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Susana Melissa Ribeiro da Silva

Abdominal Aortic Aneurysm:
a review on the role of oral antidiabetic drugs.

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Aneurisma da Aorta Abdominal:
Uma revisão acerca do papel dos antidiabéticos orais.

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"Abdominal Aortic Aneurysm: a review on the role of oral antidiabetic drugs"

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Dedicatória

Este trabalho só poderia ser dedicado àqueles que me permitiram chegar aqui hoje.

Ao meu Pai, que sempre me instigou este gosto. Que me ensinou, tão precocemente quanto me recordo de haver memória, a estipular objetivos. A desenhar metas. A consciencializar-me do esforço para as alcançar. Acima de tudo, que me ditou princípios e me deu o exemplo daquilo que mais ouso ostentar - a educação. À distância de um céu infinito, mas tão perto quanto se aqui estivesse a segurar-me pela mão – esta é a nossa vitória.

À minha Mãe, que é o meu pilar. Que se ergue, todos os dias, com motivação para enfrentar um novo dia. Que me mostra que tudo é possível, se lutarmos. Que me incentiva a olhar de frente para as adversidades e a sorrir, porque "a vida é bela". Ela, que tornou o nosso sonho em algo concreto, é a maior vencedora.

A eles, citando Nietzsche,
"Every achievement, every step forward in knowledge, is the consequence of courage, of toughness towards oneself, of sincerity to oneself."

Obrigada.

Abdominal aortic aneurysm: a review on the role of oral antidiabetic drugs

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What this paper adds

To our knowledge, this is the first literature review reporting data on human studies regarding the association between oral antidiabetic drugs (OAD) on abdominal aortic aneurysm incidence and growth. The main finding of this paper is the consistent protective association conferred by metformin, mainly regarding AAA disease progression. AMPK (5' adenosine monophosphate-activated protein kinase) signalling pathway seems to be the major mechanism through which metformin can have a protective role, by inhibiting inflammatory pathways. Studies for other classes of oral antidiabetic drugs are underpowered and thus results are not concordant enough to take conclusions. Large studies, able to isolate the effect of OAD, independently of the glycaemic status, would add important insights on this matter.

ABSTRACT

INTRODUCTION: A paradoxical negative association between Diabetes Mellitus and Abdominal Aortic Aneurysm (AAA) prevalence and growth is established. However, so far is not possible to determine whether this protection comes from the disease itself or the medication for Diabetes. The aim of this manuscript is to review the association between oral antidiabetic drugs and AAA incidence and growth.

EVIDENCE ACQUISITION: A search was conducted on Pubmed and Scopus databases until December 2019 to identify publications reporting on the association between oral antidiabetic drugs (biguanides/metformin, sulfonylureas(SU), thiazolidinediones(TZD), dipeptidyl-peptidase 4(DPP-4) inhibitors, glucagon-like peptide 1(GLP-1) agonists, sodium-glucose transporter protein-2(SGLT2) inhibitors) and the outcomes AAA incidence and growth. Only data from human studies were considered, with a minimum of 3 months follow-up.

EVIDENCE SYNTHESIS: Six studies enrolling 25810 patients were included: one reporting on the AAA risk and five reporting on AAA growth. Metformin prescription was associated with a 28% reduction in AAA occurrence, while SU and TZD were associated with a 18% decrease in AAA risk. Regarding AAA enlargement, results were concordant for a slower expansion rate associated with metformin, with a decrease ranging from -0.30 mm/y to -1.30 mm/y, but not consistent for other antidiabetic drugs.

CONCLUSIONS: Metformin seems to be associated with a decrease in AAA risk and enlargement rate. Evidence for the other classes is lacking. Studies evaluating the association between oral antidiabetic drugs and AAA progression, independently of the diabetic status, are needed.

Key words: “aortic aneurysm, abdominal”, “metformin”, “sulfonylurea compounds”, “thiazolidinediones”, “dipeptidyl-peptidase IV inhibitors”

TEXT

INTRODUCTION

Abdominal aortic aneurysms (AAAs) represent permanent dilatations of the aorta (1), more frequently located in the infrarenal aorta (2-4). The conventional definition of an AAA as an infrarenal aortic diameter of 30mm or more is now questioned by studies advocating an individualization of criteria as a mean for screening. On this regard, body-surface area is suggested to have clinical implications, since it could increase the sensibility of the diagnosis of AAA. (5)

Despite concerted efforts to understand the pathophysiologic mechanisms, there is still not a definite answer regarding the factors underlying this process (6). There are recognized pathologic processes, such as the increment of proteolytic pathways and programmed cell death, oxidative stress and immune/inflammatory cell infiltration, along with intraluminal thrombus (ILT) formation, together culminating with loss of arterial wall matrix and its compensatory disrupted remodelling. (4, 7) The loss of arterial wall is thought to result from an imbalance between proteases – most consistently matrix metalloproteinases 2 and 9 (8) - and their regulators (9), provoking enzymatic degradation of structural matrix proteins, such as elastin and collagen, as well as decreased vascular smooth muscle cell (VSMC) functions and ultimately its number(7), creating space for immune cell infiltration in the external layers – media and adventitia- rendering it prone to dilation. (7) On the other hand, ILT formation is a common finding and is yet to be clarified its role on the AAA evolution. Indeed, inflammatory activity is present in ILT and can also be a responsible for the degradation of the quality of the aortic wall. Though, from a mechanical view, ILT can function as a protective layer, wherein smaller thrombi are associated with a faster AAA growth. (10)

Despite a controversial relation between Diabetes Mellitus and all-cause mortality after AAA repair (11-13), a paradoxical negative association between diabetes and AAA prevalence and growth (14-16) is well defined. The purposed explanations for the protection conceived by diabetes involve the main pathologic features of AAA - extracellular matrix (ECM) remodelling, VSMC, advanced glycation end products (AGEs) and inflammation (3).

