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CURRENT OPINION

# Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease

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## Introduction

The potential risks associated with cardiovascular imaging (CVI) have recently been debated, partly triggered by the rapid increase in the use of imaging procedures and new imaging modalities such as cardiac computed tomography (CT).[1,2] The discussion has mainly focused only on a single-risk aspect such as radiation.[3] However, the various procedures have several risks: stressors, contrast agents, invasiveness, radiation, etc. Even more important, the test must be related to the benefit of performing or not performing the test with the risk and drawbacks associated with the disease remaining undetected.

We aimed to create a balanced analysis of immediate, short- and long-term risks associated with CVI in relation to the natural course of coronary artery disease (CAD) and to therapeutic interventions. The imaging tests for CAD were selected, since many CVI tests are commonly used. We analysed: (i) the risk of major cardiac events (MCEs) for each component of imaging test; (ii) the upper limit for each risk, in order to avoid underestimation of a risk; (iii) composite risks calculated for selected common diagnostic tests for CAD; (iv) the risks compared with the risk of the disease itself, to assess the potential benefits of tests; and (v) comparison with risks in regular life activities and that associated with trivial long-term prophylactic interventions such as aspirin use.

This analysis is based on the data available from the literature. Data for risks related to some of the procedures are quite limited, for some variable, and for some of limited quality. Still we sought to present risk estimations from all the procedures using reliable studies and databases available from an extensive search of the literature. The detailed information about risk assessments is shown in Supplementary material.

## Analysis of risks

### Definitions

In the literature, risks are described in many different ways, e.g. 'fatal, major, serious, less severe, and milder'. In the present analysis, we use 'fatal', when presented as such in the literature. 'MCEs', often used in the investigations, are presented quoting the descriptions of the citations. The degree of seriousness for 'less serious or minor adverse or side effects' vary significantly in the citations referred. In this analysis, they are defined as complications or side effects that are not life threatening. 'Adverse events (AEs) (serious and less serious) and adverse drug reactions' in relation to drug administration are described according to the WHO definitions.[4]

### Stress tests

Dynamic exercise and different pharmacological stress agents including vasodilators (adenosine, dipyridamole, selective A2A receptors agonists) and inotropic-chronotropic agents (dobutamine) are employed. The overall hard events rate of dynamic exercise has been reported to be in the range of 1.2–8.6/10 000 tests, depending on the referring population.[5,6] The overall hard event rate of pharmacological stress with dipyridamole or adenosine is comparable with that of exercise,[7,8] but minor side effects are more common. Recently, A2A selective agonists have been approved as stressors. The incidence of serious AEs and side effects appears significantly lower than with

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adenosine.[9] The complication rate with dobutamine, which is used commonly with stress echocardiography is higher than that reported for other stressors: One severe AE in 335 tests has been reported in a recent meta-analysis.[10,11] For the purpose of this study, we used a fatal event rate of 1/20 000 for exercise and 1/10 000 for pharmacological stressors.

# Imaging procedures

## Cardiac magnetic resonance imaging

Strong static magnetic field as such is unlikely to cause significant adverse biological effects. RF energy applied to the body may be responsible for tissue heating.[12] Some metallic devices, e.g. pacemaker leads, may potentially induce excessive local heating as well as arrhythmias.[13] Gradient magnetic fields could stimulate nerves and muscles, occasionally causing discomfort[14] but current cardiac magnetic resonance imaging (CMRI) systems typically operate below nerve stimulation levels. Quickly changing magnetic fields may generate electrical currents in electrically conductive devices with potential risk of arrhythmia induction in patients with pacemaker leads.[13] Ferromagnetic objects, including cerebral aneurysm clips, drug infusion pumps, cardiac pacemakers/defibrillators, accidentally introduced into a CMRI suite are quickly attracted towards the magnet and has been cause of significant injuries and even death of patients and CMRI operators. Significant increase of DNA double-strand breaks have been detected after routine 1.5 T cardiac MR examination[15,16] but obviously more information about this phenomenon is needed to make any numerical estimation about this risk.

In this paper, we estimated accidents in 0.07/10 000 examinations and 0.2/10 000 other serious AEs, including burns, arrhythmias in CMRI studies. Since no data are currently available about the clinical events caused by MR-induced DNA damage, this risk was not included.

