The Effects of Ranolazine on Hemoglobin A_{1c} in a Veteran Population

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In this observational study, ranolazine was associated with a statistically significant decrease in HbA_{1c} among veterans with diabetes mellitus.

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Diabetes mellitus (DM) is a risk factor for cardiovascular disease(CVD).[1-4] Death rates from heart disease are 2- to 4-times higher among adults with DM compared with those of adults without DM. In the US, it is estimated that 21.1 million adults have diagnosed DM, 8.1 million adults have undiagnosed DM, and 80.8 million adults have prediabetes.[3] The American Heart Association has identified an untreated fasting blood glucose level < 100 mg/dL as a component of ideal cardiovascular health.[3]

Although the use of antidiabetic agents has been shown to reduce the risks of microvascular complications among patients with DM, a cardiovascular benefit has not been consistently demonstrated with all available agents, and some used in the treatment of DM are associated with cardiovascular harm.[5] In addition, some cardiovascular medications may contribute to the development of DM or may mask the symptoms of hypoglycemia.[6] Given the risk for CVD among patients with DM, a medication with utility in both DM and CVD could be beneficial.

EVIDENCE FOR USE OF RANOLAZINE

Ranolazine is indicated for the treatment of chronic angina.[7] In clinical trials, ranolazine also was found to decrease hemoglobin A_{1c} (HbA_{1c}).[8-15] The possible mechanisms for lowering HbA_{1c} with ranolazine include preservation of pancreatic β-cells and an increase in glucose-dependent insulin secretion.[6] The most common adverse effects associated with ranolazine include dizziness, headache, constipation, and nausea.[7]

Ranolazine has been shown to be efficacious and safe in the reduction of angina symptoms among patients with and without DM.[8-12] In addition to improving symptoms of angina, studies have demonstrated a reduction in HbA_{1c} among patients taking ranolazine.[9,13-15] In an open-label extension of the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial, ranolazine 750 mg twice daily and 1,000 mg twice daily led to a greater reduction in HbA_{1c} when each was compared with placebo (-0.48% HbA_{1c}, P = .008; and -0.70% HbA_{1c}, P = .001, respectively).[9]

Among the 5,576 patients enrolled in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes—Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial with a baseline HbA_{1c}, ranolazine significantly reduced HbA_{1c} at 4 months when compared with placebo among patients with and without DM.[13] In addition, patients with DM who were treated with ranolazine were more likely to achieve a HbA_{1c} < 7% at 4 months when compared with placebo (59% vs 49%; P < .001). Ranolazine was not found to increase the incidence of hypoglycemia.

A subgroup analysis of MERLIN-TIMI 36 evaluated the effects of ranolazine compared with those of placebo on fasting plasma glucose and HbA_{1c} in patients with moderate DM (HbA_{1c} ≥ 6% but < 8%, fasting plasma glucose < 250 mg/dL) and severe DM (A_{1c} ≥ 8%, fasting plasma glucose 150-400 mg/dL).[14] A significant reduction in HbA_{1c} with ranolazine in addition to standard of care antidiabetes treatment was observed among both groups. The placebo-corrected decrease in HbA_{1c} in the moderate DM group was 0.28% (95% confidence interval [CI] -0.55 to 0;

P = .045) and in the severe DM group was 0.59% (95% CI -0.99 to -0.20; P < .001).

In a trial designed to evaluate change in HbA_{1c} in patients taking ranolazine 1,000 mg twice daily compared with that of placebo, ranolazine led to a greater decrease in HbA_{1c} compared with that of placebo (placebo corrected change in HbA_{1c} -0.56%, P = .001).[15] In addition, a higher percentage of patients achieved HbA_{1c} < 7% at 24 weeks in the ranolazine group compared with that of placebo (41.2% vs 25.7%; P = .001). No patient experienced severe hypoglycemia or had documented hypoglycemia in this study.

