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Adherence to chronic polytherapy in the secondary prevention of myocardial infarction: a matter of gender?

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Summary. Patients who have had an acute myocardial infarction (AMI) are at increased risk of mortality and morbidity. International guidelines agree on the use of a combination of the following evidence-based (EB) drugs for an effective secondary prevention: antiplatelets, β-blockers, angiotensin-converting-enzyme inhibitors/angiotensin II receptors blockers and statins. The benefits of chronic polytherapy in reducing cardiovascular diseases and mortality have been clearly shown. EB polytherapy for secondary cardiovascular prevention is equally effective in both genders. However, observational studies reported poor adherence in female patients. A real-world study on the adherence to polytherapy in the two years following the first AMI was carried out in two Italian Regions: Lazio and Tuscany. The likelihood of being adherent to EB therapy increases up to the age of 63 in men and 65 in women, while decreasing rapidly after the age of 85. At any age, women present a systematically lower adherence than men. However, the effect of gender on adherence decreases with the increasing age of the patient. Women under 55 have a 31% lower probability of adherence than men of the same age; afterwards, the effect of gender progressively decreases, until it loses any statistical significance in patients aged 85 and older. In fact, at a very old age, adherence decreases drastically in both genders. Overall, after adjusting for age and the various confounding factors, women have a 13% lower probability than men to be adherent to EB treatment.
This 'residual' gap could be due to the higher prevalence of comorbidities in women. In fact, patients suffering from more than one disease are more likely to receive complex drug regimens, which increase the risk of inappropriate prescribing, drug-drug interactions, and poor adherence. This hypothesis should be further investigated in *ad hoc* studies, in order to provide a better insight on the gender-specific adherence to chronic polytherapy after AMI, with the ultimate aim of obtaining a more effective and equitable linkage-to-care for patients with previous heart attack.

Key words. Chronic polytherapy, secondary prevention, myocardial infarction, gender differences.

Aderenza alla politerapia cronica nella prevenzione secondaria dell'infarto del miocardio: una questione di genere?

Riassunto. I pazienti colpiti da infarto miocardico acuto (IMA) sono esposti ad un aumentato rischio di mortalità e morbilità. Le linee guida raccomandano l'utilizzo congiunto e continuativo di quattro farmaci *evidence-based* (EB): antiaggreganti piastrinici, ACE-inibitori/sartani, betabloccanti e statine. La politerapia EB per la prevenzione secondaria dell'infarto riduce significativamente l'occorrenza di nuovi eventi ischemici e la mortalità per tutte le cause. Le indicazioni al trattamento sono le stesse per uomini e donne. Tuttavia, numerosi studi hanno evidenziato una ridotta aderenza al trattamento nelle donne rispetto agli uomini. Uno studio *real-world* sull'aderenza alla politerapia cronica nei due anni che seguono il primo episodio di infarto è stato condotto in due regioni italiane: Lazio e Toscana. La probabilità di essere aderenti alla politerapia aumenta sino all'età di 63 anni negli uomini e di 65 anni nelle donne, poi diminuisce rapidamente quando si superano gli 85 anni. A parità di età, le donne presentano un'aderenza alla terapia sistematicamente inferiore rispetto agli uomini. L'effetto del genere sull'aderenza, tuttavia, diminuisce all'aumentare dell'età del paziente. Le donne al di sotto dei 55 anni presentano una probabilità di aderenza del 31% inferiore rispetto agli uomini della stessa età; poi l'effetto del genere si attenua progressivamente, fino a perdere la significatività statistica nei pazienti con 85 anni e più. In età molto avanzata, infatti, l'aderenza al trattamento diminuisce drasticamente in entrambi i generi.
Complessivamente, dopo aver aggiustato per età e per diversi fattori confondenti, a due anni dall'episodio di infarto le donne presentano una probabilità di aderenza alla terapia del 13% inferiore rispetto agli uomini. Questo differenziale "residuo" potrebbe essere attribuibile alla maggiore prevalenza di comorbilità nelle donne. Infatti, è ampiamente dimostrato che i pazienti con più di una condizione patologica sono sottoposti a complessi regimi terapeutici, che aumentano il rischio di prescrizioni inappropriate, interazioni tra i farmaci e bassa aderenza. Tale ipotesi dovrebbe essere approfondita con studi *ad hoc*, per produrre maggiori evidenze sulle differenze di genere nell'aderenza alla politerapia cronica e rendere la 'presa in carico' dei pazienti con pregresso infarto più equa ed efficace.

Parole chiave. Politerapia cronica, prevenzione secondaria, infarto del miocardio, differenze di genere.

