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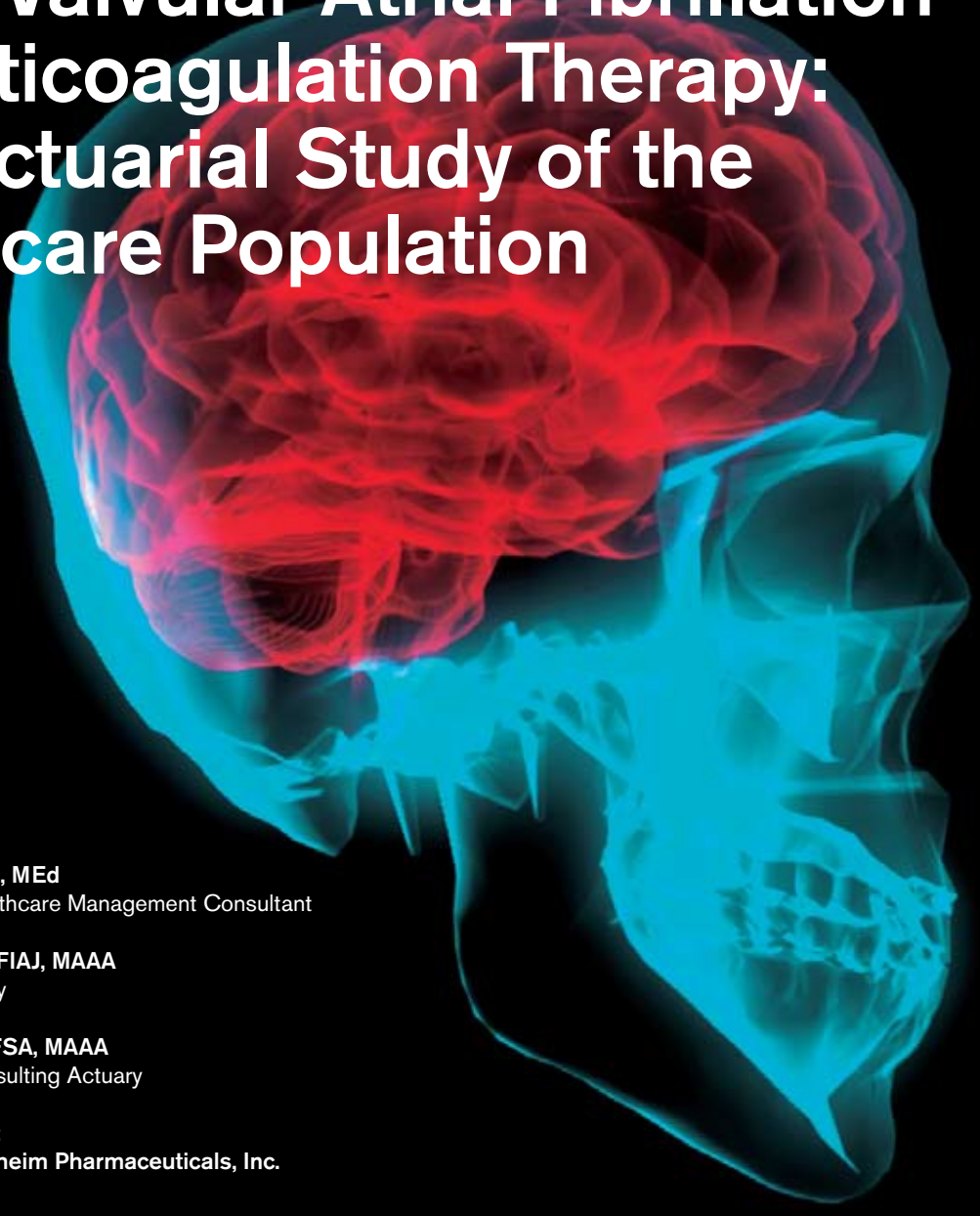
# Non-Valvular Atrial Fibrillation & Anticoagulation Therapy: An Actuarial Study of the Medicare Population



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# EXECUTIVE SUMMARY

## Background

Approximately 2.3 million U.S. adults have atrial fibrillation (AF) and that number is projected to reach 5.6 million in the year 2050.[1] [2] The prevalence rate in the 65+ Medicare population increased from 3.2% in 1992 to 6% in 2002 with much of the increase due to improved survival of AF patients.[3] Prevalence progressively increases with age, with a doubling of prevalence between ages 65-74, 75 to 84 and 85+.[3] Non-valvular atrial fibrillation (NVAF), which makes up approximately 70% of AF cases, is the focus of this report. Annual costs for the NVAF population in the U.S are estimated to be $6.65 billion.[4]

AF is of particular concern because of its association with an increased risk of stroke, heart failure and all cause mortality.[5] The Framingham Study reports that the probability of stroke in patients with NVAF is almost five-fold higher than in patients without NVAF.[6] Strokes in patients with NVAF are more severe and disabling than those in patients without NVAF.[7]

Practice guidelines have been developed based on the consistent observation in clinical trials that antithrombotic therapy significantly reduces the incidence of ischemic strokes in patients with NVAF. Two sets of evidence-based guidelines are typically considered: ACC/AHA/ESC guidelines and American College of Chest Physicians guidelines. Despite recommendations from these guidelines that oral anticoagulation (OAC) reduces the risk of stroke in patients with NVAF at moderate to high risk, anticoagulation appears to be consistently underutilized. Several studies report a prevalence of treatment with OAC for high risk patients with NVAF that ranges from only 39% to 59%. [8] [9] [10] [11]

A major factor cited for underutilization involves physician concern with OAC-associated hemorrhage. A self reported survey of physicians indicated, physicians who underutilize OAC therapy overestimate the bleed risk associated with the use of OAC therapy.[12]

Practical issues of access to care and a patient's ability to care for themselves are often not considered when studies apply the results from clinical trials to the real world. This discrepancy certainly applies to NVAF, where current oral agents used in anticoagulation therapy can be less effective in real world clinical practice because of inappropriate prescribing and management of anticoagulation.

This paper is intended to highlight the cost, utilization, mortality, and risk characteristics of Medicare beneficiaries with NVAF. We present the analysis for Medicare beneficiaries with NVAF stratified by eligibility and institutional status, for the following four populations:

- **< 65:** This population receives Medicare benefits because of disability or End Stage Renal Disease. This includes dual (both Medicare and Medicaid) and non dual eligible as well as institutionalized and non institutionalized. These people are often low income
- **65+ Institutionalized**. These beneficiaries reside in nursing homes and are often eligible for Medicaid as well as Medicare. They are disabled, often poor, and often frail.
- **65+ Non Institutionalized, Non-Medicaid**. These beneficiaries are living in the community and are not receiving Medicaid. They perhaps fit the classical image of Medicare beneficiaries.
- **65+ Non Institutionalized, Dual Eligible**. These beneficiaries live in the community, but they are eligible for Medicaid because they meet federal poverty levels.

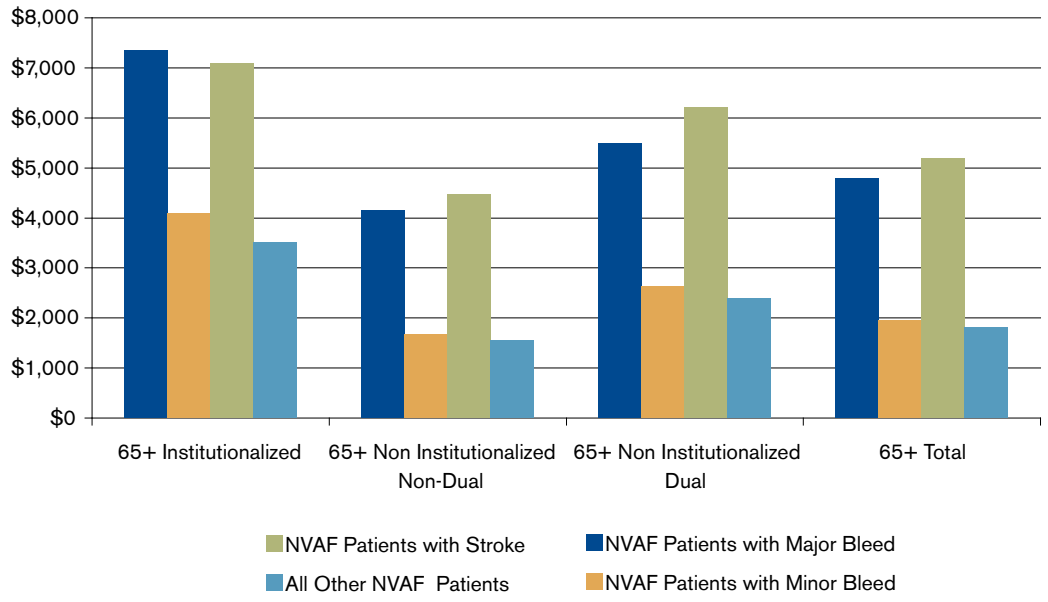
## Report Highlights

Our analysis of Medicare 5% sample identified 70% of total AF patients would be classified as NVAF (see methodology for identification criteria of NVAF). The prevalence of NVAF increases with age with an overall prevalence rate for the Medicare population of 5.3%

Among patients with NVAF, the annual frequency of stroke, a significant complication of NVAF, is approximately 3%. During the year of a stroke, NVAF patients' costs are approximately $5,000 per

patient per month (PPPM). Major bleeds (see appendix for definition), a complication associated with anticoagulation stroke prophylaxis, occur in patients with NVAF at an annual rate of 8%. During the year of a bleed, NVAF patients' costs are approximately $4,400 PPPM.

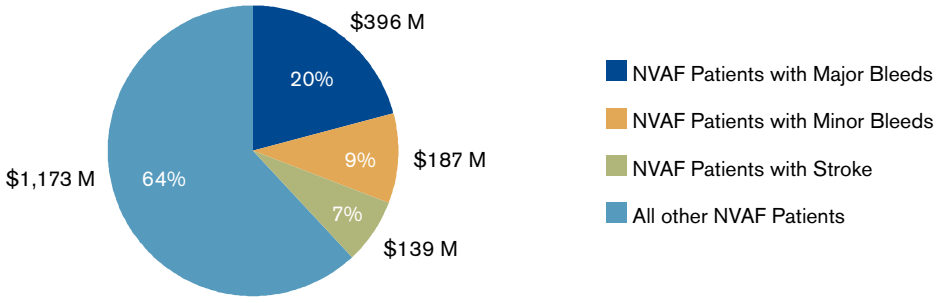
**FIGURE 1: MAJOR BLEEDS, MINOR BLEEDS, AND STROKE POPULATION PPPM TRENDED AND TO 2010**




**Source: Milliman analysis of Medicare 5% sample 2008**

Approximately 20% of patients with NVAF will have a stroke or a major or minor bleed in a given year but will account for approximately 36% of NVAF total medical cost. The pie graph below shows the annual dollar amounts incurred by patients with NVAF in a population of one million 65+ Medicare beneficiaries.

