TOPICS IN REVIEW

Antiarrhythmic effects of metformin

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Atrial fibrillation/flutter (AF) is a major public health problem and is associated with stroke, heart failure, dementia, and death. It is estimated that 20%–30% of Americans will develop AF at some point in their life. Current medications to prevent AF have limited efficacy and significant adverse effects. Newer and safer therapies to prevent AF are needed. Ventricular arrhythmias are less prevalent than AF but may have significant consequences including sudden cardiac death. Metformin is the most prescribed, first-line medication for treatment of diabetes mellitus (DM). It decreases hepatic glucose production but also reduces inflammation and oxidative stress. Experimental studies have shown that metformin improves metabolic, electrical, and histologic risk factors associated with AF and ventricular arrhythmias. Furthermore, in large clinical observational studies, metformin has been associated with a reduced risk of AF in people with DM. These data suggest that metformin may have antiarrhythmic properties and may be a candidate to be repurposed as a medication to prevent cardiac arrhythmias. In this article, we review the clinical observational and experimental evidence for the association between metformin and cardiac arrhythmias. We also discuss the potential antiarrhythmic mechanisms underlying this association. Repurposing a well-tolerated, safe, and inexpensive medication to prevent cardiac arrhythmias has significant positive public health implications.

KEYWORDS Arrhythmia; Atrial fibrillation; Metformin; Prediabetes; Ventricular fibrillation; Ventricular tachycardia

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Atrial fibrillation and flutter (AF) is a public health issue that is highly prevalent on a global scale.[1–3] Adverse outcomes related to AF include stroke, heart failure, dementia, and death.[4–6] In the United States approximately 20%–30% of adults will develop AF at some point in their life.[7] The annual economic burden of AF treatment exceeds $26 billion.[8]

Although less prevalent than AF, ventricular arrhythmias, such as ventricular fibrillation (VF) and ventricular tachycardia (VT), are frequently the final arrhythmias before sudden cardiac death.[9–12] Prevention of AF and VT/VF in high-risk populations is of utmost importance.[13–16] However, current antiarrhythmic medications have limited efficacy and significant adverse effects, thus limiting their use.[17] Determining alternative medications with favorable risk profiles is essential to reduce the societal burden of these highly prevalent and impactful arrhythmias.

Diabetes mellitus (DM) and prediabetes are prevalent risk factors for AF. The risk of AF is 34% higher in patients with DM and 20% higher in those with prediabetes compared to individuals with normal glucose tolerance.[18] Metformin, which has been in clinical use for 6 decades, is a first-line therapy for DM. It is inexpensive and has a favorable safety profile. Metformin is an activator of adenosine monophosphate-activated protein kinase (AMPK). This mechanism is primarily responsible for metformin's effect in decreasing hepatic gluconeogenesis and may also contribute to reduced inflammation and oxidative stress.[19] Clinical trials and observational data indicate that metformin may offer cardioprotective effects, including reduced risk of stroke, heart failure, myocardial infarction, and all-cause mortality.[19,20] However, less is known about potential antiarrhythmic effects of metformin. Experimental studies have shown that metformin may ameliorate the metabolic, electrical, and histologic conditions that lead to AF or ventricular arrhythmias.[19,21] Furthermore, in observational studies using administrative data, metformin use was associated with a lower risk of AF in people with DM.[19,22,23] The objective of this article is to review the current clinical observational and experimental evidence for the association between metformin and cardiac arrhythmias and to discuss the potential antiarrhythmic mechanisms underlying this association (Figure 1). Compared to a previous review on metformin and arrhythmias published in 2020, the current article is

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KEY FINDINGS

- A growing body of experimental and observational clinical evidence suggests that metformin conveys antiarrhythmic effects, potentially protecting against atrial fibrillation/flutter and ventricular arrhythmias.
- Underlying such favorable actions may be metformin's effects on activating adenosine monophosphate-activated protein kinase and attenuating inflammation, oxidative stress, dysregulated calcium handling, and pathologic structural remodeling of myocardium, while promoting myocardial oxidative metabolism and energetic integrity.
- However, starting metformin in patients without diabetes for the sole purpose of preventing arrhythmias would not be justified because the clinical evidence supporting its antiarrhythmic activity originates from observational studies, which may be affected by confounding.
- The ongoing VA-IMPACT (Veterans Affairs–Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes) trial (ClinicalTrials.gov Identifier: NCT02915198) provides a unique opportunity to test metformin's antiarrhythmic effects.

more comprehensive, including important new data that have been published since then.

Clinical evidence for antiarrhythmic effects of metformin

Atrial arrhythmias

Recent observational cohort studies indicate that metformin is associated with reduced incidence of atrial arrhythmias (Table 1). Among 645,710 patients with DM, metformin users had a lower risk of AF than nonusers after adjusting for age, sex, and traditional cardiovascular risk factors (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.76–0.86).[24] In other studies, patients using metformin had lower rates of hospitalization for AF compared to nonusers.[23,25] Furthermore, in a network meta-analysis prioritizing drug repurposing for AF, Lal et al[26] found that metformin use is associated with a lower risk of AF (OR 0.48; 95% CI 0.36–0.64) compared with other diabetes treatments (Figure 2).

