Evidence on the use of aspirin in the primary prevention of cardiovascular diseases

Evidências sobre o uso de aspirina na prevenção primária de doenças cardiovasculares

Pruebas sobre el uso de la aspirina en la prevención primaria de las enfermedades cardiovasculares

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ABSTRACT

Objective: To identify the use of aspirin recommendations for primary prevention of cardiovascular disease, weighing its benefits and risks, according to the available literature.

Methodology: This is an integrative review. Data collection took place in May 2014, accepted period of publications between 2009 and 2013 in English, Portuguese and Spanish. Results: 7 studies were selected, with excellent levels of recommendation. It was evident that the use of aspirin for primary prevention of cardiovascular disease should be based on a careful analysis of each case, assessing its benefits and risks.

Conclusion: It is concluded that are required risk stratification tools to determine if it is recommend or not the use of aspirin. Although, there is a need for special training for the nursing staff to better monitor and treat these patients.


RESUMO

Objetivo: identificar as recomendações de uso da aspirina para a prevenção primária de doenças cardiovasculares, pesando seus benefícios e riscos, conforme a literatura disponível. Metodologia: trata-se de uma revisão integrativa, a coleta de dados aconteceu no mês de maio de 2014, aceitaram-se publicações do período entre 2009 e 2013, em inglês, português e espanhol. Resultados: foram selecionados 07 estudos, com excelentes níveis de recomendação. Evidenciou-se que o uso da aspirina para a prevenção primária de doenças cardiovasculares deve ser baseado em uma análise criteriosa de cada caso, avaliando seus benefícios e riscos. Conclusão: conclui-se que são necessárias ferramentas de estratificação de riscos, para assim, recomendar ou não o uso da aspirina. Ainda que, há necessidade de capacitação especial à equipe de enfermagem para um melhor acompanhamento e tratamento destes pacientes.

RESUMEN
Objetivo: Identificar el uso de las recomendaciones de la aspirina para la prevención primaria de la enfermedad cardiovascular, sopesando sus beneficios y riesgos, de acuerdo con la literatura disponible. Metodología: Este es un examen integrador, la recopilación de datos tuvo lugar en mayo de 2014, aceptada por periodo de publicaciones entre 2009 y 2013 en Inglés, Portugués y Español. Resultados: Se seleccionaron 07 estudios, con excelentes niveles de recomendación. Era evidente que el uso de la aspirina para la prevención primaria de las enfermedades cardiovasculares debe basarse en un análisis cuidadoso de cada caso, la evaluación de sus beneficios y riesgos. Conclusión: se concluye que se requieren herramientas de estratificación del riesgo, por lo tanto, recomendar o no el uso de la aspirina. Aunque, existe la necesidad de una formación especial para el personal de enfermería para un mejor control y tratamiento de estos pacientes. Descriptores: Enfermedades cardiovasculares. La aspirina. Prevención.

INTRODUCCIÓN
El tema de estudio es la aspirina, un medicamento disponible desde 1897. Es considerado el fármaco más vendido del mundo. Sin embargo, su uso se ha visto limitado por la aparición de numerosas complicaciones. Su mecanismo de acción se debe a la inhibición de la ciclooxigenasa-1 (COX-1), que es la enzima responsable de la síntesis de prostaglandinas (PG). Estas moléculas desempeñan un papel crucial en la regulación de múltiples funciones celulares, incluyendo el dolor, la inflamación y la coagulación. La inhibición de la COX-1 puede tener efectos adversos, como el aumento del riesgo de infarto, ictus y enfermedad arterial periférica.

El presente estudio es un análisis detallado de los beneficios y riesgos asociados con el uso de aspirina en la prevención primaria de la enfermedad cardiovascular. Se revisaron estudios que contrastan el uso de aspirina y se analizó su efectividad y seguridad en el contexto de diferentes condiciones clínicas. Se identificaron experiencias clínicas que respaldan el uso de aspirina para el manejo de enfermedades cardiovasculares, así como estudios que demuestran que se requieren más investigaciones para determinar su efectividad.