Diabetic patients have a qualitative and quantitative alteration in the vascular wall structure: an increment in the basement membrane and some ECM components (17) leading to an increased arterial stiffness (18). In fact, peak wall stress levels are presumably related with the appearance of symptoms, being a biomechanical parameter suggested to provide a good estimate of the individual rupture risk. (19) The evidence is not concordant regarding the inflammatory mechanisms involved, but a correlation with

macrophage activity is suggested. On the one side, some evidence suggest that diabetic patients can have a reduction in metalloproteinase MMP-2 and MMP-9 concentration, as a protective means (20). On the other hand, diabetes is a condition known to promote a macrophage pro-inflammatory phenotype; however, its long term duration is suggested as a protective factor given the potentially associated compensatory anti-inflammatory phenotype (3, 21), boosted by the effect of glycation on interleukin-6, favouring its reduction.(22)

Antidiabetic drugs present with pleiotropic effects, and it is not completely clear whether this protection comes from the disease itself or from the anti-diabetic medications (23).

To date there is not an accepted clarification on this topic, which implies a better research on how antidiabetics drugs can have a role. Thus, the aim of this manuscript is to review the potential role of antidiabetic drugs on AAA formation and growth.

EVIDENCE ACQUISITION

Study design and literature search

A literature search was performed to identify studies investigating the role of antidiabetic drugs on AAA related outcomes – incidence and growth.

The following inclusion criteria were respected:

1- only original articles, with data related only to human studies;
2- reporting AAA formation and growth as an outcome;
3- defining, at least, one antidiabetic drug as exposure;
4- having a minimum of 3 month follow up, giving the relatively slow growth of AAA.

The last search was conducted on November 19th 2019 in Pubmed and Scopus databases, including only published results between January 1999 and November 2019, using the keywords “antidiabetic drugs”, “metformin”, “thiazolidinediones”, “PPAR-gamma agonists” “rosiglitazone”, “pioglitazone”, “sulfonylurea”, ”DPP-4 inhibitors”, “sitagliptin”, “alogliptin”, “GLP-1 agonists“, “incretins”, “liraglutide”, “exenatide”, ”SGLT2 inhibitors”, “dapagliflozin”, “empagligflozin” and “AAA” or “abdominal aortic aneurysms”, without language restrictions.

In a second step, duplicates were excluded and relevant titles selected, whose abstracts were read, when available, and checked for eligibility. Lastly, full text assessment was performed, excluding the

remaining studies that were neither original, nor presenting the same exposure or same outcome. In order to identify studies not included in the primary query, a cross-reference search was then performed.

For each study considered, the extracted characteristics were the authors, study design, published year and location, objectives of the study, number of patients and follow-up durations, definition of exposure and outcome, and when available both effect estimates and adjusted covariates.

EVIDENCE SYNTHESIS

Figure 1 represents the flowchart representative of the study selection procedure.

Six studies were included, with a total of 25810 patients: one study focus mainly in one specific drug or class (n=16), while five remaining studies reported on more than one antidiabetic drug (n=25794).

Four main classes of oral antidiabetic drugs were considered: Biguanides/Metformin (n=9326), Sulfonylureas (SU) (n=8975), Thiazolidinediones (TZD) (n=1380) and Dipeptidyl peptidase 4 (DPP4) inhibitors (n=420).

Biguanides-Metformin

AAA Incidence

Hsu et al. performed a nested case-control study including 8936 patients with DM extracted from Taiwan's National Health Insurance Research Database, representative of the majority of type 2 DM population in Taiwan. Cases (n=4468) were identified as those with either inpatient or outpatient diagnosis code of AA and controls (n=4468) matched for the duration of follow-up, age, sex, urbanization, monthly income, severity of diabetes and risk factor for AA. (24)

The authors studied the effects of four different classes of anti-diabetic drugs: Metformin, SU, TZD and DPP4 Inhibitors. Among the cases, 35% (n=1586) were prescribed Metformin, 37.8%(n=1689) were with SU, 6.6% (n=297) with TZD and 3.6% (n=163) with DPP4 Inhibitors. In the control group, 45% (n=2013) were metformin users, 46% (n=2056) were with SU, 9% (n=403) with TZD and 4.2% (n=187) with DPP4 inhibitors. (24)

Metformin use was associated with a lower risk of AA formation, with an OR=0.72 ($P<0.001$) after adjusting for comorbidities, when compared with patients without metformin (either with other antidiabetic or without any medication). Furthermore, dose-response relationship analysis was performed. Progressively

smaller odds ratios were found when increasing the duration of therapy under metformin prescription, suggesting a dose-responsive effect. (24)

AAA Growth

Itoga et al. reported the relationship between metformin prescription and AAA growth in a study including 13834 patients (entire population with DM), with a follow-up of 4.3 years. In this study 39.7% (n=5492) of the patients were prescribed metformin, 36.7% (n=5077) SU, 4.9% (n=678) TZD and 1.1% (n=152) prescribed alpha glucose inhibitors and 0.4% (n=55) prescribed DPP4 inhibitors. Metformin prescription was associated with an unadjusted annual enlargement of 1.2 mm/y (P<0.001), a 20% decrease when compared with the 1.5mm/y expansion of the remaining cohort without metformin (either with other antidiabetic medications or without any medication). When adjusting for comorbidities, metformin prescription presented a 1.17 mm/y expansion rate, a significant decrease of -0.23 mm/y (P<0.001) when compared to the mean growth rate for all the cohort (1.4 mm/y). (25)

Golledge et al. performed a three-cohort study including 1697 patients to analyse the association between diabetes treatments and AAA growth, including Metformin, SU, DPP4 Inhibitors and Insulin. The first cohort (C1), with a mean follow-up of 3.6 years, included 1357 AAA patients, of which 16% (n=217) had diabetes, 8.7% (n=118) were treated with metformin, 5.7% (n=78) with SU, 1% (n=13) with DPP4 Inhibitors and 0.8%(n=11) with Insulin. The second cohort (C2), with a follow-up of 2.9 years, was composed by 287 patients, including 24% (n=69) diabetic patients, 13.6% (n=39) metformin-treated patients and 7% (n=20) SU-treated. The third cohort(C3), followed for 1 year, included 53 patients, with 36% (n=19) diabetic patients and 30%(n=16) prescribed metformin. In all the three cohorts, mean annual growth rate was significantly slower in metformin-treated patients (C1 1.03 mm/y P= 0.012; C2 1.40 mm/y P= 0.004; C3 0.37 mm/y), when compared with patients not diabetic or not under metformin (C1 1.62 mm/y; C2 2.55 mm/y; C3 1.46 mm/y). However, growth rate was similar among other antidiabetic drugs and patients without diabetes or without metformin (C1 1.60 mm/y P=0.217; C2 2.18 mm/y P=0.514; C3 0.95mm/y P=0.693). Metformin prescription was more likely to be associated with a growth rate under the median in all the three cohorts either before or after adjustment for risk factors (C1 OR=0.59 P=0.008; C2 OR= 0.38 P=0.011); C3 OR= 0.13 P=0.010). (23)

