Current perspective

Aspirin and the prevention of ischemic heart disease.

A Socratic dialogue between a cardiologist, a clinical pharmacologist and an expert of blood platelets

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The recent publication of the results of the "Progetto di Prevenzione Primaria" by a large Italian group of researchers and general practitioners, prompts a cardiologist, a clinical pharmacologist and a blood platelet expert to review - using a Socratic dialogue style - the data on aspirin as a prototypal drug in the prevention of ischemic heart disease. The distinction between primary and secondary prevention seems to be rather artificial as it is based on past events and not on the risk of future events. Although aspirin proved to be effective in reducing both vascular mortality and non-fatal vascular events and is inexpensive, it is still underused for prevention by many physicians. The major indications on the beneficial effect of aspirin against ischemic heart disease derive from large epidemiological trials and are valid for populations rather than for single patients. Hopefully, biochemical markers such as C-reactive protein or genetic polymorphism will help to establish the effects of aspirin in more targeted groups or even in individuals.

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A young cardiologist (CARD) has invited a clinical pharmacologist (PHARM), and a platelet researcher (PLAT) to relax at his cottage on the Apennines, in the Abruzzo region, Italy. At sunset, the three friends meet along the peaceful shores of the Lake Scanno.

CARD: Dear friends, I am happy you are both here for this week-end. I'm sure you both will enjoy this beautiful environment, but I would also take advantage of your experience to discuss about the prevention of vascular disease …

PLAT: When we last met, we discussed the pros and cons of high- and low-dose aspirin, before eating those delicious trouts ...

CARD: What happened to aspirin since then?

PHARM: Well … it celebrated it's 100th birthday! We have certainly learned a lot about aspirin during the past years![1]

CARD: Well, tell me about it!

PHARM: It has been clearly established that aspirin reduces the risk of myocardial infarction and of ischemic stroke, and even of mortality after vascular events[2].

CARD: Which events?

PHARM: Well, after heart attacks, unstable angina, stroke or transient ischemic attacks, or after a coronary artery bypass graft or angioplasty ...

CARD: As I recall, last time we talked about a primary prevention study on healthy American doctors[3,4].

PHARM: Yes, indeed until a few years ago, there was no clear evidence of the benefit of aspirin in the primary prevention of occlusive vascular disease, at least as far as fatal episodes are concerned.

CARD: Does it mean that you think that the English Thrombosis Prevention Trial[5] and the HOT study on hypertensive patients[6] can be clearly interpreted in favor of aspirin? I was really impressed by both trials!

PHARM: No doubt, in subjects with a high vascular risk, aspirin, as a measure of primary prevention reduces the probability of non-fatal heart attacks.

PLAT: I'd like to mention the PPP trial ... I was actually involved in it!

CARD: What's that, a new political party?

PLAT: God forbid! PPP stands for "Progetto di Prevenzione Primaria", a study performed by a non-profit research institute and a general practice network distributed all over Italy … It has just been published[7].

