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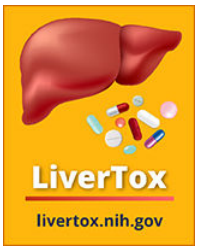


Acarbose

Updated: January 10, 2021.

OVERVIEW

Introduction

Acarbose is an alpha glucosidase inhibitor which decreases intestinal absorption of carbohydrates and is used as an adjunctive therapy in the management of type 2 diabetes. Acarbose has been linked to rare instances of clinically apparent acute liver injury.

Background

Acarbose (ay' kar bose) is an inhibitor of intestinal alpha glucosidase, an enzyme responsible for digestion and absorption of starch, disaccharides and dextrin. Acarbose is a complex oligosaccharide produced in bacteria that has activity against glucoamylase, sucrase, maltase and isomaltase, intestinal brush border glucosidases. The inhibition of the glucosidase activity blocks the breakdown of starch and disaccharides to absorbable monosaccharides, leading to delay in glucose absorption and a degree of carbohydrate malabsorption which results in a blunting of the postprandial rise in blood glucose. Acarbose was approved for use in the United States in 1995 and was the first alpha glucosidase inhibitor introduced into clinical practice. A similar alpha glucosidase inhibitor, miglitol, was approved the following year. The current indications for acarbose are for management of glycemic control in type 2 diabetes used in combination with diet and exercise, with or without other oral hypoglycemic agents or insulin. Acarbose is available generically and under the brand name Precose in tablets of 25, 50 and 100 mg. The typical initial dose in adults is 25 mg with each meal (with the first bite), followed by a gradual increase to a maximum of 100 mg three times daily. Acarbose causes malabsorption and gastrointestinal side effects of flatulence, diarrhea and abdominal boating are not uncommon. More severe but rare adverse events include skin rash and pneumatosis cystoides intestinalis.

Hepatotoxicity

In several large clinical trials, serum enzyme elevations above 3 times the upper limit of normal were more common with acarbose therapy (2% to 5%) than with placebo, but all elevations were asymptomatic and resolved rapidly with stopping therapy. These studies reported no instances of clinically apparent liver injury. Subsequent to approval and with wide clinical use, however, at least a dozen instances of clinically apparent liver injury have been linked to acarbose use. The liver injury typically arises 2 to 8 months after starting therapy and is associated with a hepatocellular pattern of serum enzyme elevations with marked increases in serum ALT levels, suggestive of acute viral hepatitis. Immunoallergic features and autoantibody formation are not typical. While most cases are mild, some are associated with marked jaundice and cases with a fatal outcome have been reported to the sponsor. No cases of chronic liver injury or vanishing bile duct syndrome have been linked to acarbose use, and most large series of cases of drug induced liver injury and acute liver failure have not identified

cases due to acarbose. Rechallenge has been carried out in several instances and resulted in recurrence with a shortening of the time to onset.

Likelihood score: B (rare but likely cause of clinically apparent liver injury).

Mechanism of Injury

The cause of liver injury during acarbose therapy is not known. Acarbose is an oligosaccharide of microbial origin and is minimally absorbed (0.5% to 1.7%), so that systemic toxicity and liver injury were not expected and remain unexplained. Liver injury from acarbose is clearly idiosyncratic and may relate to an immunological reaction to the bacterially derived oligosaccharide molecule or to alterations in the microbiome and absorption of bacterial products.

Outcome and Management

The liver injury caused by acarbose has generally been mild and self-limited with the injury resolving rapidly once acarbose is discontinued. Cross sensitivity with other hypoglycemic agents has not been described. Furthermore, liver injury has not been described in patients taking the other currently available alpha glucosidase inhibitor, miglitol. Recurrence of injury with reintroduction of acarbose has been reported and should be avoided.

Drug Class: Antidiabetic Agents

Other Drugs in the Subclass Alpha Glucosidase Inhibitors: Miglitol

CASE REPORT

Case 1. Acute hepatocellular injury due to acarbose.(1)

A 57 year old woman with type 2 diabetes developed nausea, right upper quadrant pain, dark urine and jaundice 2 months after starting acarbose (50 mg three times daily before meals). She was taking no other medications for diabetes, but had been on a laxative (cyclobutyrol) intermittently for several years. She had no history of liver disease or drug reactions, had no risk factors for viral hepatitis and did not drink alcohol. Examination showed jaundice and hepatic tenderness, but no fever or rash or signs of chronic liver disease. Laboratory results demonstrated hyperbilirubinemia (3.8 mg/dL) and marked elevations in serum aminotransferase levels (ALT 1580 U/L, AST 1090 U/L), with minimal increase in alkaline phosphatase (220 U/L). Tests for acute hepatitis A and B, cytomegalovirus and Epstein Barr virus infection were negative as were autoantibodies. An abdominal ultrasound was normal. Acarbose was discontinued and she improved within the next 10 days (Table). In follow up, all liver tests had returned to normal and she later tolerated glipizide without evidence of liver injury.