## Echocardiography

Biological effects of diagnostic ultrasound have been documented in experimental studies conducted on molecular, cellular and animal level.[17] The effects depend on the characteristics of the sound wave, sensitivity of exposed tissue, and time duration of exposure. The effects may broadly be classified into thermal and mechanical effects. With current diagnostic ultrasound technology, biological effects are unlikely to be caused directly by tissue heating.[18]

Among possible mechanical effects of ultrasound, a potential risk is cavitation: formation and rhythmic oscillation of microbubbles produced from gasses dissolved in living tissue. The mechanical index has been developed as predictor of acoustic cavitation and is displayed as a safety parameter on modern ultrasound scanners. Capillary rupture can be demonstrated when tissues containing gas-filled contrast agents are exposed to ultrasound,[19] but so far there is no evidence of significant health risk from exposure to medical ultrasound for patients or clinical staff members.

### Coronary angiography

Diagnostic invasive coronary angiography (CAG), like most invasive procedures, may cause serious complications.[20,21] Major complications of 1–2% are reported (*Table 1*), the likelihood of major complications increasing significantly with the severity of the underlying disease. Important predictors of major complications include shock, acute myocardial infarction of $<24$ h, unstable angina, cardiomyopathy, renal insufficiency, heart failure, and high age. Patients undergoing CAG in an emergency setting are at greatest risk for complications. The skill and experience of the operator and the catheterization laboratory staff, as well as the peri-procedural management and low-profile catheters are also important factors. Currently, the transradial approach decreases entry site complications as compared with the femoral approach.

In the current analysis, the acute risk of death by CAG was estimated to be 8/10 000 studies and the rate of serious AEs 177/10 000.[20,21]

# Contrast agents and tracers

## Contrast agents for cardiac computed tomography and invasive coronary angiography (iodinated)

Computed tomography and invasive CAG requires injection of an iodinated contrast agent. Adverse events after use of contrast media include local effects (extravasation), acute or delayed reactions and contrast-induced nephropathy. Extravasation occurs in ~0.2% of procedures when a power injector is used[22] and may lead to severe damage, including compartment syndrome. Mild general reactions occur in 0.4% of patients and serious reactions, including pulmonary oedema, severe hypotension, and loss of consciousness occur in 0.04%[23] with non-ionic contrast agents.

The most prominent risk of iodinated contrast agents is nephrotoxicity, rare in patients without a history or symptoms of renal disease. The incidence of kidney injury was 1.3% after percutaneous coronary intervention.[24] Nephropathy rates were substantially lower for intravenous compared with intra-arterial injections (1.1 and 1.8%, respectively).[24–26] The additional mortality of patients with clinically significant kidney failure was reported as high as 14–15.8%.[24–27]

For the purpose of this study, we estimated the rate of death due to acute general reactions for contrast agents as 0.059/10 000 and long-term risk due to nephropathy to be 6.6/10 000 for intravenous and 7.6/10 000 for intra-arterial administration. The rate of serious acute AEs was estimated to be 4.06 and long-term events 79.0 per 10 000 studies.

## Contrast agents for echocardiography

Contrast agents in echocardiography are used for cardiac chamber opacification, in particular to improve the endocardial border of the left ventricle,[28] and evaluation of myocardial perfusion. The use of contrast agents improves diagnostic accuracy and reproducibility of both rest and stress echocardiography, including left ventricular volumes, ejection fraction, and wall motion assessment.[28,29]

In the present analysis, we used a risk of serious AEs as 3/10 000 and the risk of death 0.1/10 000 after echo-contrast administration as suggested by the overall post-marketing experience with a perflutren lipid microsphere (Definity).[30] In our estimations, we assumed that contrast agents have been used in stress echo examinations.

**Table 1** Complication rates/10 000 examinations during diagnostic cardiac catheterization

| Death | MI | Stroke | Ventricular arrhythmia | Vascular | Contrast reaction | Total |
|---|---|---|---|---|---|---|
| 8 | 5 | 7 | 10 | 20 | 70 | 177 |

MI, myocardial infarction.

