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COMMENTARY

Moving from the stratification of primary and secondary prevention of cardiovascular risk in diabetes towards a continuum of risk: need for a new paradigm

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Abstract

Traditionally, patients with type 2 diabetes have been stratified according to cardiovascular (CV) risk to requiring either primary prevention (those without atherosclerotic CV disease) or secondary prevention (those with atherosclerotic CV disease in any of the vascular beds). However, this classification is misleading and arbitrary, as not all patients requiring secondary prevention have the same risk for such events, which also holds true for those requiring primary prevention (i.e. CV risk ranges from moderate to very high). In addition, in some cases, the definitions of primary and secondary prevention do not rely on symptoms but rather on the results of supplementary tests. Furthermore, patients with type 2 diabetes may also develop heart failure or chronic kidney disease. Importantly, reducing CV risk stratification to primary and secondary prevention does not provide a comprehensive approach for the management of patients with diabetes, leading to an underuse of drugs with proven CV benefit regardless of the presence of atherosclerotic CV disease. Therefore, patients with diabetes should be treated according to their CV risk considered as a continuum and not simply as falling within primary or secondary prevention.

Keywords: acute cardiovascular event, cardiovascular risk, diabetes, secondary prevention.

Citation

Garcia-Moll X, Barrios V, Franch-Nadal J. Moving from the stratification of primary and secondary prevention of cardiovascular risk in diabetes towards a continuum of risk: need for a new paradigm. *Drugs Context*. 2021;10:2021-6-3. https://doi.org/10.7573/dic.2021-6-3

Type 2 diabetes mellitus (T2DM) is a condition with important cardiovascular (CV) consequences. The presence or absence of such complications are definitory for patients to be stratified into requiring primary or secondary prevention. Traditionally, the definition of secondary prevention applied to patients who had previously experienced an acute ischemic event (i.e. stroke, acute coronary syndrome, peripheral artery disease) and that of primary prevention covered patients who had not experienced a previous ischemic event.[1] In fact, most randomized clinical trials evaluating CV outcomes have categorized patients as requiring primary or secondary prevention. However, although CV outcomes clinical trials use primary and secondary prevention to categorize patients with T2DM, not all outcomes are the same within those categories of patients. For example, in their meta-analysis, Zelniker et al.[2] found that sodium–glucose co-transporter 2 inhibitors (SGLT2i) significantly reduced major adverse CV events (MACE) only amongst patients affected by atherosclerotic CV disease (ACVD) but not in those who were not affected. However, in the DECLARE-TIMI 58 trial, dapagliflozin did not significantly reduce MACE in patients receiving secondary prevention, although it did significantly reduce the risk of MACE in those who had previously experienced myocardial infarction, suggesting that patients covered by the definition of secondary prevention in fact respond differently to CV therapies.[3] For example, similarly to patients with ACVD, guidelines state that low-dose aspirin could be considered in primary prevention in patients with T2DM at high or very high CV risk.[4,5] In addition, guidelines recommend the use of moderate-intensity or high-intensity statins for primary prevention in patients with diabetes according to CV risk.[5,6]

In summary, most guidelines on current treatments issued by scientific organizations and administrations still consider that patients requiring primary or secondary prevention are candidates for certain therapies based on their risk profiles.[4–6] However, as clinical guidelines suggest, not all patients requiring secondary prevention have the same risk of adverse outcomes; this is also true for those requiring primary prevention, leading to different beneficial effects of CV treatments that do not depend on whether a patient

requires primary or secondary prevention but, rather, on CV risk. In addition, in some cases, the definitions of primary and secondary prevention do not rely on symptoms but on the results of supplementary tests. For example, a patient with no prior stroke is considered to require primary prevention. Yet, if the same patient undergoes a carotid scan and atherosclerotic plaques are found, then they will automatically be considered to require secondary prevention.[7] Consequently, these terms may be misleading and are somehow arbitrary.