Key Points

Medication:	Acarbose (150 mg daily)
Pattern:	Hepatocellular (R=~20)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 months
Recovery:	5 weeks
Other medications:	Cyclobutyrol

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
2 months	0	1580	220	3.8	Acarbose stopped
	4 days	1344	217	1.9	
	10 days	638	154	1.2	
3 months	21 days	91	93	0.9	
4 months	2 months	34	161	0.5	Started on glipizide
Normal Values		**<42**	**<115**	**<1.2**	

Comment

Acarbose therapy has been linked to rare instances of an acute hepatitis-like injury arising 2 to 8 months after starting treatment. This case is typical of the injury described, with marked elevations in serum aminotransferase levels and mild jaundice, rapid improvement on stopping acarbose and lack of cross sensitivity with other antidiabetic medications. Several cases of recurrence of liver injury after reexposure have been described making it likely that the injury is idiosyncratic.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Acarbose – Generic, Precose®

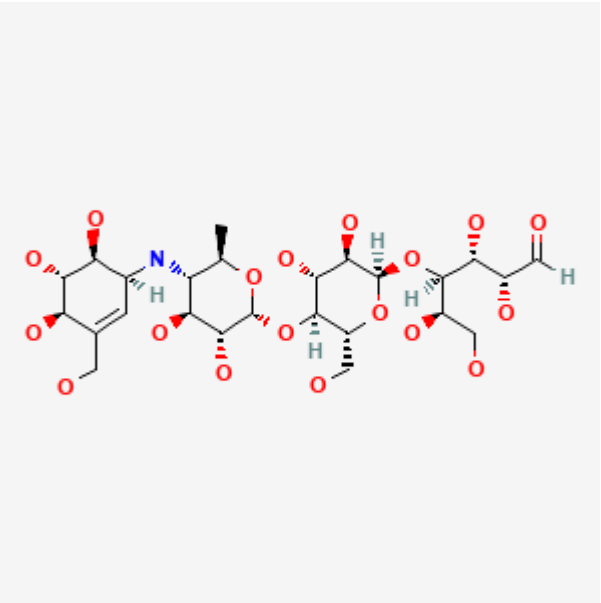
DRUG CLASS

Antidiabetic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Acarbose	56180-94-0	C25-H43-N-O18	

CITED REFERENCES

1. Diaz-Gutierrez FL, Ladero JM, Diaz-Rubio M. Acarbose-induced acute hepatitis. Am J Gastroenterol. 1998;93:481. PubMed PMID: 9517669.

ANNOTATED BIBLIOGRAPHY

References updated: 10 January 2021

Zimmerman HJ. Oral hypoglycemic agents and other diabetes therapy. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott,1999: pp. 575-9.

(Textbook of hepatotoxicity published in 1999 mentions that several instances of serum enzyme elevations and at least two cases of liver injury with jaundice have been linked to acarbose use).

De Marzio DH, Navarro VJ. Alpha-glucosidase inhibitors. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 529-30.

(Review of hepatotoxicity of drugs for diabetes mentions that acarbose has been implicated in cases of liver injury that occur 2-12 months after starting and are typically hepatocellular and resolve rapidly upon stopping).

Powers AC, D'Alessio D. Therapy of diabetes. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 863-86.

(Textbook of pharmacology and therapeutics).

Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, Ross SA, Ryan EA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Ann Intern Med. 1994;121:928–35. PubMed PMID: 7734015.

(Controlled trial of adding acarbose vs placebo to standard therapies for 1 year in 354 patients with diabetes; side effects were mild and largely gastrointestinal; "doses of acarbose as large as 200 mg three times daily had no toxic effect according to results of hematologic and biochemical profiles including liver function tests").

Coniff RF, Shapiro JA, Seaton TB. Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus. Arch Intern Med. 1994;154:2442–8. PubMed PMID: 7979840.

(Controlled trial of acarbose vs placebo in 212 obese subjects with diabetes treated for 36 weeks; ALT elevations occurred in 9% of acarbose vs 2% of placebo recipients, but no patient had symptoms and abnormal values resolved rapidly with stopping therapy).