Metformin also performed better than other diabetes medications. Ostropolets et al[22] found that compared to sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP4s), and thiazolidinediones, metformin monotherapy was associated with a lower risk of AF (Figure 3). Furthermore, in addition to a lower risk of incident AF, Zhou et al[27] observed that metformin users had a lower risk of stroke, cardiovascular mortality, and all-cause mortality when compared to users of sulfonylurea. In a case-matched study of patients with DM, users of metformin and thiazolidinediones had lower risk of AF compared to nonusers (OR 0.81, 95% CI 0.71–0.95; OR 0.72, 95% CI 0.63–0.83, respectively), whereas insulin users had a higher risk of AF (OR 1.19; 95% CI 1.06–1.35).[23]

Although these studies suggest a potential association of metformin with lower risk of AF, other studies are nonconcordant. For example, Chen et al[28] found no significant difference in the risk of AF between metformin users and nonusers (OR 1.01; 95% CI 0.88–1.15) while corroborating that insulin was associated with a higher risk of AF (OR 1.58; 95% CI 1.37–1.82). Similarly, a retrospective cohort study demonstrated similar rates of AF with metformin vs other noninsulin hypoglycemic medications.[29]

Postablation AF recurrence

Recurrent AF occurs in 30%–40% of patients after catheter ablations.[30,31] Among 271 patients with DM undergoing AF ablation, Deshmukh et al[32] observed that those using metformin were more likely to maintain sinus rhythm by 13 months compared to those not using metformin (adjusted HR 0.63; 95% CI 0.42–0.96).[32] This effect was independent of blood glucose level.

Postoperative AF

Postoperative AF complicates 30%–40% of cardiac surgical procedures and has been linked to an increased risk of stroke and mortality.[33–35] Among 1283 patients with DM who underwent cardiac surgery, Basnet et al[36] found that preoperative treatment with metformin did not reduce the risk of postoperative AF. Furthermore, a randomized controlled trial demonstrated that metformin treatment 3 days before cardiac surgery did not alter the incidence of postoperative AF.[37]

Ventricular arrhythmias

Compared to AF, fewer data are available on the association between metformin use and ventricular arrhythmias. Ostropolets et al[22] observed a lower risk of VT/VF in metformin users compared to sulfonylurea (HR 0.66; 95% CI 0.47–0.91). In a matched cohort study, participants with DM receiving sulfonylurea had a 2× times higher risk of ventricular arrhythmias and sudden cardiac death compared to those receiving metformin (Figure 4).[38] Islam et al[39] found similar results in a population-based cohort study, with sulfonylurea users experiencing higher incidence of ventricular arrhythmias compared to metformin users (HR 1.42; 95% CI 1.18–1.69). Whether these data indicate a deleterious effect of sulfonylureas and/or a favorable effect of metformin is uncertain.

Independence from blood glucose control

The association of metformin with decreased risk of cardiac arrhythmias does not seem to be a consequence of better diabetes control but an independent antiarrhythmic effect. In observational clinical studies, metformin had a similar effect on blood glucose as other diabetes medications in patients

