

Placebo and Nocebo in Cardiovascular Health

Implications for Healthcare, Research, and the Doctor-Patient Relationship

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Despite treatments proven effective by sound study designs and robust end points, placebos remain integral to elicit effective medical care. The authenticity of the placebo response has been questioned, but placebos likely affect pain, functionality, symptoms, and quality of life. In cardiology, placebos influence disability, syncope, heart failure, atrial fibrillation, angina, and survival. Placebos vary in strength and efficacy. Compliance to placebo affects outcomes. Nocebo responses can explain some adverse clinical outcomes. A doctor may be an unwitting contributor to placebo and nocebo responses. Placebo and nocebo mechanisms, not well understood, are likely multifaceted. Placebo and nocebo use is common in practice. A successful doctor-patient relationship can foster a strong placebo response while mitigating any nocebo response. The beneficial effects of placebo, generally undervalued, hard to identify, often unrecognized, but frequently used, help define our profession. The role of the doctor in healing, above the therapy delivered, is immeasurable but powerful. An effective placebo response will lead to happy and healthy patients. Imagine instead the future of healthcare relegated to a series of guidelines, tests, algorithms, procedures, and drugs without the human touch. Healthcare, rendered by a faceless, uncaring army of protocol aficionados, will miss an opportunity to deliver an effective placebo response. Wise placebo use can benefit patients and strengthen the medical profession. (J Am Coll Cardiol 2007;49:415-21)
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A placebo is a sham, often a pill, but any intervention purported to be therapeutic. Without direct physiologic or pharmacologic activity, a placebo somehow provides benefit or apparent benefit. Nocebo is a sham, without direct physiologic or pharmacological activity, that causes harm or apparent harm. This review critically examines placebo and nocebo in cardiovascular medicine.

Placebo Effect: Is it Just a Sham?

Over the past 5 decades, the influential efforts of Beecher (1), Lasagna et al. (2), Shapiro (3-5), and others have had a profound impact on how placebo is portrayed, understood, and used. The seminal work of Beecher (1) continues to shape medical, pharmaceutical, clinical, and behavioral research. With over 100,000 placebo citations in PubMed, placebo has set the standard for how clinical research is conducted.

The widely accepted notion that placebo has any effect has been challenged. Kienle and Kienle (6) argued that placebo effects can be explained by the natural history of a disease, regression to the mean, concomitant treatments, experimental subordination, methodologic defects, observer

bias (scaling bias), patient bias (conditioned answers, answers of politeness). Kienle and Kienle (6) concluded that placebo effects are grossly overrated, illusory, and the product of sloppy methodological thinking.

Subsequent analyses, comparing placebo with no treatment, rather than to treatment, suggested that placebo has a negligible impact and its effects are overestimated (7-10). Upon re-analysis of these same data, placebo was found to be effective for specific conditions (11). Methodologic and analytic issues remain unresolved. Poor study design, statistical irregularities, patient and disease selection, and lack of careful definition of what placebo is further obscures its effects and usefulness, yet, double and triple blinded placebo-controlled trials remain the best yardstick with which to measure scientific evidence.

A study designed to eliminate all real and apparent placebo effects requires that the investigator (if directly involved) and patient not know anything about the intervention or the expected outcome. An unbiased individual would administer therapy blinded to what is being given and why. The evaluator of the outcomes would not know who received "real" therapy, what it was, or why it was given. Such studies in cardiology are impractical, unethical, impossible to complete, and of little clinical significance. Double-blind placebo-controlled trials, the best generally possible in cardiology, cannot eliminate a placebo effect completely.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
ICD = implantable
cardioverter-defibrillator
VEGF = vascular
endothelial growth factor

Placebo Effects

A placebo effect represents benefit perceived by a patient or identified by a practitioner arising solely from the appearance that treatment is delivered. The placebo effect does not require that a pill be given. In 1 study, 6,000 psychiatric patients given

placebo pills blindly were told that the pills would help determine the effectiveness of subsequent therapy (12). In short order, 51% improved, 12% deteriorated, 37% had no response, and 57% had side effects. Placebo responses predicted therapeutic responses, but none of 78 patient characteristics defined a responder (13).