CARD: I understand it's an interesting

study. In general practice, indeed, unlike large multicenter trials, drugs are used by "real" people, in non-artificial conditions.
PLAT: I'm quite happy that Italian general practice finally has a role in clinical research, but adequate public incentives and financial support from the industry are needed for the future. The importance of the PPP's message cannot be underestimated and may have an impact on other countries as well. But back to aspirin ...
CARD: Yes. I'm really curious! How many subjects were enrolled in PPP? And for how long were they followed up?
PLAT: Almost 5000 persons, a cohort at lower risk than that in the Thrombosis Prevention[5] and HOT[6] trials. Unlike the HOT trial[6], cardiac risks other than hypertension were included. More than half were women, the average age was 64 years, and they were followed up for 4 years.
CARD: How was the risk defined?
PLAT: One or more of the following factors: age 65 years or over, hypertension, hypercholesterolemia, diabetes mellitus, obesity and a family history of myocardial infarction.
CARD: I'd like to know how these risk factors were defined, but I'll read the paper (Table I)[7]. Could you summarize its results?
PHARM: Let me guess: favorable trend for aspirin, but no statistical significance: small numbers and a population that was too heterogeneous ...
PLAT: Wrong! Aspirin (100 mg a day) significantly reduced not only all cardiovascular events, such as non fatal heart attack, non fatal stroke, angina, peripheral arteriopathy, revascularization procedures …, but also cardiovascular death as a separate endpoint (Table II)[7].
PHARM: Quite impressive!
CARD: But what are we looking at in practical terms?
PLAT: Aspirin prevented 6 cardiovascular deaths for every 1000 treated subjects, almost 2 a year, and 19 cardiovascular events, almost 6 a year.
PHARM: Fine, but what about the risk of hemorrhage?
PLAT: There were eight more hemorrhagic complications every 1000 treated patients in the aspirin group, about 2 or 3 a year (Table III)[7]. However, there were 4 cases of fatal hemorrhage but only one was in the aspirin group. In other words, 48 persons should receive aspirin for 4 years to avoid one cardiovascular event and 159 to avoid one cardiovascular death. In contrast, one would observe one non-fatal drug-related side effect (bleeding or gastrointestinal disease) every 96 subjects treated for 4 years.
PHARM: What surprises me most is that aspirin worked on top of the specific treatments for each risk factor. In other words, its effect was additive to that of antihypertensives and statins.
PLAT: That's right. The pathogenic mechanism inhibited by aspirin seems to be common to all the vascular risk conditions studied in PPP (Fig. 1).
PHARM: You may recall that the HOT[6] study provided a clear indication to administer aspirin only to patients whose hypertension is adequately controlled.

Table I. PPP trial: study population inclusion criteria[7].

Both sexes, aged ≥ 50 years
At least one of the following risk factors:
1. Old age: ≥ 65 years
2. Hypertension: systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg
3. Hypercholesterolemia: total blood cholesterol ≥ 6.4 mmol/l
4. Diabetes mellitus: plasma glucose ≥ 7.8 mmol/l
5. Obesity: body mass index ≥ 30 kg/m^2
6. Family history of myocardial infarction (before 55 years in parents/siblings)

Long-term pharmacological treatment for any of the conditions 2, 3 or 4 was considered as a criterion for inclusion.

Table II. PPP trial: efficacy profile of aspirin treatment[7].

	Aspirin (n=2226)		No aspirin (n=2269)		RR (95% CI)
	N.	%	N.	%	
Main endpoint (cardiovascular death, non-fatal MI, non-fatal stroke)	45	2.0	64	2.8	0.71 (0.48-1.04)
Total cardiovascular events or diseases	141	6.3	187	8.2	0.77 (0.62-0.95)
All deaths	62	2.8	78	3.4	0.81 (0.58-1.13)
Cardiovascular	17	0.8	31	1.4	0.56 (0.31-0.99)
Non-cardiovascular	45	2.0	47	2.0	0.98 (0.65-1.46)
All MI	19	0.8	28	1.2	0.69 (0.38-1.23)
Non-fatal MI	15	0.7	22	1.0	0.69 (0.36-1.33)
All strokes	16	0.7	24	1.1	0.67 (0.36-1.27)
Non-fatal stroke	15	0.7	18	0.8	0.84 (0.42-1.67)
Angina pectoris	54	2.4	67	3.0	0.82 (0.58-1.17)
Transient ischemic attack	28	1.3	40	1.8	0.71 (0.44-1.15)
Peripheral artery disease	17	0.8	29	1.3	0.60 (0.33-1.08)
Revascularization procedure	20	0.9	29	1.3	0.70 (0.40-1.24)

CI = confidence interval; MI = myocardial infarction; RR = relative risk.

Table III. PPP trial: safety profile of aspirin. Severe and unexpected non-fatal events[7].