Whilst T2DM is a major risk factor for ACVD, which remains the most common cause of death in this population, renal disease and heart failure are also frequent complications that may occur even in the early stages of the disease.[1,8] Therefore, reducing primary and secondary prevention to the presence or absence of ischaemic CV disease does not provide a comprehensive approach for the management of patients with diabetes, leading to an underuse of drugs that have been shown to positively impact these outcomes such as SGLT2i or some glucagon-like peptide 1 (GLP1) receptor agonists. In fact, clinical trials have demonstrated that SGLT2i significantly reduce the incidence of CV death and hospitalization for heart failure as well as the risk of progression of renal disease and that some GLP1 receptor agonists reduce the risk of MACE regardless of the presence of ACVD.[2,9]

Therefore, patients with diabetes should be treated by considering their CV risk as a continuum of risk – not necessarily the same as considering CV risk as requiring primary or secondary prevention.[4] European guidelines consider CV risk to be very high in patients with documented ACVD, diabetes with target organ damage (microalbuminuria, retinopathy or neuropathy), at least three major risk factors, or a long duration of diabetes (>20 years). By contrast, CV risk is considered high in patients with diabetes without target organ damage, a duration of diabetes ≥10 years, or an additional risk factor. Finally, young patients (defined as those with type 1 diabetes mellitus and aged <35 years; those with T2DM and aged <50 years) with a duration of diabetes <10 years and no other risk factors have a moderate risk.

Of note, no patient with diabetes has a low CV risk.[6] However, CV risk stratification for patients with diabetes has not been universally standardized. Thus, some authors define CV risk in patients with diabetes as follows: very high (previous ischaemic CV event), high (high clinical or instrumental evidence of CV disease, stenosis of >50% in coronary, carotid or lower extremity arteries, documented coronary heart disease, revascularization at any site), and moderate-to-high (multiple risk factors, obesity/overweight, hypertension, dyslipidaemia, smoking, family history of premature coronary heart disease, renal insufficiency, albuminuria).[1] Therefore, although CV risk must be stratified in patients with diabetes, authors disagree on how this should be conducted. In addition, based on additional imaging evaluations (i.e. arterial ultrasound, computed tomography, magnetic resonance, coronary artery calcium score with computed tomography), asymptomatic patients with diabetes may be re-classified at a higher risk level.[10] Moreover, other CV risk factors or clinical conditions that can modify CV risk should be considered when stratifying risk.[4,6]

In the light of these points, many important questions emerge. What if patients included in randomized trials were reclassified as per the risk classification suggested by guidelines instead of being classified as requiring secondary or primary prevention? Would the results be the same? By considering patients as requiring primary or secondary prevention, are we treating them appropriately according to their real CV risk? It could be argued that patients requiring secondary prevention are treated more appropriately; however, as previously mentioned, there are patients classified as requiring primary prevention who have a high or even very high CV risk equivalent to that of those requiring secondary prevention. CV risk is a continuum and patients may be better treated if we base our decisions on their risk rather than if we only consider a binary variable (primary/secondary prevention). It is necessary to perform a specific analysis of CV outcome trials in order to identify the variables associated with CV outcomes and update risk score classification for patients with diabetes as the current score seems insufficient. By stratifying patients according to their CV risk, we can tailor holistic treatment more accurately than by restricting our choices to primary or secondary prevention and thus consider blood pressure targets, lipid targets, CV prevention, and glycaemic targets. Additionally, given the high CV risk of patients with diabetes, the term 'primary prevention' may no longer be appropriate in this group of patients as it could lead to an underestimation of CV risk and, secondarily, to the underuse of CV drugs that have proven beneficial effects, not only on ischaemic outcomes but also in the slowing of progression of heart failure and renal disease. Therefore, drugs with a proven CV risk prevention profile should be used from the early stages of diabetes in order to decrease CV risk. Other families of drugs that only reduce HbA1c levels but offer no CV benefits should thus be used to ensure good metabolic control in combination with or in addition to those that have CV benefits.

Adequate scaling of CV risk in patients with diabetes is paramount and new, updated risk scales are necessary.[11]

Contributions: All authors have participated in drafting, reviewing, and/or revising the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: XGM declares no conflict of interest regarding the subject of the manuscript. VB declares no conflict of interest regarding the subject of the manuscript. JF declares no conflict of interest regarding the subject of the

manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2021/07/dic.2021-6-3-COI.pdf

Acknowledgements: Editorial assistance was provided by Content Ed Net, Madrid, Spain.

Funding declaration: Editorial assistance was funded by Boehringer Ingelheim and Lilly Alliance.

Article URL: https://www.drugsincontext.com/moving-from-the-stratification-of-primary-and-secondary-prevention-of-cardiovascular-risk-in-diabetes-towards-a-continuum-of-risk:-need-for-a-new-paradigm

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Provenance: Submitted; externally peer reviewed.

Submitted: 11 June 2021; **Accepted:** 13 July 2021; **Publication date:** 18 August 2021.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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