Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Programa de Pesquisa e Pós-Graduação em Ciências Médicas: Endocrinologia

Análise da Eficácia e Segurança Cardiovascular das Estratégias Atuais de Tratamento do Diabetes Mellitus Tipo 2

Tese de Doutorado

Dimitris Rucks Varvaki Rados

Porto Alegre, 2019.

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Orientadora: Profa. Dra. Cristiane Bauermann Leitão

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Esta Tese de Doutorado será apresentada no formato exigido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Ela é constituída de uma breve introdução em Português, três artigos em Inglês e considerações finais em Português. Os artigos dessa tese apresentam delineamento de Revisão Sistemática com Metanálise.

Dedicatória

"As melhores ideias de pesquisa que tive na minha carreira foram dentro do consultório, atendendo meus pacientes."

À memória do professor Jorge Luiz Gross.

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Sumário

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Lista de Abreviações

CABG – *coronary artery bypass grafting*

DM2 – Diabetes Mellitus tipo 2

GLP-1RA – análogos do peptídeo semelhante ao glucagon 1 (*glucagon-like peptide-1 receptor agonists*)

GRADE – *Grading of Recommendations, Assessment, Development and Evaluations*

PCI – *percutaneous coronary intervention*

PROSPERO – *International Prospective Register of Systematic Reviews*

RCT –*randomized controlled trials*

RR – *relative risk*

RRR – *relative risk reduction*

SBP – *systolic blood pressure*

SGLT2i – inibidores do co-transportador de glicose e sódio tipo 2 (*sodium-glucose-linked cotransporter 2 inhibitors*)

SH – *severe hypoglycemia*

TSA – *Trial sequential analysis*

Resumo

O *Diabetes Mellitus* tipo 2 (DM2) é uma condição de alta prevalência e com tendência a aumento da sua frequência, especialmente em países de média e baixa renda. É um dos principais fatores de risco para eventos cardiovasculares e intervenções capazes de reduzir esse risco são fundamentais.

Os estudos de revisão sistemática e meta-análise podem ser utilizados para compilar dados de estudos individuais e auxiliar no julgamento clínico. Por se tratarem de uma abordagem sistematizada aos estudos disponíveis, estão menos sujeitas a seleção de informação e direcionamento das conclusões que outros tipos de revisões e diretrizes. Utilizando-se desse recurso, nessa tese exploramos a segurança do tratamento com insulina basal, a eficácia do rastreio de cardiopatia isquêmica assintomática e os fatores que determinam os efeitos na mortalidade da farmacoterapia em pacientes com DM2.

Em relação à segurança da insulina, observa-se que o seu uso não está associado com aumento de risco de mortalidade ou de eventos cardiovasculares. Como esperado, o tratamento com insulina está associado a maior risco de hipoglicemias graves. O rastreio de doença arterial coronariana em pacientes com DM2 não é estratégia eficaz para redução de mortalidade ou eventos cardíacos (incluindo infarto não fatal, revascularização, insuficiência cardíaca e revascularizações). Por fim, a avaliação conjunta dos medicamentos antihiperglicemiantes sugerem que seus efeitos em fatores metabólicos como hiper e hipoglicemia, peso corporal e pressão arterial podem explicar parte das diferenças identificadas em termos de mortalidade e eventos cardiovasculares.

De forma agregada, esses achados auxiliam no cuidado dos pacientes com DM2. Além disso, indicam quais aspectos do conhecimento médico atual que ainda estão inexplorados e necessitam de novos estudos.

Capítulo 1

Introdução

O *diabetes mellitus* tipo 2 (DM2) é uma condição de alta prevalência e com tendência a aumento da sua frequência, especialmente em países de média e baixa renda. [1] O seu manejo exige dos profissionais, além do simples controle da hiperglicemia, cuidados abrangentes de diversos aspectos da saúde. [2] Isso inclui manejo da pressão arterial, controle do peso, rastreio de complicações, entre outros. [2] DM2 é um dos principais fatores de risco para eventos cardiovasculares, tanto em termos de prevalência quanto em magnitude. [1] Em função disso, pacientes com diabetes estão sujeitos a maior risco de morte e eventos cardiovasculares. [1] E, portanto, intervenções capazes de reduzir esse risco são fundamentais, tanto individualmente quanto em termos de saúde populacional. Por se tratar de condição de alta prevalência e interesse de pesquisa, múltiplas intervenções no DM2 já foram (e estão sendo constantemente) testadas, o que impõem aos profissionais um desafio adicional: a atualização e escolha de opções de tratamento mais eficazes e adequadas para cada paciente. Essa dificuldade ocorre tanto na decisão junto ao paciente quanto no momento de gerir recursos.

Diretrizes de manejo são úteis para auxiliar nesse problema, pois resumem o conhecimento vigente e fornecem orientações para decisão. [2] Entretanto, essas mesmas diretrizes podem ser enviesadas e contemplar apenas visões parciais do problema e representar mais opinião de especialistas do que as evidências disponíveis sobre o assunto. [3, 4] Em suma, não são obrigatoriamente um extrato do melhor conhecimento disponível naquele contexto. [3, 4] Os estudos de revisão sistemática e metanálise podem ser utilizados para compilar dados de estudos individuais (de intervenção ou não) e embasar o julgamento, apresentando de forma sumarizada as evidências disponíveis para

determinado aspecto do manejo do paciente. [5] Por se tratar de uma abordagem sistematizada ao conhecimento disponível no momento, as revisões sistemáticas estão menos sujeitas a seleção de informação e direcionamento das conclusões dependendo dos vieses dos autores que revisões não sistemáticas (narrativas). [5] Outra utilidade das revisões sistemáticas e metanálises é dirimir dúvidas em situações em que os resultados dos estudos são conflitantes ou negativos, minimizando as controvérsias em relação à melhor opção de manejo para os pacientes. Uma vez que seu método permite reunir todos os estudos existentes sobre o assunto, podem fornecer respostas mais definitivas do que cada estudo individualmente. [5]

Dentre os recursos de análises disponíveis nas metanálises temos a técnica de *Trial Sequential Analysis* (TSA). [6-8] Ela tem o objetivo de avaliar estatisticamente a confiabilidade dos resultados de metanálises, combinando técnicas de metanálise cumulativa, cálculo de tamanho amostral e ajustes para analises repetidas. [6-8] Em suma, a TSA avalia se há dados suficientes para definir que uma intervenção é benéfica, maléfica ou inócua considerando-se uma diferença mínima decidida arbitrariamente (com base em critérios clínicos, idealmente). [6-8] Dessa forma, essa é uma estimativa do poder total dos estudos incluídos.