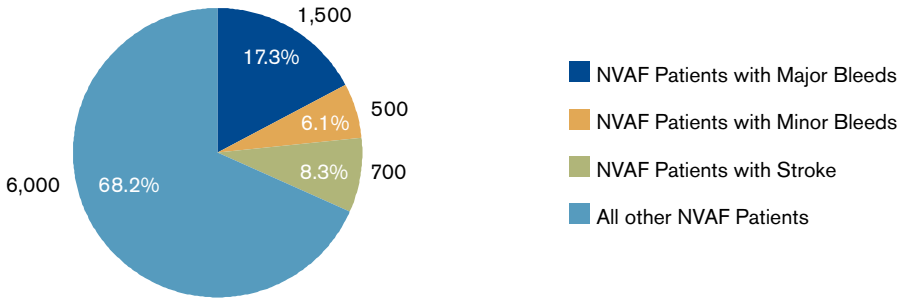
**FIGURE 2: NVAF PATIENTS WITH BLEED OR STROKES ACCOUNT FOR 36% OF COSTS OF PATIENTS WITH NVAF**




**Source: Milliman analysis of Medicare 5% sample 2008**

The mortality rate among NVAF patients with strokes and/or bleeds is high as shown below. Although 20% of NVAF patients will have a stroke or bleed in a given year, they will account for 32% of the NVAF deaths.

**FIGURE 3: NVAF PATIENTS WITH BLEED OR STROKES ACCOUNT FOR 32% OF DEATHS AMONG PATIENTS WITH NVAF (ONE MILLION 65+ MEDICARE BENEFICIARY)**




Source: Milliman analysis of Medicare 5% sample 2008

Our analysis identified that over 50% of patients with NVAF do not appear to be receiving anticoagulation therapy, the standard of care for stroke prevention in patients with NVAF without contraindications.

- Oral anticoagulation therapy (OAC) is recommended for stroke prevention in patients with AF and >1 risk factor; Warfarin is currently the only OAC available by prescription and certainly the most effective OAC treatment.[13]
- From our analysis of Medicare 5% sample 2008 data, we estimated that only 43% of the 65+ patients with NVAF would be considered on OAC therapy.

### Considerations for Payers Regarding Anticoagulation Management for Patients with NVAF

- To address patient management concerns, plans should consider disease management efforts aimed at the AF population and, in particular, monitoring of OAC therapy and INR values.
- To address the burden of OAC dosing and monitoring, specialized anticoagulation clinics with personnel trained to manage anticoagulation have been established in some regions.[14] [15] Patient self-testing with and without self reporting has been another approach to improving OAC management.[16]
- To address quality of care and safety, OAC management in patients with NVAF has received attention from Medicare as well as the Joint Commission on the Accreditation of Healthcare Organizations.

# ATRIAL FIBRILLATION IN THE MEDICARE POPULATION

In this section we establish why atrial fibrillation (AF) warrants increased attention, providing an overview of the reported prevalence, health risks, cost burden, treatment patterns, and challenges regarding oral anticoagulation therapy. The focus of this report is on Medicare beneficiaries with non valvular-atrial fibrillation (NVAF) which accounts for greater than 70% of AF cases.[17] Of particular interest is the appropriate use of oral anticoagulation therapy in the NVAF population to reduce the risk of thromboembolic events, the vast majority of which are strokes.

## Prevalence, Risks and Costs

Approximately 2.3 million U.S. adults have AF and that number is projected to reach 5.6 million in the year 2050.[1] [2] The prevalence rate in the 65+ Medicare population increased from 3.2% in 1992 to 6% in 2002 with much of the increase due to improved survival of AF patients.[3] Prevalence progressively increases with age, with a doubling of prevalence between ages 65-74, 75 to 84 and 85+.[3]

AF is an irregular heart rhythm originating in the atrial (upper) chambers of the heart. Patients with AF are often asymptomatic, although they may have symptoms such as palpitations, dyspnea, dizziness and fatigue. AF occurs most often in patients with underlying heart disease such as hypertensive heart disease, heart failure, atherosclerotic, or valvular heart disease.[13] AF is associated with an increased risk of stroke, heart failure and all cause mortality, especially in women.[5] One in every 6 strokes is associated with AF[18], with approximately 40% of the strokes in patients 80-89 years old attributed to AF.[6]

The pathophysiology of stroke associated with AF is not clearly defined. The high risk of stroke is thought to be caused by several factors. When AF occurs, the atria do not contract and blood stagnates and lingers in the left atrium and atrial appendage. This can lead to a thrombus formation which can break off, becoming an embolus, and travel and lodge in an artery causing an ischemic stroke. In addition, patients with AF have a higher prevalence of other risk factors for stroke including hypertension, diabetes and heart failure which also contributes to the higher stroke incidence rates.[19]

Specifically in regards to patients with NVAF, the Framingham Study reports the probability of stroke is almost fivefold higher than in patients without NVAF.[6] Ischemic strokes in patients with NVAF are more severe and disabling than those in patients without NVAF.[7]

The cost of care associated with NVAF can be considerable, as estimated by Coyne et al. to be $6.65 billion. Using the Healthcare Cost and Utilization Project (HCUP) data, the National Ambulatory Care Survey (NAMCS) database and the National Hospital Ambulatory Medical Care Survey (NHAMCS) the Coyne et al. study reported 350,000 hospitalizations, 5.0 million office visits, 276,000 ED visits and 234,000 hospital outpatient department visits were attributable to NVAF annually in the U.S.[4] An analysis of the Integrated Healthcare Information Systems (IHCIS) National Managed Care Benchmark Database evaluated 25 million managed care lives for readmission rates among NVAF patients. In the year following the index hospitalization, 12.5% of chronic NVAF patients were readmitted for NVAF with a mean time to readmission of 142.5 days.[20]

## Treatment Guidelines

Management of patients with AF involves 3 objectives: rate control, prevention of thromboembolism, and correction of rhythm disturbance. Drugs, cardioversion, and ablation can be used to control heart rate or in an attempt to restore normal sinus rhythm. The selection of the appropriate therapeutic approach depends on several clinical variables, including age, duration of atrial fibrillation, and coexisting conditions. Apparent restoration of sinus rhythm does not reduce the risk of stroke; as such, the need for anticoagulation remains after attempted sinus rhythm restoration.[13]

Selection of patients with NVAF for anticoagulation to prevent strokes depends on physician assessment of the relative risk of stroke versus bleeding in an individual patient. The decision can be complicated and difficult since each patient presents with a unique constellation of clinical features.

Practice guidelines have been developed based on the consistent observation in clinical trials that antithrombotic therapy significantly reduces the incidence of ischemic strokes in patients with NVAF. A meta-analysis reports an average 64% relative risk reduction of ischemic stroke in those on adjusted dose warfarin versus placebo.[21]

Two sets of guidelines are typically considered. A summary of the ACC/AHA/ESC guidelines and College of Chest Physicians guidelines appears below. Details are provided in Appendix B.

**FIGURE 4: ACC/AHA/ESC ANTITHROMBOTIC GUIDELINES FOR NVAF PATIENTS**

| PATIENT FEATURES | CLASS<br>ANTITHROMBOTIC THERAPY | RECOMMENDATION |
|---|---|---|
| AGE LESS THAN 60 YRS – NO HEART DISEASE (LONE AF) | ASPIRIN (81 TO 325 MG PER DAY) OR NO THERAPY | I |
| AGE < 60 YRS – HEART DISEASE, NO RISK FACTORS* | ASPIRIN (81 TO 325 MG PER DAY) | I |
| AGE ≥ 60 TO 74 YRS – NO RISK FACTORS* | ASPIRIN (81 TO 325 MG PER DAY) | I |
| AGE ≥ 65 TO 74 YRS WITH DIABETES MELLITUS OR CAD | ORAL ANTICOAGULATION (INR 2 TO 3) | I |
| AGE ≥ 75 YEARS – WOMEN | ORAL ANTICOAGULATION (INR 2 TO 3) | I |
| AGE ≥ 75 YEARS – MEN, NO OTHER RISK FACTORS | ORAL ANTICOAGULATION (INR 2 TO 3), OR ASPIRIN (81 TO 325 MG PER DAY) | I |
| AGE > 65 YEARS – HEART FAILURE | ORAL ANTICOAGULATION (INR 2 TO 3) | I |
| LV EJECTION FRACTION LESS THAN OR EQUAL TO 35% OR FRACTIONAL SHORTENING LESS THAN 25%, AND HYPERTENSION | ORAL ANTICOAGULATION (INR 2 TO 3) | I |
| RHEUMATIC HEAT DISEASE (MITRAL STENOSIS) | ORAL ANTICOAGULATION (INR 2 TO 3) | I |
| PROSTHETIC HEART VALVES | ORAL ANTICOAGULATION (INR 2 TO 3 OR HIGHER) | I |
| PRIOR THROMBOEMBOLISM | ORAL ANTICOAGULATION (INR 2 TO 3 OR HIGHER) | I |
| PERSISTENT ATRIAL THROMBUS ON TEE | ORAL ANTICOAGULATION (INR 2 TO 3 OR HIGHER) | IIA |

* Risk factors for thromboembolism include heart failure (HF), left ventricular (LV) ejection fraction less than 35%, and history of hypertension.
AF = Atrial fibrillation; CAD = coronary artery disease; INR = international normalized ratio; TEE =transesophageal echocardiography

**FIGURE 5: AMERICAN COLLEGE OF CHEST PHYSICIANS: 2008 GUIDELINES**

| RISK LEVEL | PATIENT FEATURES | THERAPEUTIC GUIDELINES | EVIDENCE LEVEL |
|---|---|---|---|
| LOW | • AGE ≤ 75 YEARS<br>• NO ADDITIONAL RISK FACTORS | ASPIRIN 75- TO 325-MG/DAY | 1B |
| INTERMEDIATE | • ANY ONE OF THE FOLLOWING RISK FACTORS:<br>- AGE > 75 YEARS<br>- HEART FAILURE‡<br>- DIABETES*<br>- HISTORY OF HYPERTENSION†<br>- LV SYSTOLIC DYSFUNCTION‡ | WARFARIN<br>(TARGET INR 2.5, RANGE 2.0 TO 3.0)<br>OR<br>ASPIRIN<br>75- TO 325-MG/DAY | 1A<br><br><br>1B |
| HIGH | • >1 INTERMEDIATE RISK FACTOR<br>• HISTORY OF STROKE, TIA, OR SYSTEMIC EMBOLUS*<br>• MITRAL VALVE DISEASE OR PROSTHETIC HEART VALVE§ | WARFARIN<br>(TARGET INR 2.5 RANGE 2.0 TO 3.0) | 1A |

*Not defined.
†Systolic BP > 160 mm Hg.
‡Recent (≤ 100 days) CHF or fractional shortening ≤ 25% by M-mode echocardiography.
§ If mechanical valve, target INR 3.0 (range 2.5 to 3.5).