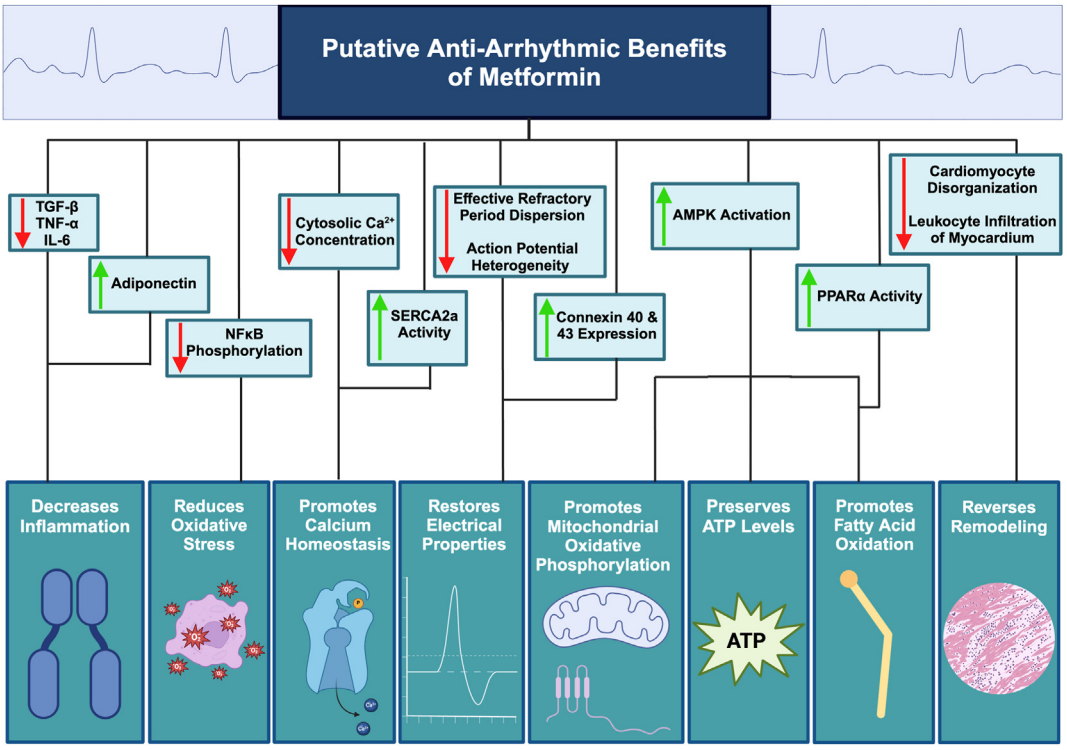

Figure 1 Putative antiarrhythmic benefits of metformin. AMPK = adenosine monophosphate-activated protein kinase; IL-6 = interleukin 6; NFκB = nuclear factor kappa-B; PPARγ = peroxisome proliferator-activated receptor-gamma; SERCA2a = sarco(endo)plasmic reticulum Ca^{2+} adenosine triphosphatase; TGF-β = transforming growth factor-beta; TNF-α = tumor necrosis factor-alpha. Created with BioRender.com.

with diabetes and had minimal effect on blood glucose in individuals without diabetes, while showing antiarrhythmic effects in both groups.[40,41] Furthermore, there is clinical and experimental evidence that AF risk is not modified by blood glucose level. *Post hoc* analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which randomized patients with diabetes to an intensive vs standard glucose control strategy, found no difference in incident AF between the treatment groups.[42] In experimental animal models of myocardial infarction, the antiarrhythmic effects of metformin on VT/VF were also independent of blood glucose concentrations.[43,44]

Mechanisms of action

Mechanisms for a putative antiarrhythmic effect of metformin are summarized in Figure 1.

Moderation of inflammation and cytokine profile

There is increasing evidence that inflammation is associated with arrhythmia development, severity, persistence, and recurrence.[45–48] Therefore, therapies that attenuate inflammation may also reduce AF incidence. *In vitro,* metformin treatment in human induced pluripotent stem cell–derived atrial-like cardiomyocytes downregulated expression of proinflammatory cytokines, such as transforming growth factor-beta1 (TGF-β1).[26] In a canine AF model of rapid atrial pacing (RAP), Li et al[49] found that metformin treatment attenuated the RAP-induced increase in proinflammatory cytokines (interleukin-6 [IL-6], TGF-β1, and tumor necrosis factor-alpha [TNF-α]). Metformin treatment also attenuated the RAP-induced reduction in adiponectin, an anti-inflammatory adipokine. In addition, the concentrations of peroxisome proliferator-activated receptor-gamma (PPAR γ), a key transcription factor controlling the expression of adiponectin, was increased.[49] With its antioxidant and anti-inflammatory properties, adiponectin may have effects on counteracting atrial fibrosis and on the development of AF.[50] Decreased levels of adiponectin and increased activity of TGF-β1, IL-6, and TNF-α have been noted in AF and may serve as therapeutic targets of metformin therapy.[51–56]

Reduction of oxidative stress

Recent evidence suggests a link between oxidative stress and AF.[57,58] In the setting of tachyarrhythmias, oxidative damage and atrial cellular remodeling induce AF.[24,59] The accumulation of reactive oxygen species (ROS) and activation of various signaling pathways augments this process. Patients with DM are thought to be more prone to developing AF in part due to increased oxidative stress and nuclear factor kappa-B (NF-κ B) signaling.[60–62]

In a canine model, RAP led to increased phosphorylation of NF-κ B and higher contents of ROS in the left atrium and epicardial adipose tissue compared to controls. Metformin therapy reduced oxidative stress that occurred in this model through decreased phosphorylation of NF-κ B.[24,49]