These trials suggest that ranolazine, in addition to decreasing anginal events, is potentially beneficial in achieving better control of DM. However, more studies are needed to determine this benefit. In addition, no trials have examined the 500-mg twice daily dose of ranolazine in HbA_{1c} reduction.

The purpose of this study was to evaluate the change in HbA_{1c} among veterans with DM after the initiation of ranolazine. The study compared the percentage of veterans achieving HbA_{1c} < 7% or < 8% after initiation of ranolazine with the baseline, to determine whether there is a dose-related change in HbA_{1c} among different ranolazine regimens and to determine whether there is a change in the incidence of hypoglycemia after the initiation of ranolazine.

METHODS

This was a multicenter, retrospective study. The institutional review board and research and development committee for 3 Veterans Affairs medical centers (VAMCs) approved this study and waived informed consent. Additionally, this study was approved for access to national patient information through the Corporate Data Warehouse (CDW).

Subjects were eligible for inclusion in this study if they were aged ≥ 18 years, had a diagnosis of type 2 DM, and received their first prescription of ranolazine at a VAMC from January 1, 2008 through March 31, 2015. Exclusion criteria included subjects with no baseline HbA_{1c} (defined as the HbA_{1c} result closest to the ranolazine initiation date and within 90 days before to 14 days after ranolazine initiation), no follow-up HbA_{1c} (defined as the first HbA_{1c} result within 60 to 180 days after the ranolazine initiation date), any change to their DM medication regimen during the follow-up period, or who discontinued ranolazine prior to collection of the follow-up HbA_{1c}.

Table 1 Baseline Characteristics (n = 66)

Variable	Total
Age, mean (SD), y	73.4 (9.3)
Male, No. (%)	66 (100)
HbA_{1c}, mean (SD), %	6.9 (0.9)
Diabetes mellitus agents, No. (%)	
Average No. of agents	1.3
Metformin	33 (50)
Sulfonylurea	24 (36.4)
DPP-4 inhibitor	0 (0)
GLP-1 agonist	0 (0)
Thiazolidinedione	1 (1.5)
Insulin glargine	3 (4.5)
Insulin detemir	0 (0)
Insulin NPH	15 (22.7)
Insulin 70/30	5 (7.6)
Insulin regular	5 (7.6)
Insulin aspart	3 (4.5)
Interacting medication (diltiazem, erythromycin, fluconazole, verapamil), No. (%)	0 (0)
Ranolazine dose, No. (%)	
500 mg twice daily	52 (78.8)
1,000 mg twice daily	14 (21.2)
Ranolazine possession ratio, %[a]	80.4

Abbreviations: DPP-4, dipeptidyl pedtidase-4; GLP-1, glucagon-like peptide-1; $HbA_{1C,}$ hemoglobin A_{1C}; NPH, neutral protomine Hagedorn.

[a]Total number of days patient was in possession of ranolazine between initiation date and follow-up HbA_{1c} ÷ total number of days between ranolazine initiation date and follow-up HbA_{1c}.

Table 2 Change in HbA_{1c}

	Baseline, %	Follow-up, %	Change in HbA_{1c}, %	*P* Value
All doses ranolazine (n = 66)	6.9	6.6	-0.3	< .001
Ranolazine 500 mg twice daily (n = 52)	6.9	6.6	-0.3	.001
Ranolazine 1,000 mg twice daily (n = 14)	6.9	6.5	-0.4	.09

Abbreiviation: HbA_{1c}, hemoglobin A_{1c}.