Several clinical schemes have been developed to estimate the risk of ischemic stroke in patients with AF. The $CHADS_2$ risk scoring methodology is the simplest and most commonly used although the risk projections produced are not considered precise.[22] The $CHADS_2$ assigns points for five factors; 1 point for **C**ongestive heart failure, 1 point for **H**ypertension, 1 point for **A**ge > 75 years, 1 point for **D**iabetes and 2 points for history of **S**troke or TIA. Risk scores correspond with the following levels: 0-1 point low risk, 2 points moderate risk, 3+ points high risk. Treatment recommendations for prophylactic anticoagulation depend on the number of risk factors.

### Anticoagulation Therapy: Challenges and Opportunities

Despite evidence that oral anticoagulation (OAC) reduces the risk of stroke in patients with NVAF at moderate to high risk, anticoagulation appears to be consistently underutilized. Several studies report a prevalence of treatment with OAC for high risk patients with NVAF that range from 39% to 59%.[8 9 10 11] For those treated with OAC, maintaining the recommended therapeutic INR level between 2.0 and 3.0 can be difficult. A large, nation-wide study of electronic medical records reported that patients spent only 48% of study days within the recommended INR range.[23] Another study found in approximately one third of patients, the INR was in therapeutic range < 20% of the time and only 19% of patients spent all or almost all of their time within the therapeutic range.[19]

Underutilization has been, in part, linked to healthcare system, physician and patient factors. Physician surveys suggest that healthcare system barriers to optimal anticoagulation include delays in laboratory reports for INRs, the general inconvenience of monitoring (recommendations are to measure at least every 4 weeks) and the lack of consultant services in anticoagulation management.[24] A major factor cited for underutilization involves physician concern with OAC- associated hemorrhage. Studies report that physicians who underutilize OAC therapy overestimate the bleed risk associated with the use of OAC therapy.[12] Without careful monitoring of INR levels, supratherapeutic INR levels can and do lead to major bleeds. Bleeds associated with OAC therapy are reported as a significant portion of emergency room visits for adverse drug events among older adults.[25] Patient factors for underutilization include physician reports that the reason for not prescribing anticoagulation in 14% of their patients was because of patient refusal or history of non-adherence.[26]

The risk for bleeding needs to be weighed when deciding on OAC therapy and the $HEMORR_2HAGES$ risk scoring tool was developed for this purpose.[27] Bleeding risk factors from existing classification schemes were combined and validated to create the $HEMORR_2HAGES$ scheme. Two points are

assigned for a prior bleed and one point for each of the other risk factors: Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age >75), Reduced platelet count or function, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk and Stroke. The bleed risk is categorized as low severity 0-1 points, moderate risk 2-3 points and high risk 4+ points. Again, as with the $CHADS_2$ risk scoring methodology, the risk scoring projections are not considered precise. Both the stroke risk score and bleed risk score should be given consideration when considering OAC therapy.

While this paper focuses on the Medicare population, we recognize that NVAF is a significant condition for younger populations; 18% of all atrial fibrillation patients are < 65 years of age.[1] Certainly, the challenges and opportunities we identify for Medicare beneficiaries with NVAF apply to all populations affected by NVAF.

# NON-VALVULAR ATRIAL FIBRILLATION (NVAF): MEDICARE 5% ANALYSIS

Our analysis found that Medicare beneficiaries with NVAF make up approximately 70% of the total AF population. Our analysis suggests the need for increased attention to the medical management of this population.

### Demographics and Eligibility Categories of the General Medicare Population

Because Medicare eligibility and health status are important determinants of access and suitable interventions, we summarize our findings for 4 eligibility/status categories of Medicare beneficiaries:

1. **< 65**: This population receives Medicare benefits because of disability or End Stage Renal Disease. This includes dual (both Medicare and Medicaid) and non dual eligible as well as institutionalized and non institutionalized. These people are often low income

2. **65+ Institutionalized**: this population resides in nursing homes and includes both dual and non dual eligible although the majority are dual eligible. This category does not include temporary skilled nursing home patients or non institutionalized LTC patients cared for in the community

3. **65+ Non Institutionalized Non-Dual**: this is what would be considered the traditional Medicare population and makes up 70% of the Medicare population.

4. **65+ Non Institutionalized Dual Eligible**: this population is eligible for both Medicare and Medicaid and resides in the community. It is older and mostly female, perhaps with a high portion of widows.

The average costs of these populations are dramatically different reflecting the scope and frequency of services provided to them.

For section I, we present basic demographic and cost information for all 4 categories of beneficiaries and narrow the detailed analysis in sections II and III to the 65+ categories.

### I. Prevalence, Cost and Utilization of the NVAF Population

We identified Medicare beneficiaries with NVAF using the methodology described in appendix B. Figure 6 shows the prevalence of NVAF is 5.3% with the institutionalized population having the highest incidence.

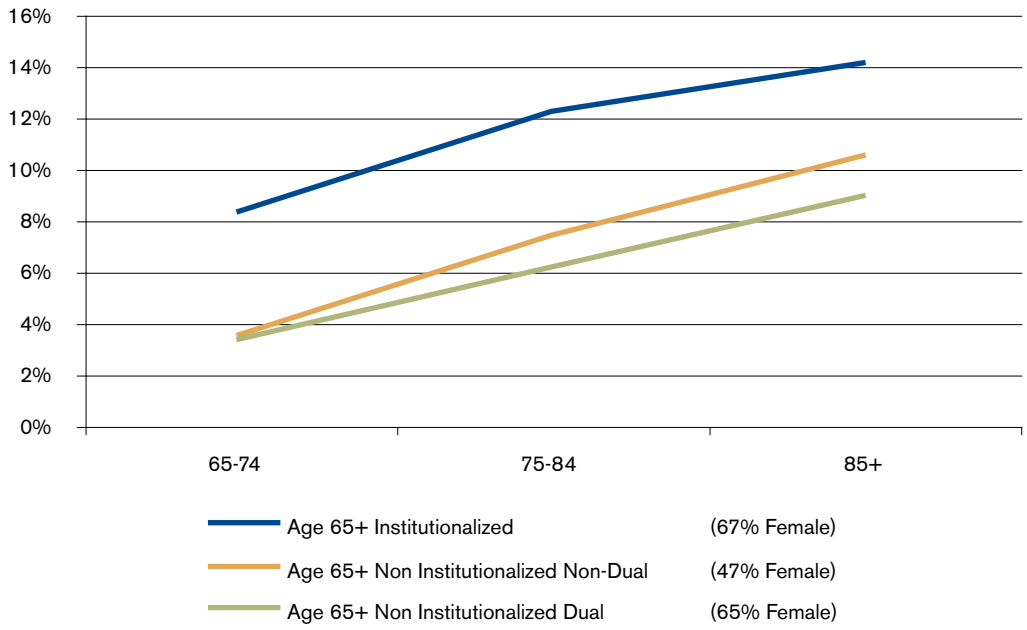
**FIGURE 6: DISTRIBUTION OF ALL MEDICARE BENEFICIARIES BY ELIGIBILITY CATEGORY, AND DISTRIBUTION OF PATIENTS WITH NVAF BY ELIGIBILITY CATEGORY**

| | TOTAL | AGE <65 | AGE 65+ | | |
|---|---|---|---|---|---|
| | | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL |
| MEDICARE POPULATION | 100% | 17% | 4% | 70% | 9% |
| PATIENTS WITH NVAF | 5.3% | 1.3% | 12.6% | 5.9% | 5.3% |

Source: Milliman analysis of Medicare 5% sample 2008

Patients with NVAF are relatively older and the prevalence of NVAF increases with age as shown in Figure 7. The <65 population has a much lower prevalence (not shown). The prevalence rate of NVAF is 12.6% for 65+ institutionalized population, 5.9% for 65+ non institutionalized non-dual and 5.3% for 65+ non-institutionalized dual Medicare beneficiaries.

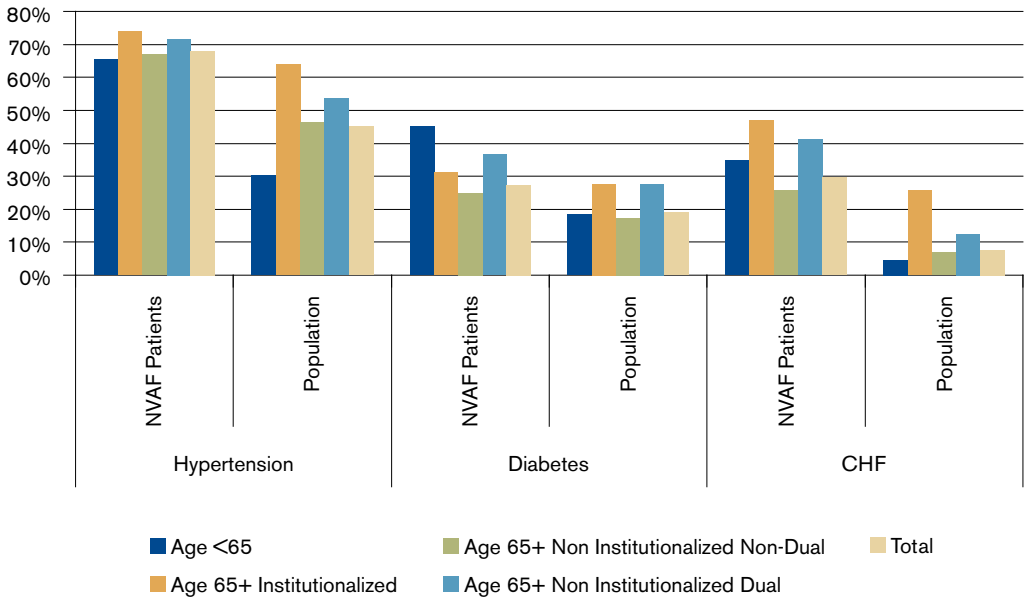
**FIGURE 7: PREVALENCE OF PATIENTS WITH NVAF BY MEDICARE ELIGIBILITY CATEGORY**




**Source: Milliman Analysis of Medicare 5% Sample Data 2008**

Patients with NVAF have a higher rate of comorbidities than the average Medicare beneficiary which adds to the cost burden. Figure 8 shows prevalence rates of 68% for hypertension, 27% for diabetes and 30% for CHF in the NVAF population.