MÉTODO
El estudio se realizó mediante una búsqueda exhaustiva de la literatura científica que se publicó entre 2009 y 2013 en inglés, portugués y español. El objetivo fue identificar estudios que evalúan el uso de aspirina en la prevención primaria de la enfermedad cardiovascular. Se seleccionaron 07 estudios, todos con excelentes niveles de recomendación. Se evaluaron los beneficios y riesgos asociados con el uso de aspirina, destacando su efectividad en la prevención de eventos cardiovasculares, y su seguridad en diferentes contextos clínicos.

En conclusión, el uso de aspirina en la prevención primaria de la enfermedad cardiovascular requiere un enfoque cuidadoso que tenga en cuenta los beneficios y riesgos asociados. Se requieren más estudios para determinar la eficacia y seguridad del uso de aspirina en diferentes condiciones clínicas.

It is known that all eicosanoids, among them prostaglandins, are synthesized by the COX pathways, which have two forms. While COX-1 acts in the regulation of normal cellular processes, COX-2 expresses constitutive function of tissues. Another difference between them is their structure, since COX-2 has a greater binding channel, which favors the development of selective COX-2 inhibitors, such as celecoxib, which inhibits COX-2 more than COX-1, being indicated similarly to other NSAIDs for pain relief and reduced risk of cardiovascular events, sometimes combined with aspirin. It is worth noting that aspirin is the only drug in the group capable of irreversibly inactivating COX; although it is rapidly deacetylated in the body, producing salicylate, which acts as an anti-inflammatory, antipyretic and analgesic.

Its use in the prevention of cardiovascular diseases (CVD) is due to the fact that aspirin inhibits COX-1, preventing the release of thromboxanes A₂ (TXA₂), responsible for platelet agglutination, thus reducing the risk of thrombus formation, coupled with the lack of antagonism to the effects of renal vasoconstrictors, usually caused by prostaglandins, but increasing the time of bleeding.

Considering the lack of studies in Brazil with this approach and focused at nursing professionals, the present study aimed to identify the recommendations of aspirin for the primary prevention of CVD, weighing its benefits and risks, according to available literature. To the extent that it is the responsible nurse, as a member of the health team, for the integral attention of the client, for the promotion of health and for the prevention of diseases, it becomes evident the necessity of appropriating knowledge such as the one produced in this study, thus facilitating the replacement of conducts previously accepted as safe, effective and accurate.

MÉTODO
It is an integrative literature review in which the following steps were considered: formulation of the research question, definition of the inclusion criteria, search for studies, selection of studies and data collection, quality evaluation of studies, analysis and summary of the results. The research question of the present review was: which are the recommendations of aspirin use for the primary prevention of cardiovascular events, evaluating benefits and risks?

For this integrative literature review, a search was made in May 2014 at the Virtual Health Library (VHL) for evidence-based reviews, systematic reviews, meta-analyses, case series, descriptive studies, expert opinion and randomized clinical trials, non-randomized, experimental, non-experimental, and quasi-experimental studies, published between 2009 and 2013 in English, Portuguese and Spanish, using the combined terms: cardiovascular diseases, aspirin use for primary prevention, and secondary prevention of CVD.

Only in 1939 was it approved by the Food and Drug Administration (FDA), being considered prototype and recommended for use in the prevention of cardiovascular events, evaluating benefits and risks.

After reading the abstracts and applying the inclusion and exclusion criteria, it was selected 7 studies in the VHL database; 1250 were excluded because they did not meet the criteria selected for this study, 253 due to the reading of the titles and abstracts, 1 was repeated, 6 because they were subject to charges and 29 because they did not meet the objective of this review.
To extract data from included articles, a data collection instrument was used, organized according to the following items: publication title, journal title, authors, language, year of publication, objective, study design, sample, technique for collection and data analysis, description of the results, conclusions and level of evidence of the study.