## Contrast agents for cardiac magnetic resonance imaging

When CMR contrast agents are used in doses producing equal attenuation as iodinated contrast agents, the risk of renal dysfunction is similar to that caused by iodinated agents.[31,32] Furthermore, gadolinium-based contrast agents are associated with the development of nephrogenic systemic fibrosis (NSF). Nephrogenic systemic fibrosis is potentially a lethal disease but it has never been seen in patients with normal kidney function.[33] Although rare, acute allergy-like reactions occur after intravenous gadolinium-based contrast agents in 0.03–0.2% of patients.[34,35] Most reactions are mild (rash, urticaria). Severe, life-threatening reactions (respiratory distress, cardiopulmonary arrest) are extremely rare: only 33 reactions after 687 000 doses[36] and very few of them fatal reactions.[37]

In the present analysis, we estimated a risk for acute fatal events to be 1/1 000 000 studies and the rate of acute severe AEs 4.8/100 000 studies. Since the literature does not present hard data for the calculation of a long-term nephrotoxic risk, we used the same risk factors as those for CT contrast agents. Thus, the estimated long-term death rate was 6.6/10 000 due to nephrotoxicity and 0.33/10 000 due to NSF. The former risk may be overestimated due to fact that smaller amounts of contrast materials are used.

## Tracers for radionuclide imaging

Radiotracers for cardiac imaging (SPECT or PET) have good safety profiles: 2–6 AEs/million for $^{99m}$Tc-sestamibi/-tetrofosmin injections.[38–40] The risk of AEs is even lower with $^{201}$thallium. No serious AEs have been reported after PET tracers. The overall the prevalence of AEs following radiopharmaceutical administration is >1000 times lower than that after ordinary pharmaceuticals and diagnostic contrast media[38–40] probably related to the very small amount of tracer injected.

For the current risk analysis, the risk of death was considered to be negligible and the rate of serious AEs 0.06/10 000 studies.

## Ionizing radiation

The harmful effects of ionizing radiation are classified into stochastic effects, which are due to radiation-induced mutations, and deterministic effects, which are due to radiation-induced cell death. Stochastic effects are the primary concern in cardiac imaging.[3]

Estimation of the risk from ionizing radiation is difficult, since no prospective trials focusing on the AEs of radiation with doses used in diagnostic procedures have ever been performed. Risks related to low doses are derived by linear extrapolation, mainly from epidemiological studies of atom bomb survivors in Hiroshima and Nagasaki.[41] Currently, one in three women and one in two men in the USA will develop cancer in his or her lifetime.[42] Since this is so much higher than any estimated effect of medical radiation, the potential minute increase in cancer due to radiation is extremely difficult to detect.

**Table 2** Typical effective doses of the most common cardiac imaging procedures

| Procedure | Effective doses (mSv) |
|---|---|
| Calcium score | 1–2 |
| CT angiography | 3–20 (mean 7) |
| Tl-201 stress + rest SPECT | 22 |
| Tc-99 m tetrofosmin or sestamibi stress + rest SPECT | 10 |
| PET perfusion stress + rest (Rb-82, N-13 ammonia, O-15 water) | 2.0–2.7 |
| FDG PET viability | 4.9 |
| Invasive CAG | 2–23 (mean 7) |

The radiation doses of cardiac examinations are displayed in *Table 2*. Recent software and hardware implementation may have reduced the patient exposition but could not be taken into account here. Since the risk due to radiation depends on several factors in populations, the European Commission Radiation protection guideline[43] (2008) makes cautious statement about using collective effective dose estimates in assessing radiation risks to patients by simple application of the nominal probability coefficients derived for a general population. Being aware of these limitations and since no better estimates are available, for the purpose of this study, we used the estimated risk by ICRP,[44] in which 10 mSv would translate to 5 additional fatal cancers/10 000 patients.

## The composite risks of diagnostic tests

The risks can be divided into acute and long-term risks. The acute AEs include allergic reactions of contrast agents, accidents during the scan and arrhythmias induced by stressors as the more important risks. Long-term AEs include malignancies and contrast-induced nephropathy as the more important risks. The risks of acute and late events were calculated separately and then pooled together to create a composite risk. With the numerous variations of each test, the selected tests are serving as examples for the composite risk profile for typical imaging of CAD.

All non-invasive tests show a very low risk of acute death (*Figure 1*) and stressors imply the highest risk for death, not the procedures themselves or the contrast agents. The acute risk of an invasive test is related to the procedure itself. When taking into account also