**FIGURE 8: PREVALENCE OF COMORBIDITIES AMONG NVAF POPULATION**




**Source: Milliman analysis of Medicare 5% sample 2008**

Patients with NVAF are at higher risk for thromboembolic – venous and arterial – events. The observed rate of venous and arterial events for NVAF Medicare beneficiaries is 33 per 1000 as shown in Figure 9. Venous events include pulmonary embolism, pulmonary infarction, phlebitis and thrombophlebitis. Arterial events include arterial embolism and thrombosis, acute myocardial infarction (MI), coronary occlusion without MI, intermediate coronary syndrome, retinal vascular occlusion and vascular disorders of the kidney.[28]

**FIGURE 9: THROMBOEMBOLIC EVENT INCIDENCE/1000 NVAF MEDICARE BENEFICIARIES**

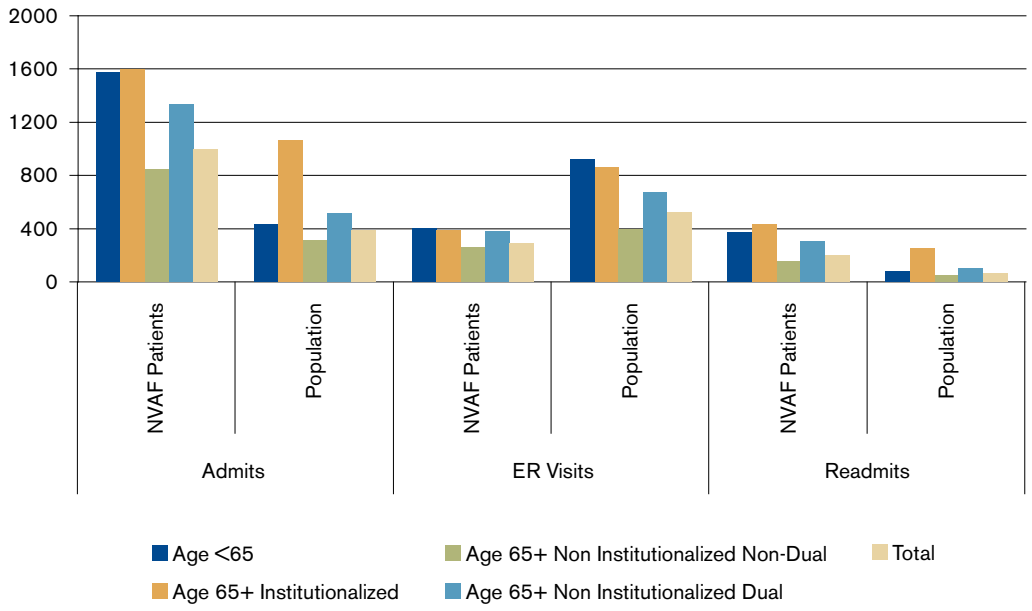
| | AGE <65 | AGE 65+ | | | |
|---|---|---|---|---|---|
| RATES/1000 NVAF MEDICARE BENEFICIARIES | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| VENOUS | 6 | 14 | 5 | 7 | 6 |
| ARTERIAL | 33 | 32 | 25 | 38 | 27 |
| TOTAL (VENOUS AND ARTERIAL) | 39 | 47 | 30 | 45 | 33 |

Source: Milliman analysis of Medicare 5% sample 2008

Patients with NVAF have higher utilization of inpatient stays and emergency room (ER) visits than the general Medicare population, some of which is related to a higher rate of comorbidities and some directly related to NVAF. We identified that 7% of admissions for NVAF patients have a primary diagnosis of atrial fibrillation. The frequency of ER visits are lower for those with NVAF, which we believe is due to the higher admission rate – ER visits that result in an admission are not billed as ER visits. Figure 10 shows the utilization rates by eligibility category.

We note that all-cause readmissions within 60 days are also higher for the NVAF population. The within 60-day rate of readmissions for the total NVAF population is 20% whereas the rate of readmission for the total Medicare population is 19.6%within 30 days and 34% within 90 days.[29]

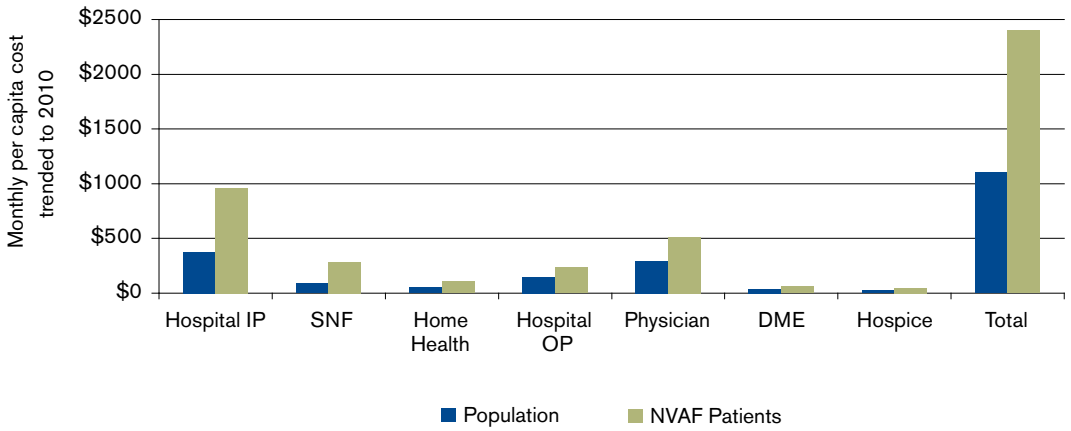
**FIGURE 10: INPATIENT ADMISSIONS, READMISSIONS AND ER VISITS/1000**




Source: Milliman analysis of Medicare 5% sample 2008

The per capita cost for patients with NVAF is more than twice that of the general Medicare population, and, as with the general Medicare population, inpatient costs are the largest component. Applying Medicare's Hierarchical Condition Category risk scoring methodology (see Appendix B) to our proprietary Part D bid tools, we estimate the Part D costs of patients with NVAF at $304 Per-Patient-Per Month (PPPM) compared to an average $181 Per-Member-Per-Month (PMPM) for the total Medicare population (not shown in Figure 4). Figure 11 shows, for 2010, patient NVAF costs as Per- PPPM figures, while the total Medicare costs are shown as PMPM. We report the PPPM inclusive of all the 4 NVAF populations.

**FIGURE 11: PMPM COSTS BY NVAF PATIENT ELIGIBILITY CATEGORY AND TOTAL MEDICARE POPULATION**




Source: Milliman analysis of Medicare 5% sample 2008

## II. Patients with NVAF are a High Risk Population

The comorbid and thromboembolic risk profiles suggest that the NVAF Medicare population is a high risk group. We present several risk characteristics of the NVAF population for the 65+ population.

For reference purposes we provide the distribution and sample size of total 65+ Medicare population and the NVAF 65+ Medicare population in Figure 12 below:

**FIGURE 12: DISTRIBUTION OF MEDICARE 65+ BENEFICIARIES BY ELIGIBILITY CATEGORIES**

| | AGE 65+ | | | |
|---|---|---|---|---|
| | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| % DISTRIBUTION OF ALL MEDICARE 65+ BENEFICIARIES (N) | 5% (64,034) | 84% (1,019,980) | 11% (132,504) | 100% |
| PREVALENCE OF NVAF IN MEDICARE 65+ BENEFICIARIES (N) | 12.6% (2,215) | 5.9% (27,994) | 5.3% (2,296) | 6.2% |

Source: Milliman analysis of Medicare 5% sample 2008

The high risk for ischemic stroke is of particular concern and the focus of antithrombotic therapy recommendations. Oral anticoagulation therapy (OAC) is recommended for stroke prevention in patients with AF and >1 risk factor; Warfarin is currently the only OAC available by prescription and certainly the most effective OAC treatment. Of interest in our analysis is the identification of appropriate use of OAC therapy based on current treatment guidelines. The remainder of our findings are reported for the 65+ Medicare population on and not on OAC, i.e. warfarin, therapy (+ OAC therapy and - OAC therapy respectively).

As noted previously, an INR between 2.0 and 3.0 is considered therapeutic in patients with NVAF on OAC to reduce the risk of stroke without increasing the risk of bleeding. The INR test is typically performed at least monthly to monitor and adjust the dose of OAC therapy if needed. An INR level < than 2.0 is associated with higher risk of stroke while an INR3.0 is associated with an increased risk of bleeding.

In the timeframe that was evaluated, we estimated that only 43% of the 65+ patients with NVAF were on OAC therapy. Patients presumed to be on treatment with OAC were older than those not treated with OAC. Although a higher percentage of patients with NVAF are women, the proportion of men on OAC is higher than women. The average member months of eligibility exposure in Medicare 5% 2008 for those on and off OAC was not significantly different. If this difference was significant, it could explain some of the difference in the rate of adverse events as those with longer eligibility exposure would have a longer time period to experience a stroke or bleed. We note the slightly longer average months of eligibility for those considered on OAC may reflect the 3+ INR methodology requirements requiring more exposure months. Figure 13 provides characteristics of the NVAF population considered on and off OAC. We did not match the on and off OAC cohorts by demographics, comorbidities or HCC risk scores.

**FIGURE 13: CHARACTERISTICS OF ON AND OFF OAC POPULATION BY MEDICARE ELIGIBILITY CATEGORY**

| | | AGE 65+ | | | |
|---|---|---|---|---|---|
| | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| % WITH OAC THERAPY | | 27% | 47% | 33% | 43% |
| AVERAGE AGE | +OAC | 84 | 78 | 78 | 79 |
| | - OAC | 85 | 79 | 80 | 80 |
| PERCENT OF MALES | +OAC | 33% | 53% | 32% | 51% |
| | - OAC | 30% | 50% | 31% | 45% |
| AVERAGE MEMBER MONTHS | +OAC | 11.4 | 11.8 | 11.7 | 11.8 |
| | - OAC | 11.1 | 11.2 | 10.6 | 11.1 |

Source: Milliman analysis of Medicare 5% sample 2008 OAC = Oral Anticoagulation.

We used the Hierarchical Condition Category[30] (HCC) system to estimate the overall health risk status of patients with NVAF (see Appendix B for a description of HCC risk scoring). We find that patients with NVAF have a significantly higher HCC score than average Medicare beneficiaries (approximately 1.0) as shown in Figure 14. Dual eligibles, both institutionalized and non-institutionalized, have higher scores than non duals. The patients with NVAF off OAC have a higher score than those on OAC (except for institutionalized), possibly reflecting physician preferences to not use OAC on very sick patients.

**FIGURE 14: HCC SCORES FOR MEDICARE BENEFICIARIES WITH NVAF**

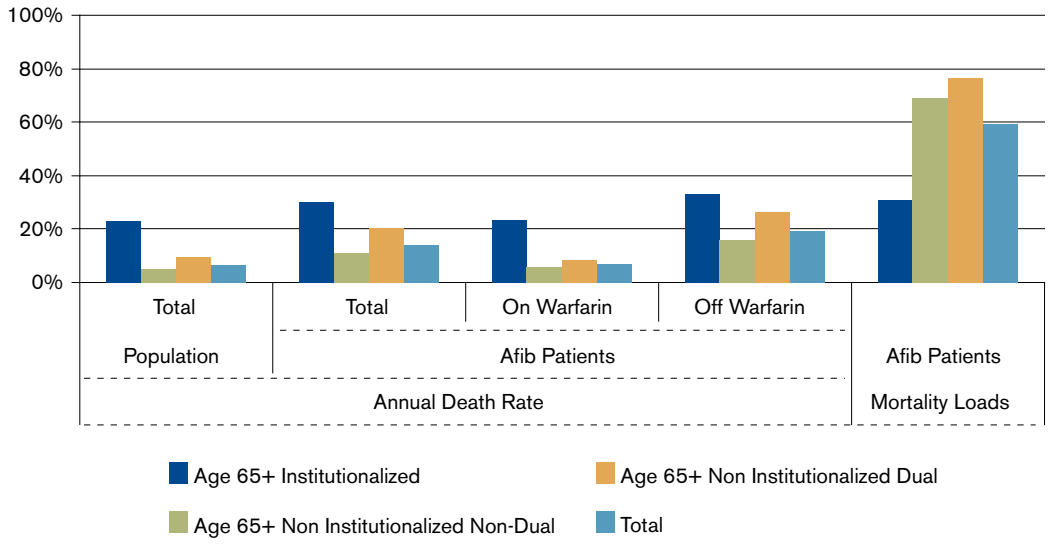
| | AGE 65+ | | | |
|---|---|---|---|---|
| | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| **NVAF ALL** | **3.06** | **2.14** | **2.93** | **2.32** |
| **+ OAC** | **3.07** | **1.93** | **2.60** | **2.06** |
| **– OAC** | **3.05** | **2.33** | **3.09** | **2.51** |

Source: Milliman analysis of Medicare 5% sample 2008
HCC Scores were calculated based on 2008 claims using the 2009 program issued by CMS.