In order to evaluate the quality of the studies and the strength of recommendation, a scale was used, for which the quality of the study is divided into 5 levels of evidence, where: 1: corresponds to the systematic review studies and meta-analyses; 2: randomized controlled trials; 3: well-delineated studies, however, without randomization, cohort studies, time series and cases; 4: well-delineated non-experimental studies, provided that these were performed in more than one research center or group; and 5: expert opinions, provided they are based on evidence and descriptive studies. As for the recommendation strength, according to the previous levels, it is classified in 3 degrees (strong: levels 1 and 2, moderate: level 3 and weak: levels 4 and 5).

Data analysis was performed in two stages. In the first stage, it was analyzed the data referring to the year of publication, indexing period, country of origin of the study, methodological approach and level and strength of evidence. The data were grouped and analyzed using mathematical operations of frequency distribution and percentage. In the next stage, the content of the studies was analyzed, observing the recommendations of the use of aspirin for the primary prevention of CVD.

**RESULTS AND DISCUSSION**

The 7 studies selected in this integrative review were classified, grouped, and subsequently discussed according to the following criteria: year of publication, origin, indexation period, methodological approach, level and strength of evidence. The following was a summary of the main results of the studies, with the purpose of recommending or not the use of aspirin for primary prevention of CVD, considering benefits and risks, synthesis is presented in tables 1 and 2.

**Table 1** - Distribution of the selected studies, according to Title/Reference, Year/Country, Periodic, and Evidence/Strength. Search Data, 2014.

<table>
<thead>
<tr>
<th>No</th>
<th>Title/Reference</th>
<th>Year/Country</th>
<th>Periodic</th>
<th>Evidence/Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Aspirin in the primary prevention of cardiovascular disease in the Women’s Health Study: effect of noncompliance</td>
<td>2012 USA</td>
<td>Eur J Epidemiol</td>
<td>Level 2/Strong</td>
</tr>
<tr>
<td>02</td>
<td>Utilización de ácido acetilsalicílico (AAS) na prevenção de doenças cardiovasculares: um estudo de base populacional</td>
<td>2012 BRAZIL</td>
<td>Cad. Saúde Pública</td>
<td>Level 3/Moderate</td>
</tr>
<tr>
<td>03</td>
<td>Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects</td>
<td>2011 USA</td>
<td>European Heart Journal</td>
<td>Level 2/Strong</td>
</tr>
<tr>
<td>04</td>
<td>Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials</td>
<td>2011 USA</td>
<td>American Heart Journal</td>
<td>Level 1/Strong</td>
</tr>
<tr>
<td>05</td>
<td>Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial</td>
<td>2010 SCOTLAND</td>
<td>JAMA</td>
<td>Level 2/Strong</td>
</tr>
<tr>
<td>06</td>
<td>Prevención primaria de la enfermedad cardiovascular con aspirina: ¿qué dicen las guías de práctica clínica</td>
<td>2010 SPAIN</td>
<td>Aten Primaria</td>
<td>Level 1/Strong</td>
</tr>
<tr>
<td>07</td>
<td>Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials</td>
<td>2009 USA</td>
<td>JAMA</td>
<td>Level 1/Strong</td>
</tr>
</tbody>
</table>

Source: Authors

The first evidence was in relation to the year of publication of the studies. The prevalence of studies published between the years 2010 to 2012 (85.7%) was identified, with two studies published per year, and in 2009 there was only one publication (14.3%). This reveals the great and recent concern in the search for new ways of preventing CVD to those who have not yet been affected by them, taking more space in scientific publications.

In relation to the country of origin, four studies (57.1%) are of American origin (USA), one Spanish (14.3%), one Scottish (14.3%) and one Brazilian (14.3%). This shows that the use of aspirin for the prevention of CVD, whether primary or secondary, was only recently of interest to Brazilian publications. This is justified by the incentive to non-pharmacological measures to prevent such events, such as the National Policy for Health Promotion - ordinance 687/GM, March 30, 2006.

In relation to the indexing journals, three were published in public health journals (European Journal Epidemiology, Atención Primaria and Caderno de Saúde Pública), two in medical journals (JAMA) and two health journals (American Heart Journal and European Heart Journal).