Thompson et al. in a prospective cohort study with a follow-up of 3.4 years included 1269 patients identified in the Chichester AAA ultrasound surveillance program between 1984 and 2007 in order to explore the relationship between commonly prescribed medications (not only antidiabetic) and AAA growth. Biguanides and SU were included, along with other non-specified oral antidiabetic drugs and

insulin. In the cohort, 3.7% (n=47) of patients were under biguanides treatment, 3.3% (n=42) under SU prescription, 0.6%(n=8) with insulin and 1%(n=13) with other antidiabetic drugs. Biguanides-treated patients presented an AAA growth rate of 0.75 mm/y, while patients without biguanides treatment had a growth of 1.55 mm/y. Biguanides-treatment was associated with a significant reduction of -0.80 mm/y in the growth rate. (P=0.05). (26)

Fujimura et al. analysed the impact of metformin in AAA growth in a cohort of 58 diabetic patients over a period of 2.6 years. Analysis for patients treated with SU, TZD, DPP4 Inhibitors, insulin and meglitinide were also performed. In this population, 25.9% (n=15) were prescribed metformin, 22.4%(n=13) were prescribed SU, 3.4% (n=2) with TZD, 3.4% (n=2) with DPP4 Inhibitors, 22.4% (n=13) with insulin and 1.7%(n=1) with meglitinide. Metformin usage was associated with a significantly slower AAA expansion, with a 0.4 mm/y enlargement rate, while the 43 patients not taking metformin (either with other antidiabetic or without) presented a mean annual growth rate of 1.7 mm/y (P<0.05). (27)

Sulfonylureas

AAA Incidence

Hsu et al. analysed 1689 (37.8%) cases and 2056 (46%) controls all diabetic patients that were only SU-treated regarding AAA occurrence. After adjusting for comorbidities, prescription of SU was associated with a significant decrease in AA incidence, with an OR=0.82 (P=0.001), when compared with patients not SU-treated (either with another antidiabetic or without any medication). Moreover, as for metformin, a dose-response relationship was present. (24)

AAA Growth

Itoga et al. studied, as previously mentioned, 5077 (36.7%) SU-treated diabetic patients.

After adjusting for baseline comorbidities, SU-treated patients presented a 1.3 mm/y expansion rate, a reduction of -0.10 mm/y (P=0.006) compared to the adjusted growth rate for the remaining cohort (1.4 mm/y). (25)

Golledge et al. analysed the 78 (5.7%) SU-treated patients included the first cohort and the 20 (7%) SU-treated patients included in the second cohort. No difference in AAA enlargement was present between SU-treated patients (C1 1.31 mm/y; C2 2.25 mm/y P=0.084) and patients without SU (either with other antidiabetic drugs or without) (C1 1.58 mm/y; C2 2.37 mm/y), with an OR=0.62 (P=0.052) for the first cohort and an OR=0.81 (P= 0.654) for the second cohort. (23)

Thompson et al. studied the AAA expansion in their 42 (3.3%) patients prescribed SU. Prescription of SU was associated with an yearly expansion rate of 0.70 mm/y, a significant difference of -0.89 mm/y

(P=0.03) when compared with the 1.59 mm/y expansion rate of the group without SU (either with other antidiabetic or without). (26)

Fujimura et al. investigated the 13 (22.4%) diabetic patients SU-treated regarding AAA enlargement. No differences were found between patients prescribed SU, whose expansion rate was 1.3 mm/y (P>0.05) and the 45 patients without SU (either with other antidiabetic or without), whose AAA growth was 1.4 mm/y. Conversely, SU prescription presented an above the unity odds ratio for the AAA enlargement above the median rate. (27)

Thiazolidinediones

AAA Incidence

Hsu et al. included 297 (6.6%) cases and 403 (9.0%) controls under TZD prescription regarding their AAA occurrence. TZD usage was associated with a significant reduction in the risk of AA, presenting an OR=0.82 (P=0.003), when compared with patients not TZD-users (either with another antidiabetic or without). Was not possible to establish a dose response relationship. Analysis for AAA growth were not performed. (24)

AAA Growth

Itoga et al. analysed the AAA expansion of 678 (4.9%) diabetic patients with TZD intake. After adjustments, TZD prescription was associated with a 1.28 mm/y expansion rate, presenting a not significant difference of -0.12 mm/y (P=0.15) when compared to the mean growth rate for all the cohort (1.4 mm/y). (25)

Fujimura et al. had only 2 (3.4%) patients under TZD prescription in their cohort. No differences were found between the 1.7 mm/y (P>0.05) TZD associated growth rate and the 1.3 mm/y expansion of the 56 patients not prescribed TZD (either with other antidiabetic or without). (27)

Motoki et al. performed a study with 16 patients, with a follow-up of 4.2 months, in order to clarify whether a PPAR-ɣ agonist could have an anti-inflammatory effect in the aorta of 16 AAA patients waiting for aneurysectomy and grafting. Two groups were created, one with Pioglitazone (P) 15mg perorally for more than two months and one control (C) group without pioglitazone, with both groups continuing their previous treatment. The Pioglitazone group included 6 (37.5%) patients and the control group 10 (62.5%) patients. In the moment of the surgery, their aorta was compared **regarding its size** and its inflammatory markers. (28)

Besides AAA growth, selected outcomes were the level of macrophage infiltration, TNFα, MMP2, MMP-9 and adiponectin gene expressions in the wall of the aorta. There was not a significant change in the aneurysm size between the two groups, despite the stated improvement in the aorta conditions. There was,

instead, a significant increase in adiponectin gene expressions and a decrease in MMP-9 and TNFα gene expressions, but not in the one's macrophage-related neither on MMP-2. (28)