	Aspirin (n=2226)	No aspirin (n=2269)
Cancer	86	80
Bleeding	24	6
Gastrointestinal	17	5
Intracranial (not parenchymal)	2	0
Ocular	1	1
Epistaxis	2	0
Other	2	0
Gastrointestinal disease (except bleeding)	8	3
Other events	36	21
Total	154	110

CARD: One could extrapolate, therefore, that aspirin would only work in populations whose risks are under control.
PHARM: Some months ago, in the *British Medical Journal* I read a paper[8] derived from the Thrombosis Prevention Trial[5]…
CARD: Any good news in it?
PHARM: Well, the *British Medical Journal* study[8] concludes that the efficacy of low-dose aspirin (75 mg a day) is inversely related to the patient's blood pressure. In other words, if you have a systolic blood pressure below 130 mmHg, aspirin reduces the risk of heart attack or stroke by 40%, if it is between 130 and 145 mmHg, risk is reduced by only 30%, but if the pressure is higher than 145 mmHg, aspirin no longer protects ... on the contrary, there is a slightly higher risk of hemorrhage, both cerebral and extracerebral …
CARD: Even at low doses?
PHARM: Yes, even at doses below 100 mg a day[9]. So patients unlikely to derive any benefit from it should not be given aspirin.
CARD: I remember that the study on American doctors[3] showed how aspirin was most effective in subjects over 50 years of age ...
PLAT: Oh my Goodness ... this means these data regard us personally!
CARD: … Hold on ... but also in subjects with blood cholesterol levels below 210 mg/dl if I'm not mistaken.
PHARM: We should be wary of conclusions derived from *a posteriori* subgroup analyses ...
CARD: Yes, of course ... I do have to say, though, that the idea of tailoring infarction therapy wouldn't be bad at all.
PLAT: During the past 20 years, large epidemiological trials have provided indications for the therapy and prevention of vascular events, but these indications are valid for populations, not for single patients.
CARD: Sure, knowing that whoever and wherever you are, if you have precordial pain you should take aspirin (any dosage, whatever you can readily find) before an ECG is done, and then call an ambulance or a taxi to take you to a hospital to receive thrombolytic therapy. This is all thanks to the clinical trials and meta-analyses which followed them[2,10] … But I would like to have clearer indications, if not for single patients, at least for less heterogeneous groups than those studied by the epidemiologists.
PHARM: Well, the transferability of clinical data to the greatest number of patients is one of the most important results of clinical trials, such as the GISSI[10] ...
PLAT: Maybe we're beginning to understand how to select *a priori* groups of subjects who could benefit from a given therapy, with results targeted to them.
CARD: Do you mean that we will no longer be forced to organize clinical trials including tens of thousands of persons, with few exclusion criteria, but select subgroups instead? ... but on what basis?
PLAT: Well, for example, on the basis of biochemical markers or of genetic polymorphisms ... In the American doctors' study[3], the doctors who had lower C-reactive protein levels had little or no protection from aspirin, whereas it was particularly active in those with higher levels of this inflammation marker[11].
PHARM: All right, calm down, my friends! The asso-

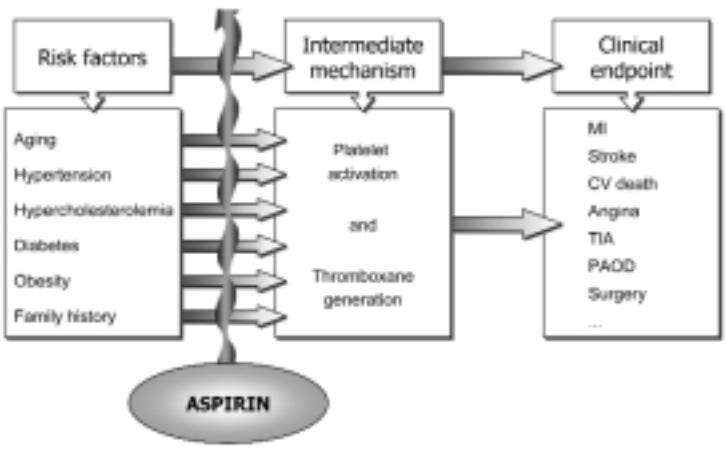

Figure 1. *PPP trial. Hypothetical effect of aspirin in different risk factor groups. CV = cardiovascular; MI = myocardial infarction; PAOD = peripheral arterial occlusive disease; TIA = transient ischemic attack.*