Table 3 HbA_{1c} Goals Achieved

Variable	Baseline (Pre-Ranolazine Initiation), No. (%)	Follow-up (Post-Ranolazine Initiation), No. (%)	*P* Value
All doses ranolazine (n = 66)			
HbA_{1c} < 7%	30 (45.5)	49 (74.2)	< .001
HbA_{1c} < 8%	56 (84.8)	60 (90.9)	.221
Ranolazine 500 mg twice daily (n = 52)			
HbA_{1c} < 7%	22 (42.3)	38 (73.1)	.001
HbA_{1c} < 8%	43 (82.7)	47 (90.4)	.371
Ranolazine 1,000 mg twice daily (n = 14)			
HbA_{1c} < 7%	8 (57.1)	11 (78.6)	.248
HbA_{1c} < 8%	13 (92.8)	13 (92.8)	NS

Abbreiviations: HbA_{1c}, hemoglobin A_{1c}; NS, not significant.

Data were collected from the electronic health record (EHR) for each subject from 6 months prior to the ranolazine initiation date through 6 months after the ranolazine initiation date. The ranolazine initiation date was defined as the date ranolazine was picked up in person at a VAMC pharmacy or 7 days after the date filled for medications sent by mail. Progress notes, laboratory values, and pharmacy records were evaluated for this time frame, and the following data were collected: ranolazine dose and initiation date, ranolazine possession ratio (total numbers of days patient was in possession of ranolazine between initiation date and follow-up HbA_{1c} divided by total number of days between ranolazine initiation date and follow-up HbA_{1c}), baseline HbA_{1c}, follow-up HbA_{1c}, hypoglycemia incidence before and after the initiation of ranolazine, concomitant DM medications and interacting medications, patient age and sex, and creatinine clearance at baseline.

The primary endpoint of this study was the change in HbA_{1c} after ranolazine initiation. The secondary endpoint was the percentage of study subjects achieving HbA_{1c} < 7% and < 8% before and after the initiation of ranolazine.

To achieve 80% power to detect a change in HbA_{1c} of 0.4%, a sample size of 52 patients was required. For the primary endpoint, a paired *t* test was used to test for statistical significance. The McNemar test was used to evaluate for a significant change in subjects achieving an HbA_{1c} < 7% and HbA_{1c} < 8% with the initiation of ranolazine.

RESULTS

A total of 523 patients were evaluated for study inclusion, of which 66 patients were included (Figure). The most common reasons for exclusion included no HbA_{1c} at baseline and changes to the DM medication regimen during follow-up. At baseline, the average age was 73.4 years, the patient population was 100% male, patients took an average of 1.3 antihyperglycemic agents at baseline, and the average HbA_{1c} was 6.9%. About 80% of patients were prescribed ranolazine at a dose of 500 mg twice daily (Table 1).

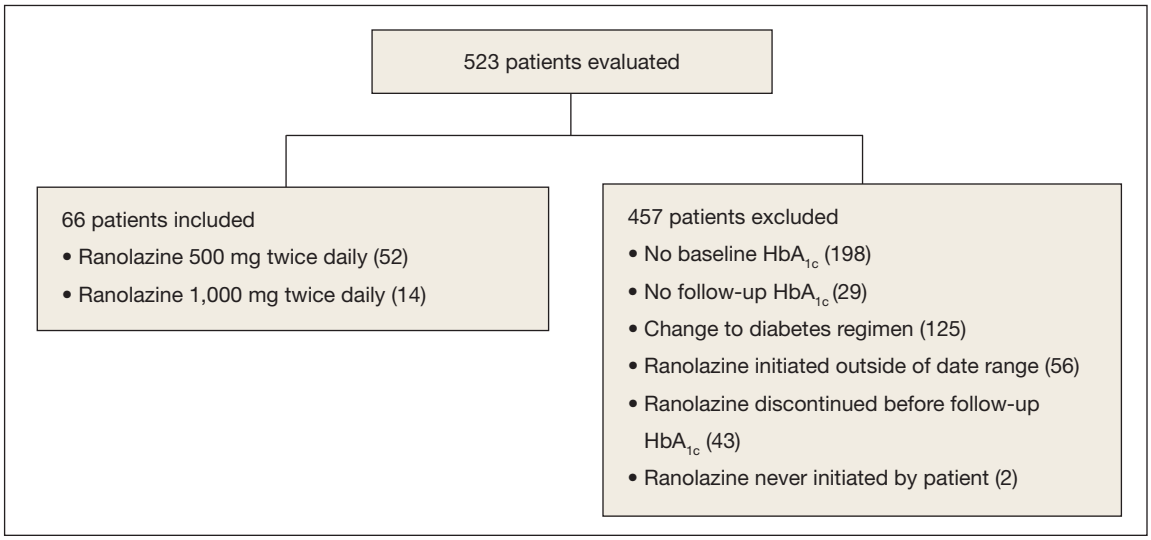
Ranolazine at any dose was associated with a change in HbA_{1c} of -0.3% ($P < .001$). In addition, the percentage of veterans achieving HbA_{1c} < 7% was significantly higher after the initiation of ranolazine ($P < .001$). More veterans achieved HbA_{1c} < 8% after the initiation of ranolazine, although this result was not statistically significant ($P = .22$).