Outros recursos disponíveis são as análises de subgrupo e metaregressões. Ambos utilizam características dos estudos para explorar resultados das metanálises, em especial em situações de alta heterogeneidade estatística. Assim são capazes de identificar situações ou subgrupos de pacientes que se beneficiariam mais ou menos das intervenções estudadas. Apesar dessas vantagens, algumas limitações devem ser apontadas. Primeiro, são análises que rompem a alocação randomizada entre os grupos e, portanto, são de natureza observacional. Como na maioria das vezes exploram variáveis (fatores da regressão ou subgrupos) no nível do estudo e não do indivíduo, outra limitação é a perda

da variabilidade dos dados. Além disso, são análises com baixo poder estatístico, então a ausência de diferença não descarta que aquele possa ter influência no desfecho.

Em relação ao manejo do diabetes, a insulina teve papel fundamental na mudança da história natural do diabetes tipo 1, transformando uma doença de mortalidade de até 70% no primeiro ano após o diagnóstico em uma doença crônica. [9, 10] Foi somente com a introdução dessa mudança que os pacientes passaram a viver tempo suficiente para enfrentar complicações cardiovasculares (macrovasculares) e microvasculares. [9] Com a disfunção progressiva da massa de células beta do pâncreas, com frequência pacientes com DM2 também necessitam desse medicamento. [11] Apesar de sua importância, estudos observacionais e de manejo intensivo da glicemia tiveram resultados conflitantes e levantaram dúvidas sobre a sua segurança em pacientes com DM2. [12-18] Especula-se que teria efeitos diretos promovendo aterosclerose, além dos riscos de hipoglicemia.

Na tentativa de reduzir o risco de eventos cardiovasculares em pacientes com DM2, o rastreio de doença arterial coronariana assintomática ou em fase "pré-clínica" parece ser uma estratégia potencialmente benéfica. Essa estratégia baseia-se no risco elevado de eventos cardiovasculares que pessoas com DM2 estão expostos e no fato de que por vezes essa manifesta-se de forma atípica ou silenciosa, devido a neuropatia cardiovascular autonômica apresentada pelos pacientes. Com esse racional, por vários anos o rastreio sistemático de doença coronariana foi recomendado no manejo do DM2 – de forma análoga ao rastreio de doença renal e retinopatia. No entanto, os resultados de alguns estudos que avaliaram o rastreio de doença cardiovascular mudaram esta conduta. [19, 20] Apesar disso, as limitações no poder desses estudos (por taxas de eventos menores que as estimadas) fazem com que essa seja uma abordagem ainda a ser explorada para o manejo dos pacientes com DM2.

Quanto ao tratamento farmacológico, existem várias classes de medicamentos disponíveis para o manejo da hiperglicemia no DM2. Apesar disso, até recentemente, apenas a metformina havia se mostrado capaz de reduzir o risco de eventos cardiovasculares e mortalidade. [21] Nos últimos anos, estudos com medicamentos das classes dos inibidores do co-transportador de glicose e sódio tipo 2 (*sodium-glucose-linked cotransporter 2 inhibitors* –SGLT2i) e dos análogos do peptídeo semelhante ao glucagon 1 (*glucagon-like peptide-1 receptor agonists*– GLP-1RA) também identificaram efeitos benéficos nesses desfechos em pacientes de alto risco. [22-24] Apesar de possuírem mecanismos de ação diversos, semelhanças nos efeitos metabólicos desses medicamentos chamam a atenção, uma vez que levam a perda ponderal e melhora do controle glicêmico sem aumento do risco de hipoglicemia. Além disso, destaca-se que há heterogeneidade não apenas entre classes, mas também dentro das classes, com medicamentos com perfis de segurança e eficácia em desfechos cardiovasculares diferentes. [22-27] Portanto, os determinantes dos diferentes efeitos dos medicamentos antihiperglicemiantes não parece estar elucidado.

Como apresentado, há vários aspectos do cuidado de pacientes com DM2 que geram dúvidas, tanto na prática clínica como em questões de pesquisa. E técnicas de metanálise podem auxiliar na elucidação desses questionamentos e, portanto, no atendimento dos pacientes. Assim, essa tese tem três objetivos:

- avaliar a eficácia e segurança do uso de insulina nos pacientes com DM2;

- avaliar o benefício do rastreamento de cardiopatia isquêmica assintomática em pacientes com DM2;

- avaliar se os efeitos dos medicamentos antihiperglicemiantes na HbA1c, frequência de hipoglicemias, peso e pressão arterial explica seus benefícios em termos de mortalidade e eventos cardiovasculares em pacientes com DM2.

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Capítulo 3

Artigo 2

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Screening for Coronary Artery Disease in type 2 Diabetic Patients: A Meta-analysis and Trial Sequential Analysis

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STRUCTURED ABSTRACT (252)

Objective: To evaluate the efficacy of coronary artery disease screening in asymptomatic patients with type 2 diabetes and assess the statistical reliability of the findings.

Methods: Electronic databases (MEDLINE, EMBASE, Cochrane Library and clinicaltrials.org) were reviewed up to July 2016. Randomized controlled trials evaluating coronary artery disease screening in asymptomatic type 2 diabetic patients and reporting cardiovascular events and/or mortality were included. Data was summarized with Mantel-Haenszel relative risk. Trial sequential analysis (TSA) was used to evaluate the optimal sample size to detect a 40% reduction in outcomes. Main outcomes were all-cause mortality and cardiac events (non-fatal myocardial infarction and cardiovascular death); secondary outcomes were non-fatal myocardial infarction, myocardial revascularizations and heart failure.

