 2010).

The Health Survey for England reported the prevalence of hypertension to be 3.3% in those aged under 40 years, 27.9% in those aged 40–79 years and 49.9% in those aged over 80 years. Similar figures are seen throughout the developed world, but these data probably underestimate the true prevalence of hypertension in the population owing to poor identification of cases (Forbes et al. 2010).

Hypertension contributes significantly to an individual’s risk of cardiovascular disease but must be considered in the context of other cardiovascular risk factors. The risk to an individual may also correlate with the severity of the hypertension. Overall, hypertension

has been estimated to confer a 3–19% increase in the risk of stroke and a 3% increase in the risk of developing heart failure. It may account for 25% of deaths from coronary artery disease. Patients with hypertension and co-morbid diabetes, obesity or hyperlipidemia have been found to be at even higher risk for cardiovascular disease and organ damage. Hypertension is associated with marked morbidity and mortality and places a high burden on health care systems (Forbes et al. 2010).

4. Azilsartan Medoxomil

Azilsartan (TAK-491) is a highly selective, long acting angiotensin II receptor blocker (ARB) that can be used alone or in combination. The target product profile for Azilsartan monotherapy is that it will exhibit best in class attributes (superior BP lowering to olmesartan by 3-5 mmHg SBP), true 24 hour BP control with QD dosing, and safety profile comparable to other ARBs. The fixed dose combination (FDC) of Azilsartan with chlorthalidone (CLD) will also exhibit best in class attributes for BP lowering, demonstrated 24-hour BP control, and safety profile comparable to other FDC's (ARB/HCT).

Azilsartan will be launched into a crowded and highly competitive antihypertensive ARB market. At Azilsartan's launch approximately 85% (volume) will be brands, but will drop to 7% 5 years later. Combination therapy (ARBs with diuretics) continues to grow. The brand vision is that Azilsartan creates additional opportunities for grade 2-3 hypertensive patients with additional risk factors to avoid life-altering events due to complications of their disease.

5. CegeDim's THIN Electronic Medical Record Database

The Health Improvement Network ('THIN') database is a computerised database of anonymised longitudinal medical records from UK primary care practices using the ViSion computer system (In Practice Systems, London, UK) to manage patient records. Currently, 479 practices participate. Data are available for a total of 9.15 million patients since 1985, including 3.36 million active cases. As of 2009, the dataset covered 5.7% of the UK population (CSD Medical Research 2011a). Data are collected on patient demographics and practice enrolment dates, diagnoses (recorded using the Read Clinical Classification version 2), referrals to secondary care (including hospital admissions and discharge diagnoses/medication data), prescriptions (recorded using the Multiflex coding system), anonymised free text, and postcode-level geographic information on socioeconomic, ethnicity and environmental variables (CSD Medical Research 2011b). Some laboratory results and measurements taken during patient visits are also recorded in THIN (Lewis et al. 2007).

THIN is a relatively young database. However, there is some historical overlap in practice sites with the well-validated GPRD database. Lewis et al. (2007) tested the strength of several well-known clinical associations in the THIN database and compared results from GPRD practices with those in non-GPRD practices. They concluded that data were equally valid in the two subsets. At least one study has attempted to externally validate data reported by primary care practices participating in the THIN data collection scheme.

Maguire, Blak and Thompson (2009) studied the reliability and timeliness of mortality reporting and developed a THIN practice-level data quality initiative. The Acceptable Mortality Reporting (AMR) indicator gives the year from which the practice is determined to reliably report all-cause mortality. Bourke, Dattani and Robinson (2004) evaluated the potential suitability of the THIN database for medical and pharmaceutical research. They concluded that data quality is assessable and that by implementing strong quality assurance procedures, THIN database records should be highly suitable for research. Since then, several studies have verified the utility of the THIN database for research on particular diseases.

The THIN database has been used in a high profile study of quality of care for patients with hypertension (Serumaga et al. 2011). MacDonald and Morant (2008) compared prevalence and treatment of clinically documented hypertension in the THIN database with that reported based on BP readings taken during a single visit as part of the Health Survey for England (HSE) in 1998 and 2003. They found lower prevalence in THIN database subjects than in the HSE. This may be partly explained by under-diagnosis and treatment of hypertension in the population.

Of particular relevance to the present proposed study, Harrison, Lancashire and Marshall (2008) investigated terminal digit bias in blood pressure readings (that is, the tendency to round the final digit of systolic and/or diastolic blood pressure readings to a round number, potentially leading to misclassification of hypertension severity) using the THIN database. They found that the extent of the problem fell dramatically over the 10 year study period from the mid-90s to mid-2000s. However, some practices continued to underestimate hypertension prevalence owing to their tendency to round the final digit of the systolic BP reading to zero.