Table 1 Clinical studies of metformin and arrhythmia risk

Study	Objective	Design	Sample (N)	Follow-up	Conclusion
Chang et al[24] (2014)	Compare the incidence of AF in patients with DM on MET to those with DM not on MET	Retrospective cohort	645,710	13 years	After adjusting for comorbidities and meds, MET reduced new-onset AF.
Ostropolets et al[22] (2021)	Determine the risk of arrhythmias in patients on single oral hypoglycemic medications	Retrospective cohort	410,000	8 years	MET reduced the risk of AF compared to sulfonylureas, DPP4s, and TZDs. MET also reduced the risk of VT/VF compared to sulfonylureas.
Tseng et al[25] (2021)	Compare the incidence of hospitalization for AF in patients who had ever used MET to those who never used MET	Retrospective cohort with propensity matching	200,000	6 years	Incidence rate of AF-related hospitalization was 56.9 vs 92.5 per 100,000 person-years for ever-users vs never-users of MET, respectively.
Deshmukh et al[32] (2021)	Determine the risk of AF recurrence after catheter ablation in patients with DM on MET vs not on MET	Retrospective cohort	271	13 months	Sinus rhythm was maintained in 55% of patients treated with MET vs 40% of patients not on MET
Basnet et al[36] (2017)	Determine the risk of postoperative AF after cardiac surgery in patients with DM on MET vs not on MET	Matched retrospective cohort	1283		No difference in the rate of postoperative AF after cardiac surgery in patients with DM on MET vs not on MET
Liou et al[23] (2018)	Compare the risk of AF between different classes of hypoglycemic medications	Nested case control	14,410		MET users had reduced rate of AF compared to nonusers.
Davis et al[104] (1998)	Determine the risk of post-MI arrhythmias with respect to hypoglycemic medications	Cohort	745	28 days	MET in combination with other hypoglycemic medications, but not alone, reduced the risk of post-MI AF. No difference in VT/VF.
Chen et al[28] (2017)	Compare the risk of AF between different classes of hypoglycemic medications	Nested case control	9790		No significant association of MET with AF incidence.
El Messaoudi et al[37] (2015)	Determine if MET pretreatment before CABG reduced adverse outcomes in patients without DM	Randomized controlled Trial	100	24 hours	MET administered 3 days before CABG did not reduce arrhythmias within postoperative 24 hours

(*Continued*)

Table 1 (*Continued*)

Study	Objective	Design	Sample (N)	Follow-up	Conclusion
Lal et al[26] (2022)	Compare the risk of AF with MET vs other hypoglycemic medications	Network meta-analysis	35,824		MET use was associated with 52% reduction in risk of AF vs those taking sulfonylureas, TZDs, and a combination regimen of hypoglycemic medications (TZD, DPP4, GLP1RA, and sulfonylureas).
Iqbal et al[29] (2022)	Determine AF incidence in patients with DM initially treated with MET vs other hypoglycemic medications	Retrospective cohort	5664	10 years	Ten-year cumulative incidence of AF in patients initially treated with MET was 5.2% vs 8.1% with other hypoglycemic medications, which was not statistically different ($P = .55$).
Zhou et al[27] (2022)	Compare AF incidence in patients with DM on MET vs sulfonylureas	Retrospective cohort with propensity matching	108,000		AF risk was higher in patients with DM on sulfonylurea monotherapy vs MET monotherapy.
Lee et al[38] (2022)	Compare risk of VT/VF or SCD in patients with DM on MET vs sulfonylurea	Retrospective cohort with propensity matching	33,192	4.9 years	Sulfonylurea use was associated with a higher risk of VT/VF or SCD than MET.
Islam et al[39] (2023)	Compare risk of VT/VF or SCD in patients with DM on MET vs sulfonylurea	Retrospective cohort with propensity matching	599,520		Sulfonylurea use was associated with a higher risk of VT/VF or SCD than MET.

AF = atrial fibrillation; CABG = coronary artery bypass graft; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4 inhibitor; GLP1RA = glucagon-like peptide 1 receptor agonist; MET = metformin; MI = myocardial infarction; SCD = sudden cardiac death; TZD = thiazolidinedione; VF = ventricular fibrillation; VT = ventricular tachycardia.

Promotion of calcium homeostasis

Calcium (Ca^{2+}) homeostasis is critical for optimal cardiomyocyte function. Intracellular Ca^{2+} handling is significantly altered in atrial myocytes in AF.[63] During the cardiac action potential, Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum (SR) allows Ca^{2+} to bind to myofilaments and initiate myocyte contraction. Atrial relaxation occurs partly through the retreat of Ca^{2+} back into the SR through a protein known as sarco(endo)plasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2a). In the atria, phospholamban regulates SERCA2a activity and cytosolic Ca^{2+} concentrations. Dysregulation of this process is thought to increase the risk of ectopic activity and the likelihood of reentry.[64–66] There is evidence that AF is triggered by delayed afterdepolarizations and spontaneous depolarizations that are propagated by alterations in calcium handling and increased cytosolic Ca^{2+}.[67,68] *In vitro,* metformin has been shown to attenuate inflammation-induced decreases in SERCA2a expression and increases in cytosolic Ca^{2+}.[49] This may occur through the upregulation of adiponectin, which increases SERCA2a expression in cardiomyocytes.[69]

Preservation of ATP levels in ischemic myocardium

Ischemic or infarcted myocardium serves as a substrate for VT/VF.[10,70–75] Myocardial ischemia causes a rundown in myocardial ATP levels. Reduced ATP concentration leads to opening of ATP-sensitive potassium channels with consequent shortening of the action potential in ischemic myocardium.[70] Heterogeneity of action potential duration and refractoriness in ischemic vs healthy myocardial regions may establish conditions conducive to VT/VF.[71,76]