DPP-4 Inhibitors

AAA Incidence

Hsu et al. included in their study 163 (3.6%) cases and 187 (4.2%) controls using DDP4 inhibitors. No differences in AAA occurrence were seen between patients under DPP4 inhibitors prescription and the comparison group without DPP4 inhibitors (either with other antidiabetic or without), with an estimated OR=1.07 (P=0.582). (24)

AAA Growth

Itoga et al. had 55 (0.4%) diabetic patients using DPP-4 inhibitors. Analysis of AAA incidence were not performed. After adjustments, DPP4 inhibitors prescription was associated with a 1.22 mm/y expansion rate, revealing a not significant difference of -0.18 mm/y (P=0.52) when compared to the adjusted growth rate for all the cohort (1.4 mm/y). (25)

Golledge et al. included for analysis of AAA expansion 13 (1%) patients using DPP4 inhibitors in their first cohort. AAA incidence analysis were not reported. No differences were seen between AAA expansion associated with DPP4-inhibitors, whose mean enlargement rate was 1.47 mm/y (P=0.677) and patients not DPP-4 users (either with other antidiabetic drugs or without), with an expansion of 1.56 mm/y, presenting an OR=0.54 (P=0.280). (23)

Fujimura et al. analysed the 2 (3.4%) patients under DPP4 inhibitors prescription regarding their AAA expansion. Analysis for AAA incidence were not performed. No differences were seen when comparing DPP4 inhibitors associated enlargement (1.0 mm/y) with the cohort without DPP4 inhibitors (either with other antidiabetic drug or without), whose growth was 1.4 mm/y (P>0.05). (27)

Discussion

DM represents a well-known cardiovascular risk factor (29). However, prevalence and growth AAA rate are lower in diabetic patients. Yet, it is not completely clear whether the above-mentioned correlation is strictly related to Diabetes Mellitus per se, or if there's a protective impact of anti-diabetic medication. This review found that anti-diabetic drugs have an impact reducing incidence of AAA, but most significantly AAA growth rate.

Regarding AAA incidence, one publication reported that metformin was associated with a 28% decrease in the risk of AA occurrence along with a 18% reduction with sulfonylureas and thiazolidinediones prescription. In contrast, no differences were seen with DPP4 Inhibitors (24).

Furthermore, the fact that was found a dose-response relationship between long-term therapy with metformin and sulfonylureas, but not with thiazolidinediones, and a decrease in AA occurrence is another argument in favour of a protection conferred by some antidiabetic medications rather than Diabetes Mellitus itself. Of note, the authors reported a lower prevalence of AAA in their population, consistent with other studies from Asian populations (30), which can compromise the applicability of the results on Caucasian populations. However, a smaller sample of AA patients would increase the probability of not finding a sufficiently powered association, which was not verified, since that also on the mentioned population the incidence of AA was significantly decreased.

Five studies reported the effect of antidiabetic drugs on AAA growth. The main conclusion is that metformin prescription, but not the other diabetes treatments, is associated with a significant reduction in AAA growth rate. While the results were concordant regarding this effect of metformin, the absolute mean annual growth rates were not similar for all the studies. While Itoga et al. presented an enlargement rate of 1.17 mm/y(25) associated with metformin, Thompson et al.(26) and Fujimura et al.(27) presented much smaller yearly expansion rates of, respectively, 0.75 mm/y and 0.40 mm/y. These are some reasons that can explain this difference. Firstly, these studies use different instruments to measure the annual growth rate (table I) and some are operator-dependent, which can compromise the reproducibility of the outcome measured; then, the sample sizes used were considerably different, which can affect the precision of the findings, as the smaller is the sample, the bigger is the margin of error; lastly, considering the type of studies analysed, systematic errors cannot be excluded, namely on the nature of the collected information and the selection of patients, since the methodology was different between studies. Even though, results are coherent regarding the protective nature of the effect of metformin on the AAA enlargement rate. On the other side, concerning the other classes of antidiabetic drugs the results were controversial. Itoga et al.(25) and Thompson et al. (26) identified a smaller growth rate associated with the prescription of sulfonylureas of, respectively, 1.30 mm/y and 0.70 mm/y, which was not supported by the results provided by Golledge et al. (23) and Fujimura et al.(27), whose growth rate was similar, of 1.31 mm/y and 1.30 mm/y, but with any statistical significance. This discrepancy can be due to the small sample sizes which increase the probability of not finding a difference that is, indeed, present. Regarding TZD and DPP4 inhibitors, all the results were concordant on the absence of effect on AAA expansion. However, analysis of the associations for these classes were relatively underpowered, which introduces the doubt whether there is a real absence of effect or if a bigger sample was needed to reach significance. Therefore, metformin was the only antidiabetic drug systematically associated with a decrease in AAA growth.

Accumulating evidence suggest that metformin can have a role on decreasing oxidative stress. According to Diaz-Morales et al., this suppression in oxidative stress, through reduced mitochondrial and

NADPH oxidase ROS levels, can be due to an overexpression of SIRT3 (sirtuin-3), a NAD+ dependent deacetylase located in the mitochondria that when overexpressed reduces ROS production in several tissues. Thus, metformin, through an enhancement in the mRNA expression of SIRT3, can potentially decrease the levels of oxidative stress, one of the hallmarks in the pathogenesis of AAA. (31)

In addition, metformin is suggested to contribute to endothelial protection by different mechanisms. On the one hand, by reducing leukocyte rolling flux and adhesion, increasing leukocyte rolling velocity and reducing serum levels of ICAM-1 and P-selectin, metformin is associated with compromised leukocyte-endothelial interactions.(31) Fujimura et al. have administered 250mg/kg/day of metformin for 14 days in experimental AAA created via intra-aortic porcine pancreatic elastase (PPE) infusion. The experiment demonstrated that metformin treatment was associated with relatively preserved aortic medial elastin and smooth muscle cell, along with a reduced mural angiogenesis and a decrease in aortic inflammation, demonstrated by a reduced accumulation of macrophage and B and T cells. (27)