Results: One hundred thirty-five references were identified and 5 studies fulfilled the inclusion criteria and totalized 3315 patients, 117 all-cause deaths and 100 cardiac events. Screening for coronary artery disease was not associated with decrease in risk for all-cause deaths (RR 0.95 [95% CI 0.66 to 1.35]) or cardiac events (RR 0.72 [95% CI 0.49 to 1.06]). TSA shows that futility boundaries were reached for all-cause mortality and a relative risk reduction of 40% between treatments could be discarded. However, there is not enough information for firm conclusions for cardiac events. For secondary outcomes no benefit or harm was identified; optimal sample sizes were not reached.

Conclusion: Current available data do not support screening type 2 diabetic patients for coronary artery for preventing fatal events. Further studies are needed to assess the effects on cardiac events.

PROSPERO: CRD42015026627.

KEYWORDS: Cardiovascular disease screening; type 2 diabetes; systematic review; meta-analysis; trial sequential analysis.

ARTICLE SUMMARY

Strengths and limitations of this study

- Electronic databases were reviewed to identify randomized controlled trials evaluating screening for coronary artery disease in type 2 diabetes.
- Results from individual studies were combined and summarized with Mantel-Haenszel relative risk.
- Trial sequential analysis was used to assess the optimal sample size for the outcomes.
- The results should be interpreted with caution as different screening methods were combined.

INTRODUCTION

Diabetes mellitus is a well-known risk factor for atherosclerosis and asymptomatic coronary disease is frequent and associated with increased mortality.[1] Intensive medical treatment with antiplatelet agents, statins, as well as blood pressure and glycemic control decrease the number of cardiovascular events in patients with established coronary artery disease.[2] It is expected that early detection and treatment of myocardial ischemia would lead to similar benefits.

Coronary artery bypass grafting reduces mortality by 40% in patients with diabetes and established multivessel coronary disease.[3] However, percutaneous coronary intervention (PCI) does not appear to influence mortality in patients with asymptomatic and stable coronary artery disease (with or without diabetes) when compared to intensive medical therapy alone.[4] BARI 2D study results showed no benefit of early revascularization in patients with type 2 diabetes. On the other hand, it suggested that coronary artery bypass grafting (CABG) might be better than medical therapy alone, but this finding must be interpreted with caution, as the allocation to PCI or CABG was not randomized.[5] Moreover, patients with diabetes and high-risk coronary lesions do benefit from CABG.[3] In summary, the goal of a screening strategy for coronary artery disease in type 2 diabetic patients would be the identification of subjects with high-risk coronary lesions (multivessel), who would be eligible for CABG and might benefit from this intervention by reducing coronary events and mortality.

Some trials directly evaluated the effects of screening for coronary artery disease vs. usual care and found no benefit for mortality or coronary events.[6 7] These trials were performed with adequate designs but in most cases have limited conclusions due to lack of power.[6 7] Meta-analysis is a valuable tool in this situation, as it combines studies in a

single analysis, which increases the sample size. Furthermore, trial sequential analysis (TSA) enables the assessment of sample size power and the need for further studies.[8 9] Therefore, our objective was to assess the efficacy of screening for asymptomatic coronary artery disease in type 2 diabetic patients compared to no screening in reducing cardiac events (non-fatal myocardial infarction and cardiovascular mortality) and all-cause mortality. Furthermore, we aimed to evaluate the statistical reliability (sample size power) of the results.

RESEARCH DESIGN AND METHODS

This study follows the PRISMA statement for reporting systematic reviews and meta-analysis.[10] The present review was registered in the PROSPERO registry under number CRD42015026627.

Search strategy

To perform the present study, we searched for randomized controlled trials evaluating the effects of screening for coronary artery disease in type 2 diabetic patients reporting any of the outcomes of interest, which were non-fatal myocardial infarction, cardiovascular and all-cause mortality, myocardial revascularizations and heart failure events. Pubmed, EMBASE, Cochrane library and clinicaltrials.org databases were searched from inception through July 2016 using the following terms: type 2 diabetes, screening of coronary heart disease and randomized clinical trial. No restrictions were made regarding study length, publication year or language. The full search terms for Pubmed were: *(screening AND coronary artery disease) AND (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])*

AND "Diabetes Mellitus, Type 2"[Mesh]. We also searched the references lists of main publications on the topic manually.

Study selection

Two authors (DVR and LCP) performed the study selection independently. We included any randomized controlled trial which included type 2 diabetic patients and that evaluated the effects of any coronary artery disease screening method on the incidence of non-fatal myocardial infarction, cardiovascular or all-cause mortality. We excluded studies that were not randomized and that compared two different screening methods. Initially, titles and abstracts were reviewed for potentially eligible studies. These studies were then evaluated in full-text and those reporting any of the selected outcomes were considered for the final review and meta-analysis.

Data extraction

The following information was extracted with a standardized form: first author´s name; study name and year of publication; screening method; study registry; baseline HbA_{1c} and age; number of men; number of patients in each group; follow-up time; number of events: non-fatal myocardial infarction, cardiovascular and all-cause deaths, revascularizations and heart failure events. We defined cardiac events as a composite of non-fatal myocardial infarctions and cardiovascular deaths.

Appraisal of study quality

We evaluated the risk of bias at the study level with the Cochrane Collaboration tool;[11] for the “other bias” item we evaluated the presence of a trial registry as low risk of bias and lack of registry as high-risk. We defined no pre-specified analysis based on the risk

of bias of the individual studies. The overall quality of the evidence of each meta-analysis was classified as 'high', 'moderate', 'low' or 'very low' based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE).[12]

Data analysis

The outcomes of interest were summarized as relative risk (RR) of screening vs. no screening and they were combined using the Mantel-Haenszel RR. The heterogeneity was assessed using the I^2 tests (I^2 >50% indicating high heterogeneity).