The placebo effect may be temporary as it is for hypertension (14), lasting weeks or months, or its effect can be longstanding as it can be with syncope (15). The diversity of responses and interventions makes temporal effects difficult to characterize.

Placebo strength varies by the type of intervention. A dose response exists (16). Blue (vs. pink) placebo pills are sedating. Yellow (vs. green) placebo pills are stimulating. Red (vs. beige) placebos encourage a cardiac response. Branded is more effective than generic. Four-times-a-day is more potent than twice-a-day. Larger capsules are stronger than smaller ones. Interventions, injections, and surgery give larger effects than pills (17,18).

Pacemaker studies provide striking insight regarding the placebo response in neurocardiogenic syncope. Comparing pacemaker to no pacemaker implantation for resistant neurocardiogenic syncope, the VPS-I (Vasovagal Pacemaker Study) was stopped prematurely due to an apparent marked reduction in syncope from the pacemaker (19). Considering the possibility that the implant itself had an important placebo effect, a controlled trial (VPS-II) of a similar population involved pacemaker implantation in all patients, but the devices were programmed off or programmed on in a double-blinded fashion (15). No significant benefit was derived from active pacing. The rate of syncope was similar to the pacing arm of the VPS-I trial.

Beta-blockers are commonly used and widely believed to be effective for neurocardiogenic syncope, but a multicenter controlled clinical trial, the POST (Prevention of Syncope Trial), comparing metoprolol to placebo indicated that any benefit from metoprolol is the same as that benefit derived from placebo (20). In retrospect, an ingenious study comparing placebo pill (atenolol) to placebo device (pacemaker) showed that placebo strengths vary by intervention type. The pacemaker was far superior to a beta-blocker (21). The duration of the placebo response lasted throughout the study. The POST-II study is now comparing fludrocortisone with placebo.

Blinded studies of pacemaker implantation for hypertrophic cardiomyopathy show a strong placebo response similar to the syncope data. Improvement occurred even when an implanted pacemaker was disabled in a blinded fashion for such patients. A large placebo response overshadowed any small or modest effect from active pacing (22-24) with no convincing explanatory mechanism identified.

Cardiac resynchronization benefits may be in part due to placebo response. The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial (25) enrolled patients who received a resynchronization device. While the heart failure would not be expected to improve, over 6 months, even with therapy programmed off in a double-blinded fashion (a sham device) functional class improved, but not to the extent as when the device was programmed on. It remains uncertain how much benefit derived from pacemakers for standard pacing indications (e.g., sinus node dysfunction or complete atrioventricular block) is due to placebo effect.

Catheter ablation is extraordinarily effective for many supraventricular tachycardias and so placebo-controlled trials appear unnecessary, but questions remain regarding efficacy of ablation to treat atrial fibrillation (AF). An apparent benefit of ablation for AF might not be surprising, given hope for cure, a reasonable explanatory mechanism, practitioner's hope for success, and the considerable interventional nature of ablation.

Over 2,000 reports have examined AF ablation, but not 1 study has had a placebo-controlled design. Many patients and clinicians report cure with ablation with excellent successes reported in the literature (26-28), but successes are not as easy to reproduce as for other types of ablation. With aggressive monitoring after ablation, episodes of asymptomatic AF and symptoms unrelated to AF can be recorded (29) although these data remain in dispute (30). As contemporary treatment for AF is to reduce symptoms with no other proven benefit, the ethics of performing a controlled clinical trial using a placebo design to provide a benchmark for safety and efficacy seems advisable.

Placebo appears to influence subjective findings more than objective measurements, but symptom recognition and interpretation is of prime importance for patients with syncope, heart failure, angina, or any other cardiac condition that affects disability or functionality or involves symptom interpretation.

Magnitude of the Placebo Effect

The magnitude of the placebo effect is difficult to quantitate due to its diverse nature (a pill, physician's advice, surgical intervention, patient beliefs, and outcome analyses) and due to the wide variety of conditions that seem to respond. An apparent effect can be immeasurable or exceed 80% of a treatment effect. A placebo can even appear to reduce the risk of death. For most situations and conditions, placebo contributes 30% to 40% to the benefit of an intervention.

Likely, 35% to 50%, if not more, of a response to an analgesic or opiate can be attributed to placebo (31–34).