On the other hand, hyperglycaemia in diabetic patients is responsible for the endothelial dysfunction mediated by poly(ADP-ribose) polymerase-1 (PARP-1) activation (32). MMP-9 regulation is controlled by transcription factors, such as NF-kB, which in turn can be regulated by PARP-1 (33), thus resulting in pro-inflammatory and pro-oxidative state in diabetic patients (32, 34). Shang et al., using a db/db mice model, speculated whether administration of 200mg/kg/day of metformin could influence the vasculature by mediating phosphorylation of AMPK and PARP-1. Metformin dose and time-dependently increased AMPK and PARP-1 phosphorylation and PARP-1 phosphorylation was AMPK-dependent. Secondly, evaluated whether phosphorylation of PARP-1 could have an impact on the endothelial function and concluded that AMPK phosphorylation of PARP-1 increased the mRNA level of eNOS (endothelial nitric oxide synthase), SIRT1 (sirtuin-1) and Krüppel-like factor 4 (KLF4) and decreased that of monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1). Lastly, metformin, through AMPK-PARP-1 phosphorylation, improved endothelial functions in db/db mouse aortas by decreasing the expression of ICAM-1 and VCAM-1 and increasing eNOS, SIRT1, and KLF4 expressions. (32) In line with this, Vasamsetti et al. administrated metformin in angiotensin II induced-AAA formation apolipoprotein E deficient mice ($ApoE^{-/-}$), in a dose of 100 mg/kg/day for 6 weeks. Then demonstrated that metformin, through AMPK phosphorylation, dose dependently decreased STAT-3 activating phosphorylation and MMP-9 activity, thereby decreasing monocyte-to-macrophage differentiation and inflammatory pathways (35) common to the pathogenesis of AAA. In addition, Yang et al., using the same mouse model, studied the connection between AMPK signalling pathway and the pathogenesis of AAA and administrated metformin, 100 mg/kg/day, as an activator of AMPK signal pathway. This study demonstrated that activation of AMPK signal pathway seems to inhibit NF-κB and STAT-3 pathways,

both crucial in the chronic inflammation involved in the AAA progression. Plus, that activation of AMPK signal pathway, including activation induced by metformin, was associated with a reduced incidence, severity and mortality of the AAA. (36). Altogether, AMPK signalling pathway seems to be the major mechanism through which metformin has a vascular protective effect on the pathogenesis of AAA. Regarding the other OAD, some mechanisms are proposed, however there is still very few evidence, mainly coming from animal studies. While Hsu et al. suggest that sulfonylureas can exert their effect through SUR2 receptor (24), expressed in smooth muscle cells, Raffort et al. proposed that thiazolidinediones can play a role by decreasing osteopontin (OPN), which in turn could decrease macrophage accumulation. (3) Along with this, rosiglitazone is suggested to decrease E-selectin, TNFα and IL-6 in the aorta of experimental AAA (7) and to reduce MMP-9 serum level in T2D patients. (37) On the other hand, DPP-4 inhibitors decreased ROS production, increasing dose-dependently the elastin content and reduced the expression and activity of MMP-2 and MMP-9 in the aneurysmal aortic wall. (38). **Figure 2** summarizes the main mechanisms through which OAD can have a protective role on AAA disease progression.

However, evidence derived from rodents' experiments is controversial and reveals difficulties in raising successful treatments for AAA without a repair indication. (39) For this reason, our study has focused on clinical studies. Despite not being possible to assess the effect of each antidiabetic drug independently of diabetes, since therapeutic applications of these drugs are limited to conditions not otherwise linked with AAA, there are some arguments in favour of the validity of our results. First, each of our studies, with the exception of Motoki et al.(28), comprise a comparison between classes of antidiabetic drugs and the results are concordant for a protection conferred by metformin but not for the other classes; in addition, the study performed by Golledge et al.(23) goes further and makes a comparison between patients with metformin, patients with other antidiabetic drugs and patients not diabetic and without metformin, supporting that the prescription of metformin is associated with an additional decrease in the AAA growth rate. This finding has not been verified for diabetic patients prescribed other antidiabetic drug, when compared with non-diabetic patients, strengthening the idea that is metformin, rather than diabetes or other antidiabetic drug, the responsible for a decrease in AAA progression.

So far, was not possible to access the effect of antidiabetic drugs on non-diabetic patients, precluding an unbiased analysis of this relationship. Hence, according to the ESVS guidelines, antidiabetic drugs are not recommended for avoiding AAA growth (40). Accessing the effect of diabetes medication in a non-diabetic population could raise ethical concerns, large studies of this nature with long follow-up periods might add important insights on this matter. Yet, there is an ongoing trial addressing the efficacy of

metformin treatment in non-diabetic AAA patients regarding AAA growth rate at 12 months, in comparison to placebo or active comparator and this may have an impact for future recommendations. (41)

Our study has recognized limitations. First, considering the large amount of different antidiabetic drugs, is possible that some keywords were not included, excluding relevant studies. Then, metformin was the most prescribed drug in most of our studies, leaving the other classes relatively underpowered. Thus, analysis for the other antidiabetic drugs may lack precision giving the relatively small sample. Moreover, giving that the absolute mean growth rate for metformin was different between studies, is probable that is present a source of heterogeneity that should be excluded, namely on the sample, follow-up period and the methodology to evaluate AAA growth used. Finally, to our knowledge, was yet not possible to dissociate the effect of antidiabetic drugs from that of diabetes itself, which introduces a confounding factor when analysing the results. In vitro studies suggest that metformin can have a relevant role in limiting AAA disease progression. Therefore, investment on future studies addressing the real effect of antidiabetic drugs could be of great value giving its potential clinical benefit.

CONCLUSIONS

Understanding the mechanisms underlying the protective association conferred by diabetes could open a new therapeutic window in the management of AAA. By mediating pleiotropic effects, metformin can be a potential therapeutic agent for patients with AAA who do not have indication for surgery. Nonetheless, clinical trials are needed in order to clarify the role of antidiabetic drugs in the progression of AAA, independently of the diabetic status. Meanwhile, investing in clinical studies including not only metformin, but also other diabetes treatments, can be ethically more accessible and provide, at some extent, some evidence regarding the real and impartial preponderance of both the effect of diabetes medication and diabetes itself.

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NOTES

Conflicts of interest.

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.

Melissa Ribeiro-Silva: design and conception of the manuscript; writing the article; final approval of the manuscript;

José Oliveira-Pinto: design and conception of the manuscript; writing the article; final approval of the manuscript;

Armando Mansilha: design and conception of the manuscript; final approval of the manuscript.