One of the aims of our study was to assess the reliability of the results – that is, to evaluate the ideal sample size to establish firm conclusions about the findings.[9] To accomplish this we performed TSA of the data. Interim analysis of a single randomized trial avoids type I error by creating monitoring boundaries for an estimated difference between groups, so if the estimated difference is reached the trial could be terminated. TSA uses a similar accurate method to create monitoring boundaries and estimate the optimal sample size in meta-analyses.[8 9] TSA performs a cumulative meta-analysis with the results of the available studies (represented by the Z-curve): as each new study is included, significance is tested and confidence intervals are estimated. It also creates adjusted boundaries for benefit, harm and futility and estimates the optimal sample size for a given difference between treatment arms, so that a smaller estimated difference would result in wider boundaries and a greater optimal sample size.[8] Because cumulative meta-analyses may lead to false positive results due to repetitive testing, this evaluation is adjusted to control for repeated analyses, while maintaining type I error at 5% and the power at 80%.[8] It is also adjusted for the variability between trials and for the amount of available evidence. If one of the boundaries (benefit, risk or futility) or if the optimal sample size is reached, firm conclusions might be made (for that predefined

difference) and further studies are deemed unnecessary; instead, if no boundaries are reached, further studies are needed to settle the question.[8] For the present analysis, we performed a TSA for a relative difference (relative risk reduction – RRR) between groups of 40% and considered as control group event rate the incidence observed in the control group for each outcome. The RRR value was chosen based on the expected benefit of revascularization in the mortality rate demonstrated by previous studies.[3] An additional TSA analysis was also performed using a RRR of 20%.

The risk of bias graph was generated with RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The meta-analyses were performed with Stata version 12.0 (Stata Inc., College Station, Texas, USA) and the TSA and graphics were generated using TSA software version 0.9 [beta] (Copenhagen Trial Unit, Copenhagen, Denmark).

RESULTS

The search in electronic databases and the manual review retrieved 135 studies for the evaluation of titles and abstracts. After screening, 7 studies were evaluated in full-text and 5 fulfilled the inclusion and exclusion criteria.[6 7 13-15] The study flowchart is depicted in supplementary material (Supplemental Material, Figure 1).

The included studies comprised patients with a mean age of 61 years, with a mean HbA_{1c} of 7.6 % and the mean follow-up was 4.1 years. Additional characteristics are presented in Table 1. Most studies performed screening with stress testing along with electrocardiography, echocardiography or scintigraphy monitoring; one study performed coronary computed tomography angiography with measurement of coronary calcium.

The studies totalized 3315 patients with 117 all-cause deaths and 100 cardiac events.

Data showed no difference between patients in coronary artery disease screening and control groups for all-cause death incidence (Figure 1a): RR 0.95 (95% CI 0.66 to 1.35). There was low heterogeneity (I^2 = 0% and p = 0.615). TSA for all-cause mortality events indicates that the futility boundary was reached, so a difference of 40% between groups is firmly discarded and no further studies are required (Figure 1b). For the RRR of 20% neither the optimal sample size (19548 patients) nor the futility boundary were reached.

There was also no difference in cardiac events (Figure 2a): RR 0.72 (95% CI 0.49 to 1.06; I^2 = 38.5% and p = 0.181). For this outcome, TSA shows that the optimal sample size is 6645 patients, which is larger than the current sample. Furthermore, neither the benefit nor the futility boundaries were reached (Figure 2b). The analysis with the (RRR of 20% showed similar results, but with a much larger optimal sample size (29763 patients).

Additional outcome analyses are presented in Table 2: the coronary artery disease screening group was similar to the control group for non-fatal myocardial infarction (RR 0.65 [95% CI 0.41 to 1.02]), heart failure (RR 0.60 [95% CI 0.33 to 1.10]) and myocardial revascularizations (PCI and CABG) (RR 1.08 [95% CI 0.83 to 1.41]). None of these outcomes reached the optimal sample size or the boundaries for futility.

Overall, the study quality was high according to the Cochrane Collaboration tool (Supplemental Material, Figures 2 and 3).[11] It must be stressed that none of the studies was blinded, but this was not considered a limitation because blinding of participants (patients and clinicians) was not feasible due to the type of intervention (screening). On the other hand, blinding of outcome assessment was reported in only one study.

According to GRADE,[16] quality of evidence was judged as high quality for both main outcomes (all-cause mortality and cardiac events).

DISCUSSION

In the present study we identified no benefit of screening for asymptomatic coronary artery disease for all-cause mortality in patients with type 2 diabetes. This conclusion is supported by a sufficient number of patients, as shown by TSA. Although we found no benefit for the other outcomes evaluated, such as cardiovascular events, these results are not definitive, as they are not supported by an adequate number of patients. This review shows that further studies evaluating coronary artery disease screening in type 2 diabetes are required before definitive recommendations on this topic can be made.

A relevant point of our analysis is the trend for statistically significant difference found in cardiac events and non-fatal myocardial infarction favouring the screening group. This finding seems to be driven by the study of Faglia et al.,[13] which was the smallest and oldest study included in our analysis. Moreover, patients in this study had an unfavourable clinical profile, represented by the worst glycemic control, the highest blood pressure, the greatest prevalence of smoking and the lowest use of statins and aspirin in comparison with the others studies. Despite this trend, TSA shows that there is insufficient data to perform firm conclusion about cardiac events and myocardial infarction. Therefore, further studies are needed to investigate the effects of screening for coronary artery disease in these outcomes.

Some limitations of this review must be acknowledged. First, the trials performed different screening tests with different specificity and sensitivity. [2] This generate two potential problems: studies using technics with lower accuracy might compromise the benefit of other technics, and combining these different tests may be questionable. Despite this, current guidelines do not define a preferable strategy for the diagnosis of coronary artery disease, [2] and a clinical trial support this position.[17] Therefore, we

believe these tests may be aggregated in a meta-analysis, as they all aim to identify high-risk patients with greater chance to benefit from CABG. [3 5 18] We cannot rule out the possibility that a test with higher sensitivity (coronary computed tomography angiography)[19] would be beneficial.[2] However the individual results of the FACTOR-64 which used a highly accurate method do not support this conclusion,[6] and, as discussed above, the potential benefit we identified in this review seems to be derived from only one study[13] that used tests with low to moderate sensitivity.

The second limitation was the somewhat choice of a relative difference of 40% between treatment arms. It was based on the benefits of CABG for patients with severe coronary artery disease.[3] Even though this evidence was published in the 90s, it is still largely used by guidelines to recommend revascularization for stable coronary artery disease. In addition, recent studies and meta-analysis have shown that CABG is superior to PCI for subjects with or without diabetes and multivessel coronary disease.[5 18 20] As only CABG is capable to reduce mortality and major cardiac events, a screening intervention aimed to identify patients with multivessel coronary artery disease assumes that patients would benefit from CABG. Therefore, a clear clinical benefit must be evident to justify the risks and costs from screening and the potential procedures resulting from it.