The mortality rate of patients with NVAF is more than twice that of the general Medicare population. Figure 15 shows the annual mortality rates for each Medicare population, the annual mortality rates for the patients with NVAF in each population, and a ratio that shows the demographically-adjusted increase in mortality associated with NVAF.

For all categories, the mortality for the NVAF population is higher than the general population; some of the higher mortality may be due to the overall older age of patients with NVAF. After adjusting for age and sex, the presence of NVAF increases mortality by 59% across the 65+ Medicare groups.

**FIGURE 15: MORTALITY RATES OF MEDICARE BENEFICIARIES WITH NVAF**




Source: Milliman Analysis of Medicare 5% Sample Data 2008

* The "mortality load" shown in Table 5 was calculated by first applying the age-sex specific mortality rate (total population) to each NVAF patient to produce the number of deaths expected if the Patients with NVAF had the general population mortality. Then, this expected number of deaths was divided into the actual number of deaths. The Loads shown are the resulting quotient minus 1.0. Mortality Loads = (Σ Number of Deaths of Patients with NVAF)/(Σ Number of Patients with NVAF × Mortality Rate of Not Patients with NVAF)-1

## III. Balancing Risk in the Management of Patients with NVAF

### *Stroke*

While OAC therapy is recommended for moderate and high risk patients with NVAF to reduce the risk of ischemic strokes and other thromboembolic events, OAC therapy can increase the risk of bleeding. The guidelines recommend evaluation of the risk of stroke and bleeding in making treatment decisions.

The $CHADS_2$ stroke risk score can be used to estimate the relative risk of stroke in patients with NVAF. The $CHADS_2$ score can be calculated from information in administrative data. We calculated the $CHADS_2$ score for patients with NVAF in our database and identified that 45% of the NVAF population are at moderate or high risk for stroke and not on OAC therapy based on the INR claim logic. Figure 16 shows the distribution of $CHADS_2$ risk scores.

**FIGURE 16: DISTRIBUTION OF $CHADS_2$ RISK SCORES AND OAC USE AMONG PATIENTS WITH NVAF**

| | | AGE 65+ | | | |
|---|---|---|---|---|---|
| $CHADS_2$ RISK SCORES | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| % OF NVAF MEDICARE BENEFICIARIES BY RISK SCORE CLASS | | | | | |
| + OAC | LOW | 1% | 12% | 5% | 10% |
| | MODERATE | 14% | 27% | 19% | 25% |
| | HIGH | 12% | 8% | 9% | 9% |
| - OAC | LOW | 5% | 13% | 10% | 12% |
| | MODERATE | 40% | 30% | 39% | 32% |
| | HIGH | 27% | 10% | 18% | 13% |

Source: Milliman analysis of Medicare 5% sample 2008 OAC = Oral Anticoagulation.
$CHADS_2$ scores: Low (0-1 points), moderate (2 points), high (3+ points)

Our analysis shows that about 3 percent of patients with NVAF, regardless of OAC therapy, will have a stroke in a given year (see Appendix B for methodology and codes for stroke identification). Figure 18 shows about 80% of these are ischemic strokes and about 20% are hemorrhagic strokes.

The incidence of all strokes (ischemic and hemorrhagic) is higher among patients with NVAF not on OAC therapy versus those on OAC therapy (Figure 17). In particular, the incidence rate of ischemic stroke is 19/1000 for patients with NVAF on OAC therapy versus 30/1000 for those not on OAC therapy. We did not match the on and off OAC cohorts by demographics, comorbidities or HCC risk scores, thus the difference in stroke incidence cannot be entirely attributed to the presence or absence of OAC therapy.

**FIGURE 17: STROKE INCIDENCE PER 1000 65+ MEDICARE BENEFICIARIES WITH NVAF**

| | | AGE 65+ | | | |
|---|---|---|---|---|---|
| | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| **STROKE INCIDENCE PER 1000 65+ PATIENTS WITH NVAF IN EACH CATEGORY** | | | | | |
| ALL STROKE | + OAC | 53 | 21 | 31 | 24 |
| | – OAC | 50 | 33 | 48 | 37 |
| ISCHEMIC STROKE | + OAC | 44 | 16 | 27 | 19 |
| | – OAC | 42 | 27 | 40 | 30 |
| HEMORRHAGIC STROKE | + OAC | 9 | 4 | 4 | 5 |
| | – OAC | 8 | 6 | 8 | 7 |

Source: Source: Milliman analysis of Medicare 5% sample 2008 OAC = Oral Anticoagulation.

Patients with NVAF who have a stroke have high mortality and high readmission rates, as shown in Figure 18. Patients on OAC have lower mortality and readmission rates than those not on OAC therapy.

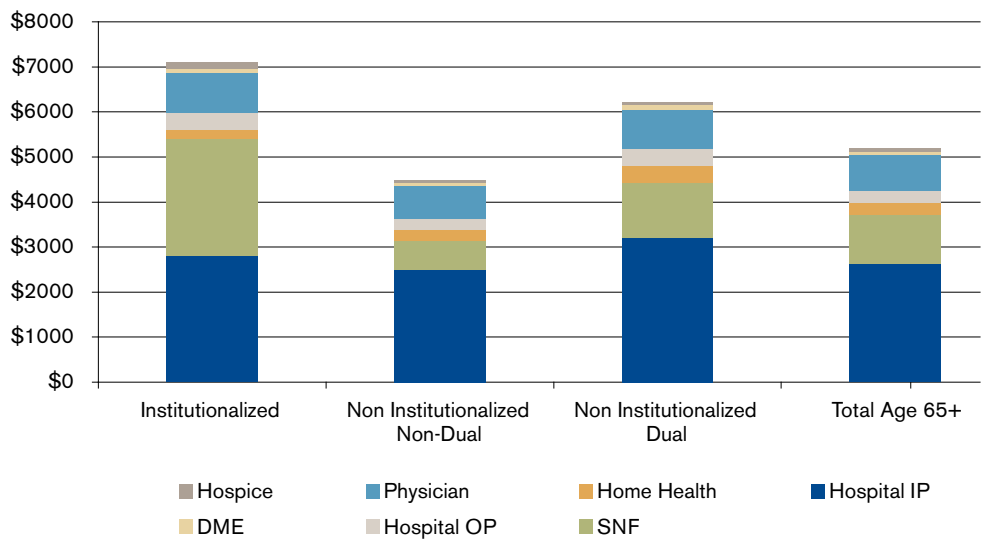
**FIGURE 18: NVAF STROKE POPULATION: ANNUAL DEATH RATE AND 60 DAY READMISSION RATES**

| | | AGE 65+ | | | |
|---|---|---|---|---|---|
| STROKE POPULATION | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| ANNUAL DEATH RATE | + OAC | 27% | 28% | 23% | 27% |
| | – OAC | 50% | 45% | 51% | 47% |
| READMISSION RATE WITHIN 60 DAYS | + OAC | 49% | 29% | 30% | 33% |
| | – OAC | 47% | 32% | 38% | 36% |

Source: Milliman analysis of Medicare 5% sample 2008 OAC = Oral Anticoagulation.

Patients with NVAF who have a stroke can be costly, as shown in Figure 19. As expected, costs are higher for those who are institutionalized or dual eligible. On average, during the year of a stroke, patients with NVAF cost about $5,000 per patient per month. The costs are the average across the NVAF stroke population assuming the stroke occurs mid year. (See methodology for cost calculation)

**FIGURE 19: NVAF STROKE POPULATION PPPM COSTS (TRENDED TO 2010)**




Source: Milliman analysis of Medicare 5% sample 2008
DME: Durable Medical Equipment; SNF: Skilled Nursing Facility; Hospital OP: Out-Patient; Hospital IP: In-Patient

### *Bleeds*

We evaluated the bleeding risk scores and the bleeding event rate (see Appendix C for bleed definition) for patients with NVAF on and off OAC therapy. We used the HEMORR2HAGES score to estimate the risk of bleeding in patients with NVAF and identified that 40% are at low to moderate risk of bleeds and not on OAC therapy. For a million Medicare beneficiaries that would amount to 24,719 patients with NVAF with a low to moderate bleeding risk not on OAC therapy. Figure 20 shows the distribution of HEMORR$_2$HAGES risk scores. We note that some of these patients may be on other anticoagulants such as aspirin, so this data may overestimate the untreated, low bleed risk population.

**FIGURE 20: DISTRIBUTION OF HEMORR2HAGES RISK SCORES AND OAC USE AMONG PATIENTS WITH NVAF**

| | | AGE 65+ | | | |
|---|---|---|---|---|---|
| HEMORR2HAGES RISK SCORE | | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| % OF BENEFICIARIES BY RISK SCORE CLASS | | | | | |
| + OAC | LOW | 1% | 12% | 6% | 10% |
| | MODERATE | 12% | 25% | 18% | 23% |
| | HIGH | 14% | 10% | 9% | 10% |
| – OAC | LOW | 4% | 12% | 11% | 11% |
| | MODERATE | 33% | 28% | 35% | 29% |
| | HIGH | 35% | 13% | 21% | 16% |

Source: Milliman analysis of Medicare 5% sample 2008

Based on our claim analysis, approximately 19% of 65+ Patients with NVAF, combining on and off OAC will have a major or minor bleed in a year (see appendix B for bleed codes and identification methodology). The rate of major bleeds is 112/1000 NVAF patients while the rate of minor bleeds is 264/1000 NVAF patients. The incidence of major bleeds is higher among patients not on OAC while the

incidence of minor bleeds is higher among patients on OAC. Because we did not match the on and off OAC cohorts by demographics, comorbidities or HCC risk scores, other factors that are known to impact the risk of bleeding could impact OAC use and subsequent related outcomes.