Recombinant human vascular endothelial growth factor protein (VEGF) research is instructive regarding how challenging it can be to measure. Vascular endothelial growth factor protein was expected to improve outcomes in ischemic heart disease, but hopes dimmed after the VIVA (Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis) study. Of 178 stable exertional angina patients randomized to placebo or low- or high-dose VEGF by intracoronary infusion, angina class and quality of life improved significantly within each group indicating a large placebo response. By day 120, placebo-treated patients had reduced benefit in all 3 measures similar to those in the low-dose VEGF group. High-dose VEGF resulted in significant improvement in angina class ($p = 0.05$) compared with placebo.

These and other (35) data indicate that placebo effects can be combined with physiological effects and have different time-to-effect curves compared with active therapy. Placebo can be difficult to distinguish from active therapies depending on expectations, follow-up, study design, and predefined end points. A study with subjective and continuous end points is more likely to show a placebo effect compared with a study with binary and objective end points.

The Nocebo Effect

A nocebo effect represents harm perceived by a patient or identified by a practitioner arising solely from the appearance that treatment has been delivered. Healthy individuals have adverse effects to a blinded sham 15% to 27% of the time (36). Adverse events have been reported spontaneously with a placebo in 109 double-blind, placebo-controlled studies of 1,228 volunteers. Repeat dosing increases nocebo effects to 28%; old age is associated with a 26% nocebo response (37,38). If patients are specifically asked about adverse effects, the percent can rise to 71% (37,39). The nocebo effect might lead to secondary gain, disability, or even death (38,39). Women report nocebo responses to therapy more than men do, but any impact of practitioner gender, culture, or other perceived biases on the nocebo response is unclear.

Adverse, often unsubstantiated, drug effects and drug side effects, a challenge in practice, may be nothing more than nocebo. Conventional wisdom that beta-blockers have common adverse effects is not substantiated (40) and may be in part a nocebo effect amplified by reading package inserts and warnings or by talking with biased physicians. Of 15 trials, in over 35,000 patients, beta-blockers were not associated with greater risk of depression (6 of 1,000 patients 95% confidence interval [CI] –7 to 19) and led only to a small associated risk of fatigue (18 of 1,000 patients; 95% CI 5 to 30) and sexual dysfunction (5 of 1,000 patients; 95% CI 2 to 8).

Nocebo can be bothersome non-specific symptoms (41). It can be cause for patients to drop out of clinical trials

thereby biasing results (38). Nocebo effects must be considered when designing clinical trials or treating patients. Subtle forms of nocebo in clinical practice may be due to undisclosed or covert emotional conflicts.

Physician advice, although an indirect form of intervention, can have powerful placebo or, unfortunately, nocebo effects. Patients can create their own nocebo effect unwittingly. From the Framingham data, women, with similar risk factors, were 4 times more likely to die if they believed they were prone to heart disease (42). Recent evidence suggests a link between emotions (such as fear or depression), cardiomyopathy, and even death. Tako-tsubo cardiomyopathy, especially prevalent in women, appears related to an adverse intense emotional stressor (43–45).

Nocebo and placebo responses remain confounders that explain much of any therapy's true benefits and risks. Active therapies could have additional placebo and/or nocebo effects.

Ethics of Placebo and Nocebo Use in Practice and Research

Deliberate placebo use occurs in clinical practice. In 1 report, 53 of 89 clinicians used placebo as a therapy with 33 of 53 using it at least once a month. Fifteen (28%) considered placebos to be a diagnostic tool. Of the respondents, 48 of 51 (94%) reported placebos to be generally or occasionally effective (46). In another report, the authors of this survey argued that placebo does not always entail deception and may even be “morally imperative” (47).

With over 3 billion prescriptions written annually, up 50% in slightly over a decade, some drugs are prescribed for the placebo response. This issue is important since medications can have adverse effect and these contribute to >100,000 deaths annually from prescription drugs in the U.S. alone (48). Use of standard, accepted therapies, without adequate evidence base, may rely in part on a placebo response. Such interventions may also cause real adverse effects and even death.