TABLES

Table I.— *Characteristics of the studies included for the association of OAD and AAA formation/ AAA growth*

Table I *– Characteristics of the studies included for the association of OAD and AAA formation/ AAA growth*

Study	Study design	Antidiabetic drug	Follow-up	Nr patients	Outcome	Adjusted OR/ mean annual	Results	Controled for
ONE ANTIDIABETIC DRUG								
Motoki et al., 2015(28) Japan	Quasi-experimental	TZD: pioglitazone [Group P: 15mg/day per os for more than 2 months before aneurystectomy]	4.2 months	16 Group P =6 Group C = 10 Patients with AAA prior to aneurysectomy	Aneurysm size (*CT);* macrophage infiltration and gene expressions; TNFα, MMP-2, MMP-9 and adiponectin gene expressions.	---	No significant difference in aneurysm size; *Group P:* ↑ *adiponectin;* ↓*MMP-9, TNF*α	---
MORE THAN ONE ANTIDIABETIC DRUG								
Hsu et al., 2016(24) Taiwan	Nested case control study	Metformin, SU, TZD, alpha-glucosidase inhibitors, meglitinide, DPP-4 inhibitors	----	8936 Cases=4468 Controls=4468 Type 2 Diabetic population >20years in Taiwan from 2000 to 2013; Cases: inpatient or outpatient diagnosis code of AA (*ICD9-CM);* Controls: eligible controls with diagnosis of type 2 diabetes mellitus (DM) but without AA	Diagnosis of AAA *(NA)*	**Met- OR= 0.72** (0.64-0.80) **SU -OR =0.82** (0.74-0.92) **TZD- OR= 0.82** (0.69 - 0.98) **α GI - OR 0.95** (0.81–1.11) **DPP-4I- OR=1.07** (0.84–1.36)	Patients receiving OADs such as metformin, sulfonylurea and TZD have lower risks of developing an AAA, but not those treated with αGI inhibitors or DPP-4 inhibitors	Follow-up duration, socioeconomic status, age, sex, adapted Diabetes complications Severity Index score, duration of DM, alpha blocker, ACE inhibitor or ARB, beta blocker, calcium channel blocker, diuretics, an antiplatelet agent, warfarin, statin, steroid, antidepressants, NSAID and insulin.

Table I (continued) – *Characteristics of the studies included for the association of OAD and AAA formation/ AAA growth*

Study	Study design	OAD	Follow-up	No. patients	Outcome	Adjusted OR/mean annual AAA growth	Results	Controled for
MORE THAN ONE ANTIDIABETIC DRUG								
Itoga et al., 2019(25) Stanford, USA	Retrospective cohort	Metformin, Sulfonylurea, Alpha glucose inhibitors (αGI), DPP-4 Inhibitors, TZD	4.2 years	13834 Patients from VA Health Care System with AAA without rupture and diabetes *(ICD-9)*	Mean annual AAA growth rate (*CT, US, MRI)*	---- Mean annual growth rate *1.4 mm/y* **Metformin: 1.17** mm/y (P<0.001) **SU: 1.30** mm/y (P=0.006) **TZD: 1.28** mm/y (P=0.15) **DPP-4I: 1.22** mm/y (P=0.52)	Metformin prescription is associated with an additional reduction in AAA enlargement rate beyond that associated with the presence of diabetes itself; sulfonylureas were also associated with a significant decrease in AAA expansion rate.	Age, ethnicity, smoking status, comorbidities, and medication use at time of AAA diagnosis
Golledge et al., 2017(23) Australia	Cohort study - 3 cohorts according to maximum aortic assessment: 1) US surveillance (1357) 2) Repeated CT (287) 3) More detailed repeated CT (53)	Metformin(met), SU; DPP-4 Inhibitors, Insulin	Cohort 1: 3.6years Cohort 2: 2.9 years Cohort 3: 1 year	1697 Patients recruited during AAA surveillance	Mean annual AAA growth rate *(US, CT)*	**C1*** **Met -OR=0.59** (0.39-0.87) **SU- OR=0.62** (0.39-1.01) **DPP-4I - OR=0.54** (0.17-1.67) **Insulin- OR= 0.41** (0.11-1.57) **C2**** **Met- OR= 0.38** (0.18-0.80) **SU- OR=0.81** (0.31-2.07) **C3***** **Met -OR= 0.13** (0.03-0.61)	Metformin, but not other antidiabetic drugs, is associated with a slower annual AAA growth rate in all the 3 cohorts.	*smoking, ischemic heart disease, initial AAA diameter, sex; **smoking, ischemic heart disease, initial AAA diameter, sex and prescription of beta-blockers; *** smoking, ischaemic heart disease, initial AAA diameter

Table I (cont.) *– Characteristics of the studies included for the association of OAD and AAA formation/ AAA growth*

Study	Study design	Antidiabetic drug	Follow-up	Nr patients	Outcome	Adjusted OR/ mean annual AAA growth	Results	Controled for
MORE THAN ONE ANTIDIABETIC DRUG								
Thompson et al., 2010(26) Chichester, UK	Prospective cohort	Biguanides, SU, Insulin	3.4 years	1269 Patients identified with an AAA through the Chichester AAA screening program.	Mean annual AAA growth rate *(B-mode US)*	---- Mean annual growth rate: *1.97mm/y;* *Estimated difference* **Biguanides: -0.80** mm/y (-1.60; -0.008) **SU: -0.89** mm/y (-1.71; -0.07) **Insulin: -1.33** mm/y (-4.44; 1.78)	Drugs used in the treatment of diabetes were associated with a 56% reduction in AAA growth rate; biguanides and sulfonylureas were particularly associated with a reduction in AAA growth rates.	Age at baseline, MAP, gender, and smoking history
Fujimura et al., 2016(27) Stanford, USA	Retrospective cohort	Metformin, SU, TZD, Insulin, DPP4 Inhibitors, Meglitinide	2.6 years	58 Patients >50 years with both DM and intact abdominal aneurysms	Mean annual AAA growth rate *(CT)*	---- Mean annual growth rate: *1.3mm/y* **Met: 0.4** mm/y (P<0.05) **SU: 1.3** mm/y (P>0.05) **TZD: 1.7** m/y (P>0.05) **DPP-4I: 1.0** mm/y (P>0.05)	Only metformin usage was negatively associated with AAA enlargement; SU therapy was associated with enlargement above the median rate.	age, gender, initial and final diameter, race, current smoking status, body mass index (BMI), comorbidities and medications

TITLES OF FIGURES

Figure 1. - Flowchart representative of the study selection procedure.