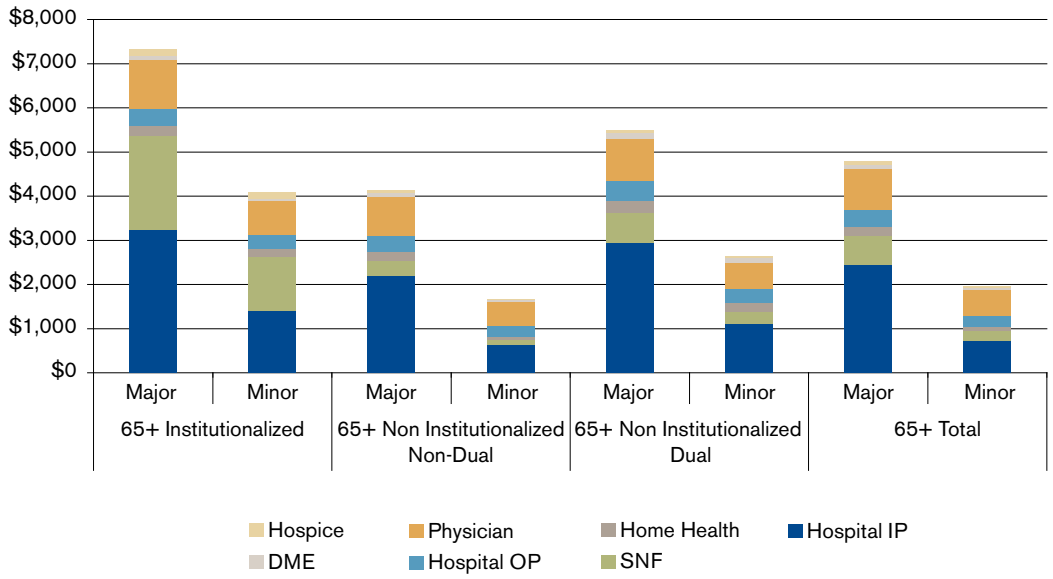
**FIGURE 21: BLEED INCIDENCE RATES FOR 65+ MEDICARE BENEFICIARIES WITH NVAF**

| | AGE 65+ | | | |
|---|---|---|---|---|
| | INSTITUTIONALIZED | NON INSTITUTIONALIZED NON-DUAL | NON INSTITUTIONALIZED DUAL | TOTAL |
| **MAJOR BLEEDS INCIDENCE PER 1000 65+ PATIENTS WITH NVAF IN EACH CATEGORY** | | | | |
| ± OAC | 164 | 100 | 151 | 112 |
| + OAC | 172 | 86 | 139 | 96 |
| – OAC | 162 | 113 | 157 | 124 |
| **MINOR BLEEDS INCIDENCE PER 1000 65+ PATIENTS WITH NVAF IN EACH CATEGORY** | | | | |
| ± OAC | 242 | 272 | 222 | 264 |
| + OAC | 328 | 380 | 357 | 375 |
| – OAC | 209 | 177 | 155 | 179 |

Source: Milliman analysis of Medicare 5% sample 2008

Patients with NVAF who have a bleed are expensive. As expected, costs are higher for those who are institutionalized or dual eligible. On average, during the year of a bleed, patients with NVAF cost about $4,400 PPPM. The costs are the average across the NVAF bleed population assuming the bleed occurs mid year. (See methodology for cost calculation)

**FIGURE 22: PATIENTS WITH NVAF PPPM COSTS (TRENDED TO 2010) DURING YEAR OF A BLEED**

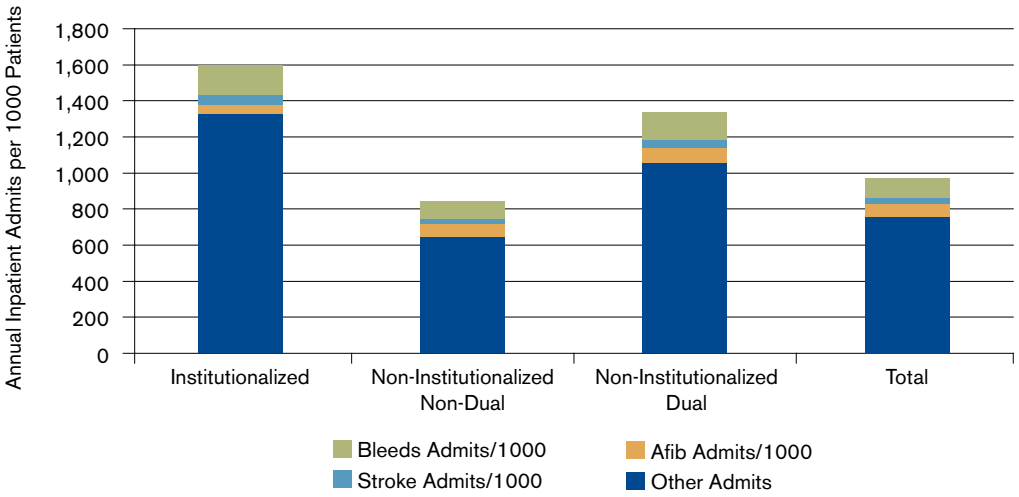



Source: Milliman analysis of Medicare 5% sample 2008
DME: Durable Medical Equipment; SNF: Skilled Nursing Facility; Hospital OP: Out-Patient; Hospital IP: In-Patient

### *Stroke and Bleeds*

The annual inpatient admission rate for Medicare beneficiaries 65+ with NVAF is 994/1000: strokes and bleeds make up 15% of the total admissions. Figure 23 shows the portion of admissions for bleeds, stroke or AF. By contrast, the average inpatient admission rate for 65+ Medicare beneficiaries is 386/1000.

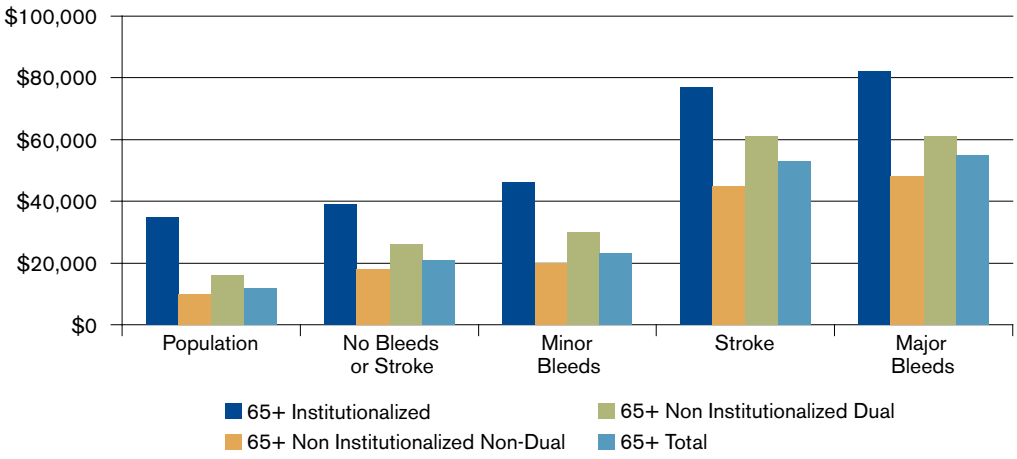
**FIGURE 23: INPATIENT ADMISSIONS FOR MEDICARE 65+ PATIENTS WITH NVAF.**




**Source: Milliman analysis of Medicare 5% sample 2008**

Figure 24 shows the average annual costs for patients with NVAF with strokes or bleeds during a 12 month period. While some of the high costs are due to age, these events bring a significant cost burden. Although the *no bleed or stroke* NVAF population is not matched on demographics and comorbidities to the stroke and bleed population, the costs during the year of a stroke or bleed are more than double that of the non bleed/non stroke NVAF population.

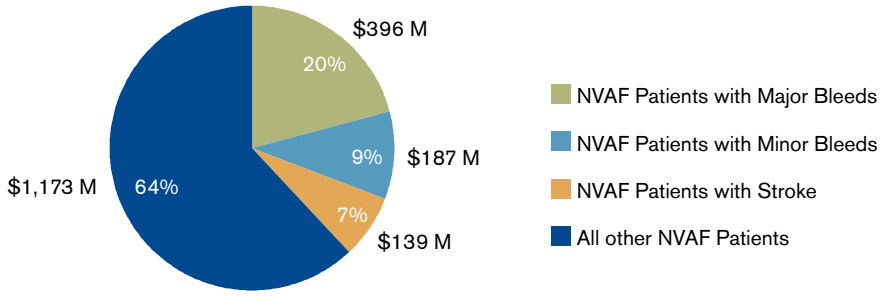
**FIGURE 24: AVERAGE ANNUAL COSTS (TRENDED TO 2010) FOR PATIENTS WITH NVAF WITH AND WITHOUT STROKE OR BLEEDS COMPARED TO TOTAL MEDICARE 65+ POPULATION**




**Source: Milliman analysis of Medicare 5% sample 2008 (numbers are rounded)**

Approximately 20% of patients with NVAF will have a stroke or a major or minor bleed in a given year but will account for approximately 36% of NVAF total medical cost. Figure 25 shows the annual dollar amounts incurred by patients with NVAF in a population of one million 65+ Medicare beneficiaries.

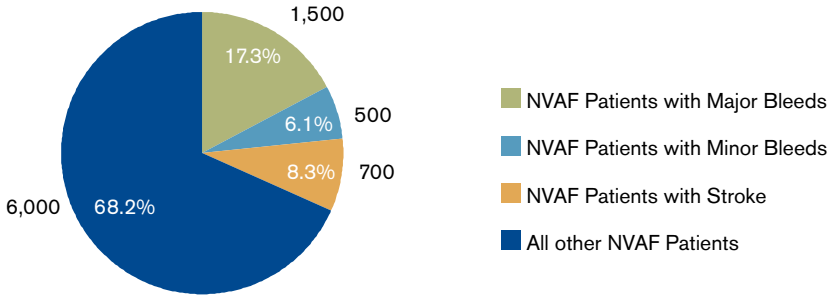
**FIGURE 25: DISTRIBUTION OF COSTS FOR MEDICARE 65+ NVAF PATIENTS (ONE MILLION 65+ MEDICARE BENEFICIARIES)**




Source: Milliman analysis of Medicare 5% sample 2008

The mortality rate among NVAF patients with strokes and/or bleeds is high as shown in Figure 20 and 21. Although only 20% of NVAF patients will have a stroke or bleed in a given year, they will account for 32% of the NVAF deaths

**FIGURE 26: DISTRIBUTION OF DEATHS FOR MEDICARE 65+ NVAF PATIENTS (ONE MILLION 65+ MEDICARE)**




Source: Milliman analysis of Medicare 5% sample 2008

## CONSIDERATIONS FOR PAYERS REGARDING ANTICOAGULATION MANAGEMENT FOR PATIENTS WITH NVAF

The 65+ Medicare population with NVAF is a high risk, high cost population. Our claim analysis identified:

- Underutilization of OAC therapy for patients with NVAF who appear to be eligible for therapy, based on treatment guidelines
- Higher rate of strokes for those not on OAC therapy
- Substantial spend associated with strokes and bleeds: 36% of total NVAF spend is for patients with NVAF having strokes and bleeds; for a population of 1 million Medicare beneficiaries, this amounts to $722 million dollars.

Our analysis as well as published studies point to the opportunity for better OAC management of patients with NVAF which can lead to a reduction in ischemic strokes. Better OAC management requires provider adherence to guidelines, patient compliance, and supportive coverage design.