ciation between C-reactive protein and the effectiveness of aspirin seems to be more a statistical game than a pathophysiological mechanism. I don't believe aspirin prevented heart attacks in the American doctors by inhibiting that inflammatory component which is so popular nowadays in acute coronary syndromes ...[12]. I do believe in inflammation, but I'm just as sure that low-dose aspirin only acts on platelet thromboxane, not on other classical inflammatory mediators[13].
CARD: Inflammation or not, it would be nice to include in primary prevention programs only those people with a certain level of C-reactive protein, or some other easily measured parameter.
PLAT: I think that C-reactive protein does not select "responders" to aspirin but that it identifies higher risk subjects for whom it may be easier to show aspirin's efficacy.
CARD: This convincing concept seems to contrast with the conclusions of the British study[8]: low blood pressure, low risk, greater effectiveness of aspirin ... or am I wrong?
PLAT: No you're absolutely right! The point is that you have to treat a lot of people to gain any benefit ... and we can't identify *a priori* the subjects who would benefit most from aspirin.
CARD: That's why we must "purify" the groups of subjects enrolled in trials according to some new criteria? You cited genetic polymorphisms. I admit I'm a bit confused about this topic ...
PHARM: You're not the only one ...
PLAT: For simplicity's sake, let's take the axiom: one gene, one protein, one function. During the past decade, quite a few researchers have wondered whether interindividual variability of a certain function – for example, angiotensin-converting enzyme activity – may depend on the variability of the levels of the corresponding protein, and if this may depend on the variability or polymorphism of the gene which codifies for that protein. Was I clear enough?
CARD: Yes, sure, but I would verify whether I remember correctly what a polymorphism is … So, a mutation is a rare variation in the DNA sequence, which is found in less than 1% of the population, while the term polymorphism indicates an interindividual difference in the DNA sequence that occurs in 1% or more of the population. Is that correct?
PLAT: Yes, sometimes up to 50% of a population carries a given polymorphism. Each individual is characterized by a sequence of three billion base pairs. One out of 300 base pairs varies from person to person …
CARD: Does that mean that any individual can be distinguished from his neighbor by about 10 million base pairs? But what does all this have to do with myocardial infarction and aspirin?
PLAT: Take the Thrombosis Prevention Trial[5]: both warfarin and aspirin were effective but warfarin mainly reduced fatal events, while aspirin mainly non-fatal ones.
CARD: Were there two different populations in this trial, responding differently to the two drugs?
PLAT: I do not know, but warfarin reduced factor VII levels to an extent similar to that observed in a population carrying a particular factor VII gene polymorphism protective against myocardial infarction[14].
CARD: What you say has an obvious implication: should we avoid giving warfarin to those people who are genetically ... anticoagulated? These subjects might benefit from aspirin instead, I hope.
PLAT: We do not know yet, but future clinical trials could enroll people not only with certain qualifying events or risk factors but also with particular genetic patterns[14]. The *Lancet* recently encouraged researchers to start trials enrolling patients according to their genetic profile ...[15].
PHARM: Do not underestimate the limitations of studies which are quick to link polymorphisms and diseases or therapies! Cardiovascular disease is multifactorial and is caused by a combination of several genes and environmental or non-genetic factors such as diet and physical exercise. These diseases are therefore difficult to dissect and the degree of correlation between genotypes and disease or drug response may be quite low. These days, genetic epidemiology is increasingly focusing efforts on controlling for potential environmental confounders.
CARD: If our vascular risk is under genetic control, should we doctors give up all efforts to keep, let's say, the blood pressure or cholesterol levels of our patients under control? I refuse to even think about it!
PLAT: Of course not, but there may indeed be a dilemma between genetics and environmental or lifestyle factors.
CARD: And where does aspirin stand with respect to genetics?
PLAT: Well, we already have some data which correlate the platelet response to the inhibitory effect of aspirin and the polymorphism of a glycoprotein of the platelet membrane[16].
PHARM: I don't see any pathophysiological connection.
CARD: … But the message is clear to me: the pharmacology of aspirin is genetically controlled!
PHARM: I wonder instead if the so-called "resistance to aspirin" could have a genetic basis. Otherwise, this "resistance" may just be a way for new and more expensive antiplatelet drugs to make headway, rather than a true pharmacological or clinical phenomenon.
CARD: You can't deny, though, that the response to aspirin, in therapeutic terms, is heterogeneous.
PHARM: Of course not. But take these two clinical cases[17]: a cardiologist has 2 patients to whom he would like to prescribe aspirin (Table IV). The first is a 45-year-old man with normal blood pressure, cholesterol, body weight and blood glucose, who is a non smoker ...
CARD: So why does he want to give him aspirin?