Figure 2. - Hypothesized mechanisms underlying the protection conferred by OAD. AMPK activation is thought to be the major mechanism through which metformin has a vascular protective effect. For SU, TZD and DPP4 inhibitors some mechanisms are purposed, but evidence is still lacking.

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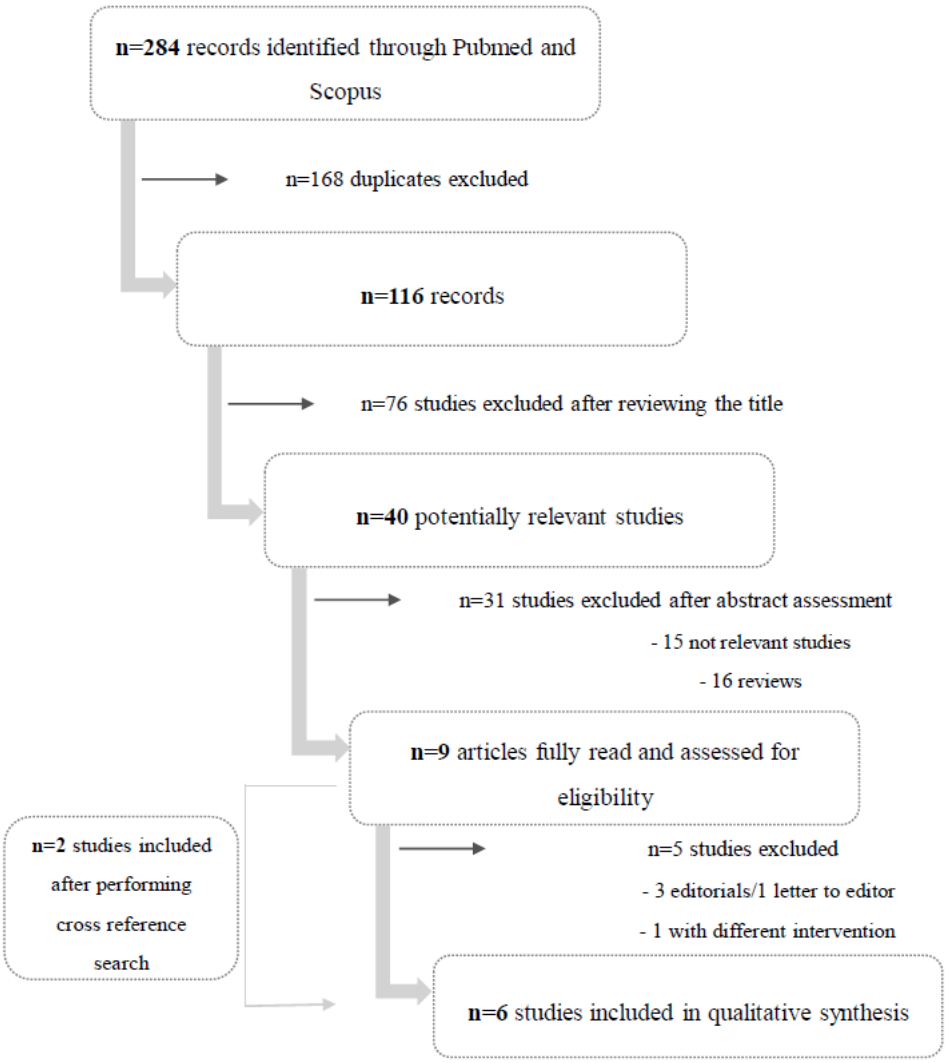
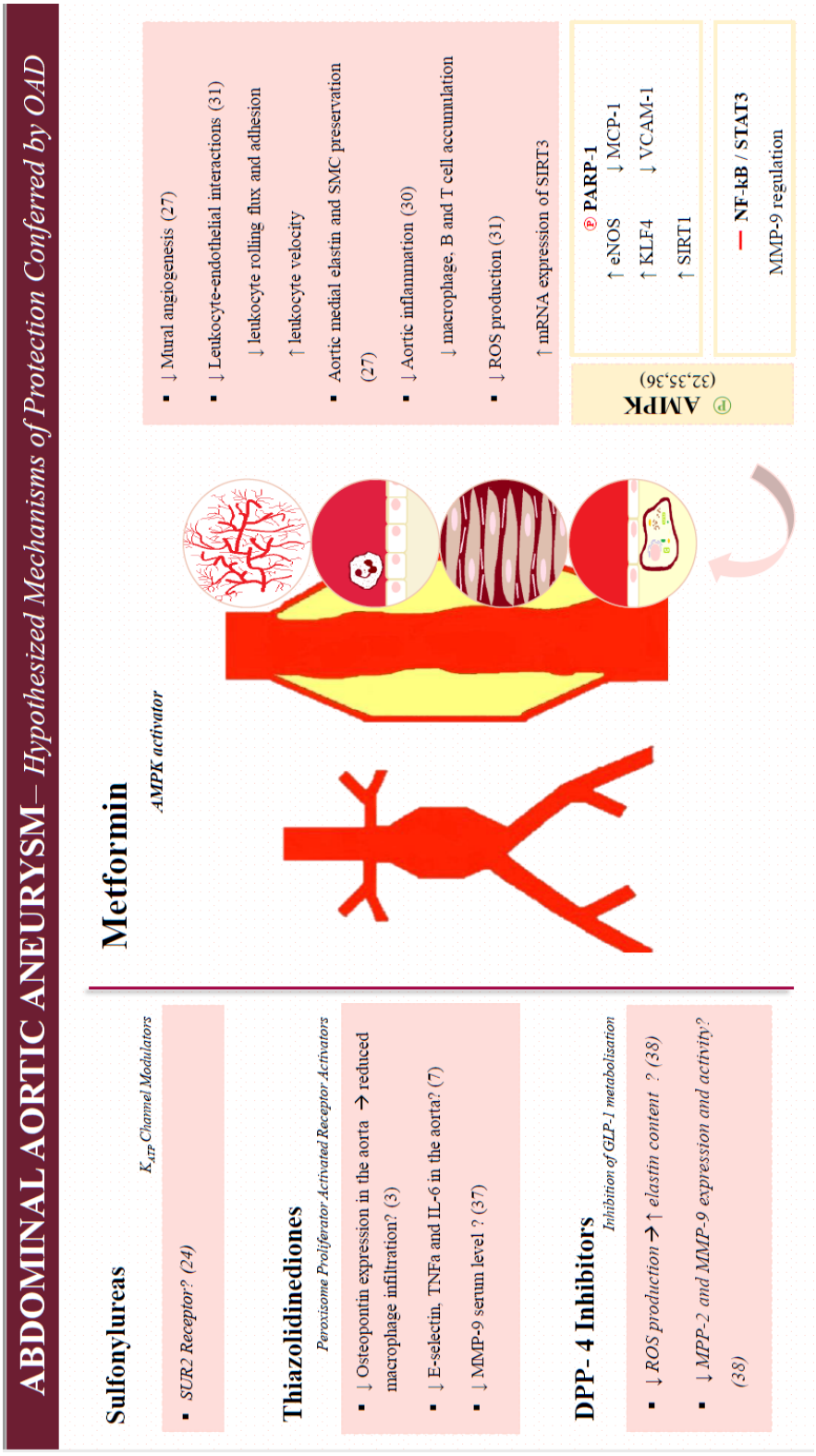


