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Effective 1/1/14 for Abilify Maintena® (aripiprazole) for Extended-Release Injectable Suspension

INDICATION and IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension

INDICATION

Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia.

- **Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.**

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Abilify Maintena is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.

FOR THE **TREATMENT OF SCHIZOPHRENIA**

An option that may help your members delay relapse

Abilify Maintena® (aripiprazole) significantly delayed the time to relapse* vs placebo (*P*<0.0001)

Visit AbilifyMaintena.com for product information and Formkit.com for formulary information.

***In a Phase III, 52-week, double-blind, randomized-withdrawal clinical trial; Abilify Maintena (n=269) vs placebo (n=134).**

IMPORTANT SAFETY INFORMATION *(continued)*

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including Abilify Maintena. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Continued on next page.

Please see IMPORTANT SAFETY INFORMATION continued, and BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

400MG

Abilify Maintena®

(aripiprazole) for extended release injectable suspension

IMPORTANT SAFETY INFORMATION for Abilify Maintena® (aripiprazole) for extended-release injectable suspension *(continued)*

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).
- **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension. Abilify Maintena should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving Abilify Maintena. In such patients, consider discontinuation of Abilify Maintena at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions: Abilify Maintena should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: Abilify Maintena may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery including automobiles until they are certain Abilify Maintena does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with Abilify Maintena; use caution in patients at risk for aspiration pneumonia.

Alcohol: Advise patients to avoid alcohol while taking Abilify Maintena.

Concomitant Medication: Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the Abilify Maintena dosage may need to be increased. Avoid the concomitant use of CYP3A4 inducers with Abilify Maintena for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels. Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

Most commonly observed adverse reaction: The safety profile of Abilify Maintena is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind Abilify Maintena and were then randomized to receive Abilify Maintena or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs placebo, respectively, was:

- Akathisia (8% vs 4%) in adult patients with schizophrenia.

Injection Site Reactions: In the open-label, stabilization phase of a study with Abilify Maintena in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for Abilify Maintena-treated patients.

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy/Nursing: Based on animal data, may cause fetal harm. Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on adjacent pages.

Otsuka Lundbeck

ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details, please see *Full Prescribing Information and Medication Guide.*)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death
- ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis

INDICATIONS AND USAGE: ABILIFY MAINTENA (aripiprazole) is indicated for the treatment of schizophrenia. Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials.

CONTRAINDICATIONS: ABILIFY MAINTENA is contraindicated in patients with a known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole.

WARNINGS AND PRECAUTIONS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, in oral aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with oral aripiprazole. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY MAINTENA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with ABILIFY MAINTENA drug discontinuation should be considered. However, some patients may require treatment with ABILIFY MAINTENA despite the presence of the syndrome.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Although the following metabolic data were collected in patients treated with oral formulations of aripiprazole, the findings pertain to patients receiving ABILIFY MAINTENA as well.

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes), who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.

  In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 1 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 1: Changes in Fasting Glucose From Placebo-controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Aripiprazole	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Aripiprazole	31/176	17.6
		Placebo	13/142	9.2

  At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

  There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

  Table 2 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 2: Changes in Blood Lipid Parameters From Placebo-controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol	Aripiprazole	34/1357	2.5
Normal to High (<200 mg/dL to ≥240 mg/dL)	Placebo	27/973	2.8
Fasting Triglycerides	Aripiprazole	40/539	7.4
Normal to High (<150 mg/dL to ≥200 mg/dL)	Placebo	30/431	7.0
Fasting LDL Cholesterol	Aripiprazole	2/332	0.6
Normal to High (<100 mg/dL to ≥160 mg/dL)	Placebo	2/268	0.7
HDL Cholesterol	Aripiprazole	121/1066	11.4
Normal to Low (≥40 mg/dL to <40 mg/dL)	Placebo	99/794	12.5

  In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/ nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

  Table 3 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

Table 3: Percentage of Patients From Placebo-controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	n (%)
Weight gain ≥7% of body weight	Schizophrenia[a]	Aripiprazole	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	Aripiprazole	719	16 (2.2)
		Placebo	598	16 (2.7)

[a]4-6 weeks' duration. [b]3 weeks' duration.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. Orthostasis occurred in 4/576 (0.7%) patients treated with ABILIFY MAINTENA during the stabilization phase, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%).

In the stabilization phase, the incidence of significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) was 0.2% (1/575).

Leukopenia, Neutropenia, and Agranulocytosis: *Class Effect:* In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including oral aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC counts until recovery.

Seizures: As with other antipsychotic drugs, use ABILIFY MAINTENA cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment: ABILIFY MAINTENA, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY MAINTENA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MAINTENA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY MAINTENA. ABILIFY MAINTENA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS: The following adverse reactions are discussed in more detail in other sections of the labeling in the *Full Prescribing Information:*

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.9)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety Database of ABILIFY MAINTENA and Oral Aripiprazole: Aripiprazole has been evaluated for safety in 16,114 adult patients who participated in multiple-dose, clinical trials in schizophrenia and other indications, and who had approximately 8,578 patient-years of exposure to oral aripiprazole. A total of 3,901 patients were treated with oral aripiprazole for at least 180 days, 2,259 patients were treated with oral aripiprazole for at least 360 days, and 933 patients continuing aripiprazole treatment for at least 720 days.

ABILIFY MAINTENA 300-400 mg every 4 weeks has been evaluated for safety in 1,287 adult patients in clinical trials in schizophrenia, with approximately 1,281 patient-years of exposure to ABILIFY MAINTENA. A total of 832 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 630 patients treated with ABILIFY MAINTENA had at least 1 year of exposure (at least 13 consecutive injections).

The conditions and duration of treatment with ABILIFY MAINTENA included double-blind and open-label studies. The safety profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. Therefore, most of the safety data presented below are derived from trials with the oral formulation. In patients who tolerated and responded to treatment with oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections under double-blind conditions, the incidence of adverse reactions was similar between the two treatment groups.

Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole: *Adverse Reactions Associated with Discontinuation of Oral Aripiprazole:* Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the incidence of discontinuation due to adverse reactions was 7% in oral aripiprazole-treated and 9% in placebo-treated patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions of Oral Aripiprazole: Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the only commonly observed adverse reaction associated with the use of oral aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

Less Common Adverse Reactions in Adults Treated with Oral Aripiprazole: Table 4 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with oral aripiprazole (doses ≥2 mg/ day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 4: Adverse Reactions in Short-term, Placebo-controlled Trials in Adult Patients Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction[a]	
System Organ Class Preferred Term	**Oral Aripiprazole (n=1843)**	**Placebo (n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a]Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Dose-Related Adverse Reactions of Oral Aripiprazole: Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed oral doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

Injection Site Reactions of ABILIFY MAINTENA: In the open-label, stabilization phase of a study with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for ABILIFY MAINTENA-treated patients. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the first to the last injection in the open-label, stabilization phase (6.1 to 4.9).

Investigator evaluation of the injection site for pain, swelling, redness and induration following injections of ABILIFY MAINTENA in the open-label, stabilization phase were rated as absent for 74%-96% of subjects following the first injection and 77%-96% of subjects following the last injection.

Extrapyramidal Symptoms of Oral Aripiprazole: In short-term, placebo-controlled trials in schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for oral aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, –0.05).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Abnormal Involuntary Movement Scale (for dyskinesias) did not show a difference between aripiprazole and placebo.

Dystonia: Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials of Oral Aripiprazole: The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for oral aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of oral aripiprazole. In addition, in a long-term, active-controlled study, the incidence of tremor was 5% (40/859) for oral aripiprazole.

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Aripiprazole: Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *Adverse Reactions (6),* or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders: ≥1/1000 patients and <1/100 patients - thrombocytopenia; Cardiac Disorders: ≥1/1000 patients and <1/100 patients - palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia; <1/1000 patients - atrial flutter, supraventricular tachycardia, ventricular tachycardia; *Eye Disorders:* ≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia; *Gastrointestinal Disorders:* ≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; <1/1000 patients - pancreatitis; *General Disorders and Administration Site Conditions:* ≥1/100 patients - asthenia, peripheral edema, chest pain; ≥1/1000 patients and <1/100 patients - face edema, angioedema; <1/1000 patients - hypothermia; *Hepatobiliary Disorders:* <1/1000 patients - hepatitis, jaundice; *Immune System Disorders:* ≥1/1000 patients and <1/100 patients - hypersensitivity; *Injury, Poisoning, and Procedural Complications:* ≥1/100 patients - fall; <1/1000 patients - heat stroke; Investigations: ≥1/1000 patients and <1/100 patients - blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased; <1/1000 patients - blood lactate dehydrogenase increased, glycosylated hemoglobin increased; *Metabolism and Nutrition Disorders:* ≥1/1000 patients and <1/100 patients - anorexia, hyponatremia, hypoglycemia, polydipsia; <1/1000 patients - diabetic ketoacidosis; *Musculoskeletal and Connective Tissue Disorders:* ≥1/1000 patients and <1/100 patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; <1/1000 patients - rhabdomyolysis; *Nervous System Disorders:* ≥1/100 patients - coordination abnormal; ≥1/1000 patients and <1/100 patients - speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia; <1/1000 patients - choreoathetosis; *Psychiatric Disorders:* ≥1/100 patients - suicidal ideation; ≥1/1000 patients and <1/100 patients - loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; <1/1000 patients - catatonia, sleepwalking; *Renal and Urinary Disorders:* ≥1/1000 patients and <1/100 patients - urinary retention, polyuria, nocturia; *Reproductive System and Breast Disorders:* ≥1/1000 patients and <1/100 patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; <1/1000 patients - gynecomastia, priapism; *Respiratory, Thoracic, and Mediastinal Disorders:* ≥1/100 patients - nasal congestion, dyspnea; *Skin and Subcutaneous Tissue Disorders:* ≥1/100 patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; ≥1/1000 patients and <1/100 patients - pruritus, photosensitivity reaction, alopecia, urticaria.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm).

DRUG INTERACTIONS: Carbamazepine or Other CYP3A4 Inducers: Concomitant use of ABILIFY MAINTENA with carbamazepine or other CYP3A4 inducers decreases the concentrations of aripiprazole. Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days *[see Indications and Usage, Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].*

Ketoconazole or Other Strong CYP3A4 Inhibitors: Concomitant use of ABILIFY MAINTENA with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with ABILIFY MAINTENA does not require a dose adjustment.

Quinidine or Other Strong CYP2D6 Inhibitors: Concomitant use of ABILIFY MAINTENA with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].* Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of quinidine or other CYP2D6 inhibitors with ABILIFY MAINTENA does not require a dose adjustment.

CNS Depressants: Given the CNS depressant effects of aripiprazole, use caution when ABILIFY MAINTENA is taken in combination with other centrally-acting drugs or alcohol.

Anti-Hypertensive Agents: Due to its α_1-adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category C: Risk Summary:* Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including ABILIFY MAINTENA) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1-10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on a mg/m^2 body surface area. ABILIFY MAINTENA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Fetal/Neonatal Adverse Reactions: Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Animal Data: Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on a mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at the oral MRHD of 30 mg/day based on AUC and 6 times, 19 times, and 65 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/ kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30 mg/day on a mg/m^2 body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

Nursing Mothers: Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ABILIFY MAINTENA in patients <18 years of age have not been evaluated.

Geriatric Use: Safety and effectiveness of ABILIFY MAINTENA in patients >60 years of age have not been evaluated. In oral single-dose pharmacokinetic studies (with aripiprazole given in a single oral dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. Also, the pharmacokinetics of oral aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment of ABILIFY MAINTENA is recommended for elderly patients *[see also Boxed Warning and Warnings and Precautions (5.1)].*

CYP2D6 Poor Metabolizers: Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Dosage adjustment is recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].*

OVERDOSAGE: Human Experience: The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

Management of Overdosage: In case of overdosage, call the Poison Control Center immediately at 1-800-222-1222.

PATIENT COUNSELING INFORMATION: Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ABILIFY MAINTENA.

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CONTENTS

VOL. 2 NO. 2 6.14 The American Journal of AccountableCare

Questions related to editorial content and submissions should be directed to associate editorial director Nicole Beagin: nbeagin@ajmc.com; 609-716-7777 ext. 131.

MISSION

The American Journal of Accountable Care provides the platform for healthcare professionals and organizations to share research and best practices in the realm of accountable care. The Journal seeks to educate its audience on how to better understand the emerging role of new payment models and policy issues surrounding healthcare reform. *The American Journal of Accountable Care* publishes timely research and analysis that encourages the sharing of best practices to ensure the improvement of healthcare quality.

The American Journal of Accountable Care™

Treat patients like you would treat your own mother.

Good advice, or common sense? For years, those of us engaged in healthcare delivery have known that common sense doesn't always apply. It's a reason why the cost of healthcare in the United States kept rising, even though chronic conditions like diabetes rose, too.

But as healthcare reform takes hold, look for common sense to matter more. This issue of *The American Journal of Accountable Care* offers plenty of advice from those who are already succeeding with new reimbursement models and through accountable care organizations, or ACOs. So much of what works in the early success stories seems obvious: *Listen to patients. Treat them like customers. Don't make them wait for hours. Let them have a say in what happens. And, understand what your patients are spending, so they don't get hit with a bill that's a surprise.*

What's challenging are the discrete steps that put ideas into practice. Successful ACO leaders, like Kelly Conroy of Triple Aim Advisory Group, who writes how the Palm Beach ACO drove home the message of "Treat patients like your mother," among other maxims, in getting physicians to adapt to changing times. Conroy writes that when unsatisfied patients can lead to a 25% loss in earnings, it's essential that doctors get serious about overlooked customer service issues. When it comes to tactics, Palm Beach ACO has learned to pay attention to small things, like making sure patients have follow-up appointments.

What we once called "beside manner" will matter, too. Brian W. Powers and Sachin H. Jain, MD, MBA, discuss the importance of a doctor's communication methods and the "tone of patient interactions." Especially when considering an elective procedure, a patient must find a doctor who shares his or her approach and values, and that will mean that not every doctor will be the right fit for every patient. Medical practices must be attuned to issues like social and cultural appropriateness, which might not be easy in an increasingly diverse nation.

ACO leaders shared these ideas and others at the first gathering of our *AJMC* ACO and Emerging Healthcare Delivery Coalition, held recently in Baltimore, Maryland. This issue includes highlights from that event, where our members were able to apply what they learned in hands-on workshops. Feedback from our event has been tremendous, and another is planned for Miami in the fall. If you have been thinking of joining our Coalition, now is the time. Healthcare delivery will keep changing, and the partnerships that are forming now may make the difference in whether your practice, hospital, or health plan succeeds in the years ahead. Join us and be among the leaders in making healthcare work better for patients. www.ajmc.com/acocoalition.

As always, thank you for reading.

Brian Haug
President
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Through coordinated care delivery, accountable care organizations (ACOs) attempt to achieve the Triple Aim: improving the patient experience of care (including quality and satisfaction); improving the health of populations; and reducing the per capita cost of healthcare.[1] When the Pioneer ACO program began in 2012, there were 32 participating organizations. Of those, 23 remain in the program and 7 have transitioned to the Medicare Shared Savings program. The Pioneer ACOs produced nearly $150 million in total savings, of which half was returned in 2012. Only 1 ACO shared in losses.[2]

The success of early ACO implementation continues to emerge. The Hill Physicians Medical Group, Inc, reported total revenue of $505.2 million in 2013, up 2.7% from 2012.[3] Anthem-HealthCare Partners, a California-based ACO created by Anthem Blue Cross and HealthCare Partners physician groups, saved $4.7 million over the first 6 months of 2013.[4] UnityPoint, a 12-hospital system in West Des Moines, Iowa, also reported that it earned $7.8 million in revenue from value-based contracts, a significant increase from $2.3 million in 2012. The organization's value-based contracts include its Trinity Pioneer ACO that began operating January 1, 2012; a commercial ACO in partnership with Wellmark Blue Cross and Blue Shield that was formed April 1, 2012; and a Medicare Shared Savings ACO that was accepted into the program July 1, 2012.[5] Rigorous evaluations examining the clinical and economic impact over the long term are highly anticipated.

Although ACO growth may been slower than anticipated, some estimate that by the end of 2014, there could be as many as 1000 ACOs operating in the United States—doubling the 500 currently established ACOs as of June 2014.[6]

The ultimate test of health reform will be whether it improves health *and* addresses rising costs. *The American Journal of Accountable Care* strives to become a valued source of information regarding the many programs occurring across the country aiming to provide better quality care at a lower rate of cost growth. We hope that the content is timely and relevant. We welcome your impressions and opinions.

"Although ACO growth may been slower than anticipated, some estimate that by the end of 2014, there could be as many as 1000 ACOs operating in the United States—doubling the 500 currently established ACOs as of June 2014.[6]"

REFERENCES

1.The IHI triple aim. The Institute for Healthcare Improvement website. http://www.ihi.org/Engage/Initiatives/TripleAim/Pages/default.aspx. Published 2014. Accessed June 16, 2014.

2. Peterson M, Muhlstein D. ACO results: what we know so far. *Health Aff Blog.* http://healthaffairs.org/blog/2014/05/30/aco-results-what-we-know-so-far/. Accessed June 16, 2014.

3. Robertson K. Revenue at Hill Physicians passes $500 million for first time. June 11, 2014. *Sacramento Business Journal.* http://www.bizjournals.com/sacramento/news/2014/06/11/revenue-at-hill-physicians-passes-500-million-for.html. Accessed June 6, 2014.

4. Terhune C. Anthem, HealthCare Partners save $4.7 million by coordinating care. June 5, 2014. *Los Angeles Times.* http://www.latimes.com/business/money/la-fi-anthem-healthcare-partners-20140605-story.html. Accessed June 6, 2014.

5. Kutscher, B. UnityPoint Health reports 34.5% boost in 2013 operating income. Modern Healthcare. http://www.modernhealthcare.com/article/20140423/NEWS/304239962. Accessed June 6, 2014.