The analysis with a RRR of 20% showed that for cardiac events, myocardial infarction, heart failure and revascularizations the results from TSA also showed that the number of patients included was not enough. In addition, for all-cause mortality the RRR of 20% analysis also lacked power and it would be required an increase in the number of patients by a factor of five, which is unlikely to happen.

Another potential source for heterogeneity in our study is the inclusion of patients with different basal cardiovascular risk due to comorbidities and risk factors. As discussed above, this might be the case of Faglia et al. study, [13] which had older patients with an

unfavorable clinical profile and found reduced risk of myocardial screening with the screening. Due to the limited number of studies, subgroup analyses could not be performed. FACTOR – 64 study included some patients with type 1 diabetes,[6] but this seems minor issue, as they represent only 10% of the sample in the original study, and 3% of the systematic review sample. We cannot rule out the risk of small study bias, as all tests performed (Begg, Egger and funnel plot inspection) do not perform well with few studies. Finally, the results of this systematic review are restricted to patients with characteristics comparable to the included patients in the individual studies. So these conclusions are not applicable to some higher risk populations, such as chronic kidney injury patients.

Some strengths of our study must be pointed out. We performed a comprehensive database search and identified all randomized trials evaluating the effects of a screening strategy for coronary artery disease in type 2 diabetic patients. Furthermore, the trials included are of high quality. As mentioned, there are some methodological differences between the studies, but the statistical heterogeneity was low or absent in the analyses. We also performed detailed analyses of the data and through TSA we could discard a significant difference between treatment arms for all-cause mortality. Unfortunately, we cannot make the same firm conclusions for the cardiac events, myocardial infarction, heart failure, and revascularization outcomes.

In conclusion, the present study supports the idea that type 2 diabetic patients without symptoms of coronary artery disease do not seem to benefit from screening for subclinical disease and that non-invasive coronary exams should be reserved for symptomatic patients. This would avoid unnecessary risks, patient distress and costs for asymptomatic patients. For other events new studies are still needed before definitive recommendations can be made.

Acknowledgment

We would like to thank Dr. Fabrizio Turrini for sharing additional data on his study (DADDY-D study).

Data sharing: no additional data available.

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Ethical Approval

Not needed.

Role of the funding source

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Conflict of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no support was received from any organization for the submitted work; JLG reports grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico, during the conduct of the study; grants and other from Eli Lilly, grants from Bristol-Myers Squibb, grants and other from Boehringer Ingelheim, grants from GlaxoSmithKline, grants and other from Novo Nordisk, grants from Janssen, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work are reported.

Table 1. Included study characteristics

Study Name	First author	Publication year	Screening method	Management recommendation
--	Faglia E[13]	2005	Exercise electrocardiogram and stress echocardiography	Yes – angiography
			No screening	No
DIAD	Young LH[7]	2009	Stress scintigraphy	No
			No screening	No
DYNAMIT	Lièvre MM[14]	2011	Bicycle exercise test or stress scintigraphy	No
			No screening	No
FACTOR-64	Muhlestein JB[6]	2014	Coronary computed tomography angiography	Yes – further testing depending on the severety of the findings
			No screening	No
DADDY-D	Turrini F[15]	2015	Exercise electrocardiogram	Yes – angiography
			No screening	No

Table 1. Included study characteristics (continued)

Patients (n)	Age (years)	HbA1c (%)	Blood pressure (mmHg)	Smoking (%)	Statin use (%)	Aspirin use (%)	Mean Follow-up (years)	Registry
71	58.7 ± 8.3	8.6 ± 2.3	143/85	46	28	9	4.4	No
70	61.5 ± 8.1	8.4 ± 1.9	141/84	55	21	12		
561	60.7 ± 6.7	7.2 ± 1.6	133/80	10	37	43	4.8	Yes
562	60.8 ± 6.4	7 ± 1.5	132/79	9	41	46		
316	64.1 ± 6.4	8.6 ± 2.2	N.R.	17	33	39	3.5	Yes
315	63.7 ± 6.4	8.7 ± 2	N.R.	14	36	24		
452	61.5 ± 7.9	7.4 ± 1.4	129/74	16	76	43	4.0	Yes
448	61.6 ± 8.3	7.5 ± 1.4	130/74	15	72	40		
262	61.9 ± 4.8	7.7 ± 1.4	140/81	40	39	29	3.6	Yes
258	62 ± 5.1	7.8 ± 1.3	141/81	37	44	25		

Table 2. Results for myocardial infarction, revascularization and heart failure of screening versus no screening

Outcome	RR (95% CI)	Accrued Population	Optimal Sample Size (RRR = 40 %)	Optimal Sample Size (RRR = 20 %)
Non-fatal Myocardial Infarction	0.65 (0.41 - 1.02)	3315	6154	17495
Heart Failure	0.60 (0.33 - 1.10)	3174	10990	49352
Revascularizations	1.08 (0.83 - 1.41)	3174	10598	47339

Figure 1. Forest plot and TSA of screening versus no screening for all-cause mortality outcome

A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.