OAC management has received attention from Medicare as well as the Joint Commission on the Accreditation of Healthcare Organizations. The CMS Physician Quality Reporting Initiative (PQRI), which created incentive payments for reporting performance on designated quality metrics, includes the measure of prescribing anticoagulation at discharge for patients hospitalized with ischemic stroke or TIA who have documented persistent or paroxysmal AF. The Joint Commission has established National Patient Safety goals for improving the safety of patients on anticoagulation therapy and recommends patient involvement and education for inpatients on anticoagulation that will be discharged on long term therapy. To support provider adherence to guidelines, plans might consider profiling physicians regarding OAC use and INR therapeutic range management. HEDIS currently does not have a quality outcome metric for OAC therapy management but quality outcome metrics can be readily established and measured for AF patients. Pay for performance (P4P) programs for OAC management should be considered after evaluating the outcomes with the PQRI program as well as P4P programs for management of other chronic disease states.

To address patient management concerns, plans should consider disease management efforts aimed at the AF population and in particular monitoring of OAC therapy and INR values. Medical management programs typically focus on major chronic conditions such as diabetes, CHF, COPD, and CAD and AF has been largely ignored. For AF patients receiving disease management services for the 5 major chronic conditions, specific AF management should be incorporated. Consideration should also be given to targeting AF patients for disease management aimed at AF management. This would be quite feasible with identification of the AF population through ICD9 codes and OAC therapy claims. Measuring the value of AF disease management programs should include targets for guideline adherence with OAC therapy and targets for meeting INR therapeutic levels.

To address the burden of OAC dosing and monitoring, specialized anticoagulation clinics with personnel trained to manage anticoagulation have been established in some regions. There are mixed results on whether the outcomes for patients receiving care at anticoagulation clinics compared to standard care are better controlled on their anticoagulation therapy. [14] [15]

Patient self testing with and without self reporting has been another approach to improving OAC management. Patients are instructed to use a device to measure INR based on a finger stick blood sample and convey the results to the physician's office which adjusts the dose accordingly as well as patients being taught to adjust the dose themselves. One study reported improved INR management with the self monitoring. [16] Web based monitoring systems to facilitate patient self monitoring are now available including the site: www.PTINR.com.

Because clinical guidelines recommend long term OAC therapy for patients with NVAF (see recommendation section), the cost can be a burden for these patients. Benefit and formulary designs should be evaluated for barriers to access and adherence to drug therapy and monitoring of INR. In March of 2008, Medicare expanded coverage of home INR monitoring to include chronic AF and venous thromboembolism patients that are on warfarin. Patients with AF must have a physician's prescription, and have been taking warfarin for 90 days or more to qualify. Reimbursement for the monitor and testing supplies requires that the patient completes face-to-face training from a healthcare professional and continue to competently use the device according to a physician's instructions.

# APPENDIX A:

# DESCRIPTION OF KEY DATA SOURCES AND THEIR APPLICATION

**Medicare 5% Sample**. This Limited Data Set contains all Medicare paid claims generated by a statistically-balanced sample of Medicare beneficiaries. Information includes diagnosis codes, procedure codes, and diagnosis-related group (DRG) codes, along with site of service information as well as beneficiary age, eligibility status and an indicator for HMO enrollment. We used Medicare 5% beneficiary sample data in 2007-2008.

**Milliman's 2009 Health Cost Guidelines**. The Guidelines provide a flexible but consistent basis for the determination of health claim costs and premium rates for a wide variety of health plans. The Guidelines are developed as a result of Milliman's continuing research on health care costs. First developed in 1954, the Guidelines have been updated and expanded annually since that time. The Guidelines are continually monitored as they are used in measuring the experience or evaluating the rates of health plans, and as they are compared to other data sources. The Standard Demographics in the Guidelines were developed to be representative of the age and sex distribution for a typical large insured group. The Standard Demographics were developed using data from large insurers combined with Department of Labor Sources. We use the Guidelines to demographically adjust our target population to a typical working age population.

## APPENDIX B: ANTICOAGULATION TREATMENT GUIDELINES

The guidelines developed by the ACC/AHA/ESC recommend:[13]

Class I Recommendations

- Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications. (Level of Evidence: A)
- The selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient. (Level of Evidence: A)
- For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity international normalized ratio (INR) of 2.0 to 3.0, unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, transient ischemic attack [TIA], or systemic embolism) and rheumatic mitral stenosis. (Level of Evidence: A)
- Anticoagulation with a vitamin K antagonist is recommended for patients with more than 1 moderate risk factor. Such factors include age 75 y or greater, hypertension, HF, impaired LV systolic function (ejection fraction 35% or less or fractional shortening less than 25%), and diabetes mellitus. (Level of Evidence: A)
- INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable. (Level of Evidence: A)
- Aspirin, 81–325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation. (Level of Evidence: A)
- For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5. (Level of Evidence: B)
- Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF. (Level of Evidence: C)

Class IIa Recommendations

- For primary prevention of thromboembolism in patients with non-valvular AF who have just 1 of the following validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable, based upon an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences: age greater than or equal to 75 y (especially in female patients), hypertension, HF, impaired LV function, or diabetes mellitus. (Level of Evidence: A)
- For patients with non-valvular AF who have 1 or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: age 65 to 74 y, female gender, or CAD. The choice of agent should be based upon the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences. (Level of Evidence: B)
- It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF. (Level of Evidence: B)
- In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 wk without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding. (Level of Evidence: C)

- It is reasonable to reevaluate the need for anticoagulation at regular intervals. (Level of Evidence: C)

The American College of Chest Physicians (ACCP) similarly recommends anticoagulation with an oral vitamin K antagonist for AF patients with more than one risk factor. [31]

- In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, TIA, or systemic embolism, we recommend long-term anticoagulation with an oral vitamin K antagonist, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). Timing of the initiation of VKA therapy after an acute ischemic stroke involves balancing the risk of hemorrhagic conversion with short-term risk of recurrent ischemic stroke and is addressed in the chapter by Albers et al in this supplement.

- In patients with AF, including those with paroxysmal AF, who have two or more of the following risk factors for future ischemic stroke, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the increased risk of future ischemic stroke faced by this set of patients (Grade 1A). Two or more of the following risk factors apply: (1) age> 75 years; (2) history of hypertension; (3) diabetes mellitus; and (4) moderately or severely impaired left ventricular systolic function and/or heart failure.

- Remark: The above recommendations correspond to a recommendation of oral VKA therapy for individuals with a score > 2 using the $CHADS_2$ classification. For these and all other recommendations of long-term therapy in this chapter, *long-term* means lifelong unless a contraindication emerges.

# APPENDIX C: METHODOLOGY

## Identification of Population

Using Medicare 5% Sample data 2008, we identified the target population for our analysis as individuals covered by Part B and not covered by HMO. Our starting population of Medicare beneficiaries was 1,459,591.

## Identification of Atrial Fibrillation Patients

We identified individuals in the population with AF if they had at least 1 IP, or 1 ER or 2 physician E&M claims with ICD9 diagnosis code for AF. The ICD9 diagnosis codes of AF and CPT E&M claims we used are below.

AF ICD9: 427.31

**Physician E&M codes**
99201-99205, 99211-99215, 99217-99220, 99241-99245, 99304-99337, 99341-99345, 99347-99350, 99381-99387, 99341-99350, 99391-99397, 99401-99404, 99411, 99412, 99420, 99429, 99455, 99456, 99499

We excluded individuals identified as having transient AF from our population.

## Identification of Transient Atrial Fibrillation Patients

We identified individuals in the population as transient AF patients if they had

- one or more valvular heart disease or valve replacement claim in prior 12 months before 1st AF claim
- one or more cardiac surgery claim in prior quarter from 1st AF claim
- one or more pericarditis claim in prior quarter from 1st AF claim
- one or more myocarditis claim in prior quarter from 1st AF claim
- one or more pulmonary embolism claim in prior quarter from 1st AF claim
- one or more hyperthyroidism claim in 12 months before first AF claim

We used the following codes to identify transient atrial fibrillation.

**Valvular heart disease or valve replacement**
ICD9 diagnosis codes: V42.2, V43.3, 394.x-397.x, 424.xx, 746.0-746.7

ICD9 procedure codes: 35.0x, 35.1x, 35.2x

CPT codes: 33400, 33401, 33403–33406, 33410–33417, 33420, 33422, 33425–33430, 33460, 33464, 33465, 33468, 33470–33472, 33474–33476, 33478,

**Cardiac surgery**
ICD9 Procedure codes 00.5x, 35.xx, 36.xx, 37.xx,

**Pericarditis**
ICD9 Diagnosis codes: 391.x, 393, 420.x, 423.2, 036.41, 074.21, 093.81, 098.83

**Myocarditis**
ICD9 Diagnosis codes: 391.2, 422.xx, 074.23, 398.0, 429.0, 032.82, 036.43, 093.82, 130.3

**Pulmonary embolism**
ICD9 Diagnosis code: 415.1x

**Hyperthyroidism**
ICD9 Diagnosis Code: 242.x

### Identification of Institutionalized Individuals

We identified individuals in the population as institutionalized if they had at least one claim with CPT code below or Place of Service code below.

CPT-4 codes 99324-99328, 99334-99337, 99339-99340 (Domiciliary, Rest Home, or Custodial Care Services)

Place of Service 32 (Nursing Facility), or 33 (Custodial Care Facility).

### On/Off OAC Therapy

Because the Medicare 5% sample does not have Part D data, we could not determine how many beneficiaries obtained warfarin through Part D benefits; therefore, we used a validated proxy for identifying patients on OAC. Patients considered on OAC therapy were identified as having 3 or more International Normalized Ratio (INR) tests; the validated proxy was found to have a sensitivity of 89% and specificity of 92%.[32] INR testing claims were identified having CPT codes below.

| | |
|---|---|
| 99263 | INR test review |
| 99364 | INR test review |
| 85610 | Prothrombin time |
| 85611 | Prothrombin time substitution plasma fractions each |

### Stroke

We identified stroke incidences as inpatient claims having Ischemic or Hemorrhagic stroke ICD9 Diagnosis code in the primary position of the claim. Ischemic or Hemorrhagic stroke ICD9 Diagnosis codes are below.