Dishonest and deceptive use of a therapy, primarily to derive covert psychological benefit, but providing no physiological or pharmacological benefit, is fraught with ethical and moral dilemmas and presently not considered acceptable. An inactive therapy may have no real benefit, be neutral, or create nocebo effects but exposes patients to unnecessary risks and may leave underlying medical conditions untreated. Patients who learn of such deceptive practices will likely lose trust.

Alternatively, if the problem being treated is benign and debilitating, if the placebo effect is strong and the risk of harm is low, if the science does not clearly indicate benefit of a therapy, or if the condition does not allow for a well tested therapy, a placebo may be justifiable. This scenario is often used under the rubric of doing what is best for the patients at a time when the data are less than clear. By so doing, the patient may be buffered from therapies with even

greater risks. A benign therapy that reduces pain by 80%, for example, even if much of the response is placebo, may be justifiable as long as the condition is benign and no other therapy is required.

Research using sham therapies help identify harmful and useless clinical interventions. They can be crucial and may be justifiable if no harm comes to the research subject. Trials comparing 2 purported active therapies using a non-inferiority or equivalence design may determine feasibility of a therapy, but without a matched placebo, it is not possible to assess any actual benefit (or harm) derived from the active treatments. No therapy is not an adequate control as it does not match expectations. There are drawbacks and difficulties with 3-way study designs involving 1 active therapy, a matched placebo, and no therapy to assess how much of an effect of a therapy is placebo and how much is active therapy. This type of study design cannot be blinded adequately.

Sham Surgeries

Research involving sham operations in cardiology help clarify the actual benefit of the therapy. Internal mammary artery ligations, once common, are no longer performed based on such investigations. Patients with suspected coronary artery disease who had angina underwent a sham procedure (skin incision) or an internal mammary ligation (an ineffective surgery). Both groups improved. Even treadmill-induced ST-segment depression improved with placebo (49). These data were reproduced (50).

Coronary artery bypass graft surgery, stent implantation, and AF ablation have not been tested against a matched sham control to show the actual benefit derived from these procedures, but such a control may be unacceptable, impossible, unethical, and impractical. One randomized controlled trial that will never be completed is comparison of a sham implantable cardioverter-defibrillator (ICD) against an actual ICD to evaluate risk reduction of mortality in a high-risk population. The SCD-HeFT (Sudden Cardiac Death Heart Failure Trial) did evaluate a placebo pill in a 3-arm study design (51). The placebo pill may be a good match for amiodarone, but hardly for the ICD. The benefit of an ICD cannot be calculated with certainty without a matched placebo. Nevertheless, such a comparison is out of line with clinical equipoise.

Neurosurgeons have performed, carefully controlled, and matched placebo surgical evaluations, so it should be possible for cardiologists and cardiovascular surgeons to do the same. One such study involved Parkinson's disease patients randomized to embryonic fetal cell brain implants or sham surgery (holes drilled in the head) (52). Both groups improved similarly regarding the primary outcome of disease severity eliminating this as a viable treatment option.

Mechanisms of Placebo Effects

Lack of consensus regarding what constitutes the placebo effect may explain in part why some data indicate a real response to placebo and other data do not. Responses that shape the placebo effect are likely an actual physiological response combined with natural history of and spontaneous fluctuations in the disease state, spontaneous remission, patient beliefs and expectations, observer enthusiasm and expectations, random variability, regression to the mean, and other obscure issues. Statistical anomalies can contribute to the placebo effect. Sample size is important. The likelihood of a placebo effect is greater in smaller data sets. Time of follow-up is important. Shorter follow-up increases the likelihood of a placebo effect that may fade with time.

Part of the response is due to expectations, culture, gender, and race of the subject and of the experimenter. Some placebo benefit may be hard-wired behavior with a genetic basis. Unwittingly (or by poor study design), the practitioner may be the one experiencing the greatest benefit of the therapy. Placebos may even work if a patient is knowingly taking one (53).

Neurophysiologic effects. Placebo can change sensitivity in perceptions related to neurocognitive pathway alterations. Placebo can release endorphin (54,55). This may initiate a cardiovascular response (56). For pain, disinhibiting nitric oxide signaling and opioid mu receptor activation could affect nigral and tegmental dopamine output by gamma aminobutyric acid neurons, ultimately affecting mesolimbic and mesocortical reward and motivation circuitries (57). Positron emission tomography brain scanning provides evidence of endogenous neurotransmitter dopamine release in Parkinson's disease patients in response to placebo (58). Electroencephalogram brain mapping suggests that a placebo response may have different mechanisms of action than an active drug even though the response is similar (59). Placebo responses could complement an active drug (or work against it).