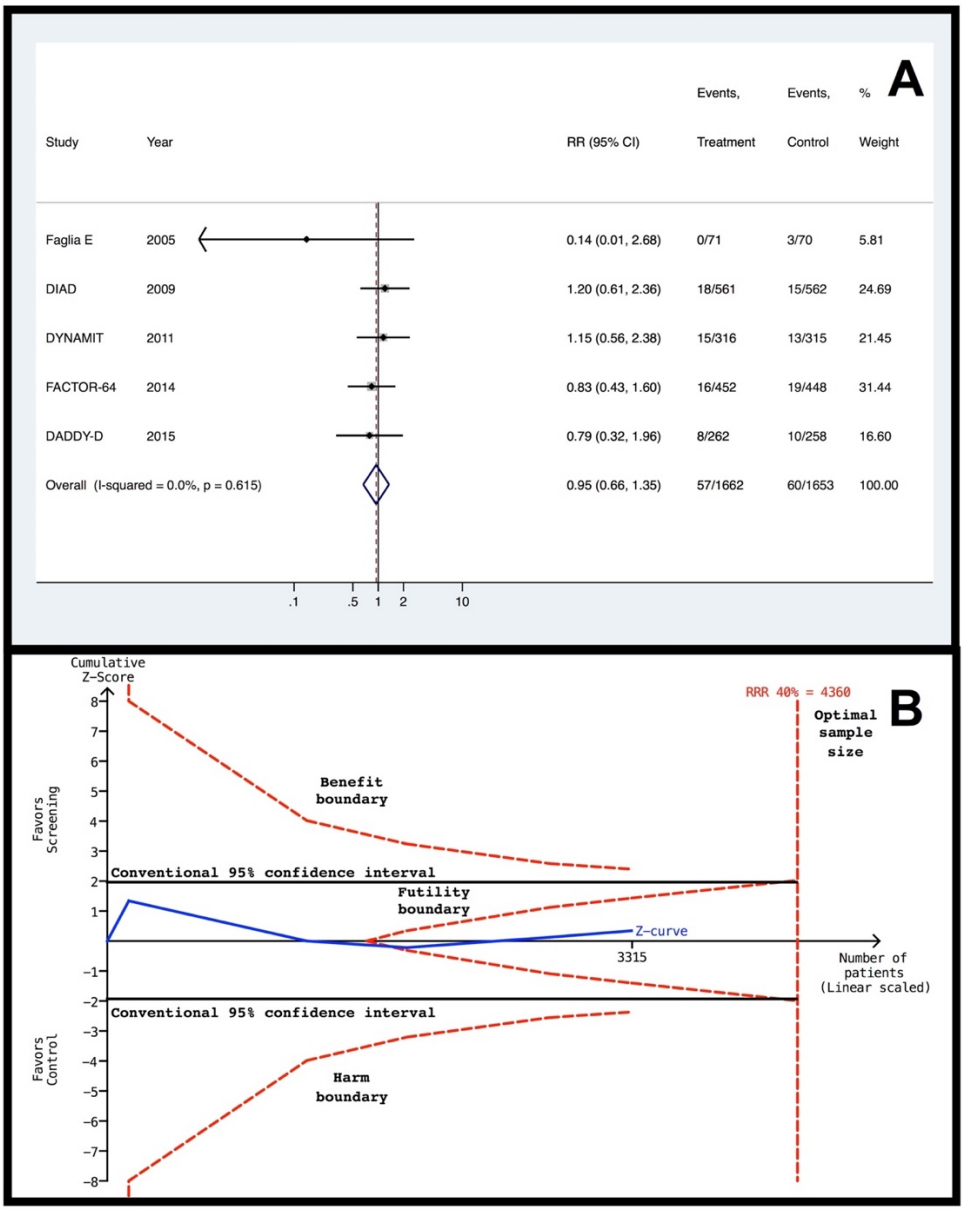
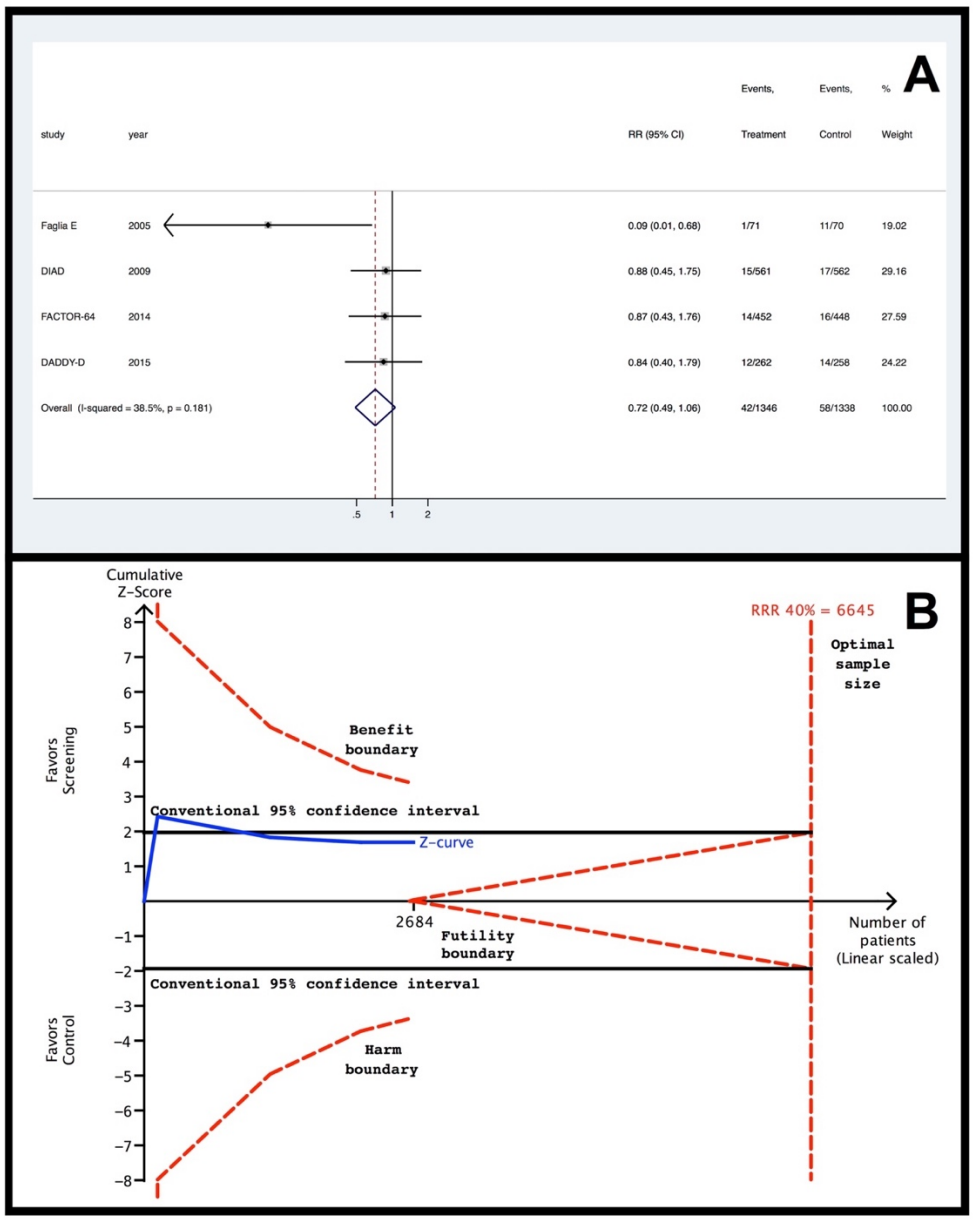


Figure 2. Forest plot and TSA of screening versus no screening for cardiac events outcome

A) Forest plot for all-cause mortality. B) TSA for a relative risk reduction of 40%. The continuous blue line represents the Z line (cumulative effect size), red dashed lines represent the harm, benefit and futility boundaries and the estimated optimal sample size adjusted to sample size and repeated analysis. The continuous black lines represent the conventional confidence intervals.