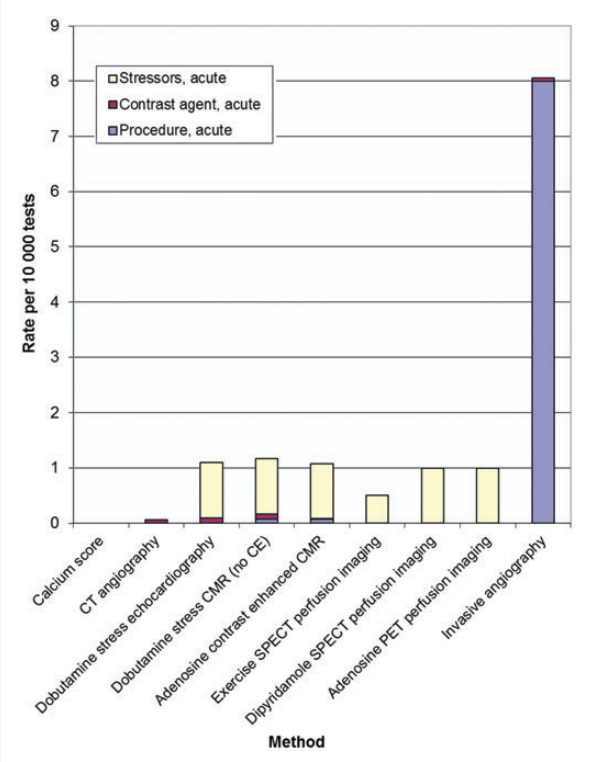


**Figure 1** Estimated risk of acute death due to an imaging procedure.

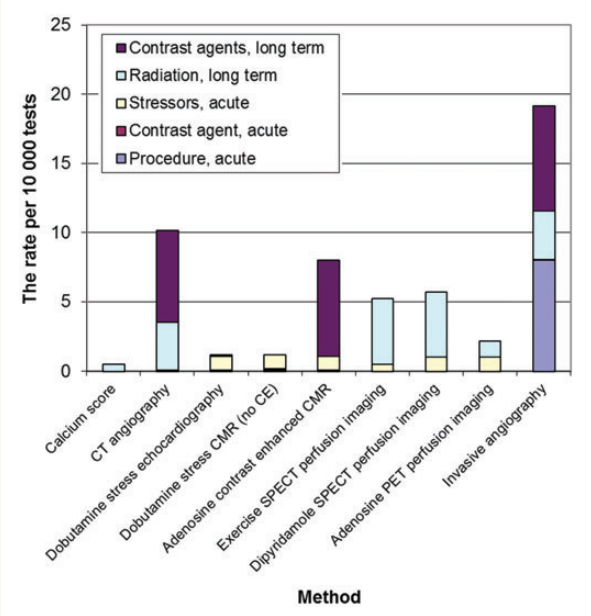


**Figure 2** Estimated risk of acute and long-term death due to an imaging procedure.

the long-term risks, the picture is somewhat changed (*Figure 2*). The risks of a fatal event by contrast agents and by radiation exposure are more important using non-invasive tests. The estimated risks of acute and long-term serious AEs due to an imaging procedure are shown in *Figure 3*.