Although demographically representative of the UK population, comparison of patients in the THIN database and the QResearch network, another UK primary care database, suggested that patients in THIN practices were more likely to be affluent (Cox et al. 2008). As socioeconomic status has been associated with health outcomes, to the extent that the THIN database is under-representative of socioeconomically deprived members of the UK general population, some findings based on THIN data should be interpreted with caution.

Approval of the THIN Scheme was granted by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2002. Studies which use only retrospective, anonymised data do not require additional MREC review. However, such studies must apply to CSD Medical Research's Scientific Review Committee for scientific approval (CSD Medical Research 2011c).

6. Study Design

Retrospective, cross-sectional, medical record database study.

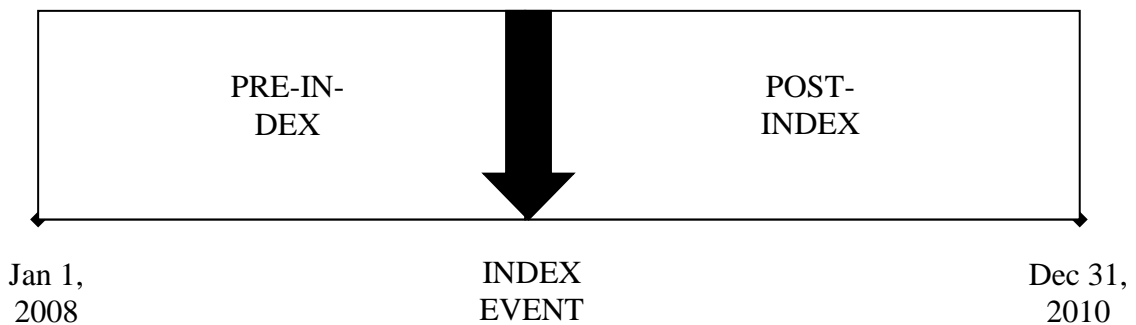
7. Study Period

Medical record data will be obtained for a three year period covering calendar years (CYs) 2008-2010. Patients will be required to be continuously registered at a practice included in the data for a minimum of 19 months during this 36 month period.

A pre-index period of a minimum of 13 months starting in January 2008 during which patients are not treated for hypertension will be sufficient to establish a ‘clean’ or ‘treatment naive’ period prior to the index event of a newly treated case of hypertension. The index date will be the date of the first prescription for an antihypertensive medication following at least 13 months free from such medication at the outset of the study period. Patients will be followed for a minimum period of 6 months post-index treatment initiation to allow time to observe the effects of treatment on hypertension outcomes (figure 2).

The use of the minimum practical study duration is recommended so as to reduce the loss of patients who are registered at practices included in the dataset for relatively short periods and may enhance the representativeness of the study population.

Figure 2. Study timeline



8. Study Population

The study population includes adults (ages 18 and older) with newly diagnosed (i.e., treatment naive) primary (essential) hypertension as identified by a Read diagnosis code in the electronic medical record (EMR) indicating essential hypertension. Patients with gestational hypertension and secondary hypertension are to be excluded.

To identify treatment naive patients, we will first select patients who were alive and permanently registered at a THIN database practice site during the study period. Patients may or may not have a diagnosis code indicating essential hypertension during the 13 month pre-index period. However, they must not have had a prescription for an antihypertensive medication during that period.

Since antihypertensive medications may be prescribed for indications other than essential hypertension, patients will be included only if they had a diagnosis indicating essential hypertension at some point during the study period and no diagnosis consistent with secondary or gestational hypertension during the same period.

Studies have shown that healthcare claims data accurately capture most patients with hypertension using diagnosis codes (Sennett 2000). The same finding would be expected with diagnoses coded in electronic medical records. This method is suggested over use of actual blood pressure readings to define hypertension since it better allows for exclusion of secondary and gestational hypertension as well as hypertensive emergencies and other causes of high blood pressure not associated with primary hypertension. However, provided that sufficient data on blood pressure readings are available in the dataset, we will confirm the diagnosis of hypertension by examining blood pressure readings from the pre-index period.

Inclusion criteria. Patients will be included if all of the following criteria are met:

- The patient is at least 18 years old at the start of the study period.
- A minimum of 19 months of continuous coverage (during a three calendar year period) in the THIN database.
- A diagnosis of essential (primary) hypertension at any point during the study period.
- A prescription for at least one antihypertensive drug (the index event) at some point after the end of the first 13 months of data and before the start of the final 6 months of data available for the patient.
- At least one blood pressure reading during the pre-index period.
- At least one blood pressure reading during the post-index period.