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Supplementary material

Figure S1. Study flowchart.

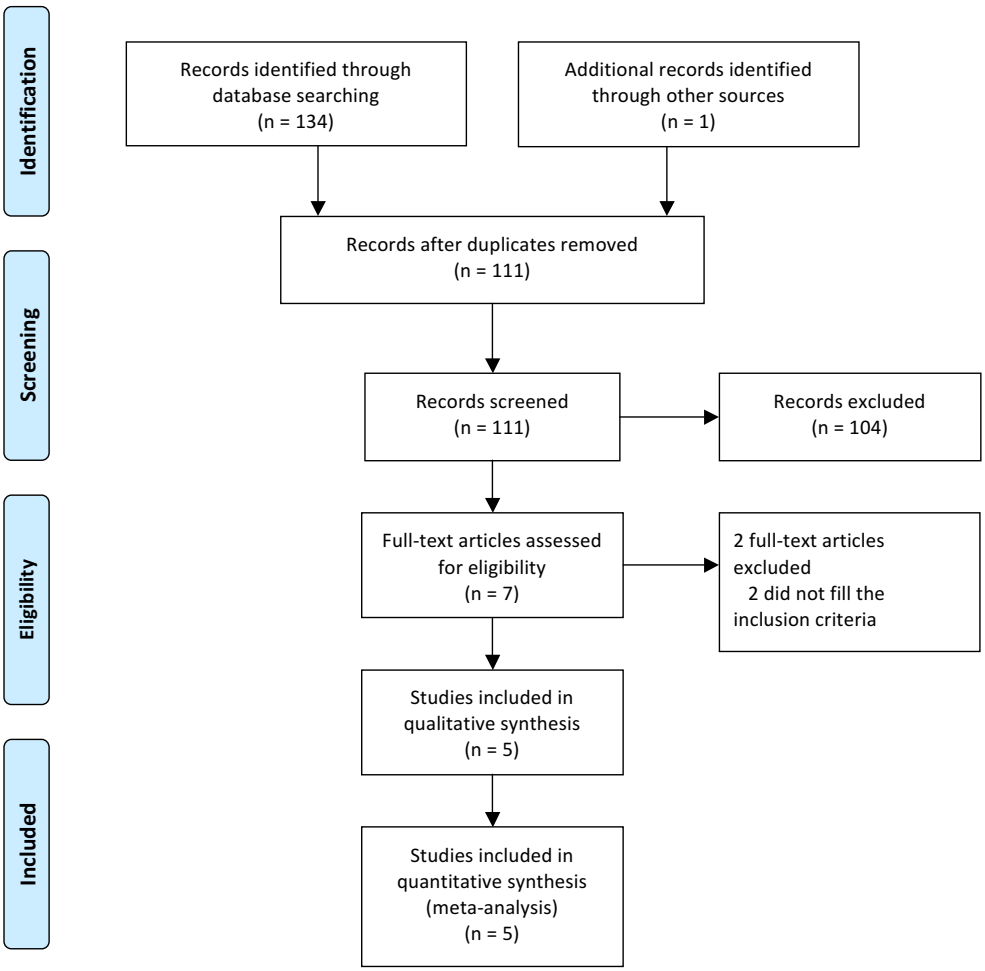


Figure S2. Risk of bias across studies.

