We agree with the main thrust of the argument in the recent article by Eriksson\(^1\) that long-term clopidogrel treatment (8 and 12 months) confers a small, or at most modest, advantage when compared to the standard 1-month treatment in patients undergoing percutaneous coronary intervention.

Eriksson should be commended for the critical analysis of the data from PCI-CURE and CREDO. In particular, for pointing out that the small absolute reductions in composite endpoints of death, myocardial infarction, revascularisation in the long-term clopidogrel treatment group compared to the standard 1-month treatment group, could easily be negated by the increased bleeding risk.

However, we wish to highlight that both trials were conducted before the era of drug-eluting stents. In fact, the main reason for prescribing clopidogrel beyond the standard 1-month period is not so much driven by the results of PCI-CURE or CREDO, but by the implantation of drug-eluting stents.

The theoretical concerns of delayed endothelialisation leading to stent thrombosis have not been borne out by trials comparing drug-eluting stents to bare metal stents. Nevertheless, all these trials of drug-eluting stents have used clopidogrel for beyond the standard 1-month period normally applied to bare metal stents.

In RAVEL,\(^2\) where short coronary lesions (mean length 9.58 mm) were treated with a single sirolimus-eluting stent, clopidogrel was prescribed for 2 months. The SIRIUS\(^3\) and TAXUS IV\(^\text{a}\) trials involved treating longer lesion lengths (mean length 14.4 and 13.4 mm, respectively) and more complex disease (diabetes, multiple stents and small vessels). The duration of clopidogrel treatment for SIRIUS and TAXUS IV trials was therefore longer, at 3 and 6 months respectively. None of these trials showed an increased risk of stent thrombosis in the drug-eluting stent group when clopidogrel was prescribed for between 2 and 6 months.

In fact, two recent reports of stent thrombosis in drug-eluting stents\(^5,6\) in the literature demonstrate a strong link to the discontinuation of anti-platelet therapy within the first month. Lemos et al.,\(^7\) has shown that even in unselected ”real world” patients outside the strict entry criteria of trials, patients with complex disease such as multi-vessel disease, bifurcation disease requiring multiple stenting can be treated with sirolimus-eluting stents effectively without an excess of stent thrombosis with clopidogrel treatment of 3–6 months duration.

Although the optimal duration of clopidogrel treatment after drug-eluting stent implantation is not known, empirical long-term treatment (3–6 months) is here to stay because of the fear of the dreaded complication of stent thrombosis and its serious consequences. Depending on lesion complexity and adverse patient characteristics such as diabetes, some authorities even recommend 6–12 months treatment with clopidogrel.\(^8\) This prolonged use of clopidogrel has economic consequences and should be considered in any cost analysis of the use of drug-eluting stents.

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Long-term clopidogrel therapy in the drug eluting stent era: beyond CREDO and PCI-CURE

Sir

In the trials comparing drug-eluting stents with bare metal stents, clopidogrel (in addition to aspirin) had been administered for 2–6 months, and no increase in the incidence of stent thrombosis has been reported to date.\(^1\) However, I share Dr. Koh’s and Dr. Kadr’s concerns about delayed endothelialisation with drug-eluting stents. Although the optimal period of clopidogrel therapy after drug-eluting stent implantation is not known, clopidogrel is prescribed for 6 months after the implantation of a drug-eluting stent in our institution, which probably provides a wide margin of safety. In contrast, anti-platelet therapy was discontinued after the procedure in four out of the seven patients with a stent thrombosis in the study of Jeremias et al.,\(^2\) cited by Koh and Kadr. This is evidently not a strong argument for long-term clopidogrel therapy.