Table IV. Summary of three clinical cases discussed in the text[17].

	Patient no. 1	Patient no. 2	Patient no. 3
Sex	M	F	M
Age (years)	45	65	40
Blood pressure	nl	↑	↑
Blood cholesterol	nl	nl	nl
Body weight	nl	nl	nl
Blood glucose	nl	↑	nl
Smoking	No	Yes	No
Previous MI	Yes	Yes (2)	No
Complications	No	Yes	No
Vascular risk (%)	2.0	30	0.10
Hemorrhagic risk (%)	0.12	0.12	0.12
Aspirin benefit (%)	0.3	4.8	–

MI = myocardial infarction; nl = normal.

PHARM: Because, despite the absence of known risk factors, this patient had a heart attack, without complications, 1 month earlier.
CARD: Hmmm! And what about the second patient?
PHARM: The second patient is a 65-year-old woman who had hypertension for 30 years, is a diabetic, a heavy smoker, and has dyspnea under the smallest effort. A few years earlier, she had a heart attack and she was recently hospitalized for another one with signs of heart failure, which responded to treatment.
CARD: It seems obvious to me that the first patient has a low risk for another vascular event, whereas the lady has a higher risk.
PHARM: Exactly! The risk of death at one year for the first patient is 2%, while it is 30% for the second patient. The absolute benefit attributable to aspirin would be about 0.3% and 4.8% respectively for them. So it's not the effect of aspirin that varies, it's the patient!
CARD: What about bleeding complications?
PHARM: As the risk of hemorrhage does not increase with that of ischemic events[18], the risk of cerebral hemorrhage for both patients is similar, around 0.12%.
CARD: I think I can see the conclusion ... In the first case – 0.3% benefit versus 0.12% risk of cerebral hemorrhage – it's not worth prescribing aspirin. In the second case – 4.8% expected benefit versus 0.12% risk – aspirin must be prescribed.
PHARM: Don't take the numbers in this exercise as absolute figures!
CARD: Of course not, but can we use the same logical process for primary prevention?
PHARM: Yes, take a 40-year-old hypertensive man (systolic pressure 165 mmHg) without other risk factors. His absolute risk of vascular events at 1 year is 0.10%[17]. If the risk of hemorrhage is 0.12%, this patient should obviously not be treated with aspirin.
CARD: But what about the results of the PPP, HOT and Primary Prevention Trials[5-7]?
PLAT: Well, that's why I insisted on being very careful about extrapolating epidemiological data from the literature and applying it to daily clinical practice! The average age of the population of the PPP trial for instance was 64, not 40 years ...
CARD: Do you think it would be prudent to affirm that the results of clinical trials must be taken as general guidelines, and that it is up to the physician to decide about their application to single patients?
PHARM: I disagree. This means surrendering again to subjective medicine, the kind considered an art and not a science, where the clinician's *ipse dixit* overrides evidence-based medicine ...
CARD: Don't be so pessimistic! Your examples imply that the distinction between primary and secondary prevention is rather artificial because it is based on past events, and not, as would be correct, on the risk of future events.
PLAT: Having suffered a vascular event is a strong element for predicting the risk of a second attack, but many other variables that contribute to the global risk of that individual should be considered ...[19].
CARD: We should therefore distinguish between low- and high-risk patients rather than between primary and secondary prevention!
PHARM: I agree now. Let me add that prevention with aspirin also has a problem regarding costs. This aspect should not be underestimated: an event avoided with aspirin costs much less than with other anti-platelet agents or with pressure or cholesterol lowering drugs.
PLAT: You are right! The poor man's prevention is aspirin and interventions such as physical exercise, smoking cessation and diet … Many could be cared for at the price for which only a few could receive expensive treatments. However, despite aspirin being inexpensive, I'm afraid it is still underused for prevention by many physicians …
PHARM: … Especially if you consider outpatients: only one third of patients randomized in the 4S trial[20] received aspirin. In the ARIC study[21], aspirin use was reported in about half of the patients with a history of myocardial infarction and only in one third of those with angina.
PLAT: Studies of hospitalized patients may show higher rates however …
CARD: … But hospitalized patients constitute only a minority of patients with cardiovascular disease! What about practice in community settings?
PHARM: General practitioners in London give aspirin to about half of the patients with coronary artery disease[22], while aspirin was used in about two thirds of similar patients seen by Scottish general practitioners[23].
CARD: Any data from the United States?
PHARM: Yes, even in the United States among outpatients with coronary artery disease, aspirin use remains suboptimal. Cardiologists however were more likely to prescribe aspirin than were internists or general practitioners[24].
CARD: Was aspirin use similar in male and female Americans?