Exclusion criteria. Patients will be excluded if any of the following criteria are met:

- A prescription for one or more antihypertensive drugs during the 13 month pre-index period.
- A diagnosis of secondary or gestational hypertension at any time during the study period.

Sample size. TBD

9. Exposures, Outcomes, and Covariates

Exposures: Antihypertensive Pharmaceuticals

Hypertension guidelines recognize five primary drug classes: thiazide/thiazide-like diuretics, beta blockers (BBs), calcium channel blockers (CCBs), ACE inhibitors (ACEIs), and ARBs [i.e., candesartan (atacand), eprosartan (teveten), irbesartan (avapro), telmisartan (micardis), valsartan (diovan), losartan (cozaar), and olmesartan (benicar)].

This study will examine the use of the five primary classes of anti-hypertensive medications, as monotherapy or in fixed dose combinations, as well as other anti-hypertensive drugs used in general practice.

Relevant drugs will be identified using codes from Chapter 2 of the British National Formulary (BNF) as follows: thiazides and related diuretics (2.2.1), loop diuretics (2.2.2), potassium sparing diuretics (2.2.3), potassium sparing diuretics with other diuretics (2.2.4), beta-adrenoceptor blocking drugs (2.4), vasodilator antihypertensive drugs (2.5.1), centrally acting antihypertensive drugs (2.5.2), adrenergic neuron-inhibiting drugs (2.5.3), alpha-adrenoceptor-blocking drugs (2.5.4), drugs affecting the renin-angiotensin system (2.5.5), including ACE inhibitors (2.5.5.1) and angiotensin-II receptor antagonists (ARBs) (2.5.5.2), renin inhibitors (2.5.5.3), and calcium channel blockers (2.6.2).

Outcomes

Identification of FDC and monotherapy patient populations. A primary purpose of this study is to classify patients according to whether or not they would benefit from initial FDC therapy, whether or not they would benefit from remaining on ARB monotherapy for as long as possible, or neither of the above treatment protocols.

A survey of guidelines and other literature on appropriate drugs and combinations will be conducted to determine the most widely accepted treatment recommendations for sub-groups of patients with particular risk factors and comorbid conditions. Patients will be categorized accordingly in preparation for analyses.

Blood pressure control. Another outcome of interest is blood pressure control during the post-index period. Systolic and diastolic blood pressure readings will be obtained from the EMR for the period following index initiation of treatment for hypertension.

High blood pressure will be defined as readings $\geq 140/90$ mmHg in general, and $\geq 130/80$ mmHg for patients identified as "high risk," based upon presence of comorbid diabetes mellitus, chronic kidney disease, carotid artery disease, peripheral arterial disease, or abdominal aortic aneurysm (Rosendorff, Black, Cannon, et al, 2007).

Target blood pressure will be defined as $\geq 90/60$ mmHg (National Heart Lung and Blood Institute, 2011) but less than the value for high blood pressure.

Patients will be identified as having high blood pressure if the most recently available measurement is in the "high" range and will be identified as being at target blood pressure if the most recently available measurement is in the target range.

Blood pressure readings will be further categorised into hypertension grade following the thresholds shown in Table 1.

Covariates

Independent Variables can be grouped into five major classes and will be constructed based upon the index date (patient demographics, socioeconomic status), pre-index period (lifestyle characteristics, illness burden, chronic/comorbid conditions), or post-index period (antihypertensive medications).

- i. Patient demographics, including age, sex, and region of residence;
- ii. Patient lifestyle variables, including tobacco use/smoking status, alcohol misuse, and body mass index.
- iii. Socioeconomic status, as proxied by Townsend Deprivation Score (available at the patient postal code level in THIN), a composite score based on census data on assets and employment in the enumeration district or ward (Adams, Ryan and White 2005);
- iv. Overall health status/illness burden as proxied by the Charlson Comorbidity Index (Deyo, Cherkin, and Ciol 1992) and following Khan et al. (2010) to map the relevant diagnosis codes from ICD-9 to Read codes;
- v. Chronic conditions, including diabetes mellitus, chronic kidney disease, carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, hyperlipidemia, stroke, ischemic heart disease, and congestive heart failure; and
- vi. Hypertensive medications prescribed, including ace inhibitors, ARBs, beta-blockers, calcium channel blockers, thiazide/thiazide-like diuretics, other antihypertensive drugs, and combination therapies.