6. Accountable Care Organization and Population Health Management Trends: Fall 2013 Economic Outlook. Premier, Inc website. https://www.premierinc.com/wps/wcm/connect/9e3ec8e7-35cf-42e3-8406-4a2d77682019/ACO-Survey-White+Paper.pdf?MOD=AJPERES. Published December 2013. Accessed June 16, 2014.

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Patient-Centered Physician Selection: A Necessary First Step for Accountable Care

BRIAN W. POWERS, BA, AND SACHIN H. JAIN, MD, MBA

There is a notable gap in our system wide efforts to promote accountable, patient-centered care: physician selection. The past decade has borne witness to significant advances in reorienting the processes and experiences of care around patient preferences and values, but the same level of focus has not been directed to helping patients identify the best physician for their needs. Instead, our prevailing approaches to matching patients with physicians remain largely agnostic to variations in patient preferences, tethered to the traditions of peer recommendation and reputation-based referral. Even recent efforts to bring more transparency and consumer choice to healthcare decisions focus primarily on costs and outcomes,[1] and neglect other domains of the patient experience.

This eschews a growing understanding of the divergent priorities many patients have when selecting a physician. Some patients place a premium on clinical reputation and technological advancement, while others are concerned more with measures of quality and value. These preferences are layered on top of additional dimensions as varied as communication style and cultural appropriateness.

Appreciating and acting on this heterogeneity is essential to improving patient ability to interact with the system and identify clinicians that best fit their needs and preferences. Strengthening the attention to patient preferences in this critical first step of a patient's healthcare experience is critical if patients are going to become engaged partners in their care and form strong therapeutic alliances with their physicians. As accountable care, value-based purchasing, and other new models of care delivery and financing intensify our focus on patient-centered care and longitudinal relationships with physicians, it is necessary to improve the healthcare system's capacity to match patients with physicians who fit their specific needs, preferences, and values.

In this perspective, we draw on the insights from research into patient preferences to propose a framework for understanding and organizing the information necessary to successfully match patients and physicians. Specifically, we outline 5 factors that should be considered when matching patients with physicians, and provide examples of the information and attributes that are important to consider within each factor.

1. *Communication and decision making.* Communication and decision making anchor the patient-physician relationship, and patient preferences in these areas vary considerably. Physician communication style and the tone of patient interactions, inclusiveness of the patient in decision making, and attitudes and approaches to uses of clinical evidence are all important variables to consider when selecting a physician. Clinical measures of individual physician performance or survey data from other patients can be important supports to patient choices in this area.
2. *Therapeutic approach.* For many elective, "preference-sensitive" conditions, the aggressiveness and intensity of treatment vary among physicians.[2] These are precisely the procedures for which patients spend the most time trying to identify the right physician, and it is important that patients understand with clarity the therapeutic options favored by their physician of choice. Similarly, a physician's willingness to provide complementary or alternative therapies, and his or her use of new technologies or investigational drugs and procedures, are important factors of consideration in this area.
3. *Social and cultural appropriateness.* Patients should be matched with physicians who can deliver care that is consistent with their social, cultural, or religious preferences. For example, patients from historically disadvantaged or marginalized groups are often more comfortable working with physicians with a special aptitude for or interest in working with those groups.[3] Other factors many patients will find important to consider are nationality, ethnicity, or fluency in their preferred language.
4. *Cost and value.* Economic considerations have a profound ef-

fect on healthcare-seeking and -utilization activities.[4] As out-of-pocket deductibles rise and patients increasingly bear the costs of care, appropriate financial data, such as expected or estimated out-of-pocket costs, will be key variables to consider in choosing a physician.

5. *Practice environment.* The attributes of the system within which a physician practices have a profound impact on a patient's experience with his or her physician. Patients are sensitive to system characteristics such as wait times, the use of patient portals, physician use of electronic health records (EHRs), and the care delivery model in which the physician operates (eg, medical home). Many patients—especially patients with complex illnesses—are especially cognizant of the extent to which clinical interactions across an extended delivery system are coordinated.

This framework is intentionally comprehensive and, in many cases, attributes of clinicians and patients will have relevance across the 5 categories. Patient preference will govern the relative importance of each dimension and its attributes; aligning a patient with the right physician requires information across all of these dimensions. **Table 1** outlines preferences of 3 sample patients to demonstrate the profound heterogeneity that must be considered and managed if patients are to be able to select physicians aligned with their unique needs, preferences, and values. True patient-centeredness will only emerge when we acknowledge this reality and build the tools, systems, and strategies to understand and manage this heterogeneity.

Fortunately, there has been a dramatic influx in the availability of the data needed to populate the various components of this framework. Patient groups and societies sometimes offer direction on choice of provider and therapy. Commercial and government websites such as Physician Compare offer information on patient experience and attributes such as communication style and cultural appropriateness. Commercial insurers are releasing tools that allow patients to receive tailored, real-time estimates of out-of-pocket expenses for different providers. Multi-stakeholder organizations such as the National Committee for Quality Assurance and the Healthcare Information and Management Systems Society have information on system-level factors such as EHR adoption and disease management capabilities. Importantly, certifications from groups like the Joint Commission and data made public by private payers and Medicare can yield information on condition-specific outcomes.

With growing quality, the infrastructure and information exist to move toward a more patient-centered approach to physician selection. But the information is siloed, housed in myriad sources that are hard for patients to navigate and even harder for them to integrate. Helping patients find the right physician requires integrating existing data sources and providing patients with the information they need to select the right physician for their needs. The responsibility for making available these integrated resources will fall on accountable care organizations, physician groups, employers, governments, and patient groups, all of whom share an interest in enabling patients to make sound decisions and begin their healthcare experience by identifying the best physician for their needs.

Table 1. Five Factors That Mediate the Physician-Patient Relationship: The Preferences of 3 Sample Patients

Health Services			
	PATIENT A	**PATIENT B**	**PATIENT C**
Communication and decision making	Defer to physician's best judgment	Shared decision making between physician expertise and patient preferences	Autonomous decision making with limited physician input
Therapeutic approach	Advanced technology and investigational therapies	Complementary and alternative therapies	Less invasive treatment and "watchful waiting"
Social and cultural appropriateness	African American physician	Physician who is fluent in their native language	End-of-life care consistent with their religious beliefs
Cost and value	Minimize total costs (enrolled in an HDHP)	Minimize co-payment	Physician in tier A of their PPO
Practice environment	Integrated primary and specialty care	Patient portal to track conditions and manage appointments	Direct care model with streamlined access

HDHP indicates high-deductible health plan; PPO, preferred provider organization.

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REFERENCES

1. Huckman RS, Kelley M. Public reporting, consumerism, and patient empowerment. *N Engl J Med.* 2013;369:1875-1877.

2. Institute of Medicine. *Patients Charting the Course: Citizen Engagement in the Learning Health System.* Washington, DC: National Academies Press; 2010.

3. Chen FM, Fryer GE Jr, Phillips RL Jr, Wilson E, Pathman DE. Patients' beliefs about racism, preferences for physician race, and satisfaction with care. *Ann Fam Med.* 2005;3(2):138-143.

4. Manning WG, Newhouse JP, Duan N, Keeler EB, Leibowitz A, Marquis MS. Health insurance and the demand for medical care: evidence from a randomized experiment. *Am Econ Rev.* 1987;77(3):251-277.

Patient-Centered Medical Home-Recognized Practices Provide a Strong Front Line for Accountable Care Organizations

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The National Committee for Quality Assurance (NCQA)-recognized patient-centered medical homes (PCMHs) provide a strong front line of support to accountable care organizations (ACOs) by achieving improved health outcomes, improved patient experience of care, and reduced costs (dabbed by the Institute for Healthcare Improvement the "Triple Aim"). The PCMH model puts the patient at the center of care, delivering "whole person" care that considers patient engagement, clinical measurement, population health management, and standard work flows designed to support the goals of the Triple Aim. The core tenets of the PCMH focus on:

- Enhanced access and continuity of care
- Delivering "team-based" care
- Identification and management of patient populations
- Planning and managing care
- Tracking and coordination of care
- Continuous commitment to quality improvement

With support of legislation outlined in the Affordable Care Act (ACA), primary care has been called on to raise the bar in identifying and managing high-risk populations, to include social determinants of health in care criteria and to deliver integrated care through co-management of behavioral/mental and physical health. Primary care practices need robust resources to meet the standardized requirements for patient engagement, shared decision making, delivery of appropriate cultural and linguistic services, and assessments of health literacy. More than 7000 NCQA-recognized PCMH practices across the country, representing more than 35,000 clinicians, have demonstrated their ability to be creative in their care team design, focused in their collaboration with specialists, and innovative in their patient engagement strategies.

PCMH standards provide a framework of standardized requirements, vetted by healthcare leaders and a national Public Comment period that invites insights and perspectives from all areas of the delivery system. This gathering of perspectives has resulted in standards that are customizable and can be adapted to a wide variety of primary care practice settings. The model continues to evolve as new research and insights into best practices are revealed, but ongoing support is necessary from health-system leaders, public and commercial payers, medical societies, and academic institutions. ACOs have a unique opportunity to leverage the knowledge they gained in working with practices that transformed to meet PCMH requirements and have exhibited a commitment to sustaining the model of patient-centered care.

Among the greatest challenges primary care practices face in meeting the charge of transformation—especially small, independent practices—is finding the financial and human resource support necessary to make the shift. With continued support from medical societies, academic institutions, regional employers, regional extension centers, and public and commercial payers, and with strong resource stewardship from ACOs, adoption of the PCMH model will grow. PCMH support continues to climb as incentives tied to PCMH transformation increase, as payers direct consumers to recognized practices and provide greater access to embedded and network case managers to support wellness, complex case management, and management of overall population health. Recognized PCMHs have been essential in driving quality improvement initiatives through CMS innovation programs, such the Multi-Payer Advanced Primary Care Practice (MAPCP) and Comprehensive Primary Care (CPCi) initiatives, which offer enhanced payment to primary care practices that coordinate better primary care for their Medicare patients. Having a strong foundational understanding of open-access scheduling, using practice staff to the highest extent of their licenses, and ensuring that patients are surveyed about their access, communication, care coordination, and self-management support needs can alleviate the burden of meeting the rigorous requirements of these programs.

Patient-centered specialty practices (PCSPs) understand the need to establish effective turnaround times for screenings and availability for consultations between physicians, to help co-manage their shared populations, to forge agreements that ensure essential, unduplicated diagnostic testing, and to collaborate on integrated care plan designs. A baseline of standards and guidelines reflects best practices in collaborative, patient-centric methods to deliver care.

Community pharmacies, urgent care sites, hospitals, rehabilitation sites, nursing homes, and home health are all vital components of a

complex delivery system and require collaboration with PCMHs to ensure comprehensive, integrated care. With support from ACA legislation and innovation grants through the Pioneer and Shared Savings programs, ACOs are accountable for achieving the goals of the Triple Aim. Tracking, monitoring, and reporting on activities that impact cost, quality, and clinical outcomes all involve support and leadership from providers armed with a solid understanding of the methods necessary to achieve these primary goals of health reform at the practice level. It is important to note that the PCMH model itself is evolutionary—and practices must evolve with the model.

The first version of NCQA's PCMH model was released in 2008. PPC-PCMH incorporated the Joint Principles as outlined by the American College of Physicians, the American Academy of Pediatrics, the American Osteopathic Association, and the American Academy of Family Physicians. Its purpose was to evaluate alignment of requirements with practice capabilities, and it focused on established policies and procedures for ensuring that practices with varied technology support could earn recognition for delivering patient-centered care. PCMH 2011 raised the bar by encouraging use of electronic health records (EHRs), clinical decision support tools, enhanced registries, and population health management solutions that aligned with criteria to meet Meaningful Use Stage 1 requirements. With support from ACA legislation, the Office of the National Coordinator for Health Information Technology provided implementation and training support through Regional Extension Centers, to help advance the movement to a more technology-based healthcare system.

PCMH 2014 standards and guidelines include annual reporting requirements to support sustainability of the model and help ensure that recognized practices remain committed to continuous quality improvement in the areas of improved outcomes, patient experience, and cost. Evaluating costs is now part of the core requirements: practices must measure quantitative data on at least 2 utilization measures, which helps ensure that they evaluate opportunities associated with all 3 points of the Triple Aim.

Since 2008, NCQA's PCMH Recognition program has been cited in health reform initiative criteria of 38 states (at the time this article was published) as a viable model for meeting key reform requirements. Provider contracts for a number of commercial payers, such as Aetna, Cigna, WellPoint, and a growing number of Blue health plans, have built PCMH recognition into their criteria for receiving pay-for-performance and enhanced fee-for-service payments. State departments of health, such as in New York, have established graduated payments for their recognized PCMHs, encouraging continued alignment with newer versions of the standards.

The value of recognition has been questioned, specifically with regard to whether practices simply "check the box" to receive enhanced incentive payments—although even the naysayers agree that requirements for recognition are patient-centric, apply to both solo practices and large, integrated systems, and can be more rigorous than other PCMH programs. The model must continue to build on lessons learned during the last 6 years. Practices recognized under PCMH 2008 requirements need support to meet the advanced requirements of PCMH 2014, and all should work to meet requirements outlined in the most recent version of the standards.

To conclude, ACOs can benefit from a strong front line of PCMH-recognized practices that provide resources and support the ongoing evolution of the medical home. Clinicians who understand the value of standardized, customizable, patient-centric best practices of care will require less oversight and can help ACOs meet the challenging goals of achieving the Triple Aim.

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Patient-Centered Outcome Assessment May Lead

To Different Conclusions and Different Treatment Decisions

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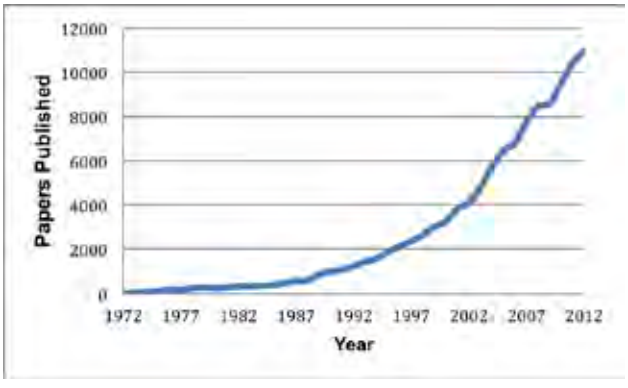
RESEARCH AND QUALITY

Discussions of how to measure health are often characterized by 2 themes: first, illness and premature death are undesirable, so at least 1 component of health is avoidance of serious illness and mortality; and second, the effects of illness and disability on everyday functioning and quality of life are important considerations as well.[1] Disease and disability would typically disrupt the usual activities of daily living. For example, cancer or heart disease may shorten life expectancy and can reduce a person's capacity to engage in meaningful life activities in the years prior to death. Even relatively minor illnesses can have disruptive effects. A common cold, for example, can interfere with social and work activities, but symptoms usually improve in a relatively short time. However, chronic illnesses, such as recurrent low back pain, can result in permanent disruption of enjoyable life activities.[2] A comprehensive conceptualization of wellness, therefore, must consider risk of death, reduced quality of life, and duration of health states.[1,3,4]

Over the last few decades, the Agency for Healthcare Research and Quality (AHRQ), clinicians, policy makers, and patient advocates have demonstrated a growing interest in measuring patient-reported outcomes. Most illnesses are now evaluated in terms of their effects on usual life activities. For example, modern medicine applies common laboratory tests, such as the blood chemistry panel, to assess wellness. Although these tests are clinically instructive, they are not always correlated with outcomes from the perspective of the patient, nor are they direct measures of the disease process. We often refer to the tests as "surrogate" markers because they serve as proxy measures of the disease process. Sometimes the surrogate markers do not correlate with either life expectancy or outcomes when viewed from the patient's perspective.[5]

Figure 1. Papers Identified in PubMed Containing Key-Word Phrase "Quality of Life": 1972-2012



Many clinical studies now apply standardized measures that address a patient's quality of life. **Figure 1** summarizes the number of scientific papers identified in PubMed between 1972 and 2012 that included the "quality of life" key-word phrase. In 1972, PubMed did not identify any papers with this phrase; but by 2012, more than 11,000 articles containing the phrase were identified. This trend has continued in recent years, with a 78% increase in the 5 years between 2007 and 2012. During the last 4 decades, many new quality-of-life tools have become available. These tools allow for a more sophisticated analysis of patient-reported outcomes specific to a variety of illnesses such as cancer,[6] diabetes,[7] and heart disease.[8]

Identifying quality of life as an important outcome was perhaps first highlighted in the 1988 Shattuck Lecture by Paul M. Ellwood Jr, MD.[9] Dr Ellwood advocated for what he referred to as "a technology of patient experience." In contrast to managing symptoms, Dr Ellwood emphasized the importance of managing patient outcomes. He saw medical care that factored in quality of life as relying on 4 techniques:

1) Developing standards and guidelines that match treatments with patient desires

2) Measuring patient well-being and functioning

3) Using normative data to interpret patient outcomes within the context of other people

4) Disseminating information in ways that could affect decision makers

This approach puts the patient at the center of healthcare and uses patient-centered reports to offer guidance and perspective for

clinical care. More recently, use of these methods has come to be known as patient-centered outcomes research (PCOR). The use of PCOR is well represented in the Affordable Care Act and in the Patient-Centered Outcomes Research Institute (PCORI). At the center of PCOR is the measurement of outcomes from the patient perspective.

Although PCOR may seem uncontroversial, the PCOR perspective often leads to different conclusions than more traditional biomedical research. PCOR gives preference to outcomes with reference to only 2 central measures: length of life and quality of life.[10,11] The central premise of PCOR is that the goal of medicine and public health is to lengthen human life and/or improve its quality during the years that people survive. This perspective argues that physiological measures are important only if they relate to life duration or life quality. Blood pressure, for example, is a meaningful biological measure because it is highly predictive of early death or disability associated with myocardial infarction (MI) or stroke. Other measures less clearly relate to the twin objectives of improved life quality or lengthened life expectancy. Catecholamine variations in response to acute stress, for example, are less clearly related to the objectives and outcomes researchers focus on.

