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Review

Aspirin underuse, non-compliance or cessation: Definition, extent, impact and potential solutions in the primary and secondary prevention of cardiovascular disease

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ABSTRACT

Despite momentous breakthroughs in unraveling the pathophysiology of many chronic conditions and developing novel therapeutic agents, everyday clinical practice is still fraught with inadequate or inappropriate use of treatments with proven benefits. Aspirin is a paradigmatic example, as it is used for the primary and secondary prevention of cardiovascular disease and appears to have a beneficial impact on cancer risk. Yet, underuse, non-compliance or cessation of aspirin are not uncommon, may have an important clinical impact, and are not aggressively prevented or managed. Increasing the awareness of the extent and impact of aspirin underuse, non-compliance or cessation, and intensifying efforts at preventing them are worthy goals likely to yield significant benefits on cardiovascular morbidity and mortality worldwide, and possibly also on cancer outcomes.

Quality: The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.

[Institute of Medicine, 1990]

1. Introduction

Cardiovascular disease remains a major cause of morbidity and mortality worldwide, despite significant breakthroughs in our understanding of this condition, and in the development of risk-beneficial and cost-beneficial diagnostic, predictive, and management strategies [1]. Even in the current era of post-genomic personalized medicine, the battle against cardiovascular disease needs to be fought at different levels, including the prescription of simple yet effective and time tested treatments and adherence to such prescription.

Aspirin has been recommended for the prevention of cardiovascular disease, and recent data preliminary support also its role in cancer prevention, with favorable effects on colorectal cancer as well as ovarian and endometrial cancer [2–8]. Indeed, aspirin appears particularly beneficial in preventing recurrent colorectal neoplasia among non-smokers [9]. Yet, several researchers and consensus groups have stated that a more selective and cautious stance to aspirin use for primary prevention is warranted, especially in low-risk or moderate-risk subjects, as the risk of bleeding may outweigh its purported benefit [10–13]. This caution has most recently been reaffirmed by the largely non-significant findings of the 14,464-patient Japanese Primary Prevention Project (JPPP), which reported after an average of 5 years a non-significant effect of aspirin in primary prevention on the risk of a composite endpoint cardiovascular death, stroke or myocardial infarction [14]. It is true that in this study aspirin was associated with a significant decrease in the risk of myocardial infarction or transient ischemic attack, but these reductions were at least partially offset by an increased risk of major bleeding.

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Table 1
Recommend definitions for aspirin underuse, non-compliance or cessation, as well as other key terms [16].

Term	Synonym(s)	Definition
Underuse	Underutilization, underprescription	Act of using (or prescribing) less than expected
Non-compliance	Non-adherence	Inaccuracy with which a patient follows an agreed treatment plan
Cessation	–	Any ceasing, discontinuation or withdrawal
Interruption	–	Physician-supervised temporary cessation for surgery or other procedures lasting <15 days
Discontinuation	–	Physician-supervised permanent cessation as perceived as no longer needed (or appropriate)
Disruption	–	Any cessation due to non-compliance or actual bleeding (brief: 1–5 days; temporary: 6–30 days; permanent: >30 days)

Accordingly, physicians and patients are often uncertain on how to proceed, and this uncertainty leads to the common phenomena of underuse, non-compliance or cessation of aspirin therapy [15–17]. Any form of non-adherence to aspirin therapy may be associated with unfavorable consequences, at least in the sense of a missed opportunity for avoiding unnecessary adverse events. However, disagreement and uncertainty persist among researchers, practitioners, and patients on the most correct definitions of underuse, non-compliance or cessation of aspirin therapy, on their precise extent and impact in real-world clinical practice worldwide, and on potential remedies to such phenomena.

We hereby present a concise overview stemming from a roundtable among international experts focusing on the four key elements which must be mastered to correctly and poignantly address aspirin underuse, non-compliance or cessation: definition, extent, impact, and potential solutions.