AMPK is activated, as a compensatory mechanism, to preserve cellular energy metabolism in ischemia.[77,78] Amplification of AMPK by metformin may serve as a safeguard against the deleterious effects of myocardial ischemia. Kawabata et al[79] showed that metformin attenuated the rundown of ATP levels in ischemic isolated rabbit hearts. Lu et al[44] demonstrated that domestic pigs treated with metformin had preserved myocardial ATP concentration, reduced heterogeneity of myocardial action potential duration, and a lower incidence of VF during ischemia compared to untreated controls. This antiarrhythmic effect was associated with amplified AMPK

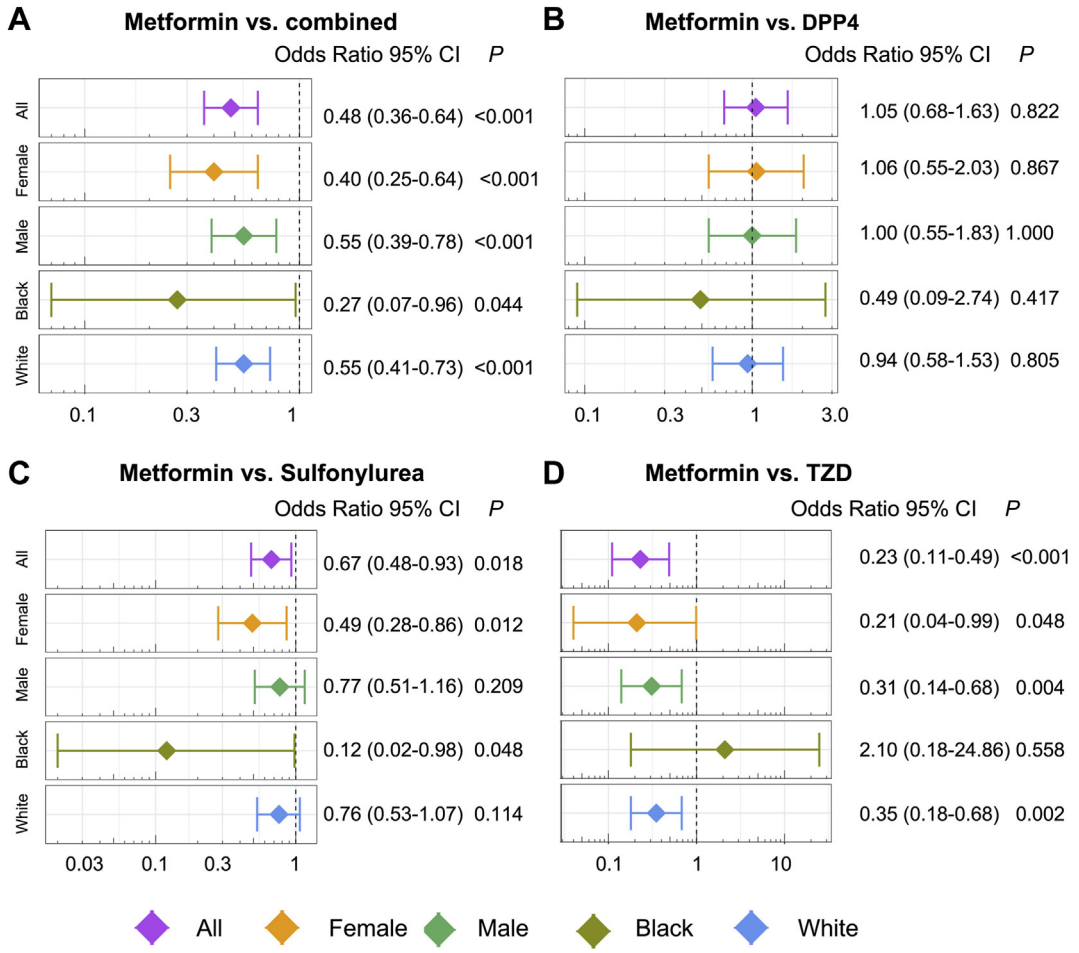

Figure 2 Pharmacoepidemiologic validation of metformin in reducing atrial fibrillation (AF) occurrence odds ratio (OR) and 95% confidence interval (CI) for metformin vs combination of the 4 drug groups (all: dipeptidyl peptidase-4 sulfonylurea [DPP4], thiazolidinedione [TZD], sulfonylurea, and glucagon-like peptide 1 receptor agonist [GLP1RA]) (n = 3578) **(A),** DPP4 (n = 1244) **(B),** sulfonylurea (n = 2352) **(C),** and TZD (n = 288) **(D).** For each of the 4 comparisons, the results for comparisons between subgroups (including female, male, Black, and White) are also shown. Patient groups were matched using propensity score matching with the variables age, gender, race, and comorbidities for the overall group comparisons. For the subgroup of male and female, the matching variables excluded gender, and for the subgroup Black and White, the matching variables excluded race. Logistic regression models were used for statistical inference of the AF ORs. Subgroup analyses were performed in females *(orange),* males *(green),* Black Americans *(dark green),* and White Americans *(blue).* $P < .05$. (Lal et al.[26] Reprinted with permission.)

activity and preserved ATP concentration in ischemic porcine myocardium but was independent of blood glucose level.