Another perspective arising from PCOR is the focus on all-cause mortality as opposed to disease-specific mortality.[12] A variety of large clinical trials have demonstrated reductions in 1 cause of death but have shown compensatory increases in other causes of death.[13] Trials on screening mammography, for example, frequently show that breast cancer screening leads to a reduction in breast cancer mortality. Yet the same trials often fail to show that breast cancer screening increases overall life expectancy.[14] Although breast cancer deaths might be reduced, other causes of death are increased.[15]

Another example of this conundrum is illustrated by the Physicians' Health Study. In this landmark study, approximately 22,000 physicians were randomly assigned to take either 325 mg of aspirin every other day or placebo. When the data were first analyzed, significantly fewer physicians in the low-dose aspirin group had died of MI than those in the placebo group. However, considering all causes of cardiovascular death, the number of physicians who had died was exactly the same in the aspirin and placebo groups (**Figure 2**). All of the deaths occurred during the study period and all were considered premature deaths. Aspirin may have changed what was recorded on the death certificate, but it did not extend participants' life expectancy.[16] Considering the specific cause of death (MI) would lead to the conclusion that using aspirin as a primary preventive was highly effective. From the outcomes perspective, though, aspirin had no effect. From the perspective of the patient, we would argue that people and families are more concerned about the person's vital status and less concerned about a specific cause of death.

Many of the controversies in contemporary medicine are related to the differences between the PCOR perspective and the emphasis on more traditional surrogate markers. For example, a current debate centers on the aggressive management of high blood pressure in the elderly. Even though aggressive management of blood pressure in older adults may reduce the chances of stroke, there is some concern that it will result in an increase in heart attacks, diminished cognitive functioning, and an increase in falls.[17] Laser focus on measures of blood pressure may miss the bigger, and perhaps more important, quality-of-life picture that is most important to patients. There are also examples of studies that fail to achieve changes in biological surrogate markers, but do find changes in important patient-reported outcomes. For example, rehabilitation for patients with chronic obstructive pulmonary disease rarely results in changes in measures of lung function. Yet, these studies consistently observe improvements in functional status and quality of life.[18]

Differences in conclusions between the PCOR perspective and traditional investigation are not rare. In large clinical trials, for example, it is common to observe changes in biological process variables without finding differences in life expectancy or health-related quality of life.[19] We expect continuing methodological discussions about the value of patient-reported experience. PCOR is a relatively new area of research investigation, and we need to learn more about how to reliably assess patient experience and how to integrate the patient perspective into the clinical decision-making process. To date, the best evidence from PCOR is rarely absorbed into clinical care.[20] But AHRQ and PCORI are committed to a rigorous research agenda on these topics. Advancing research methodologies, including new approaches to clinical research, should inform this discussion by centering medical decision-making on the preferences of the most important stakeholder—the patient.

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Figure 2. Total Mortality in the Aspirin Component of the Physicians' Health Study

CVD indicates cardiovascular disease; MI, myocardial infarction
Overall, the number of physicians who died was identical in the aspirin and the placebo conditions (adapted from Kaplan, *New Engl J Med*. 1989;321(8):501-507).

REFERENCES

1. Kaplan RM, Ries AL. Quality of life: concept and definition. *COPD.* 2007;4(3):263-271.

2. Smith WB, Safer MA. Effects of present pain level on recall of chronic pain and medication use. *Pain.* 1993;55(3):355-361.

3. Brown DS, Jia H, Zack MM, Thompson WW, Haddix AC, Kaplan RM. Using health-related quality of life and quality-adjusted life expectancy for effective public health surveillance and prevention. *Expert Rev Pharmacoecon Outcomes Res.* 2013;13(4):425-427.

4. Cherepanov D, Palta M, Fryback DG, Robert SA, Hays RD, Kaplan RM. Gender differences in multiple underlying dimensions of health-related quality of life are associated with sociodemographic and socioeconomic status. *Med Care.* 2011;49(11):1021-1030.

5. Kaplan RM. *Diseases, Diagnoses, and Dollars.* New York, NY: Springer; 2009.

6. Yost KJ, Thompson CA, Eton DT, et al. The Functional Assessment of Cancer Therapy - General (FACT-G) is valid for monitoring quality of life in patients with non-Hodgkin lymphoma. *Leuk Lymphoma.* 2013;54(2):290-297.

7. Speight J, Sinclair AJ, Browne JL, Woodcock A, Bradley C. Assessing the impact of diabetes on the quality of life of older adults living in a care home: validation of the ADDQoL Senior. *Diabet Med.* 2013;30(1):74-80.

8. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. *Cardiol Young.* 2013;23(4):473-485.

9. Ellwood PM. Shattuck lecture--outcomes management: a technology of patient experience. *New Engl J Med.* 1988;318(23):1549-1556.

10. Kaplan RM. Two pathways to prevention. *Am Psychol.* 2000;55(4):382-396.

11. Kaplan RM. Quality of life: an outcomes perspective. *Arch Phys Med Rehabil.* 2002;83(12, suppl 2):S44-S50.

12. Kaplan RM. Behavior as the central outcome in health care. *Am Psychol.* 1990; 45(11):1211-1220.

13. Kaplan RM. The Ziggy theorem: toward an outcomes-focused health psychology. *Health Psychol.* 1994;13(6):451-460.

14. Gøtzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev.* 2013;6:CD001877.

15. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty-five-year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ.* 2014;348:g366.

16. Kaplan RM. Health outcome models for policy analysis. *Health Psychol.* 1989;8(6): 723-735.

17. Mancia G, Grassi G. Aggressive blood pressure lowering is dangerous: the J-curve: pro side of the arguement. *Hypertension.* 2014;63(1):29-36.

18. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med.* 1995;122(11):823-832.

19. Gerstein HC, Miller ME, et al.; Action to Control Cardiovascular Risk in Diabetes Study G. Effects of intensive glucose lowering in type 2 diabetes. *New Engl J Med.* 2008;358(24):2545-2559.

20. Han PK, Kobrin S, Breen N, et al. National evidence on the use of shared decision making in prostate-specific antigen screening. *Ann Fam Med.* 2013;11(4):306-314.

Cardiologists start more patients on XARELTO® than any other anticoagulant[1]

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IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including XARELTO®, increases the risk of thrombotic events. If anticoagulation with XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Please see Important Safety Information on following pages.
Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO® in patients with active pathological hemorrhage.
  - A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable.
  - Concomitant use of other drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and NSAIDs.
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia)

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO®. The next XARELTO® dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO® is to be delayed for 24 hours.

- **Use in Patients With Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Avoid the use of XARELTO® in patients with creatinine clearance (CrCl) <15 mL/min, since drug exposure is increased. Discontinue XARELTO® in patients who develop acute renal failure while on XARELTO®.

SIX INDICATIONS STRONG

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled
- For the treatment of deep vein thrombosis (DVT)
- For the treatment of pulmonary embolism (PE)
- For the reduction in the risk of recurrence of DVT and of PE following initial 6 months treatment for DVT and/or PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee replacement surgery
- For the prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery

*Among Factor Xa inhibitors and direct thrombin inhibitors.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.
- **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.
- **Use in Patients With Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use With P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with combined P-gp and strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan). Avoid concomitant use of XARELTO® with drugs that are P-gp and strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort).
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing and is not readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients With Prosthetic Heart Valves:** The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.

DRUG INTERACTIONS

- Avoid concomitant use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.
- XARELTO® should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit outweighs the potential risk.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** XARELTO® should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus.

References: 1. Data on file. Janssen Pharmaceuticals, Inc. Based on IMS Health, NPA Market Dynamics New to Brand, July 12, 2013. **2.** Data on file. Janssen Pharmaceuticals, Inc. Data as of 7/1/13. **3.** Data on file. Janssen Pharmaceuticals, Inc. Based on IMS Health, NPA Weekly, Total Prescriptions, July 2011–August 2013. **4.** Mega JL, Braunwald E, Wiviott SD, et al. *N Engl J Med*. 2012;366(1):9-19. **5.** The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. **6.** The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. **7.** Patel MR, Mahaffey KW, Garg J, et al; and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. **8.** Lassen MR, Ageno W, Borris LC, et al; for the RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358(26):2776-2786. **9.** Kakkar AK, Brenner B, Dahl OE, et al; for the RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet*. 2008;372(9632):31-39. **10.** Eriksson BI, Borris LC, Friedman RJ, et al; for the RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358(26):2765-2775. **11.** Hori M, Matsumoto M, Tanahashi N, et al; on behalf of the J-ROCKET AF study investigators. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation: the J-ROCKET AF study. *Circ J*. 2012;76(9):2104-2111. **12.** Cohen AT, Spiro TE, Büller HR, et al. *N Engl J Med*. 2013;368(6):513-523. **13.** Mueck W, Eriksson BI, Bauer KA, et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban—an oral, direct Factor Xa inhibitor—in patients undergoing major orthopaedic surgery. *Clin Pharmacokinet*. 2008;47(3):203-216. **14.** Data on file. Janssen Pharmaceuticals, Inc. Based on IMS Health, NPA Weekly, August 2013.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS (cont'd)

There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing.

- **Labor and Delivery:** Safety and effectiveness of XARELTO® during labor and delivery have not been studied in clinical trials.
- **Nursing Mothers:** It is not known if rivaroxaban is excreted in human milk.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Females of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

OVERDOSAGE

- Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable.

ADVERSE REACTIONS IN CLINICAL STUDIES

- The most common adverse reactions with XARELTO® were bleeding complications.

K02X121084IR2

Please see Important Safety Information on preceding pages.
Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.

Xarelto®
rivaroxaban tablets

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

XARELTO® (rivaroxaban) tablets

Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)
XARELTO® (rivaroxaban) tablets, for oral use
See package insert for full Prescribing Information

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information].*

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**

[see Warnings and Precautions and Adverse Reactions].

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions].*

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thrombo-prophylaxis *[see Warnings and Precautions].*

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation: XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information].*

Treatment of Deep Vein Thrombosis: XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

Treatment of Pulmonary Embolism: XARELTO is indicated for the treatment of pulmonary embolism (PE).

Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism: XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) and Clinical Studies (14.1) in full Prescribing Information].*

Risk of Bleeding: XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information].* Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents

(tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered but has not been evaluated in clinical trials.

Concomitant use of other drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions]*.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

Use in Patients with Renal Impairment: Nonvalvular Atrial Fibrillation: Avoid the use of XARELTO in patients with CrCl <15 mL/min since drug exposure is increased. Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Discontinue XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population *[see Use in Specific Populations]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations]*.

Use in Patients with Hepatic Impairment: No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

Use with P-gp and Strong CYP3A4 Inhibitors or Inducers: Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Drug Interactions]*.

Risk of Pregnancy Related Hemorrhage: In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Patients with Prosthetic Heart Valves: The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning* and *Warnings and Precautions]*
- Bleeding risk *[see Warnings and Precautions]*
- Spinal/epidural hematoma *[see Boxed Warning* and *Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 16326 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 4728 patients who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

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Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF study.

Table 1: Bleeding Events in ROCKET AF*

Parameter	XARELTO N = 7111 n (%)	Event Rate (per 100 Pt-yrs)	Warfarin N = 7125 n (%)	Event Rate (per 100 Pt-yrs)
Major bleeding†	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ‡	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

* For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for XARELTO vs. 2.9 per 100 Pt-yrs for warfarin.

‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of PE: EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	XARELTO† N = 4130 n (%)	Enoxaparin/ VKA† N = 4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

EINSTEIN Extension Study: In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.

Table 3: Bleeding Events* in EINSTEIN Extension Study

Parameter	XARELTO† 20 mg N = 598 n (%)	Placebo† N = 590 n (%)
Major bleeding event‡	4 (0.7)	0
Decrease in Hb ≥2 g/dL	4 (0.7)	0
Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.3)	0
Gastrointestinal	3 (0.5)	0
Menorrhagia	1 (0.2)	0
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)
Any bleeding	104 (17.4)	63 (10.7)

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.
† Treatment schedule: XARELTO 20 mg once daily; matched placebo once daily
‡ There were no fatal or critical organ bleeding events.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N = 4487 n (%)**	**N = 4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N = 3281 n (%)**	**N = 3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N = 1206 n (%)**	**N = 1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

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Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN Extension study are shown in Table 5.

Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study

System Organ Class Preferred Term	XARELTO N = 598 n (%)	Placebo N = 590 n (%)
Gastrointestinal disorders		
Abdominal pain upper	10 (1.7)	1 (0.2)
Dyspepsia	8 (1.3)	4 (0.7)
Toothache	6 (1.0)	0
General disorders and administration site conditions		
Fatigue	6 (1.0)	3 (0.5)
Infections and infestations		
Sinusitis	7 (1.2)	3 (0.5)
Urinary tract infection	7 (1.2)	3 (0.5)
Musculoskeletal and connective tissue disorders		
Back pain	22 (3.7)	7 (1.2)
Osteoarthritis	10 (1.7)	5 (0.8)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	6 (1.0)	2 (0.3)

* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication.
† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole), increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. The increases in exposure ranged from 30% to 160%. Significant increases in rivaroxaban exposure may increase bleeding risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

When data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors *[see Warnings and Precautions]*.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Results from drug interaction studies and population PK analyses from clinical studies indicate coadministration of XARELTO with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions]*.

Anticoagulants and NSAIDs/Aspirin: Single doses of enoxaparin and XARELTO given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and XARELTO resulted in an additive effect on factor Xa inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Coadministration of the platelet aggregation inhibitor clopidogrel and XARELTO resulted in an increase in bleeding time for some subjects *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions]*.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Patients with renal impairment receiving full dose XARELTO in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) may have increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.

XARELTO should be used in patients with CrCl 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus *[see Warnings and Precautions]*.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

Labor and Delivery: Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

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Nursing Mothers: It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information]*.

Females of Reproductive Potential: Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Renal Impairment: In a pharmacokinetic study, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE: In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery: The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Hepatic Impairment: In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

OVERDOSAGE:

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

Revised: August 2013

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Connected Care Is Key to Accountable Care: The Case for Supporting Telehealth in ACOs

KRISTA DROBAC, EXECUTIVE DIRECTOR, ALLIANCE FOR CONNECTED CARE
CLIF GAUS, PRESIDENT AND CEO, NATIONAL ASSOCIATION OF ACOS

The vision of accountable care organizations (ACOs) is forcing new ways of thinking about care coordination, continuous population management, and maximization of appropriate treatment options outside high-cost settings. At the same time, patient engagement and empowerment are pushing the boundaries on how the medical community thinks about the patient and caregiver experience. Connected Care is an essential tool for achieving the goals of accountable care while improving patient and caregiver satisfaction. However, despite the rapidly developing technology and increasing interest among patients and providers in using Connected Care, statutory and regulatory barriers continue to limit its use in Medicare. These limitations can be lifted for ACOs without an act of Congress.

What Is Connected Care?

Connected Care is the real-time, electronic communication between a patient and a provider, including telehealth, remote patient monitoring, and secure e-mail communication between clinicians and their patients. Through Connected Care, healthcare providers can remotely communicate with their patients and other healthcare providers across care settings through iPads, laptops, and smartphones; patients and their caregivers can be more engaged in the delivery of their own care; and patients with limited access to healthcare providers can be treated in less costly and more accessible care settings, such as in their homes or at local retail clinics.

Evidence Around The Use Of Connected Care

A growing body of evidence is demonstrating how the benefits of Connected Care are improving healthcare access and quality and reducing costs for payers. A literature review that will be published in *Telemedicine and eHealth*, principally authored by Rashid Bashshur, PhD, of the University of Michigan, looked at the evidence related to 3 chronic diseases prominent in the Medicare population—congestive heart failure (CHF), stroke, and chronic obstructive pulmonary disease (COPD). Among CHF patients, telemonitoring was significantly associated with reductions in mortality, ranging from 15% to 56% compared with traditional care. Meanwhile, telestroke provided an advantage for stroke patients without readily available access to stroke specialists. The various modalities of telestroke have demonstrated the ability to reduce mortality in the range of 25% during the first year after the event. Ultimately, the evidence supports the economic benefit of telemonitoring compared with traditional care among CHF, stroke, and COPD patients.

St Vincent Health in Indiana—a member of Ascension Health, the country's largest not-for-profit healthcare system—enrolled patients with CHF and COPD in a remote care management program following discharge from a group of its hospitals. The intervention consisted of daily monitoring of patients' biometrics, including blood pressure, body weight, and oxygen saturation. There were also regular videoconferencing visits with the patients as well as educational videos to help patients with their needs. Initial results showed that the care management program reduced hospital readmissions to 5% compared with 20% in the control group—a 75% reduction. Given that Medicare spends an estimated $26 billion each year on readmissions, of which over $17 billion is preventable, it is clear that the Medicare program has the potential to generate significant savings through similar remote care management solutions.[1]

As for primary care, there is evidence that Connected Care is effective for managing care outside of provider settings. A recent RAND study published in *Health Affairs* found that patients who participate in primary care telemedicine "visits," which consisted of remote physician consultations by phone or videoconference, were less likely to require follow-up visits for a similar condition in any setting.[2] Only 6% of patients sought follow-up care compared with 13% in the control group, whose participants instead visited a physician office or emergency department (ED). While cost savings were

not the focus of the study, the authors noted that the $38 telemedicine visit as a replacement for physician office and ED visits could generate savings for payers.

Connected Care is also improving patient satisfaction in various ways. A recent Massachusetts General Hospital study examined the impact of online follow-up care for patients with the 10 most common chronic diseases: hypertension, arthritis, diabetes, anxiety, depression, GERD, headaches, asthma, back pain, and weight control issues.[3] Patients completed online questionnaires regarding their condition in lieu of in-person follow-up visits and participated in telehealth consults with their physicians as necessary. Patients found the online consults to be quick and convenient, and reported high satisfaction with the clinical efficacy of the consults. Physicians found that remote care sessions, which included the online questionnaires, saved time, allowed for more regular follow-up, and provided a more complete picture of their patient's well-being. This study is another example of how Connected Care is finding alternative ways to improve care delivery for both patients and their providers.