The clinical value of long-term therapy with clopidogrel in addition to aspirin has recently been called into question.\(^3,4\) Now the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with
Recent Transient Ischemic Attack or Isc-
chastic Stroke (MATCH) trial\(^2\) also raises
serious concerns about the safety of com-
bining aspirin and clopidogrel long-term.
In MATCH, clopidogrel and aspirin (\(n = 3797\)) were compared with clopido-
grel alone (\(n = 3802\)) after an ischemic
stroke or transient ischemic attack.
There was a non-significant 0.73% absolute
risk reduction in the composite of cardio-
vessel death, myocardial infarction or isch-
aemic stroke during 18 months of fol-
low-up in patients receiving both aspirin
and clopidogrel, compared with those re-
ceiving clopidogrel only. However, the
absolute risk of life-threatening or major
bleedings increased by 2.62% in patients
who were given both aspirin and clopido-
grel (\(p < 0.001\)). Accordingly, the
number needed to harm was only around
38.

Obviously, further study is needed to
determine the risks and benefits of
combining aspirin and clopidogrel for
more than a few months in patients with
atherothrombotic disease, including
those receiving a drug-eluting stent.
Remember Voltaire’s bright reflection:
"The best may be the enemy of the
good".

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Cardiovascular disease, periodontitis, and the
monocyte relationship

To the Editor

One investigative approach to linking
periodontal disease to atherosclerotic cardio-
vascular disorders is demonstrating a
shared risk factor with the potential for ac-
tually mediating cardiovascular disease. This
in regard, the Buhlin et al.\(^1\) report com-
paring cardiovascular risk factors between
patients with severe periodontal disease
(without known history of cardiovascular
disorders) and healthy individuals suggests
discovery of an important relationship.
Their meticulous and innovative investiga-
tion discloses that a unique haematological
index, the peripheral blood monocyte
count, associates strongly with severe
periodontal disease. Yet the investigators
dismiss any potential for clinical relevance
of this finding on the stated ground that the
monocyte levels were within the "normal"
range, and consequently they excluded this
variable from their reported multivariable
models and analyses.

The discovery of novel risk factors in
exploratory studies like the Buhlin study
requires entertaining scenarios beyond the
entrenched paradigms. Moreover, several
bases do exist to support an inference that
peripheral blood monocyte indices, within
today’s reference range, may in fact op-
erate to confer substantial cardiovascular
disease risk. The true healthy range for
peripheral blood monocyte levels vis à vis
cardiovascular disease is not known. This
conundrum persists because an appropri-
ate reference population cannot be con-
stituted. Present day technology does not
enable physicians to validate the absence
of underlying atherosclerosis. Therefore
the statistical approach used today to de-
fine the reference range, for example, as
two standard deviations above and below
the mean is problematic in that it relies on
a group of apparently healthy individuals.
However a more meaningful approach,
defining abnormal values as those associ-
ated with adverse physiological or clinical
consequences, is feasible. Several initial
developments in this direction are re-
ported. First, the available longitudinal
epidemiological studies indicate that mi-
nor increments in monocyte counts and propor-
tions (that fall well within their
reference ranges) do convey long-range
predictive value for clinical cardiovascular
disease and mortality.\(^2\)\(^\text{–}\)\(^4\)
Second, the available longitudinal clinical imaging
studies show that minor incremental dif-
fences in monocyte counts or propor-
tions within today’s reference range
associate with near-term augmentation in
rates of atherosclerotic vascular lesion
progressions. The putative athrogenic
effect of circulating monocytes manifests
at native lesions in non-manipulated ar-
teries\(^5\)\(^\text{–}\)\(^7\) as well as at iatrogenically triggered
lesions such as restenosis after angioplasty
or endovascular stent placement.\(^5\)\(^\text{–}\)\(^7\)

In summary, this cumulative evidence
enables the conclusion that it is both valid
scientifically and clinically relevant for
investigators to pursue evaluating mono-
cyte levels in future risk factor analyses
des of cardiovascular disease. This logic is ger-
mance to the aim of the Buhlin study seek-
ing to identify independent risk factors for
periodontal disease that might be shared
with cardiovascular diseases. Therefore
the inclusion of peripheral blood monocyte
indices (absolute count and relative propor-
tion) as variables into their multivari-
ate models is warranted. This more
comprehensive modelling might also serve
to illuminate interactions between circu-
lating monocytes and the inflammatory
mediators and biomarkers discussed (e.g.,
C-reactive protein, TNF-\(\alpha\) receptor 1, IL-
6), where such physiological relationships
in vivo have yet to be articulated.

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