The studies were classified as to the type of methodology, in order to identify the use of quantitative and qualitative methods. Prevalence of quantitative studies (6 studies - 85.7%) is justified by the large number of controlled and randomized trials (3 studies), meta-analyzes (2 studies) and cross-sectional population studies (1 study). It is important to highlight the quantitative research for the identification and recommendation of the use of aspirin in the primary prevention of CVD, since these provide precision and reliability of the data for analysis. However, the importance of qualitative studies, due to
their subjectivity, and the ability to know deeply what is being investigated, is emphasized. In this study, we have a (14.3%) qualitative research of the systematic review type.

When considering the level of evidence and strength, the USA is highlighted again with four important works of strong evidence, being two level 1 of evidence, and two level 2 of evidence. When evaluating all this review with a great level of recommendation, therefore, it presents, besides the four American publications with a strong level of evidence, a level 1 (Spain), a level 2 (Scotland) and a level 3 (Brazil), as can be observed in table 1, strong, strong and moderate, respectively.

Table 2 shows the methodological outlines and main conclusions of the selected studies in the integrative review.

**Table 2 - Presentation of the methodological outline and main conclusions of the selected studies. Research Data, 2014.**

<table>
<thead>
<tr>
<th>Nº</th>
<th>METHODOLOGICAL DESIGN / CONCLUSIONS</th>
</tr>
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<tbody>
<tr>
<td>01</td>
<td>A randomized study of aspirin 100 mg taken on alternate days by women over 45 years without prior CVD. The analysis allowed us to conclude that the use of aspirin for primary prevention is effective in women as well as men; besides it is also effective in reducing mortality in patients with previous CVD, that is, in secondary prevention.</td>
</tr>
<tr>
<td>02</td>
<td>A cross-sectional population study with a sample of 2,710 individuals aged 45 years or older with at least 2 risk factors for CVD (Diabetes Mellitus - DM, Hypertension and/or dyslipidemia), who would need ASA for primary and/or secondary prevention. Prevalence of 24.8% and 34.3% of ASA use in primary and secondary prevention, respectively, is below the recommended level for CVD prevention.</td>
</tr>
<tr>
<td>03</td>
<td>Randomized and controlled study with 39,876 women aged 45 years or older, using aspirin 100 mg taken every other day. The study showed that aspirin use was ineffective and even harmful in the majority of the study population, as well as an association between individual characteristics and treatment.</td>
</tr>
<tr>
<td>04</td>
<td>Meta-analysis of 9 randomized trials that evaluated the effect of aspirin on primary prevention of major cardiovascular events. All the evidences investigated allow a modest recommendation of aspirin for the primary prevention of CVD due to its risks, such as severe hemorrhage.</td>
</tr>
<tr>
<td>05</td>
<td>A randomized controlled trial conducted between April 1988 and October 2008 with 28,980 men and women aged 50 to 75 years without prior CVD to evaluate the efficacy of 100 mg enteric coated aspirin. Comparing the aspirin and placebo / control groups, it was found to be significant the use of aspirin for the primary prevention of CVD, and not significant in secondary prevention and in reducing the risk of CVD mortality, and even though 34 participants in the Aspirin group compared to 20 in the placebo group developed severe bleeding requiring hospital admission.</td>
</tr>
<tr>
<td>06</td>
<td>Systematic review of 14 guidelines for primary prevention of CVD (9) and for prevention in DM (5). It was evidenced that most of the guides recommend the use of aspirin for the primary prevention of CVD in diabetic patients, however, there are discrepancies between international centers and even in different documents of the same society.</td>
</tr>
<tr>
<td>07</td>
<td>Meta-analysis of 18 prospective and/or randomized studies of aspirin therapy involving 5,269 individuals with peripheral cardiovascular disease, with or without dipyridamole. Evidence has shown that the use of aspirin alone or in combination with dipyridamole for primary prevention of CVD is not significant, however, the use of non-fatal stroke reduction is significant. It also raised the need for randomized trials to evaluate the benefit / risk ratio of aspirin use for CVD prevention.</td>
</tr>
</tbody>
</table>

Source: Author

This study represents an attempt to build a consensus of the available evidence regarding the recommendations for primary prevention of CVD with the use of aspirin, providing a more careful and precise decision-making for care. CVD is a group of conditions that affect both the cardiovascular system and the blood vessels. They lead to a high rate of premature mortality in adults, and when not mortal, cause total or partial disability, reducing autonomy, and entailing repercussions not only for the individual, but also for the family and society. This is a major challenge for health policies.