Promotion of mitochondrial oxidative phosphorylation

A potential mechanism for metformin's benefit on metabolism is through AMPK-mediated reversal of the Warburg effect, a metabolic shift from mitochondrial oxidative phosphorylation to glycolysis even when oxygen supply is sufficient (so-termed "aerobic glycolysis").[80,81] Decreased activity of AMPK is associated with aerobic glycolysis and the development and persistence of AF. By activating AMPK, metformin may diminish aerobic glycolysis, enhance oxidative metabolism, and reduce the incidence of AF.[82]

Promotion of myocardial fatty acid oxidation

The antiarrhythmic effect of metformin in experimental models may be related to enhancement of fatty acid oxidation. Dysregulated cardiac fatty acid metabolism with accumulation of intracellular lipids is known to contribute to AF progression.[83] Compared to patients in sinus rhythm, those with AF have been noted to have higher plasma levels of saturated fatty acids, lower plasma levels of unsaturated fatty acids, and increased atrial expression of fatty acid binding protein 3, which is involved in fatty acid uptake and intracellular transport.[83,84] Furthermore, cardiac adiposity has been associated with an increased risk and severity of AF.[85] Promotion of fatty acid oxidation and autophagy by metformin may protect against development of AF by attenuating lipotoxicity.[83,86,87] Liu et al[21] demonstrated that RAP increased the expression of factors that augment aerobic glycolysis, such as hypoxia inducible factor-1a (HIF-1a). RAP also downregulated AMPK and peroxisome proliferator-activated receptor coactivator 1α (PPAR-α) activity, reducing fatty acid oxidation and leading to intramyocardial lipid accumulation. Treatment with metformin blunted these effects by increasing AMPK and PPAR-α

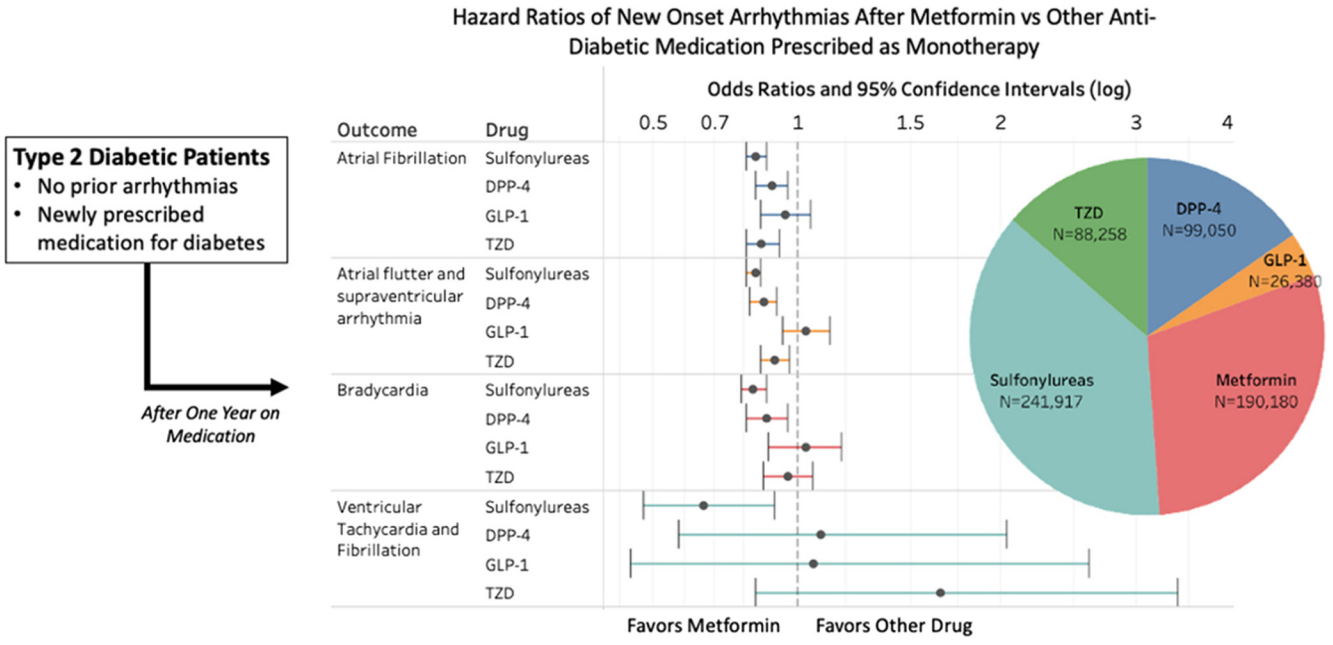

Figure 3 Association of metformin monotherapy with arrhythmias compared to other medications for treatment of diabetes mellitus. Abbreviations as in Figure 2. (Ostropolets et al.[22] Reprinted with permission.)

activity.[21] Bai et al[88] demonstrated that while RAP decreased transcription and expression of PPAR-α, leading to intracellular lipid accumulation in atrial myocytes, those effects were attenuated by metformin treatment.