Barriers to Use Of Connected Care in ACOs

While a handful of ACOs have invested in Connected Care and are using it with great success, the majority are reluctant to adopt such technology because of Medicare program coverage and reimbursement limitations. Specifically, section 1834(m) of the Social Security Act (the Act) only enables the Medicare program to cover and reimburse for a limited number of Part B services furnished to beneficiaries located at certain originating sites in rural areas.[4] This serves as a disincentive for the vast majority of ACO providers, many of whom practice in urban areas, to use this type of technology.

Implementing a telemedicine or remote patient monitoring program requires up-front investment, mostly in the area of process design and training. Making the case to the chief financial officer of an ACO in a time when hospital budgets are being reduced and the future is uncertain is difficult. For many physician-led and smaller ACOs without access to a lot of capital, it is not even an option.

The Solution

Allowing ACOs to be reimbursed for Connected Care technologies will further the goals of the ACO program by providing additional tools to improve quality and reduce costs. Furthermore, it is consistent with the language of the Affordable Care Act (ACA), which directed ACOs participating in the Medicare Shared Savings Program to "define processes … to coordinate care, such as through the use of telehealth, remote patient monitoring, and other such enabling technologies."[5] To that end, in the final regulations for the program, CMS indicated that it wanted to give ACO providers the flexibility to choose those tools that best facilitate care coordination for their practitioners and patients.[6] However, this is not the case under the current statutory and regulatory framework.

Fortunately, the Secretary has the tools in place to address these barriers. Section 1899(f) of the Act gives the HHS Secretary the authority to "waive such requirements of sections 1128A and 1128B and title XVIII of [the] Act as may be necessary to carry out the [program]."[7] Separate from the waiver authority for the Center for Medicare and Medicaid Innovation demonstration projects, this authority applies only to ACOs. To date, this authority has been used to grant 5 waivers to the fraud and abuse laws and to the timing of ACO repayment for shared losses.[8] The waiver of the 1834(m) restrictions is equally critical to achieving the success of ACOs and can be done without waiting for Congress to act.

Conclusion

Connected Care technologies can help achieve the core goals of ACOs and should be widely deployed. Although there is already evidence of its success in improving care and reducing costs, the current operational structure of the healthcare system makes investment in Connected Care technologies without reimbursement difficult, even for ACOs. The authority exists within HHS to waive the restricting language that limits reimbursement of telehealth to rural areas for ACOs. HHS should use its authority to lift those restrictions so more ACOs can serve patients with technology that will improve care and patient satisfaction, while lowering costs.

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REFERENCES

1. The Revolving Door: A Report on US Hospital Readmissions. Robert Wood Johnson Foundation website. http://www.rwjf.org/content/dam/farm/reports/reports/2013/rwjf404178. Published February 2013.

2. Usher-Pines L, Mehrotra A. Analysis of Teladoc use seems to indicate expanded access to care for patients without prior connection to a provider. *Health Aff (Millwood).* 2014;33(2):258-264.

3. Dixon RF, Rao L. Asynchronous virtual visits for the follow-up of chronic conditions [published online May 2. 2014]. *Telemed J E Health.*

4. Section 1834(m) of the Social Security Act, 42 USC §1395m(m).

5. Section 1899 of the Social Security Act, 42 USC §1395jjj.

6. 76 Fed. Reg. 67802 (Nov. 2, 2011).

7. Section 1899(f) of the Social Security Act, 42 USC §1395jjj(f).

8. 76 Fed. Reg. 67992 (Nov. 2, 2011) and 76 Fed. Reg. 67802, 67941 (Nov. 2, 2011).

How We Did It: How One Physician-Owned ACO Earned Shared Savings

KELLY CONROY,
EXECUTIVE DIRECTOR,
PALM BEACH ACO;
CEO, TRIPLE AIM
ADVISORY GROUP

The world of healthcare is no longer changing: it *has* changed. Embracing that change and understanding what it means is at the core of Palm Beach Accountable Care Organization's (ACO's) success in its first year participating in the CMS Medicare Shared Savings Program, earning a total of $22 million in shared savings. Palm Beach ACO, which has about 30,000 Medicare beneficiaries and 275 participating primary care physicians and specialists, is one of the 29 ACOs in the nation that earned shared savings in the first performance year.

Achieving this success required laser focus on simple steps proven to make measurable differences. We quickly learned that building a large, expensive infrastructure was not going to bring the results that would be necessary to earn shared savings. Instead, a grassroots approach was taken that centered on physicians and their patients. Our strategy started with gaining a clear understanding of the rules, and then engaging physicians in real and meaningful ways to create a belief that this approach to healthcare would work.

That belief in the ACO model began with the realization that the government is a partner in this process—CMS's goal is to create a collaboration that is good for both physicians and their patients. Treating patients as consumers who are willing to pay for quality outcomes is the ultimate mission, which means that the reimbursement system must change. Yet, we believe that the concept of rewarding quality makes sense and can work.

Success also means a huge cultural shift, but one that has the potential to return medicine to its roots. Our physicians began to believe in the ACO model because it put them in the driver's seat. Making doctors part of the solution is critical, as no one is better able to improve the delivery of healthcare and redefine population health management than doctors. Thanks to the experience and insight of Hymin Zucker, MD, chief medical officer at Palm Beach ACO, it quickly became clear that success would hinge on the creation of strong patient-doctor bonds and a full knowledge of the population, as they exist both inside and outside the doctor's office.

This completely changes the image of population health management in today's healthcare model. With primary care physicians managing the process, medicine takes care of itself and the practice of medicine returns to what it was always meant to be. In turn, knowing and building close ties with everyone surrounding that physician can lead to better healthcare for the patient.

We concentrated on defining expectations and improving coordination with all stakeholders, including specialists, hospitals, home healthcare agencies, and skilled nursing facilities. We didn't try to control where the patient went, but instead created a competition among providers in the community. We communicated about those who got results and it had a positive domino effect; that improvement in work flow and collaboration moved the needle in measurable ways.

Everything we did tied back to the overarching goal of understanding each patient's experience and building enduring connections between doctor and patient. We continually measured our progress against the 33 quality measures and looked for ways to achieve ongoing improvement in each area.

We realized that dissatisfied patients could mean as much as 25% in lost savings, so it made sense to spend time in this area. One surprising discovery was the substantial number of patients who walked out of the office without follow-up appointments. That loss of control over a patient's healthcare often resulted in the loss of the patient altogether, which means lost revenue and decreased shared savings.

So our team spent countless hours engaging physicians and navigating them through the cultural shift and the environment of constant measurement. We held both group and face-to-face meetings to demonstrate how even just a few simple changes

could result in tremendous savings and improved quality measures, all without creating additional work for physicians.

Once the message was delivered, the results became increasingly clear. Dr Zucker made tremendous strides in helping physicians and their teams see the importance of quality patient-physician interactions. He helped physicians remember the value of creating a constant state of "wow" for each patient. Physicians were encouraged to create systems, hire staff, and do whatever was necessary to create positive patient experiences by treating those patients as they would treat their own mothers, for example. Patients who winter in Florida but live elsewhere the rest of the year were called and asked how they were doing; follow-up visits were scheduled before patients left the office; and patients who hadn't been seen for a while were called and reminded to schedule wellness visits. These closer relationships resulted in more—and better—transitional care management, fewer emergency department visits, and increased overall satisfaction for patients. In short, we worked to create a culture where physicians are involved with their patients.

It didn't take long for the physicians to see the value of their role as patient advocates, and the pieces began to fall into place. The successful physicians made changes in their offices, whether it was staffing, extended hours, or increased patient outreach. As a result, patients enjoyed the benefits of more detailed care plans and of the shared decision making with their doctors regarding their individual health issues, and their overall satisfaction increased. That satisfaction translates into real savings when those patients give their doctors high marks on satisfaction surveys.

When doctors solved the access issues and created happier patients, they realized the value in truly taking care of their population. We went as far as creating "The Big 7" patient satisfaction tips and posting them in physician offices. We determined that the areas with the best potential for improvement were:

1. Providing patients with timely care, appointments, and information
2. Ensuring effective communication with the doctor
3. Creating an environment that encourages patients to rate their doctors favorably
4. Providing easy and convenient access to specialists
5. Offering health education
6. Finding ways to involve patients in shared decision making
7. Staying current on each patient's health status.

Simply being more proactive in getting patients in for wellness visits and preventive screenings covers 11 of the required 33 quality measures. Increasing clinical outcomes and improving revenue translates into a win-win for the patient and physician.

The primary lesson learned on the path to shared savings was that small changes make big differences. Improving patient outcomes and experiences, all while reducing unnecessary expenditures, creates a better healthcare system for everyone. Our bottom-up approach allowed us to help physicians to more thoroughly understand and thus manage their population, and help earn shared savings.

Table. GPRO Outcomes

Do you know how many wellness visits you did NOT do this year?
GPRO WELLNESS VISIT 11/33 QUALITY MEASURES
Preventive Health Domain
1. Influenza 2. Pneumococcal 3. Adult weight screen and f/u 4. Tobacco use and intervention 5. Depression screening 6. Colorectal cancer screening 7. Mammography screening 8. Proportion of adults 18+ who had their blood pressure measured within the preceding 2 years
Care Coordination Domain
9. Screening for Fall risk
At-Risk Population Domain
10. Diabetes composite (aspirin use) 11. Ischemic vascular disease (use aspirin and other antithrombotic)
Copyright 2014 Triple Aim Advisory Group Brookings Presentation June 2014.

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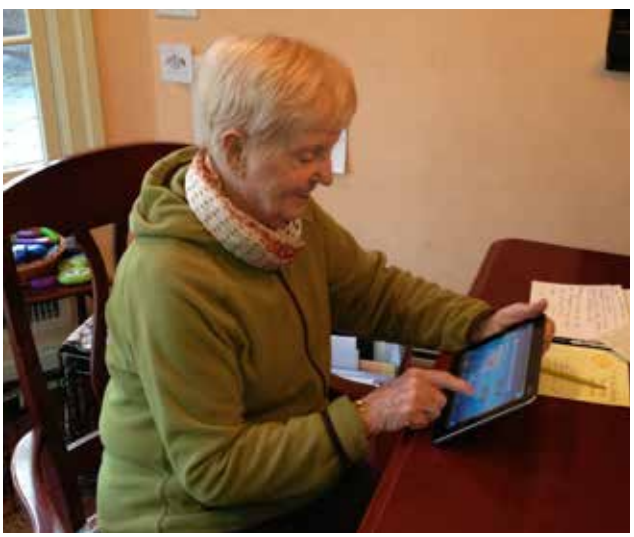
Study: Health Recovery Solutions Uses Tablets to Reduce Cardiac Readmissions

JUDITH KUTZLEB, DNP, AND JOAN SHEA, MBA, JD

Health Recovery Solutions (HRS) has made great strides in solving the readmission problem, and HRS is gaining national attention for its clinical successes and commitment to significantly improving outcomes for both patients and hospitals.

Health Recovery Solutions was co-founded by Jarrett Bauer at Johns Hopkins University after his grandmother was unnecessarily readmitted to the hospital for heart failure. The lack of attention that contributed to his grandmother's illness led him to mobilize doctors, nurses, developers, and engineers to develop technology for leading medical centers to reduce readmissions and empower patients to improve their own lives once discharged. "From day 1, we set out to give patients the tools to succeed after they leave the hospital's care," said Mr Bauer.

HRS provides leading medical centers with the most advanced patient monitoring devices, focusing on managing their highest-risk patients through changing patient behavior to reduce readmissions. Upon admission, patients are provided a 4G Internet-ready tablet that is preloaded with HRS software. Patients are able to use informational videos and teach-back quizzes to educate themselves on their condition, which includes dietary information and more. At discharge, patients leave with integrated wireless monitoring devices (including blood pressure monitors, pedometers, digital scales, and pulse oximeters) in addition to their tablets. Patients also receive daily reminders to enter important data such as medication compliance, blood pressure, weight, physical activities, and any symptoms they might be experiencing. Patient data are then recorded and transmitted back to care teams.



After the program was implemented, HRS, Hackensack University Medical Center, and Holy Name Hospital launched a multidisciplinary study to evaluate the impact of an advanced practice, nurse-directed patient education approach to heart failure treatment while integrating an interactive 4G android tablet. The effect on 30-day readmission, as well as patient activation and engagement, were the primary end points of the 50-patient randomized study, and the results were impressive. Patients utilizing a tablet had an 8% readmission rate compared with a 28% readmission rate for patients who did not receive a tablet. The average patient age was 71 years, with an ejection fraction below 40%. The average medication adherence percentage was 84.38%; average adherence to recording weight was 89.82%; and adherence to daily exercise was 77.09%. Additionally, patients who received the tablet lost an average of 5 pounds during the 30-day study period.

HRS Clinical Trial Data

HRS Tablet Group

- 30-day readmission percentage: 8%
- Average ejection fraction: 37.71%
- 25 patients (14 male, 11 female)

Usual Care Group

- 30-day readmission percentage: 28%
- Average ejection fraction: 40.8%
- 25 patients (13 male, 12 female)

Patients were enamored with the HRS platform. One female patient reported that "Medication reminders were a huge help, and the video chat enabled me to ask my nurse small questions that had a big impact." Similarly, a male patient in his 80s said, "The tablet kept me motivated and organized. I wasn't readmitted and I owe a big thank you to this program."

Nancy Elmann, heart failure advanced practice nurse and outpatient ventricular assist device coordinator, praised the program for reducing readmissions and improving patient lifestyles, stating that "It's the only tool that gives the patient control when managing their chronic illness. It allows them to be the person engaging with the tablet on their own. The results showed that elderly patients could utilize technology for their own well-being."

Furthermore, Morey J. Menacker, DO, of Hackensack Medical Center, reflected on a patient who in 2012 was hospitalized every 2 months for chronic heart failure, but hadn't been hospitalized once in 2013 after being placed in the tablet program. "It's a dramatic change to a patient's quality of life," he said. "You can't put a cost on that. The cost is miniscule compared to the benefit."

The program has not only helped patients, it has helped accountable care organizations (ACOs) save money and helped hospitals see a return on their investment by reducing medical penalties associated with readmissions. As a result of the study, HRS has enabled both Hackensack and Holy Name to reduce their Medicare penalty by preventing 5 excess readmissions. The average New Jersey hospital is losing approximately $25,000 for these types of readmissions.

HRS has gained national attention from CNN Money, *Time* Magazine, and Fox Business News as a result of this study. The HRS tablet program directly helped Hackensack Physician Hospital Alliance ACO to receive Level 1 ACO Accreditation. Other top national medical centers have also begun using the HRS platform, including Massachusetts General Hospital, Penn Care at Home, Valley Hospital, Beth Israel Deaconess Medical Center, and First Health of the Carolinas.

HRS feels fortunate to be in a position to help hospitals and ACOs save money. But as HRS CEO Jarrett Bauer explains, "In the end, it's all about the patient. The most important thing we do is to help patients take care of themselves."

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INVOKANA™ is the #1 branded therapy prescribed by endocrinologists when adding or switching non-insulin type 2 diabetes medications*

ENVISION NEW **POSSIBILITIES**

Invokana™
canagliflozin tablets

*Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data through 9/20/13.

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

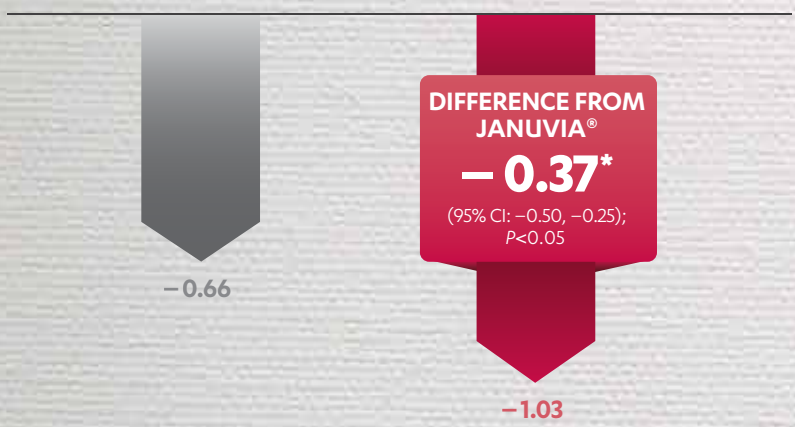
CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

INVOKANA™ 300 mg demonstrated greater reductions in A1C vs Januvia® 100 mg at 52 weeks…

Adjusted Mean Change in A1C From Baseline (%): INVOKANA™ 300 mg vs Januvia® 100 mg, Each in Combination With Metformin + a Sulfonylurea[1]



Incidence of Hypoglycemia

With metformin + a sulfonylurea over 52 weeks: INVOKANA™ (canagliflozin) 300 mg: **43.2%**; Januvia® 100 mg: **40.7%**[1]

- Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue[1]

Convenient Once-Daily Oral Dosing[1]

- Recommended starting dose: INVOKANA™ 100 mg
- Dose can be increased to 300 mg in patients tolerating 100 mg who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control

*INVOKANA™ + metformin is considered noninferior to Januvia® + metformin because the upper limit of the 95% confidence interval is less than the prespecified noninferiority margin of 0.3%.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.
- **Impairment in Renal Function:** INVOKANA™ increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

COVERED FOR >**75%** OF COMMERCIALLY INSURED PATIENTS WITHOUT PRIOR AUTHORIZATION[3]

...as well as greater reductions in body weight† and systolic blood pressure (SBP)†

Change in Body Weight†

Significant reductions in body weight at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[1]

»Difference from Januvia®‡:
300 mg: **–2.8%**

Change in SBP†

Significant lowering of SBP at 52 weeks, each in combination with metformin + a sulfonylurea (*P*<0.001)[2]

»Difference from Januvia®‡:
300 mg: **–5.9 mm Hg**

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.

†Prespecified secondary endpoint.

‡Adjusted mean.