Coniff RF, Shapiro JA, Seaton TB, Bray GA. Multicenter, placebo-controlled trial comparing acarbose (BAY g 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. Am J Med. 1995;98:443–51. PubMed PMID: 7733122.

(Controlled trial of acarbose vs placebo with and without tolbutamide in 290 patients with diabetes; while overall rates of ALT elevations were similar with and without acarbose, elevations >3 times ULN occurred in 5 patients [4%] on acarbose and none on placebo; all abnormalities were reversible with discontinuation of treatment).

Andrade RJ, Lucena MI, Rodríguez-Mendizábal M. Hepatic injury caused by acarbose. Ann Intern Med. 1996;124:931. PubMed PMID: 8610937.

(65 year old woman developed malaise followed by jaundice 2 months after adding acarbose to chronic glyburide therapy [bilirubin 9.9 mg/dL, ALT 690 U/L, Alk P 221 U/L], resolving within few months of stopping).

Coniff R, Krol A. Acarbose: a review of US clinical experience. Clin Ther. 1997;19:16–26. PubMed PMID: 9083705.

(Review of safety of acarbose based on results from 1108 patients treated for an average of 6 months; most common adverse events were gastrointestinal pain, diarrhea and flatulence; rates of ALT elevations were no different than with placebo).

Carrascosa M, Pascual F, Aresti S. Acarbose-induced acute severe hepatotoxicity. Lancet. 1997;349:698–9. PubMed PMID: 9078205.

(40 year old woman developed jaundice 2 months after adding acarbose to glyburide therapy [bilirubin 11.0 mg/dL, ALT 2350 U/L, Alk P 325 U/L], resolving within 3 months of stopping and ALT elevations developing within a week of restarting).

Diaz-Gutierrez FL, Ladero JM, Diaz-Rubio M. Acarbose-induced acute hepatitis. Am J Gastroenterol. 1998;93:481. PubMed PMID: 9517669.

(57 year old woman developed jaundice 2 months after starting acarbose [bilirubin 3.8 mg/dL, ALT 1580 U/L, Alk P 220], resolving within 2 months of stopping: Case 1).

Fujimoto Y, Ohhira M, Miyokawa N, Kitamori S, Kohgo Y. Acarbose-induced hepatic injury. Lancet. 1998;351:340. PubMed PMID: 9652620.

(Brief descriptions of 3 women, ages 52 to 62 years, with hepatic injury arising within 2.5-8 months of starting acarbose, one with jaundice [bilirubin 0.6-4.5 mg/dL, ALT 907-1837 U/L, Alk P not given], biopsies showing hepatitis-like injury, resolving within 1 month of stopping).

Andrade RJ, Lucena M, Vega JL, Torres M, Salmerón FJ, Bellot V, García-Escaño MD, et al. Acarbose-associated hepatotoxicity. Diabetes Care. 1998;21:2029–30. PubMed PMID: 9802764.

(45 year old man and 54 year old woman had onset of liver injury 5 and 6 months after starting acarbose [bilirubin normal and 4.7 mg/dL, ALT 153 and 2556 U/L, Alk P normal and 174 U/L], resolving within a few months of stopping).

Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes Care. 1999;22:960–4. PubMed PMID: 10372249.

(Controlled trial of acarbose vs placebo for up to 3 years in 3309 patients with diabetes; side effects and ALT results were not discussed).

Gentile S, Turco S, Guarino G, Sasso FC, Torella R. Aminotransferase activity and acarbose treatment in patients with type 2 diabetes. Diabetes Care. 1999;22:1217–8. PubMed PMID: 10388994.

(Among 770 patients with diabetes treated with acarbose, preexisting liver disease was common and mild de novo ALT elevations occurred in 1.9%, usually near the beginning of therapy and none were clinically apparent).

Mennecier D, Zafrani ES, Dhumeaux D, Mallat A. Gastroenterol Clin Biol. 1999;23:1398–9. [Acarbose-induced acute hepatitis]. French. PubMed PMID: 10642627.

(59 year old man developed liver injury 3 months after restarting acarbose [bilirubin normal, ALT 22 times ULN, Alk P 1.1 times ULN], resolving within 2 weeks and recurring within 4 weeks of restarting [eosinophilia and ALT 12 times ULN]).

Krähenbühl S. Acarbose and acetaminophen.a dangerous combination? Hepatology. 1999;29:285–7. PubMed PMID: 9862881.