Conditioning effects. Conditioning can elicit a placebo response. Rats drinking saccharin-flavored water with cyclophosphamide had immunosuppression. Ten days later, after recovery, one-half the rats received saccharin; the other half received nothing. Saccharin lowered antibody titers versus control 8 days after antigenic stimulation (60). Similarly, patients may be "hard wired" to develop a conditioned placebo response. Conditioning may be more important than expectation (61).

Expectation effects. An expectation of, or hope for, benefit from a treatment can explain placebo effects. Low expectations will reduce or eliminate the placebo effect (61). Expectation has neurophysiological impact as measured by a functional magnetic resonance imaging (62) and can affect outcomes based on patient and practitioner interpretations (63). Several types of expectation responses exist (Table 1).

Table 1 Definitions of Some Expectation Effects Behind the Placebo Response

Hawthorne effect	Subjects respond to knowledge of being evaluated and observed
Jastrow effect	Subjects respond to explicit expectation about outcome
Pygmalion effect	Evaluators expect therapeutic benefit, so they see it
John Henry effect	Control subjects attempt to emulate expected outcomes
Halo effect	Subjects respond to treatment novelty (i.e., new technology)
Experimenter effect	Evaluators consciously (or not) interpreted outcomes differently
Socialization effect	Others reporting feigned (apparent) benefit influence outcomes
Value effect	Costs influence expected outcomes

Expectation in clinical trials can affect a placebo response if the participant has past clinical trial experience, has undergone medication changes, has had procedures, has fear of being a placebo responder, gets input from or has trust in study or non-study doctors, or has a fear of side-effects (64). This is most patients. Paying a high price for a therapy may affect expectations.

The meaning response: a form of expectation. The “meaning response” is a plausible, understandable, explanation of an illness (even if a manufactured concept) and/or treatment. Interpretation of the meaning and impact of a condition affects patient responses. “The chest pain is benign and due to a problem in the esophagus” is completely different than: “The chest pain is due to blocked arteries supplying blood to your heart. You will probably die soon.”

Sox et al. (65) found that performing a series of tests in patients with non-specific chest pain could reduce disability from 45% to 20% even if the tests were negative or unnecessary. Simply performing tests in patients with atypical chest pain can have a beneficial effect even though structural heart disease is not present. While these results do not necessarily represent a modern population of patients with chest discomfort and there may be issues of study rigor, the point is clear—evaluation can change the perceptions and expectations regarding outcomes.

As part of the meaning response, apparent rational therapy can influence outcomes even if the therapy is a sham. Consider a patient with a coronary artery that is 99% blocked. It makes sense, and has meaning to the patient and to the physician, that opening the artery to augment coronary blood flow will improve the outcome. This line of reasoning makes sense whether or not it really is true and whether the therapy is effective or not, but it offers a placebo effect. Transmyocardial revascularization may provide placebo response due to its proposed mechanism of action. Vascular endothelial growth factor may have had benefit by this same mechanism overshadowing other possible benefits. Angioplasty, stent placement coronary artery bypass graft surgery, and AF may work partially by this mechanism.

Patient Compliance and Adherence: Indicators of Expectation?

Compliance and adherence to placebo affects outcomes or at least differentiates therapy responders from non-responders. The Coronary Drug Project enrolled about 5,000 men in the 1960s. High-risk men received clofibrate or placebo. Over 5 years, mortality was the same in both groups, but patient outcomes varied by compliance. For those >80% compliant to placebo, the mortality was 15%, similar to clofibrate, but for those compliant <80%, the mortality was 28% (similar to clofibrate) ($p < 10^{-16}$) making this the most statistically significant study in cardiology to date. No specific parameters predicted compliance (66). At the time, the authors stated that, unless this response was understood, it could be very difficult to understand any study results or make sense of clinical trials.