2. Definition

For several years there has been limited room to standardize the terminology regarding aspirin underuse, non-compliance and cessation. However, recent efforts have led to more uniform definitions agreed upon by several stakeholders (Table 1) [16]. Indeed, underuse can be defined as any act of using (or prescribing) aspirin less than expected or deemed clinically appropriate. Of course, underuse may actually be considered appropriate use if the threshold for appropriateness is increased, and is potentially mirrored by overuse, a topic which has however been studied only in part [18]. Alternatives to underuse are underutilization and underprescription. None of these terms clarifies whether the issue is in the prescriber or in the patient, but the responsibility is typically awarded to the prescriber or the healthcare institution.

Table 2
Clinical extent of aspirin underuse.

Finding	Source	Study features
Underuse of aspirin occurred in 4% to 16% of patients in secondary prevention.	Welton (1999)	Survey in 123 physicians in the UK.
Underuse of aspirin in the secondary prevention of stroke was explained by general practitioners with difficulties in applying guidelines, patient resistance to aspirin, prioritization of other issues during busy visits, and problems in reviewing medications of stroke patients.	Short (2003)	Qualitative study in 15 general practitioners in the UK.
Underuse of aspirin occurred in 84% of patients in primary prevention and in 67% of subjects in secondary prevention, being more common in females, in younger patients, in the case of polypharmacy, at first visit, in those managed by non-cardiologists or with few cardiovascular risk factors.	Stafford (2005)	Cross-sectional study exploiting the NAMCS and ODcNHAMCS in the USA.
Underuse of antiplatelet agents (including aspirin) occurred in 42% of patients with peripheral artery disease and 9% of patients with coronary artery disease.	Hasimu (2007)	Cross-sectional study in 5263 patients in China.
Underuse of aspirin occurred in 43% of cases in primary prevention and 31% of cases in secondary prevention, with use being more common after having had a discussion with a provider about aspirin, those with high objective risk of cardiovascular disease, or those with higher subjective risk of cardiovascular disease.	Pignone (2007)	Survey in 1299 patients in the USA.
Underuse of aspirin 12 months after an acute coronary syndrome occurred in 13% of patients.	Bi (2009)	Observational study in 2901 patients in China.
Underuse of aspirin in secondary prevention of cardiovascular disease occurred in 15% of cases, and was more common in older patients, those with a clinical event >1 year before, without a history of coronary revascularization, or those with lower socio-economic status.	Niu (2009)	Survey in 2803 patients in China.
Underuse of aspirin occurred in 5% to 15% of patients in secondary prevention.	Al Omari (2012)	Survey in 124 physicians in Jordan.
Underuse of aspirin in women occurred in 59% of cases in primary prevention and 52% of cases in secondary prevention, with use being more common with dyslipidemia or a family history of cardiovascular disease.	Rivera (2012)	Survey in 29,701 women in the USA.
Underuse of antiplatelet agents (including aspirin) in primary prevention occurred in 83% of patients, and was more common in males and the elderly, whereas in secondary prevention occurred in 53% of subjects, and was more common in females, the elderly, those of Hispanic ethnicity, or managed by non-cardiologists.	George (2012)	Cross-sectional study in 15,943 patients in the USA.
Underuse of aspirin in primary prevention occurred in 31% of eligible patients, and was more common in younger people, and women; this was mirrored by unsubstantiated use in 18% of subjects without formal indications, and was more common in older and among Hispanic people.	VanWormer (2012)	Cross-sectional study in 831 patients in the USA.
Underuse of antiplatelet agents (including aspirin) in secondary prevention occurred overall in 75% of patients (ranging from 48% in North America and Europe to 94% in Africa), with underuse associated with lower country income and rural setting.	Yusuf (2012)	Cross-sectional international study in 153,996 patients.
Underuse of aspirin in primary prevention was less common in patients at higher level of education, in the insured, and those with a regular source of care.	Mainous (2014)	Survey in 3435 patients in the USA.

NAMCS = National Ambulatory Medical Care Survey; ODcNHAMCS = Outpatient Department component of the National Hospital Ambulatory Medical Care Survey.