(Editorial discussing a study of the effects of acarbose in rats fed alcohol demonstrating increased sensitivity to hepatic injury from acetaminophen; mentions that there have been 200 reports of liver injury due to acarbose reported to the WHO, but none associated with acetaminophen toxicity).

de la Vega J, Crespo M, Escudero JM, Sánchez L, Rivas LL. Gastroenterol Hepatol. 2000;23:282–4. [Acarbose-induced acute hepatitis. Report of two events in the same patient]. Spanish. PubMed PMID: 15324623.

(57 year old woman developed jaundice 2 months after adding acarbose to glyburide therapy [bilirubin 20 mg/dL, ALT 2300 U/L], having a recurrence within 1 week, 3 years later when acarbose was restarted [bilirubin 3.9 mg/dL, ALT 2778 U/L, Alk P 624 U/L], resolving within 2 months of stopping).

Madonia S, Pietrosi G, Pagliaro L. Acarbose-induced liver injury in an anti-hepatitis C virus positive patient. Dig Liver Dis. 2001;33:615–6. PubMed PMID: 11816556.

(74 year old woman developed jaundice 3 months after adding acarbose to glyburide [bilirubin 8.9 mg/dL, ALT 519 U/L, Alk P 258 U/L], resolving within 1 month of stopping; patient was also positive for anti-HCV and HCV RNA and no follow up provided).

Benavente Fernández A, Maraver Gacía A, Talavera Fabuel A, Barrios Merino A. Med Clin (Barc). 2001;117:317–8. [Acute hepatitis induced by acarbose]. Spanish. PubMed PMID: 11571129.

(73 year old woman developed jaundice 3 months after starting acarbose [bilirubin 25 mg/dL, ALT 2500 U/L, Alk P not given], resolving with stopping).

Chitturi S, George J. Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. Semin Liver Dis. 2002;22:169–83. PubMed PMID: 12016548.

(Overview of hepatotoxicity of antidiabetic medications mentions that acarbose has been incriminated in hepatotoxicity, generally arising within 2-8 months of starting therapy with an acute hepatitis-like clinical picture, but that miglitol has not).

Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359(9323):2072–7. PubMed PMID: 12086760.

(Controlled trial of acarbose vs placebo in 1429 patients with impaired glucose tolerance with follow up for an average of 3.3 years; serum enzyme results and liver injury not mentioned).

Segal P, Eliahou HE, Petzinna D, Neuser D, Brückner A, Spengler M. Long-term efficacy and tolerability of acarbose treatment in patients with type 2 diabetes mellitus. Clin Drug Investig. 2005;25:589–95. PubMed PMID: 17532703.

(Controlled trial of acarbose vs placebo in 139 patients with diabetes; 2 patients [3%] on acarbose developed ALT elevations above 3 times ULN, both apparently receiving high doses [>600 mg daily]).

van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care. 2005;28:154–63. PubMed PMID: 15616251.

(Review of 41 studies, 30 of acarbose, 7 miglitol, 1 voglibose and 3 combined; discusses relative rates of side effects in comparison to placebo overall, but does not mention hepatic effects specifically).

Hsiao SH, Liao LH, Cheng PN, Wu TJ. Hepatotoxicity associated with acarbose therapy. Ann Pharmacother. 2006;40:151–4. PubMed PMID: 16317107.

(57 year old woman developed abdominal pain 6 months after starting acarbose [bilirubin normal, ALT 454 U/L, GGT 109 U/L]; ALT decreased but remained elevated after reducing dose of acarbose, but resolved completely only when it was stopped; review of 10 cases in literature).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver injury in the US collected from 2004 to 2008, none were attributed to acarbose).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury, none of which were due to acarbose).

Drugs for type 2 diabetes. Treat Guidel Med Lett. 2011;9(108):47–54. PubMed PMID: 21778966.

(Concise review of the role of current antidiabetes medications in management of type 2 diabetes).

Wu QL, Liu YP, Lu JM, Wang CJ, Yang T, Dong JX, Li CJ, et al. Efficacy and safety of acarbose chewable tablet in patients with type 2 diabetes: a multicenter, randomized, double-blinded, double-dummy positive controlled trial. J Evid Based Med. 2012;5:134–8. PubMed PMID: 23672220.

(Among 207 patients with type 2 diabetes treated with a standard or chewable tablet of acarbose three times daily for 12 weeks, there were no "clinically relevant changes in biochemical parameters").

Wang JS, Huang CN, Hung YJ, Kwok CF, Sun JH, Pei D, Yang CY, et al. acarbose/metformin fixed-dose combination study investigators. Acarbose plus metformin fixed-dose combination outperforms acarbose monotherapy for type 2 diabetes. Diabetes Res Clin Pract. 2013;102:16–24. PubMed PMID: 23993469.