Reversal of remodeling

Atrial fibrosis creates conduction disturbances that facilitate reentry and AF.[89] Once established, AF worsens the progression of atrial fibrosis.[90] Therefore, mitigating fibrosis may be a potential therapeutic target to prevent AF.

Metformin treatment has been shown to attenuate or reverse atrial fibrosis *in vivo*.[21,49] In diabetic and arrhythmogenic rodents, metformin limits cardiomyocyte disorganization and leukocyte infiltration in atrial tissue.[82,91] This is thought to occur through activation of AMPK, which protects against the dysregulation of transcription factors needed to maintain expression of ion channels and gap junction proteins. Decreased activity of AMPK in the atria promotes electrophysiological changes and ectopic activity that may lead to AF.[92,93] The relationship between metformin and AMPK has been observed on a genetic level. Approximately 100 AF susceptibility loci have been identified through genomewide association studies. In an AF network module consisting of differentially expressed genes in atrial tissue, metformin was shown to target genes encoding subunits of AMPK, such as *PRKAB1*.[26] Thus, experimental data indicate that metformin, through activation of AMPK, may prevent deleterious fibrotic changes that are both a cause and a consequence of AF.

Restoration of electrical properties

Shortening and increased dispersion of the atrial effective refractory period (ERP) increases vulnerability to AF.[49,94,95] Li et al[49] demonstrated that RAP decreased atrial ERP in dogs. However, treatment with metformin attenuated this effect. RAP also increased ERP dispersion compared to controls; however, metformin treatment fully reversed this effect.[49] In another AF canine model, Liu et al[21] observed that metformin treatment restored ERP values and significantly reduced ERP dispersion, AF inducibility, and window of vulnerability.

Gap junctions, such as connexin43, are critical for cell-to-cell electrical conduction and are downregulated in AF. Whereas RAP downregulated connexin43 in canines, treatment with metformin minimized this effect.[96] Furthermore, Ozcan et al[82] noted restoration of connexin40 and connexin43 concentrations in an AF mouse model after treatment with metformin.

Small conductance calcium-activated potassium channels (SK channels) also play a critical role in the action potential repolarization of cardiomyocytes, although their role in the pathophysiology of AF is less clear. The genetic knockout of SK2 channels and pharmacologic inhibition of SK channels in atrial myocytes have been shown to induce early afterdepolarizations that create arrhythmogenic substrates.[97,98] In contrast, the knockdown of SK3 channels has been shown to reduce the number of AF episodes and AF duration in rats.[99] In concordance with these studies, Fu et al[91] demonstrated in diabetic rats that metformin treatment upregulates SK2 and downregulates SK3 channels. These findings suggest that SK channels could play a role in AF and may partially explain the antiarrhythmic benefits of metformin.

Under conditions of ischemia, susceptibility to ventricular arrhythmias such as VT and VF increases.[100] One reason for this is shortening of action potentials.[101] In metabolically normal pigs that underwent experimental myocardial