INVOKANA™ provides SGLT2 inhibition, reducing renal glucose reabsorption and increasing urinary glucose excretion.[1]

Adverse Reactions

In 4 pooled placebo-controlled trials, the most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.[1§]

References: 1. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013. **2.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36(9):2508-2515. **3.** Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ. Data as of 9/17/13.

SGLT2 = sodium glucose co-transporter-2.

§Included 1 monotherapy and 3 add-on combination trials with metformin, metformin + a sulfonylurea, or metformin + pioglitazone.

Learn more at **INVOKANAhcp.com/journal**

- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

Please see additional Important Safety Information and brief summary of full Prescribing Information on the following pages.

ENVISION NEW
POSSIBILITIES

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.
- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.

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» **Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

» There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

» The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritus, thirst, nausea, and constipation.

K02CAN13149

Please see brief summary of full Prescribing Information on the following pages.

Invokana™
canagliflozin tablets

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA or any other antidiabetic drug.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to

INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

INVOKANA™ (canagliflozin) tablets

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0

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Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including

UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

INVOKANA™ (canagliflozin) tablets

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

10282400

K02CAN13080B

janssen

A Transitional Care Model for Patients With Acute Coronary Syndrome

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ABSTRACT

IMPORTANCE: Hospital readmissions place a substantial burden on the US healthcare system, especially those related to cardiovascular disease. Patients with acute coronary syndrome (ACS) constitute many of these readmissions, yet little is known about reducing such events.

OBJECTIVES: This study aimed to measure the effectiveness of the Bridging the Discharge Gap Effectively (BRIDGE) program in reducing readmissions and improving medication persistence in patients with ACS.

DESIGN: This was a retrospective outcomes study that used consecutive data for all patients referred to the BRIDGE program between March 2008 and March 2009.

SETTING: Ambulatory visit post-discharge from an academic hospital.

PARTICIPANTS: A total of 424 patients were referred to the BRIDGE program. ACS comprised 25.2% (n = 107) of the diagnoses. Patients were excluded if they died or were rehospitalized prior to their scheduled BRIDGE appointment (n = 9, 8.4%). The final study sample included 80 patients after excluding patients with missing data (n = 18, 18.4%).

INTERVENTION: BRIDGE is a nurse practitioner–led model for providing transitional care to cardiac patients. The intervention consists of a 1-time visit within 14 days of discharge. Patients received AHA/ACCF guideline-based care, examinations, education, follow-up, and referrals.

MAIN OUTCOME MEASURES: Prior to data collection, it was hypothesized that patients who attended BRIDGE would have lower 30-day readmission rates and superior 6-month medication persistence rates over nonparticipants (ie, follow-up only with primary care providers or cardiologists).

RESULTS: Of 80 patients, 77.5% (n = 62) attended. Their mean age was 62.5 years, 58.7% were female, and 86.3% were white. Patients who attended BRIDGE had lower rates of readmission at 30 (9.7% vs 27.8%, *P* = .112), 60 (11.3% vs 38.9%, *P* = .012), 90 (16.1% vs 38.9%, *P* = .052), and 180 (27.4% vs 50.0%, *P* = .072) days postdischarge compared with nonattenders. There were no significant differences between groups in medication persistence 6 months after discharge.

CONCLUSIONS: Patients who attended their BRIDGE appointment had fewer readmissions than patients who received usual care. Further, these reductions were not explained by better medication persistence. Models such as this should be developed and analyzed across institutions and patient types to ensure patient safety at home after hospital discharge and reduce excessive and unnecessary health-system costs.

It was estimated that 15.4 million Americans suffered from coronary heart disease between 2007 and 2010, and nearly 635,000 more would have a new coronary event.[1] Of the latter, 419,100 will likely survive and approximately 67% of those (280,000) will suffer a recurrent event warranting rehospitalization (not including those who will have a silent event).[1] Despite these projections, little is known about the circumstances culminating in a hospital readmission for patients with acute coronary syndrome (ACS). Possible contributors, however, have been speculated to include premature discharge, lack of prompt access to cardiology follow-up after hospital discharge,[2] insufficient discharge education, lack of patient understanding of education provided, and poor patient and provider adherence to American Heart Association/American College of Cardiology Foundation (AHA/ACCF) guidelines.[3] Whatever the cause of these hospital readmissions, especially those deemed avoidable,[4] they place a substantial burden on an already stressed US healthcare system.[5] To address these high rates of readmission, many clinical scientists and care providers are looking to new models of care that focus specifically on the transition period between hospital discharge and home.

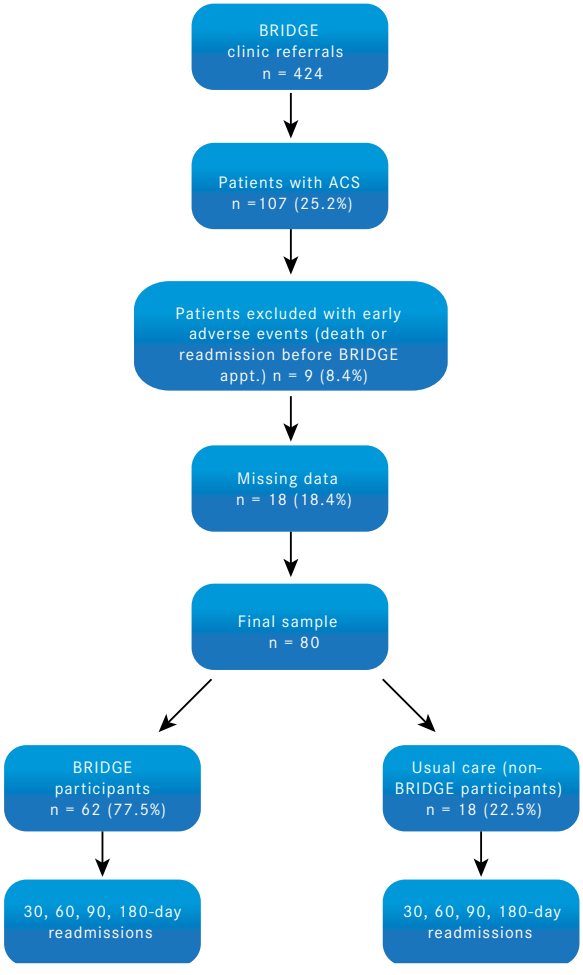
Transitional care begins prior to hospital discharge and terminates once an outpatient care team has seen the patient and assumed care responsibility. Most transitional care models are designed around direct patient assessment, diagnosis, treatment, and education during this interim phase.[6-9] This is achieved by facilitating communication among providers, improving discharge education and medication management, resolving outstanding diagnostics, and instructing patients when to seek care.[10]

Healthcare providers have long recognized the consequences of poor patient follow-up, but lack of provider accountability between discharge and ambulatory care follow-up has allowed a gap in care transitions to go largely unchecked.[11] As an example, Jencks and colleagues[5] reported that 50.2% of Medicare patients rehospitalized within 30 days of discharge had no record of being seen by a healthcare provider postdischarge. One consequence of such oversight is the rising number of potentially preventable hospital readmissions.[12] Initially, the aim of reporting

hospital readmission rates was to draw attention to the dilemma and allow patients to make informed choices about where to seek care.[13] Later, readmission rates became part of pay-for-performance programs.[14] Now, as a result of the Patient Protection and Affordable Care Act (ACA), hospitals with above-average readmission rates will be penalized with a reduction in the percentage of their Medicare reimbursement. Initial fines were imposed in 2013 and levied against 2012 readmission rates.

We developed the Bridging the Discharge Gap Effectively (BRIDGE) program to facilitate timely postdischarge care for patients discharged with a cardiac diagnosis. Operating since 2008, BRIDGE provides a 1-time ambulatory transitional care visit within 14 days of discharge, and stresses the importance of developing trusting relationships between patients and providers.[15] The BRIDGE clinic is staffed by 5 specialty-certified cardiovascular nurse practitioners (NPs) who function in collaboration with the discharging cardiologist. The goal of the NPs is to eliminate many of the aforementioned contributors to hospital readmissions by conducting thorough examinations, reviewing diagnostic tests postdischarge, evaluating response to treatment, performing medication reconciliation, making therapeutic adjustments when necessary, and ensuring that appropriate follow-up and referrals are scheduled. The NPs tailor education about the individual's event, condition, disease process, and signs and symptoms that should trigger a call to a physician or an emergency department visit. The BRIDGE visit functions as an extension of the hospital discharge team, differing from usual care in 3 distinct ways: (1) the BRIDGE clinic ensures that the time between a patient's hospital discharge to their first outpatient follow-up is no longer than 14 days; (2) the visit with a NP, while providing traditional evaluation and treatment, emphasizes education and support; and (3) patients are seen by NPs who are integrated within the health system and better able to facilitate and coordinate care within that system compared with those external to the system.

Figure 1. Patient Flow Diagram



This figure demonstrates how the study cohort was determined, which patients were included and excluded, and how groups were divided.

This study aimed to measure the effectiveness of the BRIDGE program by comparing the 30-day to 180-day readmission rates for ACS patients who attended BRIDGE with those who chose not to attend in lieu of usual care. Additionally, it aimed to determine whether medication persistence contributed to the readmission rates. It was hypothesized that patients who attended BRIDGE would have lower 30-day readmission rates and superior 6-month medication persistence rates over nonparticipants.

Methods

This was a retrospective study using consecutive data (extracted from an electronic medical record) for all patients referred to the BRIDGE program in a deidentified clinical database. The Human Subjects Internal Review Board of the University of Michigan Medical Center approved this study (HUM00035421).

All patients discharged with a diagnosis of ACS (acute myocardial infarction or unstable angina) from the inpatient adult cardiology service between March 30, 2008, and March 30, 2009, were eligible for this study. Referrals were made to the BRIDGE program based on the lack of availability of a cardiology or primary care follow-up appointment within 14 days of discharge. Patients included in the analysis were divided into 2 cohorts: those who were referred and attended ("attenders") and those who were referred and did not attend ("nonattenders"). Patients were excluded from the study if they became pregnant, sought follow-up outside the institution, or died within 30 days of discharge. The Social Security Death Index was queried for patients lost to follow-up; only the result of this query was recorded.

The study cohort (**Figure 1**) included 424 patients referred to the BRIDGE program. ACS comprised 25.2% (n = 107) of the diagnoses referred. Patients were further excluded if they died or were rehospitalized prior to their scheduled BRIDGE

Table 1. Demographic Differences Between BRIDGE and Usual Care Participants, No. (%)

VARIABLE N = 80	ALL n = 80 (100%)	Attend n = 62 (77.5%)	Did Not Attend n = 18 (22.5%)	*P*
Age (mean + SD)	62.4 ± 13.9	62.9 ± 14.1	60.9 ± 14.8	.60
Gender (% female)	47 (58.8)	35 (56.5)	12 (66.7)	.44
Race				
White	69 (86.3)	53 (85.5)	16 (88.9)	1.00
Non-white (black, Asian, Native American, Hispanic)	11 (13.7)	9 (14.5)	2 (11.1)	1.00
Comorbidities				
Afib	5 (6.3)	4 (6.5)	1 (5.6)	1.00
CVD	4 (5.0)	4 (6.5)	0	.57
Hx TIA	2 (2.5)	2 (2.8)	0 (0)	1.00
Hx CVA	1 (1.3)	1 (1.6)	0	1.00
CHF	11 (13.8)	7 (11.3)	4 (22.2)	.26
CAD	77 (96.3)	59 (95.2)	18 (100.0)	1.00
Current smoker	19 (23.8)	16 (25.8)	3 (16.7)	.54
Diabetes	6 (7.5)	2 (3.2)	4 (22.2)	.41
Dyslipidemia	58 (72.5)	49 (79.0)	9 (50.0)	.03
HTN	50 (62.5)	41 (66.1)	9 (50.0)	.21
Obesity	14 (17.5)	13 (21.0)	1 (5.6)	.17
Peripheral vascular disease	9 (11.3)	5 (8.1)	4 (22.2)	.11
Psychiatric disorder n = 27 (43.5%)	**27 (33.8)**	**n = 17 (27.4)**	**n = 10 (55.6)**	–
Anxiety	14 (51.9)	9 (52.9)	5 (50.0)	1.00
Dementia	4 (14.8)	3 (17.6)	1 (10.0)	1.00
Depression	20 (74.1)	12 (70.6)	8 (80.0)	.68
Substance abuse	6 (22.2)	4 (23.5)	2 (20.0)	1.00
GRACE risk score (mean ± SD)	99.69 ± 30.8	100.8 ± 30.9	104.8 ± 32.9	.53
Charlson Comorbidity Index (mean ± SD)	3.98 ± 1.79	4.05 ± 1.74	3.98 ± 1.96	.75

Afib indicates atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; HTN, hypertension; Hx CVA, history of cardiovascular disease; Hx TIA, history of transient ischemic attack.

appointment (n = 9; 8.4%). The final study sample included 80 patients after excluding patients with missing variables (n = 18; 18.4%).

Instruments

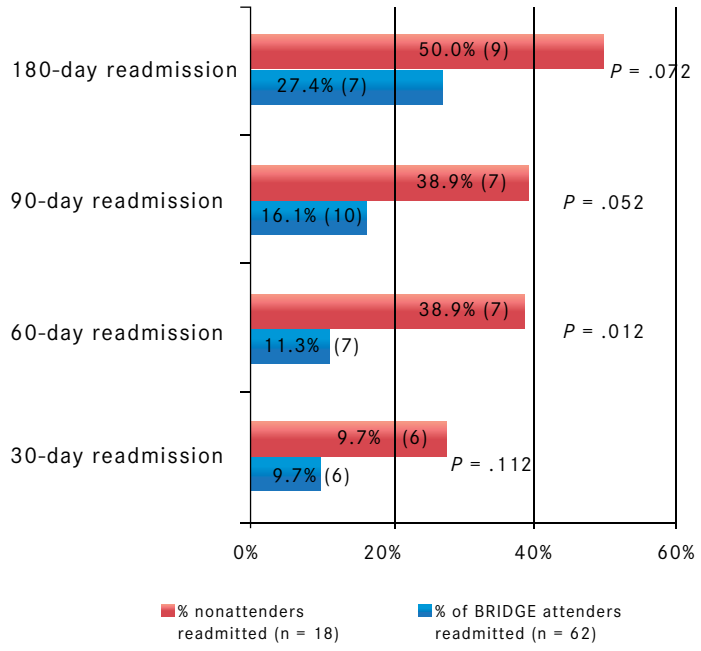
Two principal instruments were used to describe patients' overall state of health. The first measure, the Charlson Comorbidity Index (CCI), quantified the combined effects of 19 comorbid conditions on mortality.[16] Tested across a variety of populations, the CCI has consistently proved valid for predicting mortality.[16-18] The second measure, the GRACE Risk Model for Discharge, predicted the risk of death in patients with ACS from hospital discharge to 6 months out[19] with excellent discriminatory and predictive validity (C statistic, 0.70-0.80).[20,21]

Data Analysis

Data were analyzed using SPSS 18.0 (IBM, Armonk, New York). All variables were assessed for compliance with statistical assumptions. Missing data were excluded from the sample.

Baseline equivalencies were assessed for all demographic variables, comorbidities, CCI scores, and GRACE risk scores. Associations between variables were assessed with Pearson's correlation coefficient. Independent student *t* tests and χ^2 were used to compare differences between the BRIDGE intervention group and the usual care group. Pearson's χ^2 test for significance was reported except in cases where the expected count would violate an underlying assumption; in those cases, Fisher's exact test was reported. Hierarchical logistic regression models were used to evaluate whether BRIDGE attendance influenced readmissions and/or medication persistence, after adjusting for comorbidities

Figure 2. Readmission Rates for BRIDGE Attenders Versus Nonattenders, % (n)



Readmission rates between acute coronary syndrome patients who attended BRIDGE and those who did not at 30, 60, 90, and 180 days postdischarge.

(CCI) and severity of events (GRACE). ORs and 95% CIs were reported for all independent variables. The significance level was set at .05 for all analyses.

Readmission rate. The hospital readmission rate was calculated as the number of patients discharged from the hospital with a diagnosis of an ACS event and readmitted within 30, 60, 90, or 180 days, divided by the total number of people who were discharged alive with the same diagnosis.[5] The BRIDGE and non-BRIDGE–specific rates of readmission were calculated as the total number of readmissions for the BRIDGE and non-BRIDGE groups divided by the total number of subjects in each group. Only the first readmission following discharge for an ACS event was counted.

Medication persistence. Medication persistence was defined as self-reported continued use of prescribed AHA/ACCF-recommended pharmacotherapy regimens of β-blockers, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers [ARBs]), aspirin, statins, or clopidogrel at 6 months, postdischarge. Six-month persistence rates were determined by comparing self-reported medication regimens from the most complete cardiology or primary care follow-up notes at 6 months, postdischarge (no more than 2 weeks before and no more than 1 month beyond the 6-month discharge date) to the medication regimen prescribed at discharge. Six-month medication persistence rates for each drug and for the 4 (β-blockers, ACE inhibitors [or ARBs], aspirin, statins) and 5 (β-blockers, ACE inhibitors [or ARBs], aspirin, statins, plus clopidogrel) drug combination regimens were compared between BRIDGE attendees and nonattendees. This methodology is consistent with the methodology employed by the GRACE Registry.[22] Patients with known contraindications or hypersensitivity reactions to certain medications, such that they could not be prescribed or continued, were excluded.

Results

Of 107 ACS patients discharged from the study hospital and referred to the BRIDGE program, 80 were included in the final readmission analysis. To isolate the BRIDGE effect, patients who died or were readmitted prior to their scheduled appointment were excluded, as were patients with missing data (n = 27; Figure 1). Excluded patients, compared with patients remaining in the study, were noted to have higher CCI and GRACE risk scores, suggesting that these patients either had more comorbid conditions, worse events, or both.

The mean age of the final sample was 62.4 years. The majority (58.8%) were female, and white (86.3%), with a median length of initial hospital stay ranging from 2 to 4 days. **Table 1** shows a comparison of patients who attended BRIDGE versus non-attenders. With the exception of a higher percentage of dyslipidemia among BRIDGE users, there were no significant differences between the 2 groups.