(Among 233 patients with type 2 diabetes treated with acarbose alone or acarbose and metformin for 16 weeks, serious adverse events were rare [~3%] and none were hepatic; no mention of ALT elevations).

Yang W, Liu J, Shan Z, Tian H, Zhou Z, Ji Q, Weng J, et al. Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial. Lancet Diabetes Endocrinol. 2014;2(1):46–55. PubMed PMID: 24622668.

(Among 784 patients with type 2 diabetes treated with either metformin or acarbose for 24-48 weeks, serious adverse events were rare [2%] and none were hepatic; no mention of ALT elevations).

Rocha-Honor E, Polo-Romero FJ, Sánchez-Beteta P, Martínez-Peguero J, Santisteban-López Y, Beato-Pérez JL. Acarbosa y propofol: ¿una peligrosa combinación? Rev Esp Anestesiol Reanim. 2014;61:109–11. [Acarbose and propofol: a dangerous combination?]. Spanish. PubMed PMID: 23276378.

(67 year old woman developed pruritus, nausea and fatigue 3 months after starting acarbose, which improved on stopping but had an acute hepatitis 2 weeks later following cataract surgery [ALT 1345 U/L, Alk P 273 U/L, bilirubin 2.8], resolving within 2 months).

Drugs for type 2 diabetes. Treat Guidel Med Lett. 2014;12(139):17–24. PubMed PMID: 24566424.

(Concise review of current therapy of type 2 diabetes mentions that acarbose and miglitol are generally less effective than other drugs in lowering A1c levels; no discussion of side effects).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, four were attributed to antidiabetic agents, including metformin, sitagliptin and glibenclamide, but none specifically to acarbose or miglitol).

Komatsu M, Tanaka N, Kimura T, Fujimori N, Sano K, Horiuchi A, Sugiura A, et al. Miglitol attenuates non-alcoholic steatohepatitis in diabetic patients. Hepatol Res. 2018;48:1092–8. PubMed PMID: 29935004.

(Among 17 adults with type 2 diabetes and nonalcoholic steatohepatitis treated with miglitol for 12 months, ALT and HbA1c levels and body weight decreased overall as did liver biopsy scores for steatosis and inflammation but not for fibrosis or ballooning; there were no serious adverse events and no mention of ALT elevations or hepatotoxicity).

Chao CT, Wang J, Huang JW, Chien KL. Acarbose use and liver injury in diabetic patients with severe renal insufficiency and hepatic diseases: a propensity score-matched cohort study. Front Pharmacol. 2018;9:860. PubMed PMID: 30131698.

(Analysis of the Taiwan National Health Insurance Research Database identified patients with type 2 diabetes and end stage renal disease found rates of development of acute hepatic injury were not affected by acarbose use in those with or without preexisting liver disease or cirrhosis).

Hedrington MS, Davis SN. Considerations when using alpha-glucosidase inhibitors in the treatment of type 2 diabetes. Expert Opin Pharmacother. 2019;20:2229–35. PubMed PMID: 31593486.

(Review of the role of alpha glucosidase inhibitors in the therapy of type 2 diabetes mentions that side effects are largely gastrointestinal [diarrhea, abdominal pain, flatulence] and are transient and mostly dose dependent; no mention of ALT elevations or hepatotoxicity).

Drugs for type 2 diabetes. Med Lett Drugs Ther. 2019;61(1584):169–78. PubMed PMID: 31770362.

(Concise review of the mechanisms of action, clinical efficacy, side effects and costs of currently available drugs for type 2 diabetes mentions that miglitol and acarbose must be taken with each meal and can lower HbA1c levels by 0.5-1.0%; side effects are not discussed).

Lin WH, Yang CY, Kuo S, Kuo TH, Roan JN, Li CY, Wang MC, Ou HT. Hepatic and cardiovascular safety of acarbose among type 2 diabetes patients with end-stage renal disease: a nationwide population-based longitudinal study. Diabetes Res Clin Pract. 2020 Oct 6.:108489. [ePub ahead of print]. PubMed PMID: 33035600.

(Analysis of the Taiwan National Health Insurance Research Database between 1999 and 2013 identified 32,531 patients with diabetes and end stage renal disease, of whom 6263 were treated with acarbose and had a slightly lower rate of development of hepatic disease [1.25 vs 1.34 per 100 patient years] as well as lower rates of cardiovascular events and all-cause mortality).