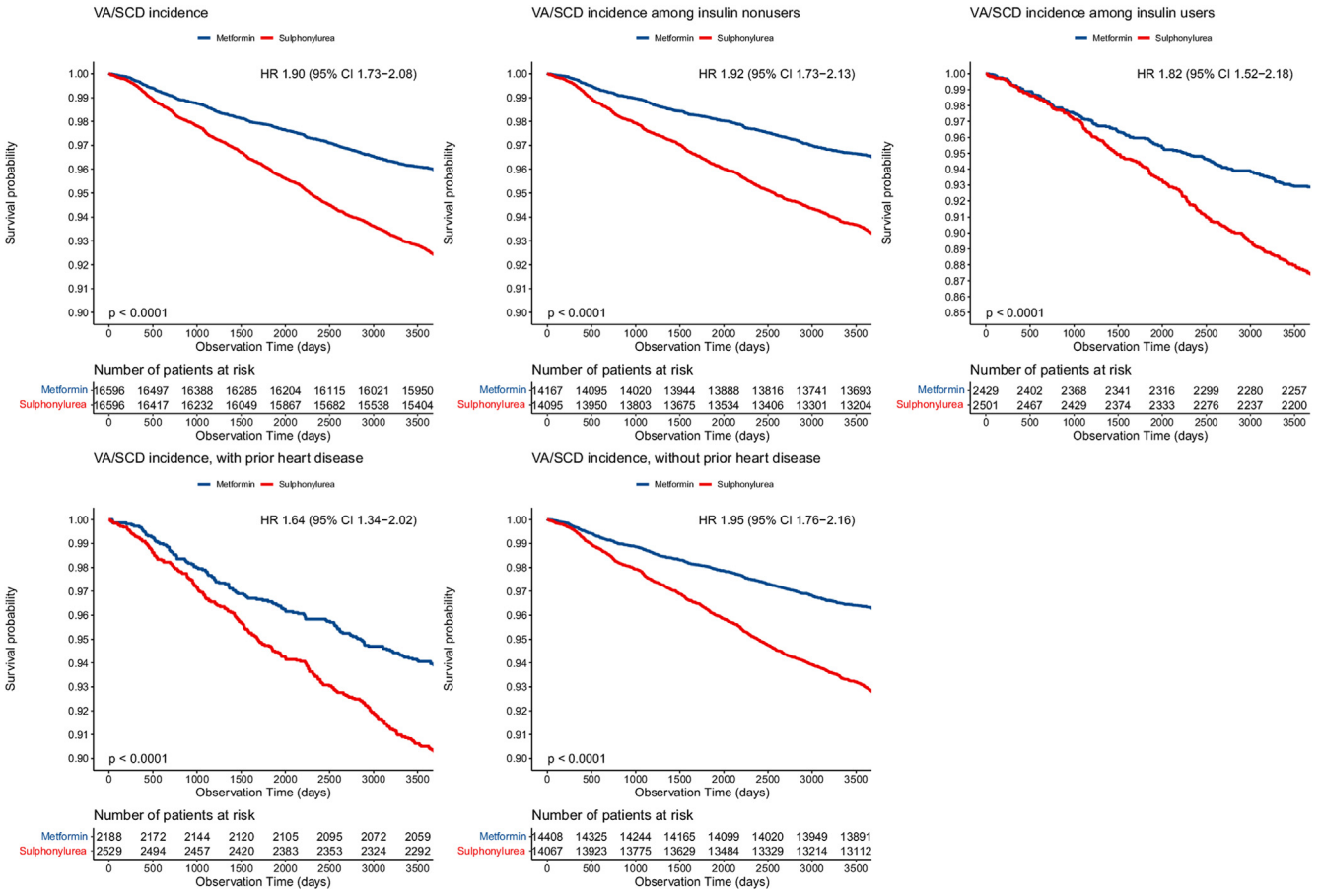

Figure 4 Kaplan-Meier survival curves of ventricular arrhythmias and sudden cardiac death associated with metformin vs sulfonylurea. CI = confidence interval; HR = hazard ratio; SCD = sudden cardiac death; VA = ventricular arrhythmia. (Lee et al.[38] Reprinted with permission.)

ischemia, those treated with metformin demonstrated less heterogeneity of action potential duration between ischemic and healthy regions and a lower incidence of ischemic VF compared with untreated pigs.[44] Regional heterogeneity in the action potential duration (dispersion) between ischemic and nonischemic regions is also known to precipitate VF.[100,102,103]

Conclusion

A considerable and growing body of experimental and clinical evidence suggests that metformin conveys antiarrhythmic effects, potentially protecting against both atrial and ventricular arrhythmia. Underlying such favorable actions may be metformin's effects in activating AMPK and attenuating inflammation, oxidative stress, dysregulated calcium handling, and pathologic structural remodeling of myocardium while promoting myocardial oxidative metabolism and energetic integrity (Figure 1). Each of these effects could stabilize or ameliorate the electrophysiological conditions leading to arrhythmias.

However, starting metformin in patients without diabetes for the sole purpose of preventing arrhythmias would not be justified because the clinical evidence supporting the antiarrhythmic activity of metformin originates from observational studies, which may be affected by confounding (Table 1). Randomized controlled trials are needed to establish metformin as an effective antiarrhythmic medication. The TRIM-AF (Targeting Risk Interventions and Metformin for Atrial Fibrillation) trial (ClinicalTrials.gov Identifier: NCT03603912) is testing the effects of lifestyle risk modification and metformin on AF burden detected on cardiac implantable devices. The VA-IMPACT (Veterans Affairs–Investigation of Metformin in Pre-diabetes on Atherosclerotic Cardiovascular OuTcomes) trial (ClinicalTrials.gov Identifier: NCT02915198) is randomizing patients with prediabetes and cardiovascular disease to metformin or placebo to test the hypothesis that metformin reduces major adverse cardiovascular outcomes. In the trial, all new clinical AF events will be collected as adverse events, and patients with cardiac implantable devices are being followed centrally for arrhythmias. In this regard, the VA-IMPACT trial provides a unique opportunity to test metformin's antiarrhythmic effects.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2024.04.003.

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