In Italy, ischemic heart disease is the main cause of mortality among both genders. Furthermore, with the aging of the population, the subjects affected by these conditions are destined to increase.[1]

For patients in secondary prevention after an acute myocardial infarction (AMI), national and international guidelines recommend the joint and continuous use of four evidence-based (EB) drugs: ACE-inhibitors/sartans, platelet aggregation inhibitors, beta blockers and statins.[2] EB polytherapy significantly reduces the occurrence of new ischemic events and all-cause mortality.[3,4] Indications for treatment are the same for men and women. In terms of efficacy of the therapy, there is no difference with regard to gender.[5-7] However, numerous studies have shown that women are less adherent to treatment than men.[8,9]

This differential was confirmed by a recent observational population study conducted in two Italian Regions: Lazio and Tuscany. Using the current health information systems, data relating to 32,962 patients over 35 years of age, at their first episode of heart attack, were identified and analyzed. Drug treatment was evaluated in a two-year follow-up, starting from the date of discharge (*index date*). Patients who presented a medication possession ratio (MPR) ≥0.75 for at least three of the four EB drugs were defined as "adherent to chronic polytherapy".[10] The MPR measures, for each individual, how much part of the follow-up period has been adequately covered by the pharmacological treatment, in accordance with the defined daily doses (DDD) established by the World Health Organization.[11]

The cohort of infarcted patients was characterized by a greater prevalence of male gender, equal to two thirds of the total. Important and statistically significant differences were found in the distribution by age: the average age at discharge in women was 74, compared to 65 in men (Table 1). These age differences "upon the first episode of AMI" confirm a phenomenon already known in the literature: women develop heart disease with a delay of about 10 years compared to men.[12]

Table 1 shows, separately by gender, the proportion of patients being treated with the ten drug classes most prescribed in this cohort in the 12 months prior to the AMI episode. The difference between the two genders was expressed through the prevalence ratio (PR, prevalence in women/prevalence in men), both crude and adjusted for numerous potential confounders, such as age, previous use of EB drugs, duration of hospitalization, discharge ward (cardiology vs others), presence of revascularization procedures during hospitalization, type of heart attack (STEMI vs N-STEMI), 21 presence of comorbidities identified in the index hospitalization and in the previous 9 years.

Figure 1 shows the probability of adhering to chronic polytherapy with increasing age. This relation was analyzed separately in the two genders. The relationship between adherence to treatment and age is not linear, but takes the form of an "inverted" *J-shaped relation*. The probability of adhering to polytherapy increases up to the age of 63 in men, and up to the age of 65 in women. This probability decreases very quickly after the age of 85. The most relevant aspect is that, at the same age, women present a systematically lower adherence to therapy than men.

Table 1. Drug therapies ongoing in the 12 months prior to the heart attack episode: prevalences separated by gender

	Men	Women	Total		
Gender (no.) **Gender (%)**	21,783 66.1	11,179 33.9	32,962 100.0		
Years of age (median ± SD)	65 ± 13	74 ± 13	68 ± 13		
Drugs taken in the 12 months before the AMI episode (%)			**PR**	**PR adjusted**	**95% CI**
ACE-inhibitors/ARBs	39.8	55.3	1.39*	1.09*	1.07-1.12
Drugs for acid secretion-related disorders	25.7	43.0	1.67*	1.28*	1.24-1.33
Anti-infective agents for systemic use	27.1	36.8	1.35*	1.18*	1.14-1.23
Antithrombotic agents	24.1	39.3	1.63*	1.03*	1.01-1.05
Anti-inflammatory and antirheumatic agents	18.3	32.5	1.78*	1.58*	1.51-1.65
Lipid-modifying substances	17.6	23.1	1.31*	1.07*	1.03-1.12
Antidiabetic agents	16.3	20.6	1.27*	1.01	0.98-1.05
Calcium channel blockers	16.0	20.5	1.28*	0.94*	0.90-0.99
Beta-blockers	12.3	21.4	1.74*	1.37*	1.29-1.44
Diuretics	8.0	19.4	2.42*	1.33*	1.25-1.41

SD: standard deviation; AMI: acute myocardial infarction; ARBS: angiotensin II receptor blokers; PR: prevalence ratio.
*Statistically significant difference (p-value ≤0.05).

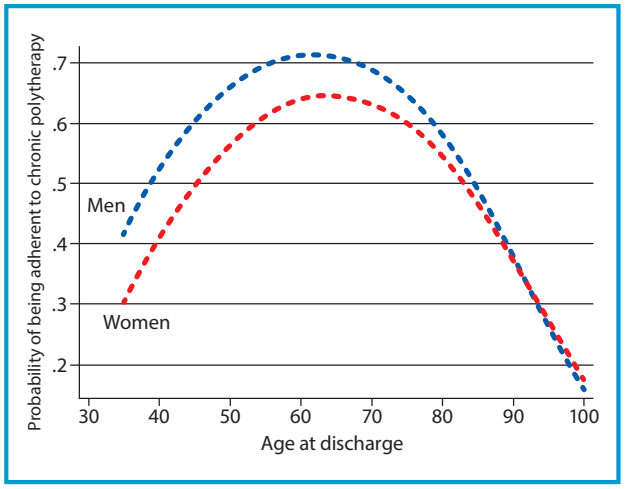

Figure 1. Adherence to chronic polytherapy by age: gender differences.