There are complex, if not multivariable, factors in the genesis of CVD. Hence, Brazil's investments, for example, in the creation of public health policies and programs, such as HiperDia, a program focused on clients with hypertension and/or diabetes. The focus of treatment is on prevention, changing habits and reducing risk factors, through dietary reeducation, exercise, smoking cessation, glycemic control, actions that can significantly reduce the incidence of CVD. However, today, we question the use of drugs with inhibitory action of platelet aggregation for the primary prevention of cardiovascular alterations, with aspirin being the object of our discussion.

Currently, some associations recommend the use of aspirin for primary prevention of CVD, such as the American Diabetes Association (ADA), which recommends the use of 75-162 mg of aspirin a day for the prevention of CVD in high-risk diabetic patients, ie, men over 50 and women over 60 years old, with multiple risk factors, provided that they are at low risk of gastrointestinal bleeding and without contraindications to the use of ASA. This recommendation, to a certain extent, extends to the entire group of individuals at high risk of developing CVD. This is justified by the fact that there are no studies comparing different doses of aspirin, the dose of 100 mg/day being the most used in the studies.

A large meta-analysis of 9 randomized trials evaluating the effect of aspirin on primary prevention of major cardiovascular events has shown that for every 1,000 patients treated for 5 years, there were 3 avoided cardiovascular events associated with 3 major bleeding events, indicating that there was no net benefit, suggesting that strategies can be developed to maximize the benefits and minimize the risks. These results can be compared to a randomized clinical trial conducted with 28,980 men and women aged 50-75 years without prior CVD to evaluate the use of 100 mg aspirin for primary prevention, in which it
demonstrated 34 aspirin group participants compared to aspirin 20 from the placebo group who developed severe hemorrhage, requiring hospital admission.15

Thus, studies do not recommend the use of aspirin for the primary prevention of CVD when considering the most relevant risks when compared to the benefits. Among the risks, the studies mention: gastric mucosal lesion, upper gastrointestinal bleeding and gastrointestinal bleeding, also report that individuals undergoing anticoagulant therapy, recent gastrointestinal bleeding, liver disease, tendency to bleeding and allergy to aspirin are not candidates for this strategy (100 mg of aspirin daily).12-14,17

In this sense, knowing that nursing act as a member of the health team, has the most diverse ways of promoting health, such as home visit, nursing consultation, individual and/or collective educational process19, it is verified that it is essential for the nurse to know and take advantage of the recommendations, as well as the benefits and risks of the use of aspirin for the primary prevention of CVD, in order to provide the best care, providing an comprehensive patient care.

CONCLUSION

In clinical practice, the use of aspirin for primary prevention of CVD should therefore be weighed on a case-by-case basis, meaning that patients at risk should be identified, using stratification tools adapted to the specific population.

These tools must be adapted, through rigorous studies to the population of a given geographical area, of the population of each country of origin. There is also a need for tools to assess the individual risk of bleeding, in order to know if, in fact, primary therapy will benefit with minimum risk. Another aspect to highlight is the optimal dose of aspirin. However, further studies and dose-specific adaptation to the target population are needed. In addition to a special training, the nursing team must be fit for a better follow-up and treatment for patients with CVD.

This research was limited because it included only articles in Portuguese, English and Spanish. The necessity of other randomized and controlled clinical trials that use the same intervention to evaluate such use is corroborated, because the studies included in this paper are very heterogeneous, not allowing the comparison between them. It is also concluded that, in addition to the reduced publications included in this review, the scientific production regarding pharmacological therapies for primary prevention of CVD is still incipient.

REFERENCES


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