Figure 2. - Hypothesized mechanisms underlying the protection conferred by OAD. AMPK activation is thought to be the major mechanism through which metformin has a vascular protective effect. For SU, TZD and DPP4 inhibitors some mechanisms are purposed, but evidence is still lacking.



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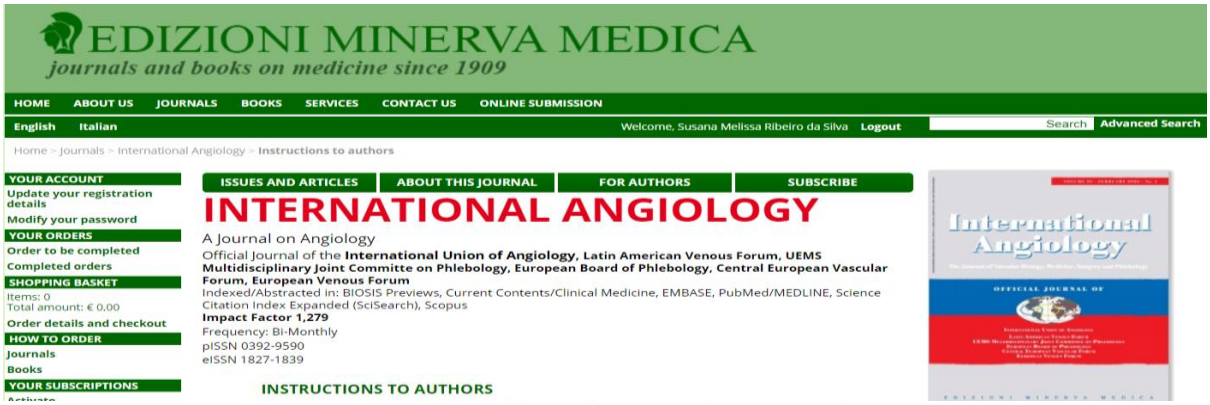
Anexo(s)

Normas de publicação da revista "International Angiology"



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Original articles. These should be original contributions to the subject. The text should be 3000-5500 words (8 to 16 typed, double-spaced pages) not including references, tables, figures. No more than 50 references will be accepted. The article must be subdivided into the following sections: introduction, materials (patients) and methods, results, discussion, conclusions. The introduction should describe the theoretical background, the aim of the study and the hypothesis to be tested. The materials and methods section should describe in a logical sequence how the study was designed and carried out, how the data were analyzed (what hypothesis was tested, what type of study was carried out, how randomization was done, how the subjects were recruited and chosen, provide accurate details of the main features of treatment, of the materials used, of drug dosages, of unusual equipments, of the statistical method ...). In the results section the answers to the questions posed in the introduction should be given. The results should be reported fully, clearly and concisely supported, if necessary, by figures, graphs and tables. The discussion section should sum up the main results, critically analyze the methods used, compare the results obtained with other published data and discuss the implications of the results. The conclusions should briefly sum up the significance of the study and its future implications. For randomised controlled trials it is suggested to the

authors to conform the structure of their paper to the checklist requirements of the following guidelines reported by the CONSORT statement: **http://www.consort-statement.org**.

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Articles should include an abstract of between 200 and 250 words. For original articles, the abstract should be structured as follows: background (what is already known about the subject and what the study intends to examine), methods (experimental design, patients and interventions), results (what was found), conclusions (meaning of the study). For systematic reviews and meta-analyses, the abstract should be structured as follows: introduction, evidence acquisition, evidence synthesis, conclusions. Key words should refer to the terms from Medical Subject Headings (MeSH) of MEDLINE/PubMed. No abstracts are required for editorials or letters to the Editor.

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Identify methodologies, equipment (give name and address of manufacturer in brackets) and procedures in sufficient detail to allow other researchers to reproduce results. Specify well-known methods including statistical procedures; mention and provide a brief description of published methods which are not yet well known; describe new or modified methods at length; justify their use and evaluate their limits. For each drug generic name, dosage and administration routes should be given. Brand names for drugs should be given in brackets. Units of measurement, symbols and abbreviations must conform to international standards. Measurements of length, height, weight and volume should be given in metric units (meter, kilogram, liter) or their decimal multiples. Temperatures must be expressed in degrees Celsius. Blood pressure must be expressed in millimeters of mercury. All clinical chemistry measurements should be expressed in metric units using the International System of Units (SI). The use of unusual symbols or abbreviations is strongly discouraged. The first time an abbreviation appears in the text, it should be preceded by the words for which it stands.

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Table body	*Table body*	*Table body*	*Table body*
Table body	*Table body*	*Table body*	*Table body*

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