Overall, after adjusting for all the potential confounding factors previously indicated, two years after hospital discharge, women have a 13% lower probability of adherence to polytherapy than men. However, as shown in Figure 1, there is a significant interaction between the patient's gender and age. With increasing age, the effect of gender on adherence decreases. This effect is very strong in patients under the age of 55: in the 35-54 age group, the probability of adherence to EB treatment is 31% lower in the female gender than in the male one: relative risk (RR) = 0.69; p <0.001; 95% CI = 0.60-0.81. In the two subsequent age groups (55-69 and 70-84), the effect is attenuated and remains almost constant, with a statistically significant RR close to 0.90. Therefore, in the intermediate classes, the female disadvantage is reduced to 10%. Finally, no significant gender difference emerges in patients aged 85 or older (RR = 0.95; p = 0.455; 95% CI = 0.83-1.09). Among the oldest old, the worsening of the general state of health, the onset of problems related to disability or non-self-sufficiency, especially if not supported by effective welfare policies, level out (downward) the probability of adherence to treatment. Very advanced age makes men and women equal, drastically limiting the adherence to treatment in both genders.

Interestingly, the gender differential in terms of adherence to treatment varies substantially according to the class of drug considered. Statins are the class for which the greatest gender gap is identified: in fact, for a woman, the probability of adherence to the treatment with statins is 27% lower than for a man (adjusted RR = 0.73; p <0.001; 95% CI = 0.69-0.77). The female disadvantage is reduced in the case of ACE inhibitors/sartans, for which women show a 16% lower probability of adherence (RR = 0.84; p <0.001; 95% CI = 0.80-0.89). The only drugs for which men are less adherent are beta-blockers (RR = 1.09; p = 0.001; 95% CI = 1.03-1.15). Finally, for antiplatelet agents, the gender difference in the adherence levels is not statistically significant (RR = 0.97; p = 0.295; 95% CI = 0.91-1.03).

Many studies attempted to identify factors that could explain women's reduced adherence to the drug therapy for the secondary prevention of heart attack. Some focused on the age at which the acute event occurs for the first time, others on the severity of the episode, still others on the symptoms, which in women can lead to an initial misclassification of the diagnosis. It is interesting to note that, in a recent study conducted in Lazio, a gender differential was observed in the time of access to coronary angioplasty for patients affected by AMI.[13]

Some authors have gone so far as to speculate that part of the under-treatment found in women may be attributable to a reduced 'attention' or 'risk awareness' by healthcare professionals in the cases where the acute event occurs in a woman.[14-16] However, none of these studies has clearly demonstrated what the causes of the phenomenon are, and the results are often conflicting.

In an attempt to overcome these limitations, in this study several confounding factors were considered, in addition to age. By adjusting for these factors, however, the difference in the probability of adherence to polytherapy between men and women is still high and statistically significant.

This 'residual' differential could be attributable to the higher prevalence of comorbidities in women. At the same age, women present a greater number of chronic conditions, with substantial differences starting from the age of 55.[17] The presence of concomitant diseases, especially if chronic, could contribute to the reduced therapeutic adherence observed in the female gender. In fact, it has been widely demonstrated that the presence of comorbidities, and the related pharmacological treatments, makes it more difficult to establish and maintain a correct therapeutic regimen.[18,19]

This hypothesis could provide several insights for the conduct of new epidemiological studies, as well as open wide margins for a further in-depth investigation on the topic of the 'female disadvantage' in the adherence to EB drugs after a heart attack. A brief discussion on this issue may be helpful. The adjustment model used in the study also included some concomitant conditions. However, the conditions considered were 'traced' using exclusively the hospital information system, through which it is possible to reconstruct only a limited portion of the patient's overall clinical picture, thus generating a phenomenon known as *unmeasured confounding* (confusion caused by unmeasured variables). Should the 'negative' effect of comorbidities on gender differences be confirmed, through the conduct of *ad hoc* studies, the health policy implications could be very relevant. In fact, in the case of multi-chronic patients with previous organ

damage, the care path should be based on the integration between different professional figures. However, in clinical practice, the therapeutic approach is still oriented towards the treatment of the individual condition. If patients are 'de-structured' in the individual diseases they are affected by, the risk increases that they are exposed to an excessive number of pharmacological treatments. This form of care, on the one hand reduces the adherence to treatments and, on the other, can generate harmful interactions between different drugs. Therefore, in cases where people with previous heart attacks present numerous concomitant conditions – a situation likely to be more frequent in women than men – a multidisciplinary approach is needed, aimed at the overall evaluation of male and female patients, for a more equitable and effective 'linkage-to-care'.[20]

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