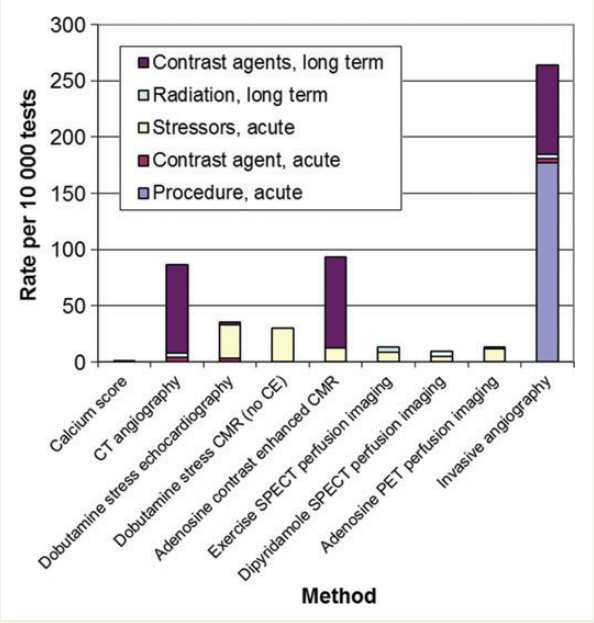


**Figure 3** Estimated risk of acute and long-term serious adverse events due to an imaging procedure.

## Comparison of risks of diseases, therapies and activities of daily life in healthy subjects

In *Figure 4*, the composite long-term risks of a fatal event due to imaging are compared with the risks of CAD, aspirin medication and the risks of daily-life activities. Based on SCORE,[45] an asymptomatic male at the age of 50–60 years with more than one risk factor for atherosclerosis has a 10-year risk of cardiovascular death ~1000/10 000. In a symptomatic population, the risk will definitely be higher and dependent on the severity of disease. The life-time risk of fatal bleeding by aspirin medication is 140/10 000.[46] The life-time risk of dying in a fatal motor vehicle accident is 119/10 000.[47] The corresponding risks of fatal accidents for pedestrians, by drowning and by bicycling, are 16, 9 and 2 per 10 000 subjects, respectively. The risk of fatal bleeding due to aspirin is about seven times higher than the risk of an invasive imaging test and 14–280 higher than any non-invasive imaging test. Correspondingly, the risk of death due to CAD even within 10 years is about 50 times higher than the risk of an invasive imaging and 100–2000 times higher than any non-invasive imaging procedure.

# Discussion

To the best of our knowledge, this is the first study that has analysed acute and long-term composite risks related to CVI. Our analysis shows several important findings: stress agents are relatively major contributors to acute risks related to CVI. However, in absolute figures, the risk is small. In invasive tests, the procedure itself is the most important risk factor. For long-term risks of fatal events, the

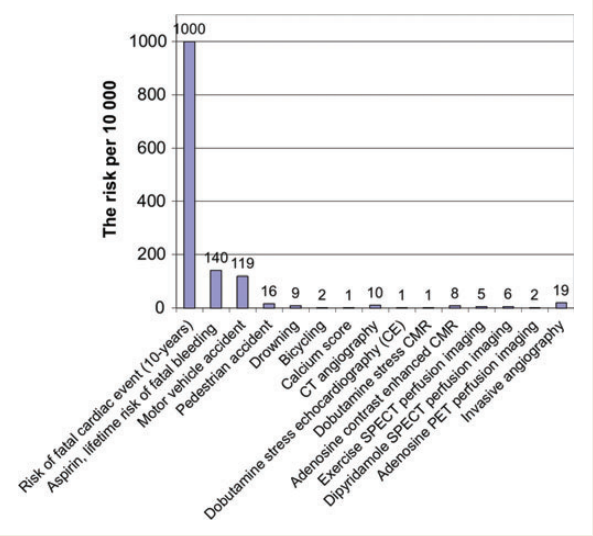


**Figure 4** Risk of fatal events after imaging compared with other risks. The graph displays the risks of fatal cardiac events in asymptomatic 50- to 60-year-old men with more than one risk factor for atherosclerosis, fatal bleeding during aspirin therapy, risk of fatal events due to selected activities in daily life, and fatal events after cardiovascular imaging procedures.

risks of contrast agents and the radiation risk have high impact on the composite risk of the procedure. The risks of non-fatal events are mostly related to stressors and contrast agents.

It is to be noted that the life-time risk of imaging procedures for fatal events is small as compared with the general risk of fatal cardiac events by CAD both in asymptomatic and symptomatic populations. Although the risk of aspirin therapy has no clear link with the risks of imaging test, we used that for a comparison to get an idea about the scale of various risks. Aspirin therapy is commonly suggested as a safe therapy for patients with coronary atherosclerosis and is used liberally in patients with mild and asymptomatic CAD. We found that the risk of imaging tests at the highest is less than one-seventh of the life-time risk of fatal bleeding by aspirin. The risk associated with revascularization is of course markedly higher than any medical or diagnostic intervention but the benefit is also well documented when used appropriately.

The risk associated with imaging procedures is small as compared also with other risks. In patients with suspected or known CAD, the risks from the disease left untreated is obviously much higher and increases with the severity of the disease. Therefore, the relative risk from the natural course of the disease as compared with the risk of imaging is even more striking. The relative low risk of imaging is further emphasized when comparing risks of imaging tests with daily-life activities and imaging risk appears in the same range as that related to walking, swimming, or bicycling.

The benefit of imaging, both in known and suspected CAD, is presently intensively debated: What is the best algorithm for demonstrating CAD in order to offer a therapeutic intervention? The economic consequences of the recent increases in number of imaging procedures also play a significant role in the debate. There is no doubt that benefit of imaging is not only achieved, but indispensable for patients, both to offer optimal therapeutic interventions and to eliminate the fear and anxiety in symptomatic subjects without CAD.

# Conclusions

The CVI tests are all related to small but detectable risks. Different components of imaging tests contribute to the acute and long-term risks. The composite risks of imaging tests are in the same range as the risks of common daily-life activities and are only a minor fraction of the risk of CAD or common therapeutic or prophylactic medical interventions.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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