**Ischemic Stroke**

| | |
|---|---|
| 433.01 | Occlusion and stenosis basilar artery w cerebral infarct |
| 433.11 | Occlusion and stenosis carotid artery artery w cerebral infarct |
| 433.21 | Occlusion and stenosis vertebral artery w cerebral infarct |
| 433.31 | Multiple and bilateral w cerebral infarct |
| 433.81 | Other specified precerebral artery w cerebral infarct |
| 433.91 | Unspecified precerebral artery w cerebral infarct |
| 434.01 | Cerebral Thrombosis with Cerebral infarction |
| 434.11 | Cerebral Embolism with Cerebral Infarction |
| 434.91 | Cerebral Artery Occlusion, Unspecified, with cerebral infarction |
| 436.xx | Ischemic stroke |

**Hemorrhagic stroke**

| | |
|---|---|
| 430 | Subarachnoid hemorrhage |
| 431 | Intracerebral Hemorrhage |
| 432.0–432.9 | Other & Unspecified Intracranial Hemorrhage |

### Bleeds

We identified major bleed incidences as inpatient or ER claims coded with a bleed ICD9 Diagnosis code in any position of the claim. Minor bleeds were identified as physician office visit claims with a bleed ICD9 Diagnosis code in any position of the claim:

| | |
|---|---|
| 246.3 | Hemorrhage and infarction of thyroid |
| 286.5 | Hemorrhagic disorder due to intrinsic circulating anticoagulants |
| 362.81 | Retinal hemorrhage |
| 363.61 | Chorodial hemorrhage and rupture |
| 363.62 | Expulsive chorodial hemorrhage |
| 379.23 | Vitreous hemorrhage |
| 388.69 | Otorrhagia |
| 448.9 | Other and unspecified capillary diseases - hemorrhage, hyperpermeability, thrombosis |
| 456 | Esophageal varices with bleeding |

| | |
|---|---|
| 456.2 | Esophageal varices in diseases classified elsewhere |
| 459.0 | Hemorrhage, unspecified |
| 523.8 | Other specified periodontal diseases |
| 528.9 | Mouth bleed |
| 530.82 | Esophageal hemorrhage ( excluding varices) |
| 531 | Gastric ulcer-acute with hemorrhage |
| 531.2 | Gastric ulcer -acute with hemorrhage and perforation |
| 531.4 | Gastric ulcer-chronic or unspecified with hemorrhage |
| 531.6 | Gastric ulcer-chronic or unspecified and perforation |
| 532 | Duodenal ulcer-acute with hemorrhage |
| 532.2 | Duodenal ulcer-acute with hemorrhage and perforation |
| 532.4 | Duodenal ulcer-chronic or unspecified with hemorrhage |
| 532.6 | Duodenal ulcer-chronic or unspecified with hemorrhage and perforation |
| 533 | Peptic ulcer-acute with hemorrhage |
| 533.2 | Peptic ulcer-acute with hemorrhage and perforation |
| 533.4 | Peptic ulcer-chronic or unspecified with hemorrhage |
| 533.6 | Peptic ulcer-chronic or unspecified with hemorrhage and perforation |
| 534 | Gastrojejunal ulcer-acute with hemorrhage |
| 534.2 | Gastrojejunal ulcer-acute with hemorrhage and perforation |
| 534.4 | Gastrojejunal ulcer-chronic or unspecified with hemorrhage |
| 534.6 | Gastrojejunal ulcer-chronic or unspecified with hemorrhage and perforation |
| 537.83 | Angiodysplasia of stomach and duodenum with hemorrhage |
| 562.03 | Diverticulitis of small intestine with hemorrhage |
| 562.13 | Diverticulitis of colon with hemorrhage |
| 568.81 | Hemoperitonetum-nontraumatic |
| 569.3 | Hemorrhage of rectum and anus |
| 569.83 | Perforation of intestine |
| 578.xx | Gastrointestinal hemorrhage |
| 596.8 | Other specified disorders of bladder -includes hemorrhage, hypertrophy |
| 599.7 | Hematuria |
| 626.6 | Metrorrhagia-bleeding unrelated to menstrual cycle |
| 627.1 | Postmenopausal menorrhagia-excessive bleeding associated with onset of menopause |
| 719.1x | Hemarthrosis -varied sites |
| 727.89 | Bursa bleed |
| 784.8 | Hemorrhage from throat |
| 784.7 | Epistaxis |
| 786.3 | Hemoptysis |
| 958.2 | Secondary or recurrent hemorrhage |
| 998.1x | Hemorrhage or hematoma or seroma complicating a procedure |

### Thromboembolic Events

We identified Thromboembolic events as inpatient claims having venous or arterial events ICD9 code in the primary position of the claim. Venous or arterial events ICD9 Diagnosis codes:

**Venous events**

| | |
|---|---|
| 415.1x | Pulmonary embolism and infarction |
| 451.1x–451.9x | Phlebitis and thrombophlebitis |
| 453.x | Other venous embolism and thrombosis |

**Arterial events**

| | |
|---|---|
| 444.x | Arterial embolism and thrombosis |
| 410.xx | Acute myocardial infarction |
| 362.30–362.34 | Retinal vascular occlusion |
| 593.81 | Vascular disorders of kidney |
| 411.1 | Intermediate coronary syndrome |
| 411.81 | coronary occlusion without MI |

### $CHADS_2$ Scores

We developed CHADS2 scores (risk for stroke) for each AF patient. CHADS2 scores were the sum of the points defined below.

| CHAD ITEM | POINTS |
|---|---|
| CONGESTIVE HEART FAILURE | 1 |
| HYPERTENSION (SYSTOLIC >160 MMHG) | 1 |
| DIABETES | 1 |
| AGE GREATER THAN 75 | 1 |
| PRIOR STROKE OR TIA | 2 |

For identification of prior stroke (ischemic and hemorrhagic) or TIA, we looked back 12 months using Medicare 5% Sample data 2007.

### $HEMORR_2HAGES$ Scores

We developed HEMORR2HAGES risk scores (risk for bleeds) for each AF patient. HEMORR2HAGES risk scores were the sum of the points defined below.

| HEMORRHAGE ITEM | POINTS |
|---|---|
| HEPATIC OR RENAL DISEASE | 1 |
| ETHANOL ABUSE | 1 |
| MALIGNANCY | 1 |
| OLDER THAN 75 YEARS OF AGE | 1 |
| REDUCED PLATELET COUNT OR FUNCTION | 1 |
| HISTORY OF STROKE | 2 |
| HYPERTENSION | 1 |
| EXCESSIVE FALL RISK | 1 |
| ANEMIA | 1 |

### Hierarchical Condition Category (HCC) Scores

HCCs are used by the Medicare program to risk adjust the premiums it pays to Medicare Advantage Plans (MA) under Medicare Part C and Prescription Drug Plans (PDPs) under Medicare Part D. The HCC system captures information about an individual's diagnoses, institutional status, and demographic characteristics, and converts that information into a risk score. A higher risk score for an individual indicates the medical or drug costs for that individual are expected to be higher. We note that, due to the complexity of the system, the average score for the entire Medicare population in any year may not be exactly 1.00.

The HCC methodology assigns a condition category to individuals based on a diagnosis appearing in only one claim (excluding lab, radiology and some other claims). We note that our identification of patients with NVAF is somewhat more rigorous in that we required that the diagnosis appear in two or more office visits, 1 inpatient claim or 1 ER claim. Therefore, our analysis does not necessarily correspond to the premium adjustment Medicare would make to MAs or PDPs.

### Identification of Death and Readmission Rates

The readmission rates and death rates are those observed in 2008 for patients having a stroke in 2008. The death rate underestimates the annual mortality rate because they are the observed number of deaths within the year among patients with NVAF who had a stroke. The readmission rates measure the probability of a readmission in the stroke population, within 60 days of an admission.

# REFERENCES


1 Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370-2375.

2 Miyasaka Y, Barnes ME, Gersh BJ, et al, Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence. Circulation. 2006;114:119-125

3 Lakshminarayan K, Solid CA, Collins AJ, et al. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). Stroke. 2006;37:1969-1974.

4 Coyne KS, Paramore C, Grandy S, et al. Assessing the direct costs of treating non-valvular atrial fibrillation in the United States. Value Health. 2006;9:348-356.

5 Stewart S, Hart CL, Hole DJ et al. A population based study of the long term risks associated with atrial fibrillation. 20 year follow-up of the Renfrew.Paisley study. Am J Med 2002;113:356-364.

6 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke. 1991;22:983-988.

7 Lin HJ, Wolf PA, Kelly-Hayes M. et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke.1991;27:1760-1764.

8 Fang C, Stafford R, Ruskin J, et al. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. Arch Intern med. 2004;164:55-60.

9 Waldo AL, Becker RC, Tapson VF, et al. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am College of Card. 2005;46:1729-1736.

10 Samsa GP, Matchar DP, Goldstein LB, et al. Quality of anticoagulation management among patients with atrial fibrillation. Arch Intern Med. 2000;160:967-973.

11 Glazer N, Dublin S, Smith NL, et al. Newly detected atrial fibrillation and compliance with antithrombotic guidelines. Arch Intern med. 2007;167:246-252.

12 Gross CP, Vogel EW, Dhond AJ, et al. Factors influencing physicians' reported use of anticoagulation therapy in nonvalvular atrial fibrillation: a cross-sectional survey. Clin Ther. 2003;25:1750-1764.

13 Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). Circulation. 2006;114:e257-e354.

14 Gaughan GL, Dolan C, Wilk-Rivard E, et al. Improving management of atrial fibrillation and anticoagulation in a community hospital. It Comm J Qual Improv. 2000;26:18-28.

15 Matchar DB. Do anticoagulation management services improve care? Implications of the Managing Anticoagulation Services Trial. Card Electrophysiol Rev. 2003;7:379-381.

16 Sawicki PT. A structured teaching and self management program for patients receiving oral anticoagulation: a randomized controlled trial. Working group for the study of patient self management of oral anticoagulation. JAMA. 1999;281:145-150.

17 Stettin G. Treatment of nonvalvular atrial fibrillation. West J Med. 1995;162:331-339.

18 Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. Ann Intern Med. 1999;131:688-695.

19 Walker AM, Bennett D. Epidemiology and outcomes in patients with atrial fibrillation in the United States. Heart Rhythm. 2008;5:1365-1372.

20 Kim MH, Lin J, Hussein M, Battleman D. Incidence and temporal pattern of hospital readmission for patients with atrial fibrillation. Current Medical Research and Opinions. 2009;25:1215-1220.

21 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation Ann Intern Med. 2007;146:857-867.

22 Gage BF, Waterman AD, Shannon W. et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;13:2864-2870.

23 Boulanger L, Kim J, Friedman M, et al. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. Int J Clin Pract. 2006;60:258-264.

24 Bungard TJ, Ghali WA, Teo KK, et al. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med. 2000;160:41-46.

25 Budnitz DS, Shehab N, Kegler SR, et al. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007;147:755-765.

26 Hylek EM, D'Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice. The challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke. 2006;37:1075-1080.

27 Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151:713-719.

28 Harley CR, Riedel AA, Hauch O, et al. Anticoagulation therapy in patients with chronic atrial fibrillation: a retrospective claims data analysis. Curr Med Res Opin. 2008;21:215-222.

29 Jencks SF, Willimans MV, Coleman EA. Rehospitalizations among patients in the Medicare fee for service program. N Engl J Med. 2009;360. 1418-1428.

30 Pope GC, Kautter J, Ellis RP, et al. Risk Adjustment of Medicare Capitation Payments Using the CMS-HCC Model, Health Care Fin Rev, Summer 2004/V25, N4.

31 Singer DE, Albers GW, Dalen J, et al. Antithrombotic therapy in atrial fibrillation. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:546S-592S.

This report reflects the findings of the authors and does not represent a position or endorsement by Milliman or any product or policy. The findings presented in this report are based on data and research. These findings may not be suitable for any particular individual or group of people. Treatment and pathophysiology of NVAF will need to be revised as new data becomes available. Accordingly, the reader should seek updated information before applying our findings.

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