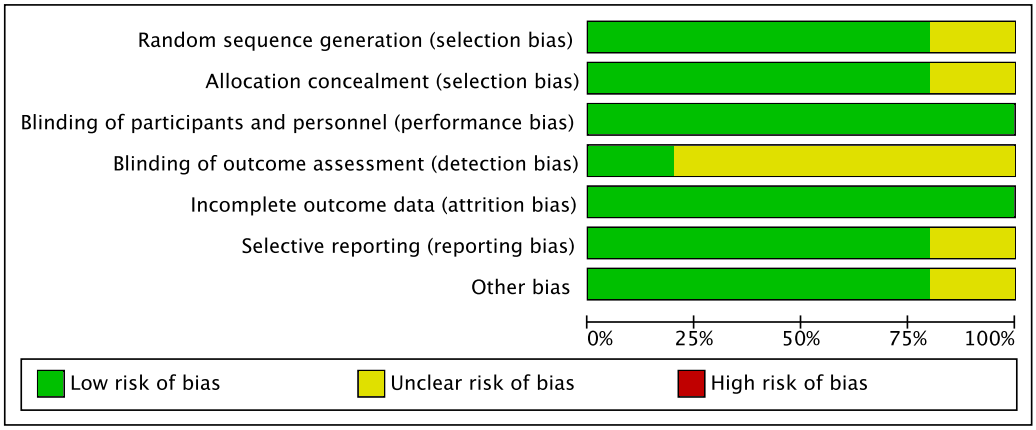
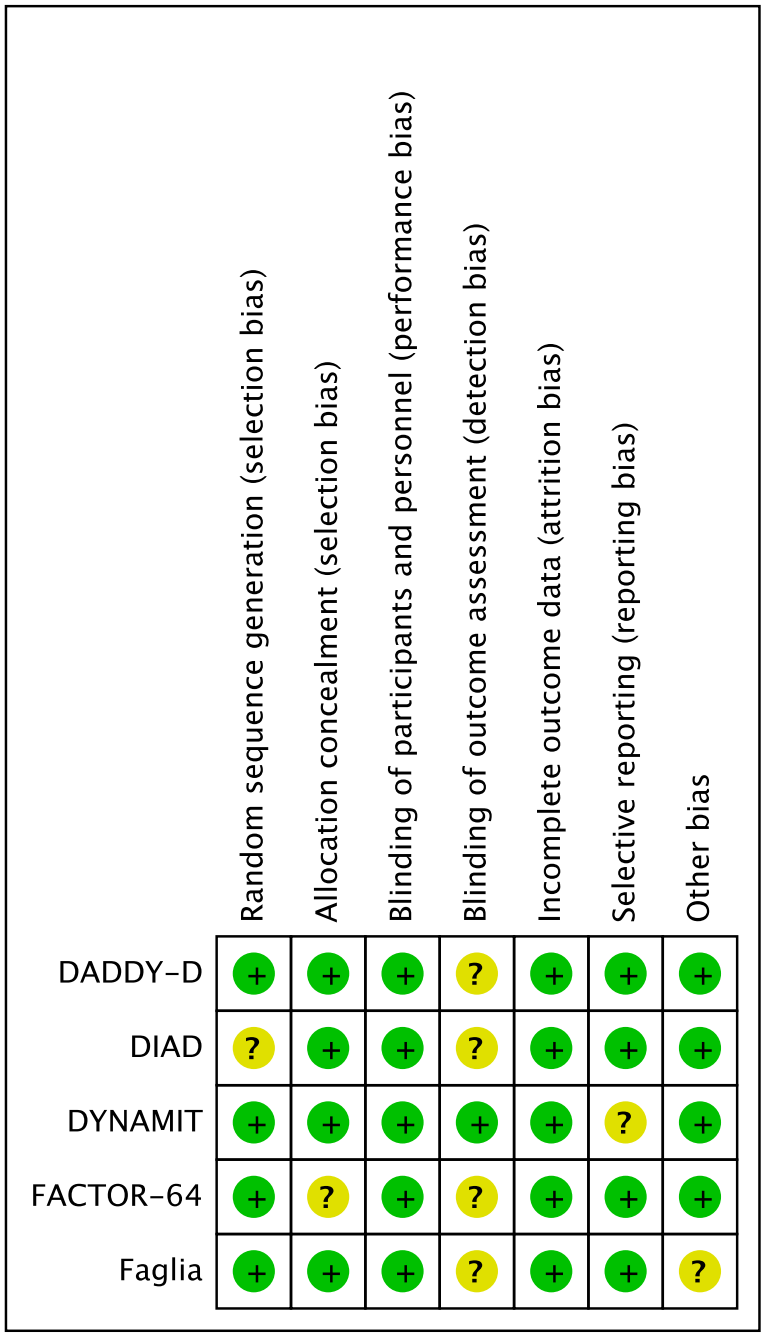


Figure S3. Risk of bias for individual studies.



Capítulo 5

Considerações Finais

Os resultados apresentados podem ser interpretados com duas óticas. Do ponto de vista clínico, pode-se concluir que o tratamento com insulina basal no tratamento do DM2 é seguro, o rastreio de cardiopatia isquêmica assintomática para pacientes assintomáticos não é benéfico e intervenções farmacológicas que promovem um perfil metabólico mais favorável estão associadas com menor chance de morte e eventos cardiovasculares. Por outro lado, do aspecto metodológico, confirma-se que revisões sistemáticas são ferramentas úteis para explorar e sumarizar o conhecimento disponível, bem como indicar quais discussões no manejo do DM2 podem ser consideradas "encerradas", com conclusões definitivas e quais ainda precisam ser melhor exploradas. [1]

Na avaliação da segurança do tratamento com insulina basal em pacientes com DM2, observa-se que não há evidências que justifiquem preocupações com o uso desse medicamento. Essa conclusão baseia-se na ausência de risco na meta-análise e na observação da TSA que descartou uma diferença de 20% para maioria dos desfechos avaliados. A importância clínica desses achados tem repercussão prática direta, uma vez que frequentemente pacientes com DM2 necessitam de tratamento com insulina basal ao longo do seu tratamento. Como já discutido, esses resultados também remetem a comparação entre achados de estudos observacionais e de intervenção [2, 3] e apresenta uma vantagem adicional das revisões sistemáticas com meta-análise: expandir a população sendo analisada, sem perder o benefício dos estudos observacionais de possuírem grandes amostras.

Não se identificou benefício do rastreio de doença arterial coronariana em pacientes com DM2. A TSA descartou uma diferença de 40% entre os grupos intervenção

e controle para mortalidade por todas as causas, mas para os demais desfechos o número de pacientes não foi suficiente para conclusões definitivas. Permanecem incertezas sobre a eficácia do rastreio nos outros desfechos (eventos cardiovasculares, infarto não fatal, revascularização, insuficiência cardíaca e revascularizações) e sobre a presença de diferenças menores que 40% para mortalidade por todas as causas. Uma questão fundamental nessa discussão é a diferenciação entre rastreio e investigação: se o rastreio de pacientes assintomáticos não é útil, a avaliação clínica minuciosa e a atenção a sintomas atípicos é fundamental para a identificação precoce dos pacientes que podem se beneficiar de estratégias de revascularização. [4]

Com o surgimento de novas classes de medicamentos antihiperglicemiantes (e dentro delas, diferentes representantes), surgem dúvidas dos motivos da heterogeneidade nos benefícios dos medicamentos. O conceito de que fatores intermediários explicam essa variabilidade clínica foi explorado nessa tese. Os resultados encontrados sugerem que efeitos glicêmicos (tanto na hiper, quando na hipoglicemia), no peso e na pressão arterial podem explicar essa variabilidade. Diversas limitações inerentes às revisões sistemáticas exigem que essa hipótese seja confirmada em outras bases de dados. Ainda assim, esses achados estão de acordo com as diretrizes atuais.

Por fim, esses resultados reforçam o uso de insulina basal, descartam abordagens rotineiras de rastreamento de cardiopatia isquêmica em favor da atenção aos achados clínicos e sugere que medicamentos com um melhor perfil metabólico tem maior chance de benefício em pacientes com DM2. Se por um lado, indicam o melhor conhecimento disponível e consequentemente resultam no melhor cuidado para os pacientes, por outro, apresentam verdades transitórias, válidas dentro para as intervenções e populações testadas e com as publicações disponíveis no momento atual. Assim, os resultados

apresentados nessa tese refletem uma visão mais ampla do conhecimento atual, útil para prática clínica e capaz de indicar novos caminhos de pesquisa.

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