Table 2. Odds of Being Readmitted 30, 60, 90, and 180 Days After Discharge for Patients Who Participated in the BRIDGE Program

DAYS AFTER DC	OR	95% CI	ADJUSTED OR CCI	95% CI	ADJUSTED OR GRACE	95% CI
30	.179	.042-.761	.268	.069-1.038	.285	.075-1.091
60	.138[a]	.037-.514	.191[a]	.054-.669	.203[a]	.059-.699
90	.233[a]	.007-.776	.268[a]	.078-.922	.306	.093-1.009
180	.378	.128-1.112	.311	.095-1.021	.373	.119-1.167

CCI indicates Charleson Comorbidity Index; DC, discharge; OR, odds ratio.
[a]$P < .05$

Attendance

As seen in Table 1, 77.5% (n = 62) of the patients referred to the BRIDGE program attended their scheduled appoint-

ment. The median time from discharge to attending a BRIDGE program appointment was 15 days (range, 11-20 days). The time elapsed between discharge and being seen by any medical provider (considered usual care) was 20 days longer for patients who did not attend BRIDGE. However, patients who did not attend BRIDGE were seen by cardiology sooner (31 days vs 59 days; $P < .05$) than attenders. Patients who missed or cancelled their BRIDGE appointment (n = 58) were contacted by phone to ascertain the reason. Approximately one-third (34.5%) reported that they were able to get an earlier appointment with either cardiology or their primary care provider. Other reasons for not attending included not wanting the appointment (17.2%), no-show (12.1%), problems with appointment location (5.2%), rehospitalization (5.2%), schedule conflict (5.2%), and other unspecified reasons (19.0%).

Readmissions

It was hypothesized that patients who were referred and chose to attend the BRIDGE program would have lower readmission rates than patients who received usual care. In fact, as shown in **Figure 2**, patients who attended the BRIDGE program had lower rates of readmission at 30, 60, 90, and 180 days after hospital discharge for an ACS event than did nonattenders, but only 60-day data were significantly different between the groups.

Patients participating in the BRIDGE program were .138 to .378 times less likely to be readmitted compared with those who received usual care (**Table 2**). The maximum benefit was observed at 60 days postdischarge, though at all points post discharge, BRIDGE attenders were less likely to be readmitted. Data were subsequently and independently risk adjusted both for CCI and GRACE risk scores, as these measures have a linear relationship ($r = .812$). Both models (CCI and GRACE) fit the data equally well with Hosmer-Lemeshow goodness of fit test significance levels between 0.447 and 0.915.

Table 3. Rates of Medication Persistence by BRIDGE Attendance Number (%)

Variable	N[a]	Overall	Attenders n = 70 (72.2)	Nonattenders n = 27 (27.8)	*P*	OR	95% CI
Prescribed at discharge							
Aspirin	97	95 (97.9)	69 (98.6)	26 (96.3)	.48	2.654	[.160-44.004]
β-blockers	97	86 (88.7)	62 (88.6)	24 (88.9)	1.00	.969	[.237-3.960]
ACE inhibitor/ARB	97	73 (75.3)	57 (81.4)	16 (59.8)	.02	3.014	[1.136-7.998]
Statin	97	92 (94.8)	68 (97.1)	24 (88.9)	.13	4.250	[.669-26.995]
Clopidogrel	97	72 (75.5)	53 (75.7)	19 (73.1)	.79	1.149	[.412-3.199]
4-drug combination[a]	97	59 (60.8)	47 (67.1)	12 (44.4)	.04	2.554	[1.030-6.335]
5-drug combination	97	46 (47.4)	36 (51.4)	10 (37.0)	.20	1.800	[.724-4.476]
Persistence at 6 months							
Aspirin	44	42 (95.5)	33 (97.1)	9 (90.0)	.41	3.667	[.208-65.548]
β-blockers	40	36 (90.0)	29 (93.5)	7 (77.8)	.21	4.143	[.494-34.746]
ACE inhibitor/ARB	31	25 (80.6)	20 (80.0)	5 (83.3)	1.00	.800	[.076-8.474]
Statin	44	40 (90.9)	31 (91.2)	9 (90.0)	1.00	1.148	[.106-12.427]
Clopidogrel	35	30 (85.7)	22 (81.5)	8 (100.0)	.32	–	–
Of patients prescribed 4 agents							
Still on 0 agents	27	–	–	–	–	–	–
Still on 1-2 agents	32	8 (25.0)	1 (16.7)	7 (26.9)	1.00	1.842	[.182-18.65]
Still on 3-4 agents	27	24 (88.9)	19 (86.4)	5 (100.0)	1.00	–	–
Of patients prescribed 5 agents							
Still on 0 agents	21	–	–	–	–	–	–
Still on 1-2 agents	23	4 (17.4)	3 (16.7)	1 (20.0)	1.00	.800	[.065-9.919]
Still on 3-4 agents	34	20 (58.8)	14 (53.8)	6 (75.0)	.42	.389	[.112-2.024]
Still on 5 agents	21	12 (57.1)	10 (58.8)	2 (50.0)	1.00	1.429	[.161-12.701]

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; OR, odds ratio.
Total sample size for the analysis of medication persistence was 97 rather than 80 as in the readmission analysis. Only 1 participant had missing data on 6-month medication persistence, while 18 patients had missing data on readmissions.
[a]Aspirin, β-blockers, ACE-inhibitor/ARB, statin.
[b]Four agents plus clopidogrel.

Medication Persistence

To explicate why patients who participated in the BRIDGE program had lower readmission rates, we further analyzed whether patients seen in the BRIDGE program were more likely to adhere to their prescribed AHA/ACCF-recommended pharmacotherapy regimens. Given the breadth of literature suggesting that transitional care models with NPs fill a critical gap in care delivery to effect outcomes,[23,24] it was hypothesized that patients who participated in the BRIDGE program would have higher medication persistence rates at 6 months than individuals who did not participate.

Overall rates of medication prescribing at discharge for secondary prevention in the study cohort exceeded published rates for aspirin, β-blockers, and statins.[25,26] **Table 3** describes patterns of attendance by medications prescribed at discharge and patterns of persistence with medications 6 months after discharge. All patients referred to BRIDGE without an early adverse event (n = 98) were included in this analysis. Patients with missing medication data were excluded at each time point such that at 6-month follow-up, sample sizes were smaller and varied by group.

Nearly all patients discharged with ACS were prescribed aspirin (97.9%) and statins (94.8%), and use of β-blockers (88.7%) and ACE inhibitors (or ARBs; 75.3%) was high compared with published literature.[26,27] Of patients meeting the criteria for clopidogrel, 75.0% received a prescription at discharge. Most subjects remained on their prescribed pharmacotherapy regimens 6 months after discharge. However, there were no differences in medication persistence between BRIDGE participants or participants receiving usual care 6 months after discharge.

Logistic regression was used to predict the likelihood of medication persistence at 6 months after hospital discharge. The analysis was limited by the number of patients for which there were medication persistence data available. Because of the small sample size, it was necessary to test a series of models rather than a single model. Therefore, 3 series of analyses were performed (BRIDGE attendance; BRIDGE attendance adjusted for CCI; and BRIDGE attendance adjusted for GRACE risk score). Each series tested the likelihood of medication persistence to aspirin, ß-blockers, ACE-inhibitors, statins, and clopidogrel individually and to the 4- and 5-drug combined pharmacotherapy regimens of aspirin, ß-blockers, ACE inhibitors, and statins (4-drug regimen) plus clopidogrel (5-drug regimen). Only 4 of the 21 models tested were predictive of medication persistence at 6 months: ß-blockers or ACE-inhibitors adjusted for either the CCI or GRACE risk score. For ß-blockers, the addition of the CCI to attendance explained between 22.9% (Cox and Snell R^2) and 47.8% (Nagelkerke R^2) of the variance in persistence. Likewise, testing attendance with the GRACE risk score explained between 25.4% (Cox and Snell R^2) and 53.1% (Nagelkerke R^2) of the variance. The ACE-inhibitor model adjusted for the CCI explained between 25.0% (Cox and Snell R^2) and 39.0% (Nagelkerke R^2) of the variance in persistence; and in combination with the GRACE risk score explained between 31.7% (Cox and Snell R^2) and 49.5% (Nagelkerke R^2) of the variance.

Discussion

This study was designed to measure the effectiveness of the BRIDGE program in reducing hospital readmission rates for ACS patients. It was hypothesized that compared with patients who had usual care, BRIDGE attenders would have lower rates of hospital readmissions. BRIDGE attenders were seen at a median of 15 days postdischarge--the same timeframe in which nonattenders were seen by their primary care providers, but 16 days earlier than nonattenders were seen by a cardiologist. The NP-driven, single-dose, transitional care program was a successful strategy to lower all-cause hospital readmissions for ACS patients. Even after adjustments for severity of illness and severity of event, patients who chose to attend their BRIDGE appointments fared better than patients who received usual care. Although this study was designed to address readmissions within 30 days of hospital discharge, the maximum benefit was observed at 60 days postdischarge, with a positive trend at all other time points.

Reductions in readmissions cannot be explained simply by better medication persistence for those who attended BRIDGE. There were no significant differences in 6-month medication persistence for any single medication (aspirin, β-blocker, ACE inhibitor, statin, clopidogrel) or combined regimen. With the exception of risk-adjusted β-blocker and ACE inhibitor models, no other models were predictive of medication persistence 6 months after discharge. Further research is thus needed to more fully understand what elements of the BRIDGE program contribute to its success.

Limitations

There are some limitations that should be considered with regard to this study. Study data were collected retrospectively, and thus, causality should not be assumed. As the study also lacks randomization, the results may not be generalizable. The sample size was small, with readmission rates as low as 9.7%, such that there were insufficient outcomes to adequately power a multiple regression analysis. Despite this, significantly lower readmission rates were found at both 60- and 90-day postdischarge points.

Optimal time to follow-up was another limitation of this study. When the BRIDGE program began (2008), postdischarge follow-up within 14 days was reasonable. However, this design was problematic for assessing 30-day outcomes, as the measurement period was not truly 30 days, but rather only the 14 days between

Continued on page 51

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ELIQUIS® (apixaban) is

- **indicated** to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- **newly indicated** for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip replacement surgery
- **newly indicated** for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone knee replacement surgery

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

(A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE: Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

(B) SPINAL/EPIDURAL HEMATOMA: ELIQUIS use in patients undergoing spinal epidural anesthesia or spinal puncture increases the risk of epidural or spinal hematoma which may cause long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurologic impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated.

See adjacent pages for complete Boxed WARNINGS.

Please see Important Safety Information and Brief Summary of Full Prescribing Information, including **Boxed WARNINGS**, on following pages.

IMPORTANT SAFETY INFORMATION

WARNINGS: (A) DISCONTINUING ELIQUIS® (apixaban) IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

(A) Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

(B) When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary. Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- Increased Risk of Stroke with Discontinuation of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation: Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

Bleeding Risk:

- ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal bleeding. Concomitant use of drugs affecting hemostasis increases the risk of bleeding including aspirin and other anti-platelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
- There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban.

WARNINGS AND PRECAUTIONS

Bleeding Risk (continued):

- Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. For patients receiving 5 mg twice daily, the dose of ELIQUIS should be decreased when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.

- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke.

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see Brief Summary of Full Prescribing Information, including **Boxed WARNINGS**, on following pages.

Reference: ELIQUIS® (apixaban) Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY; March 2014.

Bristol-Myers Squibb Pfizer

Eliquis® (apixaban) tablets 5mg 2.5mg

ELIQUIS® (apixaban) tablets for oral use **℞ ONLY**

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

(B) SPINAL/EPIDURAL HEMATOMA

(A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered *[see Dosage and Administration and Warnings and Precautions]*.

(B) SPINAL/EPIDURAL HEMATOMA

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.

Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Stroke with Discontinuation of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation

Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation *[see Clinical Studies (14.1) in full Prescribing Information]*. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant *[see Dosage and Administration (2.5) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.2) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to an emergency room. ELIQUIS should be discontinued in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS (apixaban). The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

ADVERSE REACTIONS

The most serious adverse reactions reported with ELIQUIS were related to bleeding *[see Warnings and Precautions]*.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per year) in ARISTOTLE and AVERROES.

Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

	ELIQUIS N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI*)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI)‡	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Intraocular§	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal¶	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM**	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

* Confidence interval.

† International Society on Thrombosis and Hemostasis (ISTH) major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

‡ GI bleed includes upper GI, lower GI, and rectal bleeding.

§ Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).

¶ Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.

** CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, ELIQUIS dose, type of atrial fibrillation (AF), and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

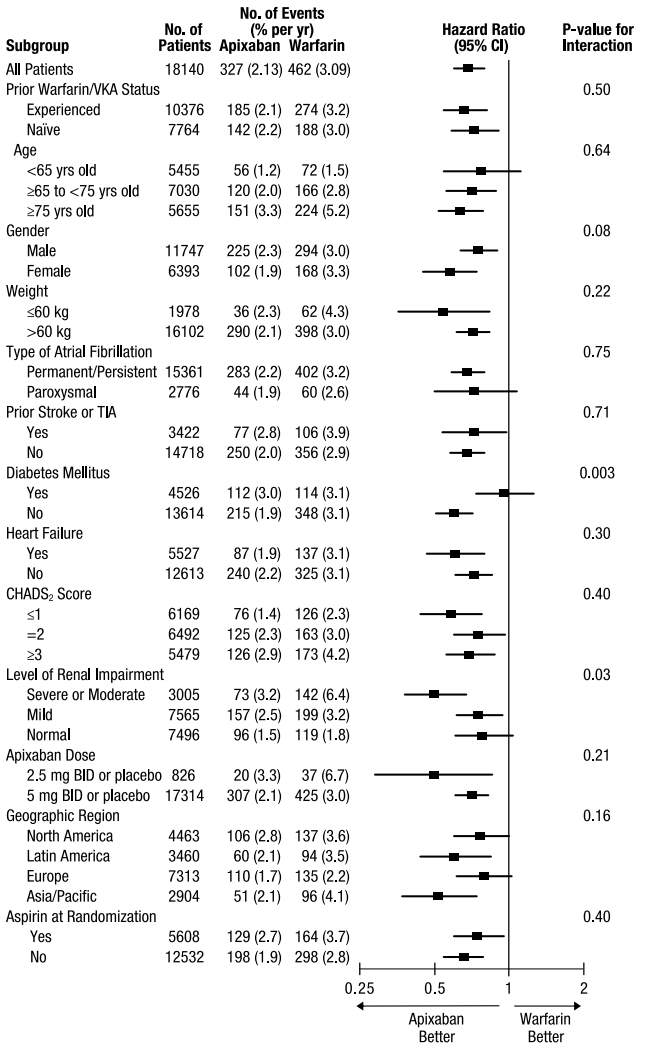

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS (apixaban).

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.

† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶ CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS, n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke.

Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving 5 mg twice daily, the dose of ELIQUIS (apixaban) should be decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

In patients already taking ELIQUIS at a dose of 2.5 mg daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS (apixaban) with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.77% per year with apixaban versus 0.62% per year with placebo in patients receiving single antiplatelet therapy and was 5.91% per year with apixaban versus 2.50% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

End-Stage Renal Disease Patients Maintained with Hemodialysis

Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS (apixaban); therefore, the dosing recommendation for patients with nonvalvular atrial fibrillation is based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis. The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age ≥80 years or body weight ≤60 kg, reduce dose to 2.5 mg twice daily *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.2, 12.3) in full Prescribing Information]*.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patients have had neuraxial anesthesia or spinal puncture, and particularly if they are taking concomitant medicinal products affecting hemostasis, they should be informed to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

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BRIDGE appointments and the 30 days postdischarge date.

A further limitation of this study was the use of self-report data for medication persistence. Information as to whether medication omissions or discontinuation were the result of a patient or provider decision was inconsistently documented. Thus, it is not possible to determine whether this over or underestimates the potential benefits of BRIDGE. A more formal study is needed to investigate these findings.

Conclusions

The general cardiology BRIDGE program is a novel and effective model for providing transitional care and lowering all-cause hospital readmissions for ACS patients. The NPs provide a high level of service in ensuring the health of their patients, providing education to the patients and their families, reconciling medications, and communicating with the patient's discharge team and outpatient care provider. Even after adjustments for severity of illness and severity of event, patients who chose to attend their BRIDGE appointments had lower readmission rates at 30, 60, 90, and 180 days postdischarge than those with usual care. Furthermore, these reductions were not explained by better medication persistence. Though the relative value of this NP model of early postdischarge transitional care compared with a timely primary care or cardiology physician visit remains to be seen, models such as this should be developed and analyzed across institutions and patient types (diagnoses) to maintain patient safety at home after hospital discharge and reduce excessive and unnecessary health-system costs.

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REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6-e245.

2. Fye WB. Cardiology workforce: a shortage, not a surplus. *Health Aff (Millwood)*. 2004;(suppl):W4-64-W66.

3. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458-2473.

4. Report to the Congress: Promoting Greater Efficiency in Medicare. Washington, DC: Medicare Payment Advisory Commission; June 2007.

5. Jencks S, Williams M, Coleman E. Rehospitalizations among patients in the Medicare fee-for-service program. *N Eng J Med*. 2009;360(14):1418-1428.

6. Coleman E, Parry C, Chalmers S, Min S. The care transitions intervention: results of a randomized controlled trial. *Arch Intern Med*. 2006;166(17):1822-1828.

7. Naylor M, Brooten D, Campbell R, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *J Am Geriatr Soc*. 2004;52(5):675-684.

8. Sinclair A, Conroy S, Davies M, Bayer A. Post-discharge home-based support for older cardiac patients: a randomised controlled trial. *Age Ageing*. 2005;34(4):338-343.

9. Stewart S, Pearson S, Luke C, Horowitz J. Effects of home-based intervention on unplanned readmissions and out-of-hospital deaths. *J Am Geriatr Soc*. 1998;46(2):174-180.

10. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA*. 2010;303(17):1716-1722.