PHARM: No, it was less likely in women (21 vs 30%) a significant difference[24]!
CARD: This finding is consistent with the fact that women receive less aggressive treatment for coronary disease … What can be done to increase the awareness of aspirin's benefits?
PHARM: Well, nurses or information systems might complement physicians in chronic disease management strategies … But the problem of health care strategies is a complex one and may vary from one country to another.
CARD: I have a last question, perhaps a stupid one … Is it true that wine is just as good as aspirin in preventing vascular disease?
PLAT: Yes indeed, epidemiological studies and a recent meta-analysis agree that constant, moderate use of alcohol, especially wine, prevents cardiovascular disease by about 30%, even if one eats plenty of cheese …[25].
CARD: Is there any dose-response effect of wine?
PLAT: Well, just as in the case of aspirin, protection against cardiovascular events can be seen at a wide range of doses (or glasses?!) and just as for aspirin, low doses of wine are more effective than higher ones. In addition, the effect of wine or aspirin is stronger for heart disease than for cerebrovascular disease ...
CARD: What a fascinating analogy!
PHARM: Come on! There are numerous examples in the cardiovascular literature of studies that have documented consistent population and mechanistic data that have not held up in clinical trials! See the same PPP trial for vitamin E …[7]. Without a large-scale, randomized, clinical endpoint trial of wine intake, there is little justification to recommend wine intake as a cardioprotective strategy!
PLAT: It is hard for me to imagine a trial in which half of a large group of randomized persons would agree – at least in Italy – to avoid wine for 5 years to assess their chance of developing myocardial infarction … The evidence for the beneficial effect of wine should critically include molecular biology, animal and observational epidemiological studies[26].
CARD: Whilst awaiting the best levels and kinds of evidence, I all the same propose to end this chat with a dignified homage to Bacchus! But, before that, let me ask a very last question: are there any recent data on aspirin and stroke prevention?
PHARM: Yes, about 3 years ago, two large trials were published: one was international and the other Chinese; they each enrolled 20 000 patients immediately after an acute ischemic stroke. A meta-analysis of these two studies has just been published[27].
CARD: What are the conclusions?
PHARM: A significant reduction of 7 cases of recurrent ischemic stroke and of 4 deaths every 1000 patients treated (160 or 300 mg of aspirin a day) against an increase of two hemorrhagic episodes every 1000 patients; therefore, we're talking about a net benefit of 9 events/1000 people during a hospitalization period lasting 2-4 weeks. None of these events were correlated with risk factors, such as hypertension.
CARD: These results are certainly comforting, but I wonder whether we should really treat 1000 patients just to avoid 11 episodes only, no matter how serious they may be.
PHARM: Well, consider that if we have 100 000 cases of stroke every year – as in Italy, the number of events avoided would be 1100, not insignificant, even considering the 200 cases of hemorrhagic stroke or hemorrhagic transformation of the initial infarction which occur if not because of, at least in conjunction with, aspirin use.
PLAT: Hopefully, in the years to come, associations and effects will be established in wide populations enabling us to apply them to single subjects ...[28].

The three friends walk towards an Abruzzese restaurant, for a memorable struggle between risk factors and protective effects (the Mediterranean diet ...). They will go back to aspirin another time ...

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