This observation has been reproduced. The same results were seen after myocardial infarction (67). In the Beta-Blocker Heart Attack Trial, among 2,175 participants, those who did not adhere well to treatment (taking $\leq 75\%$ of prescribed medication) were 2.6 times more likely than good adherers to die within a year of follow-up (95% CI 1.2 to 5.6). Poor adherers had an increased risk of death taking placebo (odds ratio 2.5), and this risk was not accounted for by severity of disease, sociodemographic features, smoking, or psychological characteristics. The same finding was seen in patients with congestive heart failure patients (68) and with hypertension (69).

Is Placebo Powerful or Powerless?

Perhaps the greatest single observable consistent and reproducible effect seen over time in medicine is the placebo effect. If it is simply a fake, then perhaps all of medicine is largely a sham. This hypothesis is untenable.

Taking the tact that placebo is powerless, Hrobjartsson and Gotzsche (10) sought to prove this based on a meta-analysis of 130 trials involving 3,795 patients. The placebo compared with no therapy had no effect in the conditions tested. The analysis showed no difference for pharmacologic, physical, or psychological placebos leading some to abandon the idea that a placebo has an effect. Not all agree. For specific conditions, re-analysis of the same data has shown different results (11) perhaps revealing biases. That aside, much of what is considered placebo may be due to expectation effects, built in biases in patient assessment, and reporting and conditioning responses.

The difference between powerful and powerless placebo may relate to what the placebo is considered to be. The lack of a singular criterion for placebo definition across studies might underlie the core of the debate. The issue is often related to how a placebo is used and/or how the results of a study are observed and evaluated. Apparent and actual benefit can be difficult to separate. The common denominator, the core of the placebo response, is not the therapy

but the dynamic between patient and physician. This dynamic cannot be factored out in studies performed and those analyzed by Hrobjartsson and Gotzsche (10). Other data point to this interaction as being crucial (70).

Physicians—the unwitting contributor to the placebo response. Placebo responses are seen because they are expected or predicted. The doctor can enhance the placebo response and be a knowing or unwitting contributor to it. In a double-blinded trial for pain, 1 group received a narcotic analgesic, narcotic antagonist, or placebo and the other received a narcotic antagonist or placebo. Doctors who knew which group was which gave the therapy. The first group had a better outcome (71).

Concealed random allocation (to counterbalance experimenter and subject expectancies) may offset these issues. Selective reporting, focusing only on positive outcomes, can be misleading but may represent part of the placebo effect. Evaluating specific clinical conditions rather than looking at the group as a whole may be another contributor. All these issues must be considered in order to design a robust double-blinded placebo-controlled clinical trial in which expectancies are eliminated.

Future Research

A standardized (narrow) definition of placebo will help better identify how placebos work. Until placebo is better defined and understood, the placebo effect will remain a real phenomenon. More carefully designed studies that identify and compare placebos may help clarify the issues. Such studies are underway.

Conclusions

Placebo and nocebo effects are common in practice. An understanding of these effects is vital to evaluate outcomes fairly in research. Placebo and nocebo ultimately involve salutary and deleterious interactions (and their interpretation) between patient and doctor. Placebo is time-tested and is an intricate part of successful medical care.

A cold, uncaring, disinterested and emotionless physician will encourage a nocebo response. In contrast, a caring, empathetic, physician fosters trust, strengthens beneficent patient expectations, and elicits a strong placebo response. A compassionate, hands-on approach may be more valuable than any single medical therapy. Generally undervalued, often unrecognized, placebo helps define our profession. The doctor, the nurse, the healthcare provider are the most valuable resources for healing patients.

A 2005 *U.S. News and World Report* cover stated: “Who Needs Doctors? Your next doctor may not be an MD and you may be better off.” Have we finally come this far, where the human touch of the physician can be replaced by healthcare reduced to guidelines, tests, algorithms, procedures, and drugs?

It is unlikely that patients would accept depersonalized medicine no matter how far technology progresses and no

matter how hard the benefits of the doctor-patient relationship are sterilized, dissected, and disregarded. The personal role doctors have in patients’ lives has made the medical profession one of the most respected and time-honored professions. If the placebo response as part of the doctor-patient dynamic is alive, patients will be happier and healthier. Without placebos, the doctor’s role will deteriorate or disappear, and patients will suffer. Placebos work!

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