と両立できる薬剤とされる[52]。

免疫グロブリンは生理的な母乳含有成分の一つであり，少数サンプルにおける免疫グロブリン大量療法（IVIG）中の母乳免疫グロブリン検査では，IgG 濃度は正常～増加，IgM 濃度は正常～低下と報告されている[52]。IVIG 治療（0.4 g/kg/日を 5 日間連続投与後，分娩後 6 週と 12 週に 1 日ずつ投与）の多発性硬化症患者 69 名から授乳をうけた 108 名の児において，重篤な副作用が報告されていない[53]。一方，IVIG 治療（月 1 回 10 g 投与）中の多発性硬化症 43 名の授乳児において IVIG 関連と考えられる一過性の皮疹を 1 例に認めたが，それ以外に重篤な副作用はなかった[54]。

アザチオプリン，シクロスポリンは授乳を介した児への免疫抑制作用の可能性があり，成長や発がん性への影響が不明であるため，授乳の安全性は確認されていない。また，難治性 ITP に対して最近使用されるようになったトロンボポエチン受容体作動薬は，人の母乳移行の程度および授乳児への影響は不明である。しかし，動物実験（ラット）で乳汁中への移行が示唆されることから，現時点では授乳婦への投与は避けるか，投与中は授乳を避けることが望ましい[55]。

他ガイドラインとの比較

欧米の ITP ガイドライン[3~5]において，治療を要する患者の授乳制限については言及されていない。その背景として，この問題が ITP に限らず，一般的な薬剤と授乳の安全性に関する課題であるためと考えられる。従って，この課題はその様な視点から判断されるべきである。

CQ16. 新生児の出血のリスクは？ また分娩前に児の血小板数を予測する方法はあるか？

推奨グレード：2C

1. 新生児の血小板が 5 万/μl 未満に減少する頻度は約 10%，頭蓋内出血を合併する頻度は 1%弱と推定される。
2. 分娩前に新生児の血小板数を予測する方法として，前子と次子の血小板数の相関が高いことが有用である。

解説：

ITP 合併妊婦から出生した児のうち出生後に，血小板数が 5 万/μl 未満，2 万/μl 未満に減少する割合は，各々約 10%，約 5%である[6, 56]。

もっとも重大な出血症状は頭蓋内出血である[43, 56]。通常は生後 1~3 日以内で発生するが，胎内発症の報告例[57]もある。頻度は 1%弱[56]と低いが一旦発症すると予後は悪い[43]。半数程度が死亡又は重篤な神経学的後遺症を残す[7, 43]。帝王切開が経膣分娩と比較して，頭蓋内出血の危険を減らすというエビデンスはない。頭蓋内出血症例には，血小板数が 5 万/μl 以上の場合や無症候性の場合もある[43]。

分娩前の予測因子については，母体側の因子（ITP の発症時期，血小板数，治療の有無，脾摘の有無）について複数の研究で検討されてきた[6, 56]。これらの因子の中で，母体血小板数[43, 58]や，脾摘の既往[2, 43]（特に脾摘後も血小板数が回復しない場合）が，出生児の血小板数と関連を示す論文もある。しかし同時にこれらの二つの因子の関連性を否定する報告も多い[6, 56]。反復して確かめられている唯一の因子は，前子の血小板数と次子の血小板数がよい相関関係にあることである[2, 7, 43, 59]。従って，分娩歴のある ITP 妊婦では，出産前に前子の出生時や出生後の血小板数をあらかじめ把握することが極めて重要である。第 1 子の場合には有用な予測因子は存在しない。

他のガイドラインとの比較

- 英国血液学会ガイドライン[3]：母体の血小板数，抗血小板抗体の抗体価，脾摘の有無のいずれも新生児血小板数の予測因子にならないと記載されている。
- 国際コンセンサス報告書[4]：英国血液学会ガイドラインと同様に，母体の血小板数，抗血小板抗体の抗体価，脾摘の有無のいずれも新生児血小板数の予測因子にならないと記載されている。