11. Naylor M, Aiken L, Kurtzman E, Olds D, Hirschman K. The importance of transitional care in achieving health reform. *Health Aff (Millwood)*. 2011;30(4):746-754.

12. Goldfield NI, McCullough EC, Hughes JS, et al. Identifying potentially preventable readmissions. *Healthcare Finance Rev*. 2008;30(1):75-91.

13. Outcome measures. CMS website. http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html. Published 2013. Accessed February 2, 2013.

14. Conrad DA, Christianson JB. Penetrating the "Black Box": financial incentives for enhancing the quality of physician services. *Med Care Res Rev*. 2004;61:37S-68S.

15. Albert NM. Improving medication adherence in chronic cardiovascular disease. *Crit Care Nurse*. 2008;28:54-64.

16. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.

17. Needham D, Scales D, Laupacis A, Pronovost P. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *J Crit Care*. 2005;20(1):12-19.

18. Charlson M, Szatrowski T, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251.

19. Eagle K, Lim M, Dabbous O, et al. A validated prediction model for all forms

of acute coronary syndrome: estimating the risk of 6-month post-discharge death in an international registry. *JAMA*. 2004;291(22):2727-2733.

20. Elbarouni B, Goodman S, Yan R, et al. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute myocardial coronary syndrome in Canada. *Am Heart J*. 2009;158(3):392-399.

21. Ramsay G, Podogrodzka M, McClure C, Fox K. Risk prediction in patients presenting with suspected cardiac pain: the GRACE and TIMI risk scores versus clinical evaluation. *QJM*. 2007;100(1):11-18.

22. Eagle K, Kline-Rogers E, Goodman S, et al. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. *Am J Med*. 2004;117(2):73-81.

23. Brown SA, Grimes DE. A meta analysis of nurse practitioners and nurse midwives in primary care. *Nurs Res*. 1995;44(6):332-339.

24. Horrocks S, Anderson E, Sallisbury C. Systematic review of whether nurse practitioners in primary care can provide equivalent care to doctors. *BMJ*. 2002;324(7341):819-823.

25. Margulis AV, Choudhry NK, Dormuth CR, Schneeweiss S. Variation in initiating secondary prevention after myocardial infarction by hospitals and physicians, 1997 through 2004. *Pharmacoepidemiol Drug Saf*. 2011;20:1088-1097.

26. Simpson E, Beck C, Richard H, Eisenberg MJ, Pilote L. Drug prescriptions after acute myocardial infarction: dosage, compliance, and persistence. *Am Heart J*. 2003;145:438-444.

27. Vasaiwala S, Nolan E, Ramanath VS, et al. A quality guarantee in acute coronary syndromes: the American College of Cardiology's Guidelines Applied in Practice program taken real-time. *Am Heart J*. 2007;153:16-21.

AHIP: 2014 National Health Policy and Health Insurance Exchanges Forum Event Highlights

KATIE SULLIVAN

On March 5-7, America's Health Insurance Plans (AHIP) held its 2014 National Health Policy and Health Insurance Exchanges Forum conferences. Both events highlighted the opportunities, challenges, and trends of the healthcare marketplace under the Affordable Care Act (ACA).

ACA Implementation in the States

Three state representatives shared their unique experiences with Medicaid expansion, approaches to health insurance exchanges, and the other efforts they are making to promote choice and competition in the healthcare marketplace. Their experiences are important to reflect upon as state representatives throughout the nation are implementing health reform in various ways.


Michael Bousselot

Michael Bousselot, policy advisor, Office of the Governor for the state of Iowa, said that Iowa is all about making people healthier. A healthier population is the best reformed population, he argued. In 2013, Iowa became the 10th-healthiest state in the United States. This was a merit worth celebrating, especially because the state ranked only 19th healthiest in 2010. The state aspires to reach the number 1 position by 2016, and plans to do this by encouraging lifestyle changes among Iowa residents through programs that promote smoking cessation and healthier eating habits.

Mr Bousselot also described Iowa's Health and Wellness Plan, which intends to improve the health outcomes of Iowa residents. The wellness plan will replace IowaCare, the state's limited benefit program.

Following Mr Bousselot's lead-in, Emily Whelan Parento, executive director, Office of Health Policy, Cabinet for Health and Family Services in Kentucky, described Kentucky's healthcare landscape. She said Kynect, Kentucky's health benefit exchange, opened insurance to an estimated 640,000 people. She also noted that 308,000 individuals were eligible for Medicaid under the new rules, and that over 330,000 individuals became eligible for premium assistance. This success was due in part to Kentucky governor Steve Beshear's initiative to sign an order which customized the exchange, as well as his decision to establish an advisory board to guide the rollout.

Ms Parento also discussed kyhealthnow, a program that focuses on advancing wellness for Kentucky residents. Like Iowa, the states' administration seeks to increase its ranking among the healthiest states in the nation. Some of their strategies include reducing Kentucky's rate of uninsured to less than 15%, reducing the smoking rate by 10%, and reducing the rate of obesity by 10%. Tobacco use/smoking is by far the biggest priority, Ms Parento noted. All of these initiatives are not just for health's sake, but for controlling state costs related to health expenditures.


Greg Moody

To wrap up the discussion, Greg Moody, director at the Governor's Office of Health Transformation, State of Ohio, described Ohio's Health and Human Services Innovation Plan, or the state's "innovation framework." The 3 main strategies of this plan include modernizing Medicaid, streamlining Ohio's health and human services, and paying only for value-based services. Mr Moody noted that these particular aims became necessary when the state's health spending began to increase at an unsustainable rate during 2011, after a 9% increase in Medicaid spending coupled with an $8 billion state budget shortfall.

To address the problem, officials competitively rebid managed care contracts in 2012. Currently, the state has rebalanced its health budget, has $1.5 billion in "rainy day" funding (it had $0.89 in this fund at the end of 2011), and boasts that Medicaid underspending has topped $950 million. Ohio also has uniquely eliminated the coverage gap for childless adults, and for those who did not qualify for subsidies even with the expansion of the federal poverty level under the ACA.

ACA's Future: The Good, the Bad, and the Ugly

Avik Roy, senior fellow, Manhattan Institute for Policy Research, and Jonathan Cohn, senior editor of *The New Republic*, discussed how the future of the ACA will require a more bipartisan ap-

proach. They also noted that it will need more positive stories from the media to frame the highlights of health reform.


Avik Roy

In fact, according to Mr Roy, one of the most difficult aspects of healthcare reform is the reservations of some conservative parties. He said that reform will likely never go back to "what was," and suggested there are myriad pathways to what the future of healthcare could look like. However, while the ACA improves access for many consumers, it still does not address the underlying costs of healthcare in the United States. Mr Avik suggested that a "superior" form of coverage would involve alternative legislation, not a repeal.

Mr Cohn added that the media has skewed the ACA picture, and that all too often, the more harrowing stories of individuals' challenges with the ACA overshadow the good news that happens because of reform. He, like Mr Roy, suggested that the "now versus the past" discussions about healthcare are irrelevant and fruitless. He stressed the importance of a stronger focus on the future and what "could be" through legislative reform.

Mr Avik and Mr Cohn also conversed about implications of the individual mandate, which has been delayed 1 year; essential health benefits; and the advantage of private payers in insurance exchanges.


Cass R. Sunstein

Simplifying the Complex: Educating and Engaging Consumers

Cass R. Sunstein, professor, Robert Walmsley University, Harvard Law School, presented a session that had 1 concept in mind: think simple. He suggested that patients require both freedom of choice and steering. He said that greater access to information can empower consumers with the knowledge they need to make informed decisions about their healthcare.

How to make that simple, he said, is through "nudges and nudging." This is because every person operates with 2 systems in mind: the first is automatic, such as when we navigate the halls of our dark homes late at night without thinking about it; and the second is more deliberate and slow, such as when we try to compute complicated math problems in our heads.

It's important to think about those simple solutions that speak to the "first system" of people's minds. For instance, if a physician is seeking to improve medication adherence with a patient, using a text messaging program to send reminders has been found to be effective. He also offered the example of the FDA's ChooseMyPlate initiative. In an effort to promote better nutrition and reduce national obesity rates, the FDA now uses a plate with colored portions instead of a pyramid to demonstrate food serving sizes. Overall, Mr Sunstein said "nudges" should be automatic, simple and easy, intuitive, and meaningful. The goal is to incite engagement that does not strain "system 2."

Nudges are also important because many patients are much too "present biased," and experience some form of realistic optimism (meaning they believe bad things can't happen to them, that they only happen to other people). He added that time and patience are essential to improving patient outcomes. Mr Sunstein concluded that the future is bright if we are willing to consider ways to save money, simplify the system, and improve patient engagement.

Healthcare Cost Containment and Its Impact on US Economic Competitiveness

Paul Howard, PhD, senior fellow and director, Center for Medical Progress, Manhattan Institute for Policy Research, said that the question in healthcare, especially when comparing the United States with other countries, is whether our spending is giving us good value for the dollars spent. He said stakeholders broadly agree that spending in the United States does not currently buy great value. Dr Howard also said that despite much criticism, the United States actually ranks in the middle of the pack globally when it comes to health outcomes. Still, it's difficult to determine or blame specific systems for specific outcomes, especially when issues such as a patient lifestyle or behaviors are factored into the equation.

He also added that the United States isn't the only country that faces challenges with spending and outcomes. Anywhere from 20% to 30% of Organization for Economic Cooperation and Development (OECD) countries waste healthcare dollars on inappropriate care, ineffective drugs, and fraud. He suggested that if OECD countries could cut their wasteful spending by between 10% and 15%, it would raise longevity at birth by 1 year. If you estimate each person's life worth at $150,000, that would save trillions of dollars in spending, and it would have an enormous effect on an economy of 300 million people.


Paul Howard, PhD

"The healthcare system can obviously become more efficient in that, but also have benefits for us in terms for outcomes and our longevity," Dr Howard said. "So it's a win-win situation if you can find the right way to reduce spending."

As US healthcare spending levels rise, other spending and investments in areas such as infrastructure and education are crowded out. The same is true for state spending—including Medicaid programs. "Healthcare spending squeezes out other priorities," he said.

Effects of reduced spending, increased efficiency, and improved productivity are necessary to improve costs/wage compensation and out-of-pocket costs. He also suggested that consumer education, public purchasing services, and retail clinics or telehealth have a role in controlling US healthcare spending.

Paul Van de Water, PhD, senior fellow, Center on Budget and Policy Priorities, said that healthcare containment is not just about competitiveness. He started by saying that in recent years, the rate of healthcare spending has slowed, and that national health expenditure growth reported by CMS or total spending data demonstrates this trend. He also said that Medicare cost growth for beneficiaries has been as small as 0% to 1% between 2013 and 2014. However, this is not a total victory—there have been other periods in which cost growth has slowed and then ramped back up.

"What I think we need is what I call the 'all-of-the-above strategy,'" he said. "All too often, advocates with particular approaches like to, from my point of view, exaggerate the likely benefits of their particular approach to cost control and by the same token, perhaps exaggerate or downsize the other approaches. There are many tools available, and my suggestion is that to be properly used, we really need to be making use of all of them. There are very few approaches we can rule out."

Dr Van de Water also said that cost control will not be painless. It may require a balancing act of making hard choices and sacrifices, and as we manage a mixture of approaches to reducing costs, tradeoffs will have to be made.

Championing Innovation: Partnering With Providers to Reward Quality and Reduce Costs

Andrew Dreyfus, president and CEO, Blue Cross Blue Shield of Massachusetts, discussed how next-generation network strategies could be designed to encourage value and affordability. In particular, he addressed the 2006 Massachusetts health insurance reform law known as An Act Providing Access to Affordable, Quality, Accountable Healthcare. Most industry stakeholders are no strangers to the fact that this policy gave way to what has become the ACA. Mr Dreyfus said that rather than making the ideological case for health reform, Massachusetts made the business case for reform.

"We have a bill [the 2006 bill] in which all stakeholders—business and labor, and hospitals and health plans, and consumer advocates, and those who pay for the market—came together," he said.

Mr Dreyfus said that other concepts within the Act, including individual mandates and Medicaid expansion, also later became cornerstones of the ACA. As well, Mr Dreyfus said the bill resulted in 97% of adults and 100% of children having health insurance in Massachusetts. He said that the bill maintains its effect in the state, even as the national policy lags in popularity. However, the policy has not been without challenges. Expanding coverage in the absence of cost containment didn't work because Massachusetts is one of the "most expensive places to get healthcare in the world."

In addition, the state faced pressure from cities and small businesses watching their premiums grow by 10% to 15% per year. The governor even lost his patience and initiated the "great healthcare standoff" in which he rejected rates from payers until they were affordable. But, thanks to the strength of reform coalitions and the persistence of bill supporters, differences were worked out and the resulting health models were much stronger.

Mr Dreyfus added that while they had a few early adopters that agreed to the model at the very beginning, they faced their fair share of opposition. So they had to quickly build momentum by demonstrating success, publically declaring that fee-for-service increases would no longer be funded, and by encouraging the public sector to make alternative payment models the norm (eg, the Alternative Quality Contract, or AQCs). As a result, 85% of doctors and specialists are actively participating in the state's health model. It's working across the state in a variety of practice types and businesses.

He also mentioned that a team of researchers at Harvard Medical School, led by Michael Chernew, PhD, have been publishing independent results about the ACA annually, and they are finding that AQCs improve quality and slow spending growth.

"On health outcomes, which are kind of the gold standard of quality measurement, you can see enormous progress," Mr Dreyfus said. "For example, some of our AQC groups have 9 out of 10 of their diabetes patients with their blood sugar under good control. The national average is about 70%. That means less renal illness and fewer overall complications."

Best of all, he said, is that physicians are embracing the model. This is leading to better and more efficient engagement, and improved health outcomes. He added that it will never be politicians who make reform effective—it will be physicians taking accountability and starting to change how they practice. The problem must be solved from within.

"We're all part of the problem—health plans, employers, hospitals, physicians, patients—and we're the ones who can solve this problem. We can initiate this model of better care and lower costs for all," he said.

The ACA's Unintended Consequences for Medicare

Katherine Baicker, PhD, professor of health economics, department of health policy and management, Harvard School of Public Health, and Mark E. Miller, PhD, executive director, MedPAC, discussed several of the ACA's effects on Medicare. Both speakers reflected on how Medicare Advantage payment cuts, new reimbursement models, and the influx of baby boomers might affect future change in the Medicare program.

Dr Miller said that professionals should pay attention to Medicare accountable care organizations (ACOs). He described them as "organized fee-for-service models" in which providers are given incentives for meeting certain benchmarks. A variety of models have been established throughout the country, covering around 5.5 million beneficiaries. Many ACOs view themselves as an alternative to managed medical assistance programs because they believe they have strong patient engagement and lower overhead, which removes a need to recruit. Some may even begin to

assume risk, even though this technically questions the fee-for-service model.

"You now have these 3 delivery systems: FFS, ACO, MMA; they're paid differently. The benchmarks, if they have them, are different; the quality measurement is different; if they beat the benchmark, what they can do with the money is different; their regulatory burdens are different; how the beneficiary is engaged is different," he said. "The commission, at the macro level, is starting to look across all 3 of these. We have to think about rationalizing payment, risk adjustment, quality measurement, how the patient is engaged, and regulatory burden. And that is a good way to think about our agenda going forward."

Dr Baicker discussed what Medicare is doing in terms of helping to slow the spending growth. She noted 2 goals of healthcare reform, including expanding the access of care to cover uninsured, which she suggested is "easy," and slowing the healthcare spending growth, which she said is a more difficult task.

"The goal is not just to spend less on healthcare. That's actually a pretty easy goal to achieve. If we just wanted to spend less on healthcare, we would eliminate Medicare. Problem solved, we'd spend billions less every year," she quipped. "That's clearly not desirable public policy. Healthcare provides much-needed benefits to beneficiaries—eliminating health insurance or public subsidies is terrible policy."

Dr Baicker further suggested that the goal is to slow spending growth while promoting high-value care. How we do that, she said, is the "billion-dollar question." She said that while it would be nice if healthcare services came with a label that determined value, very few people in the system currently face the true cost of the healthcare they're using.

Next-Generation Data Analytics to Transform Healthcare

Keith R. Dunleavy, MD, president, CEO, and chairman of the board, Inovalon, Inc, discussed the 4 vertical components of capitated managed care. They include Medicare Advantage, managed Medicaid, commercial health insurance exchanges, and accountable care organizations (ACOs). He suggested that the 4 components have common cornerstones that make them relevant to the "data picture." Those cornerstones are risk/accuracy, clinical and quality outcomes, utilization efficiency, complexity/compliance reporting, and consumerism. He suggested that consumerism is particularly critical to success.

"Data is, at the core, something that healthcare has as an industry underleveraged compared to its peer industries [like] financial services or retail," he said. "We see that now rapidly changing."

He said "accelerated Darwinism" is forcing healthcare to change. This term is used because the theorist Charles Darwin suggested that only the strongest survive. Those who are succeeding in achieving the aforementioned cornerstones are more likely to succeed over those who do not.

"The future is data being able to predict what you should be doing with your patient population," Dr Dunleavy said. "Big data is not just large sets of data, big data is the total set of tool capabilities that allow for advancements in extracting value out of large data environments."

Marcus D. Wilson, PharmD, president, HealthCore, Inc, added that analytics are all about improving quality and affordability through empowering patients in the decision-making process with physicians. He suggested that this is possible through complete evidence development and improving the depth of understanding we have of an individual.

"It's not just about Dr Jones understanding the therapeutic condition that Ms Atkins has, but also now understanding everything about Ms Atkins, where she fits within that evidence," Dr Wilson said. He cited a study suggesting that decisions were guided by sufficient evidence only about 11% of the time.

Charles D. Kennedy, MD, MBA, CEO, Accountable Care Solutions at Aetna Inc, said he believes the underlying business model in healthcare is changing. Value-based care, he said, helps to support this transformation.

Dr Kennedy said the first thing you have to do to make value-based contracting successful is "define value." He defined it as quality over cost. The challenge is to then get all the clinical data in place, as well as to address the lack on interoperability.