10. Statistical Analysis

The proposed methods comprise a mix of descriptive analyses and logistic regression analyses.

1. Guideline review: Conduct a review of UK/European and other relevant guidelines and summarize key recommendations with particular emphasis on recommendations pertaining to initial treatment with FDC therapy and contraindications to FDC therapy. This will provide information on current clinical best practices in the treatment of newly diagnosed hypertension and identify exceptions to standard recommendations based on clinical findings and other important patient characteristics.

2. Descriptive analysis: To better understand the potential market for Azilsartan Medoxomil in fixed dose combination versus ARB monotherapy, determine the percentage of newly diagnosed patients that are indicated for initial FDC treatment and the percentage of patients who would benefit from sustained ARB monotherapy.
 - a. Use the THIN medical record database to identify the number of newly diagnosed/treated patients with risk factors indicating the potential need for initiation with fixed dose combination therapy according to clinical guidelines. Identify patients with markedly elevated BP and those who are at high or very high risk of cardiovascular complications.
 - i. Compute the percentage of such patients from among all patients eligible for ARB therapy owing to elevated BP and cardiovascular risk.
 - ii. Compute the percentage of patients in this FDC risk group who are treated initially with FDC (versus monotherapy) and compare this to the percentage of patients who are not in the FDC risk group who are treated initially with FDC (versus monotherapy).
 - b. Use the THIN medical record database to identify the number of newly diagnosed/treated patients with risk factors indicating that FDC therapy would not be optimal (e.g., patients with, or at risk of developing, diabetes).
 - i. Compute the percentage of patients who are identified as being poor candidates for FDCs from among all patients eligible for ARB therapy owing to elevated BP and cardiovascular risk.
 - ii. Compute the percentage of patients in this risk group who are treated initially with monotherapy (versus FDC) and compare this to the percentage of patients not in this risk group who are treated with monotherapy (versus FDC).
 - c. Compute the percentage of patients who try multiple ARBs prior to switching to FDCs and the percentage who switch directly from an ARB to an FDC during the study period. Compute mean time-to-switch between groups of patients who switch between ARBs versus switching from an ARB directly to an FDC.
3. Multivariate analysis: To better understand which patient characteristics are predictive of initial FDC therapy versus sustained monotherapy,
 - a. Prior to conducting multivariate adjusted analyses, descriptive statistics of all independent and dependent variables will be provided. Differences in means will be examined using t-statistics and differences in categorical variables will be examined using chi-square statistics.

- b. Logistic regression analysis will be used to examine which patient characteristics (e.g., age, sex, baseline BP range, clinical conditions, BMI, etc.) are associated with initial FDC treatment (versus initial monotherapy treatment) in practice.
- c. Logistic regression analysis will be used to estimate the relationship between different treatment regimes and BP goal outcomes, controlling for patient characteristics and time from diagnosis to most recent BP reading. If sufficient data exist, separate models will be estimated for patients who are expected to benefit from initial FDC therapy and those who may be advised to avoid FDC therapy.

11. Limitations of the Study Design, Data Sources, and Analytic Methods

In addition to the usual limitations of retrospective analyses based on medical records that were collected for administrative purposes rather than for research, there are several potential pitfalls of the proposed analyses. These may limit the ability of phmr to undertake the analyses as specified above and/or may limit the robustness and generalisability of findings. Although we will endeavour to obtain information on the data limitations prior to data acquisition, some issues may not become fully apparent until data have been acquired and data processing begins.

Potential pitfalls include the following:

- Cell sizes may be limited owing to relatively small numbers of newly diagnosed patients with high risk characteristics in the data.
- Lack of complete data from inpatient and other encounter types may limit our ability to identify high risk patients.
- Missing data on BMI and lifestyle factors may limit the regression analyses.
- Insufficient data on blood pressure readings prior to diagnosis and later in the study period may limit analysis on the relationship between treatment regimen and success in meeting blood pressure goals.
- Given that most patients with primary hypertension are ages 40 and older, it is likely that a relatively small portion of the study population will be ages 18-39, and individuals in this cohort will be unrepresentative of the market as a whole. Consequently, it may be sensible to limit analyses to middle age and older adults.

12. Plans for Disseminating and Communication Study Results

The investigators and sponsors are committed to wide dissemination of the study findings. The study plan approved by the sponsors includes a timeline for submitting abstracts to major European and international cardiovascular and hypertension society meetings. This plan also includes a provision for one or more manuscripts to be prepared and submitted for peer-reviewed academic publication. The STROBE guidelines for reporting observational studies will be followed (von Elm et al. 2007).

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