A dose of 500 mg ranolazine twice daily also was associated with a significant decrease in HbA_{1c} by 0.3% ($P = .001$). A significant increase in veterans achieving HbA_{1c} < 7% after ranolazine initiation was observed (42.3% before ranolazine initiation vs 73.1% after ranolazine initiation; $P = .001$), and a nonsignificant increase in veterans achieving HbA_{1c} < 8% was observed (82.7% before ranolazine initiation vs 90.4% after ranolazine initiation, $P = .37$).

At a dose of 1,000 mg twice daily, a 0.4% decrease in HbA_{1c} was observed. However, this result was not found to be statistically significant ($P = .09$), and the study was underpowered to detect a significant change in HbA_{1c} at this dose. A nonsignificant increase in veterans achieving HbA_{1c} < 7% was observed after ranolazine initiation (57.1% before ranolazine initiation vs 78.6% after ranolazine initiation, $P = .25$), but no difference was found in veterans achieving HbA_{1c} < 8%.

Hypoglycemia was not reported in a ma-

Figure Inclusion and Exclusion Criteria



Abbreviation: HbA_{1c}, hemaglobin A_{1c}.

jority of study patient progress notes; thus, it was not evaluated further.

DISCUSSION

In this study of a veteran population, ranolazine was associated with an HbA_{1c} decrease of 0.3%. This change is less than that observed in previous studies, which may be related to a lower baseline HbA_{1c} for the patients in this study. In addition, a greater percentage of veterans achieved an $HbA_{1c} < 7\%$ after initiation of ranolazine compared with that of the baseline.

To the authors' knowledge, this is the first study evaluating ranolazine and HbA_{1c} in a veteran population. It also is the first study to demonstrate an association between HbA_{1c} lowering and ranolazine at a dose of 500 mg twice daily. These results suggest that in patients with chronic angina and type 2 DM, ranolazine could potentially play a dual role in therapy.

Limitations

The authors recognize several limitations in this study. Given its observational design, it cannot be definitively concluded that the decrease in HbA_{1c} was due to the initiation of ranolazine. While excluding patients with changes to their antidiabetic medication regimen was done in an effort to minimize confounding factors, it is possible that other factors, such as lifestyle, also could explain changes in HbA_{1c}. It is possible that changes to the DM medication regimen were made but not documented in the EHR. In addition, information on hypoglycemia was not readily available; thus, the safety of ranolazine among patients with DM could not be evaluated fully. Finally, the patient population characteristics may limit external validity.

CONCLUSION

In this observational study, ranolazine was associated with a statistically significant decrease in HbA_{1c} among veterans with DM, which supports previously published literature.[9, 13-15] However, no randomized controlled trials have been performed specifically studying the impact of ranolazine on HbA_{1c} among patient with DM. Ideally, future prospective, randomized placebo-controlled studies will take place to further evaluate the association between ranolazine use and HbA_{1c} lowering.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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tigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

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