Second, value-based decisions must be made on an individual level. If you don't have a way to individualize information so that people can make value-based decisions upon that information, it can limit the value of analytics. You have to find ways to capture and share information in an effective way, among different systems. Only a few companies have managed this. He also cited timeliness as another challenge for professionals.

"You're looking at populations of patients trying to glean understandings and new knowledge, but the ability to actually apply that knowledge at the point of care in real time and with appropriate context still remains something that we have a bit of development to get to." However, he suggested that the expansion of big data analytics will be valuable to clinical value-based decision making.

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This exciting addition to our AJMC Live portfolio will focus on some of the most challenging issues facing payers and providers in the treatment of a variety of infectious diseases.

This meeting promises to bring together payers, providers, patient advocates, and other key stakeholders dedicated to improving the quality of care of infectious disease patients, and will provide the ideal environment to align your brand messaging with this one-of-a-kind meeting.

This conference is just around the corner; but limited sponsorship opportunities are still remaining!

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- Improving Outcomes in Viral Hepatitis
- HCV: The Changing Treatment Landscape

THE AMERICAN JOURNAL OF MANAGED CARE®

AJMC's ACO and Emerging Healthcare Delivery Coalition: First Live Meeting Coverage

KATIE SULLIVAN

The American Journal of Managed Care hosted its very first ACO and Emerging Healthcare Delivery Coalition meeting in Baltimore, Maryland, on April 17-18, 2014. The 2-day event engaged coalition members as they discussed important issues surrounding accountable and patient-centered care delivery models.

Marketplace Overview and Real-World Perspectives


Ira Klein, MD, MBA, FACP

The opening session was presented by Ira Klein, MD, MBA, FACP, chief of staff, office of the chief medical officer, national accounts clinical sales & strategy, Aetna, Inc, and Anthony D. Slonim, MD, DrPH, CPE, FACPE, executive vice president and chief medical officer, Barnabas Health, and executive director, Barnabas Health ACO North and Central Jersey ACO.

Dr Klein opened with a discussion that analyzed the findings of a survey performed by *The American Journal of Managed Care* and Health Research & Analytics (HRA), both part of Intellisphere, LLC. The brief survey was sent to 41 ACO Coalition members, including Johnson & Johnson, Aetna, Walgreens, and the National Pharmaceutical Council. Findings centered on everything from the challenges they faced with collaboration to some of the innovative solutions they have implemented within their ACOs.

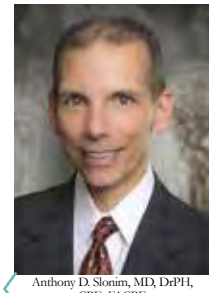
Dr Klein suggested to audience members that the survey was used as a "map" by which speakers could guide the conversation on topics that audience members had the most interest in. The poll asked Coalition members to rank, on a scale of 1 through 5, the most important topics in 4 categories:

- **Patient Experience**—Patient engagement was ranked as the most important aspect to "progress collaboration in activating patient interest to engaging them long term" (2.6/5). Patient satisfaction was ranked least important in this category by survey takers (0/5).
- **Quality**—Survey takers ranked "quality metrics" (2.7/5), followed by "enhancing care management" (2.2/5) as the top 2 important under quality topic discussions.
- **Cost/Financial**—Contracting was deemed to be the most important for members (5/5), but cost-effectiveness (2.6/5) and value-based reimbursement (2.9/5) were not far behind.
- **Data Technology**—The most significant results here were what was found to be *not* important by survey takers. This included "tracking measures" (4.2/5). Dr Klein noted that most survey takers seemed not to care about sharing data as much as they did about sharing information.

Overall, Dr Klein determined that one of the most crucial and beneficial aspects of the Coalition and of the meeting was that every life cycle of the ACO presents a variety of opportunities and challenges. With such a diverse group of members from organizations such as ACOs, pharmacies, and insurers, members are able to share their unique experiences and learn from one another.

ACOs and the Evolving Healthcare Marketplace

Anthony D. Slonim, MD, DrPH, CPE, FACPE, Barnabas Health, provided a very thorough analysis of ACOs and how they function. With an estimated one-third of care offering little to no value, Dr Slonim said that many want to know what the value proposition of an ACO is, and what it will mean for patients. The value proposition says that value is subject to quality as it relates to total costs of care. To increase value, one must improve quality or lower costs. Value decreases when quality is reduced or costs increase.


Anthony D. Slonim, MD, DrPH, CPE, FACPE

Dr Slonim explained that current care models can be chaotic in non-hospital settings. To improve managed care settings, beyond controlling costs, organizational processes must be reengineered and health-system employee roles must be clearly defined. ACO models have been perceived as a potential solution to ensuring that doctors practice better, specifically when dealing with a panel of patients.

ACOs also offer a variety of payment/reimbursement models, including shared savings (both 1-sided and 2-sided risk models), bundled payments, partial capitation, and global payments. An ACO's structured network can allow physicians to take risks with

payment models where they might not otherwise be able to do so in other care delivery settings.

As an ACO matures, its priorities will change, as will the opportunities within the industry. Dr Slonim suggested that many within ACOs simply are "learning as they go." Additionally, he recommended that the doctor-patient relationship remain front and center in all that ACOs do. As the healthcare landscape evolves, conversations amongst health professionals such as those at the ACO Coalition meeting will be needed to determine the best path to successful ACO management.

Healthcare Delivery Implementation Strategies

Ed Cohen, PharmD, FAPhA, Walgreens, presented a session that focused on WellTransitions, a Walgreens program which "bridges gaps in care by supporting patient recovery through several hospital-to-home transition steps." These steps aim to reduce patient readmissions, increase patient satisfaction, and lower the costs of overall care.

Patients who participated in the program were:

- 46% less likely to have an unplanned readmission
- 26% less likely to be readmitted with non-CMS–targeted conditions, while those with CMS–targeted conditions were 55% less likely to be readmitted
- 44% less likely to be readmitted under age 65 years, while those age 65 years or older were 48% less likely to be readmitted.

Dr Cohen provided a study which took place at DeKalb Medical Group, which partnered with Walgreen pharmacists to increase patient education about their medication following a hospital admission. The collaborative pharmacist-hospital relationship enabled DeKalb to improve its Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) score, which monitors patient satisfaction, just 90 days after it was initiated. In fact, they reported a 26% relative increase in HCAHPS domain score. Dr Cohen stressed that Walgreens functions not as a vendor at DeKalb, but as a department of hospital system operations.

"We don't want to be looked at as an outside vendor, we want to be looked at as another department in the hospital, so we work really hard to integrate, we have our staff go through all of the orientation as though they were an employee at the hospital, so we are really proud about that," said Dr Cohen.

With nearly 1 in 3 patients nonadherent to the medications that manage their disease, health systems require treatment programs supported by a collaborative team to ensure patient wellness and healthy outcomes.

ACOs: Key Functions & PCMH Support

Paige Cooke, National Committee for Quality Assurance, defined an ACO as a provider-based governing body responsible for the provision of resources to meet the triple aim. It is supported by stakeholders that include payers, purchasers, pharmacy, and ambulatory care sites. The foundation of building any strong ACO model, she said, is the patient-centered medical home (PCMH).

She provided 2 testimonials that described the ACO experience. The first group was Bon Secours Virginia Medical Group. Bon Secours achieved savings in the first year of participation in the CMS Medicare Shared Savings Program, with enterprise-wide electronic medical record use, early adoption of the medical home model, and other patient engagement initiatives.

She also shared the example of the Montefiore Medical Center in New York, a group which also integrated patient engagement as well as implementing "innovative nurse-driven interventions that supported patient outcomes and experience."

Ms Cooke noted that the PCMH model is the fastest growing delivery system innovation in the United States. As of March 2014, there were 7118 PCMH sites throughout the country. The National Committee for Quality Assurance (NCQA) ranks several PCMH quality standards on a score-based scale. PCMHs can help:

- Enhance access and continuity
- Encourage team-based care
- Identify and manage patient populations
- Plan and manage care
- Track and coordinate care
- Highlight performance measurement and quality improvement.

In 2014, there were various quality-standard updates to team-based care, behavioral health, and measuring costs. Ms Cooke noted that ACOs can provide valuable resources to support the delivery of patient-centered primary care including access and coordination of patient management.

"One of the most important concepts that ACOs need to embrace is that the patient-centered medical home model is an evolutionary one, it's one that is designed to align with the growth and evolution of what is happening in health reform," said Ms Cooke. She praised NCQA's PCMH Recognition Program, which provides accolades to those ACOs and PCMHs which demonstrate success with implementing evidence-based practices within their health systems.

Real-World Best Practices: Financial Structures, Quality Measurement, Medication Management

Kelly Conroy, Palm Beach Accountable Care Organization (PBACO), LLC, provided insight into experience with managing patients at the PBACO. CMS accepted the group on July 1, 2012. As with other accountable care models, PBACO focuses on a triple aim of care, which includes improving the patient experience, improving population health, and decreasing per capita healthcare costs. Additionally, as a member of CMS's Medicare Shared Savings Program, they are able to be rewarded for achieving specific quality and cost-saving benchmarks.

Ms Conroy noted that initial implementation was difficult. They had to put pressure on the community stakeholders, like hospitals,

to buy into the accountable care model. It was difficult to convince providers and doctors that transitioning from the fee-for-service model to and ACO was not only possible, but the financially responsible and logical choice. It was important to reach out to physicians and let them know that their contributions were making a difference once they agreed to join PBACO's efforts.

"We created this outside component of competition with our community stakeholders pushing on the doctors, and eventually, the doctors started answering the phones, and then eventually, the doctors started to appoint a point of contact in their office to get it," said Ms Conroy. "And then, after they made $22 million or saved $22 million, then they got really interested in doing things."

They quickly discovered that patient satisfaction was key to improving outcomes. Even something as a simple as a follow-up call was found to improve the patient experience. As a "low-tech" ACO, PBACO still found ways to engage patients in their care plans. She provided the example of their In-Form-A-Doc document which allows the patient to document health concerns and questions in between visits. She noted that it is important to keep track of patients and to treat the same patients prospectively assigned in the beginning of year as at the end of a tracking period. Still, patient engagement and outcomes can be improved, even solutions are low-tech.

"Patient engagement: I see a lot of ACOs went really high-end; patient portals, all kinds of patient engagements. We went very, very low end," said Ms Conroy. "We used the Medicare opt-out letter that you have to send to patients as a good way to start talking to the patients, and it turns out once the physician had that conversation with the patient, the patient wants to save Medicare, wants to work closer with the doctor, and it made them feel good."

Achieving Quality in ACOs: Are They Ready to Maximize the Value of Pharmaceuticals in Patient Care?

Kimberly Westrich, MA, director for health services research, National Pharmaceutical Council (NPC), said ACOs intertwine quality and cost-effectiveness like yin-yang.

"We're moving to an ACO world, a value-based world," she said, and changing to a different reimbursement model provides the opportunity to develop a strategic framework "where lowering costs and raising quality can really be merged."

There is also a large opportunity for pharmaceuticals, and the collaboration between the American Medical Group Association, Premier Health Alliance, and NPC has been focusing on just that. These partners seek to develop and implement a framework that will define the role of pharma in ACOs, and how that will aid in the success of meeting financial targets and quality benchmarks. They have considered several recommendations which include a reduction of the "one-size-fits-all" mind-set in medication therapy management.


Kimberly Westrich, MA

"We heard about silos this morning, that's the way the system is currently built," said Ms Westrich. "One part of really optimizing medication value is getting out of that silo world, thinking about the resources as being a pooled thing that we can access, not silos; medications are something that in many conditions can help cost offsets."

Aside from de-siloing care systems, Ms Westirch recommended moving away from the one-size-fits-all approach by using composite risk to identify the patients who may require an intervention, and putting into place a system of checks and balances to ensure that patients—especially those with chronic diseases—are receiving optimal care. These quality checks will also certify that there are not incentives that inappropriately lower costs.

Health providers should also assess how "ready" pharmaceutical companies are to enter an ACO arrangement. After identifying existing gaps in care, they can develop a partnership with pharma companies that improve patient outcomes. Pharmacists will ultimately play an important role in many ACOs' success if the infrastructure can be built.

How to Decrease Cost While Improving Quality and Safety: Medication Therapy Disease Management Program

As a pharmacist, Michael A. Evans, BS, RPh, said that his organization—Geisigner Health System—has taken a risk by implementing pharmacist-run disease management clinics. Mr Evans suggested that clinical pharmacists are the "drug experts" who can teach pharmacology to everyone in a system, including physicians, physician assistants, and nurse practitioners. They also work with physicians and utilize electronic health records (EHRs) to coordinate patient care. He said that while there remains a challenge with coordinating care with retail pharmacies, Geisigner has already begun to explore ways to close that gap.

The organization's medication therapy disease management program (not to be confused with CMS's definition of medication therapy management, or MTM) includes 51 pharmacists in 47 locations. It focuses on anemia management, pain therapy, heart failure, geriatrics, and several other conditions.

"In our process—prior to the patients being referred into the program—their adherence to medications was about 50% of the time; the normal population that we see across the country," said Mr Evans. "But once we start managing the patient, we're touching them, we get the patient on a therapy that they accept, we get the patient on a therapy that's not causing them side effects, [and] we get them on a therapy that the patient is willing to accept the burden of the cost. Patients now will become adherent to the therapy 81% of the time."

Pharmacists can improve adherence rates and increase medication cost savings by having a role in a patient's continuum of care. For instance, he said, a patient may be prescribed a medication, but there is no way to ensure they are taking it as prescribed. Patient questionnaires and EHR documentation are just some of the ways that pharmacists and providers can monitor patient activity and prevent adverse drug reactions.

"Remember, we're touching these patients 1.44 times per month. Primary care, they're not touching that often, or the specialist, they're not touching the patient that often, nor do we want them to be touching them that often, right? We want the physicians practicing at the top of their license, seeing patients and diagnosing conditions, referring the patient over to the pharmacist for their care. Patients love it; you can see the satisfaction. Satisfaction surveys are greater than 95%," said Mr Evans.

Overall, Mr Evans said that the pharmacy and the pharmacist are integral resources in accountable care models. Data integration and management, combined with effective communication, will be key as well.

Accountable Care Organization Best Practices in Specialty Pharmacy

Michael Baldzicki, CRCM, executive vice president of industry relations and advocacy for Armada Health Care, said there are a variety of innovative opportunities for collaboration with new delivery models like ACOs. Specialty pharmacy is a new segment for most participants, but it is quickly becoming an area of strategic focus. Technology has played a large role in boosting the importance of specialty pharmacies, especially as biosimilars may impact cost utilization management techniques.


Michael Baldzicki, CRCM

"Specialty pharmacy has evolved from a more lick-and-stick game to now a service-oriented program initiative, so a lot of these specialty pharmacies are trying to prove their value stake not only to the payer, but also to the manufacturer, and really hone in on key therapeutic areas, saying, 'I'm going to be good at these 4 things, or maybe 1 thing because I'm a local specialty pharmacy and I'm going to be really good at hep C," said Mr Baldzicki. "And that's where they're sitting, kind of putting their anchor, to really put their stake in the game, not only get into the payer network, but work with local physician groups."

There are a variety of opportunities for specialty pharmacy. One is that they have the capability to share and integrate data analytics. They also can offer and integrate disease management therapy programs. They can even enter risk-sharing agreement contracts with ACOs. By collaborating, specialty pharmacies can improve outcomes for ACOs, including in hospital readmissions, quality metrics, and overall adherence.

Mr Baldzicki noted that health reform and other shifts in care will impact the exact partnership that specialty pharmacy will have in accountable care models.

"A specialty pharmacy model really entails their relationship with the physician. Most physicians have about 2 or 3 likable specialty pharmacies that they really refer to, and then, patient care management programs and guidelines and protocols all focus around cost," he said. "So again, there's a lot of opportunity where specialty pharmacies can come into the game and really integrate… it's just how, when, and where."

Our Healthy Perspective: Healthcare Transformation Through Accountable Care

Bob Kropp, MD, MBA, CHIT, regional medical director for Aetna, put it simply: the status quo cannot be sustained. The current health system is wasteful due to disorganization, fragmentation, and incoordination. The Institute of Medicine has identified drivers of the waste inside the system, and those include unnecessary services, higher-priced services that are necessary based on site of service, duplicate care, and administrative services.

He likened the patient experience with the health system to going through a maze where no 2 pathways lead to the same outcome. Payers, Dr Kropp said, are able to provide solution that can make this system work better.

To make changes, providers must be incentivized to make decisions that will allow the system to function differently than it does today. Plan members must also be incentivized and be provided with opportunities to make different choices within the healthcare system.

"Our mission is to create an environment, a relationship with our ACOs, that addresses the drivers of waste within the system, and allow you folks to do the things that we've been hearing about all day today that are the right things to make the system work better," said Dr Kropp.

Aetna's strategy focuses on 4 main areas:

- Creating an environment where incentives are aligned
- Identifying inconsistent delivery of care and unnecessary services
- Addressing episodic and reactive care
- Technology, especially as it relates to provider-payer communication.

"So our strategy involves incentives, information, different kinds of interventions, and innovative technology that we offer in various combinations. And the combination or the solution that we offer is really based on the concept of collaboration," said Dr Kropp. "Rather than coming in with a one-size-fits-all kind of strategy, which you usually associate with managed care, our philosophy is that we have recognized that the community is at different stages of maturation, has different needs at different times. Our overarching philosophy here is to be a partner wherever the physician organization is."

To learn more or sign up for the AJMC's ACO and Emerging Healthcare Delivery Coalition, email: ACO_Coalition@ajmc.com

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Coalition Goals

- Gather insights into current "real-world" best practices and strategies for care management interventions
- Gather insights into current ACO physician challenges and best practices in executing successful ACOs and healthcare models, including consideration of the impact of incentive structures for ACO providers—implementation of strategies and measurement
- Identify operational lessons and best practices, including key components of transition-of-care programs; patient and physician engagement; quality measures; formulary decisions; and ACO protocol development
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