CQ17. 胎児血小板数を測定すべきか？

推奨グレード：1C

経皮的臍帯穿刺を用いた胎児血小板数測定も，胎児頭皮からの血液採取による血小板数測定も推奨しない。

解説：

経皮的臍帯穿刺を用いた胎児血小板測定は，1~2%の確率で胎児死亡が合併すると推定されている[60]。この合併率は生後の死亡率と同等またはやや高く，利益より危険が上回るために，経皮的臍帯穿刺を用いた胎児血小板測定は実施すべきではない。また，胎児頭皮からの血液採取は手技的に困難であり[61]，また採取途中の血液凝固や羊水混入などにより不正確な血小板数を示す[62~64]ため，推奨されない。2000 年以降に発表されているガイドライン[3, 4]と総説[65, 66]においても，いずれも同様のコメントである。

他のガイドラインとの比較

- 英国血液学会ガイドライン[3]：経皮的臍帯穿刺も胎児

頭皮からの血液採取も推奨しないと記載されている。
・国際コンセンサス報告書[4]：経皮的臍帯穿刺も胎児頭皮からの血液採取も推奨しないと記載されている。

CQ18. 出生した児の評価はどのようにするのか？

推奨グレード：2C
1. 臍帯血または新生児末梢血を用いて出生時に血小板数を評価する。出血症状の有無にかかわらず全児に推奨する。
2. 出生時の血小板数が15万/μl未満に減少している場合には，反復して評価する。通常最低値は日齢2～5であるが，それ以降に遷延する場合もある。

解説：

ITP合併妊娠の妊婦から出生した児は，出生時から血小板数が減少している場合もあるが，出生数日後（通常最低値は日齢2～5）に減少することもある[6, 56, 65]。出血症状の有無にかかわらず全例，出生時に臍帯血を用いてまたは生後早期に末梢血を用いて，血小板数の評価を推奨する。15万/μl未満の血小板減少の場合には，反復採血して正常化するか少なくとも上昇傾向を確認する。経過中に血小板数が5万/μl未満になった場合には，頭部エコーなどの画像検査を積極的に施行すべきである。

2013年の米国血液学会誌に掲載された総説では，出生時の血小板数が正常の場合には反復採血を推奨していないが，両親に1週間以内の出血症状に注意して観察することを推奨している[8]。わが国では，日齢4～5に実施する先天性代謝異常スクリーニング検査時に血小板数を再評価できる機会を利用して採血（ヒールカット法ではなく，静脈採血）をすることにより，退院の安全性をより客観的に判断することも可能である。

新生児血小板減少をきたす原因として，母体ITP以外にも付加的な因子がありうることに注意する。早産・低出生体重児では血小板減少症の頻度は高く，新生児集中治療室で管理する低出生体重児の22～33%に認めるという報告がある[66]。さらに，同種免疫性血小板減少症[67]，Upshaw-Shulman症候群，先天性血小板減少症[68, 69]なども鑑別が必要になる場合もある。特に同種免疫性血小板減少症は頭蓋内出血の頻度が高く，次子では血小板減少が重篤化するため評価が重要である[67]。

他のガイドラインとの比較

・英国血液学会ガイドライン[3]：ITP合併妊婦から出生した新生児は，全例臍帯血または新生児末梢血を用いて，血小板数を評価することが推奨されている。最低値を確認するまで連日採血することが推奨されている。
・国際コンセンサス報告書[4]：ITP合併妊婦から出生した新生児は，全例臍帯血または新生児末梢血を用いて，血小板数を評価することが推奨されている。最低値を確認するまで反復採血することが推奨されている。

CQ19. 新生児の血小板減少の治療は？

推奨グレード：2C
1. 出血症状のない場合，血小板数3万/μl未満であれば免疫グロブリン大量療法あるいは副腎皮質ステロイド薬の投与を考慮する。
2. 出血症状がある場合，血小板数3万/μl未満であれば免疫グロブリン大量療法あるいは副腎皮質ステロイド薬の投与とともに，血小板数5万/μl以上を目標に血小板濃厚液の輸血を考慮する。

解説：

ITP合併妊婦から出生した新生児の血小板減少症の治療は，臍帯血および生後の2～5日の間での血小板数の推移と出血症状から治療の要否を判断する。血小板減少は，臍帯血より生後さらに減少する場合があることに留意する。治療は，免疫グロブリン大量療法あるいは副腎皮質ステロイド薬による薬物治療と血小板濃厚液の補充療法がある。

血小板数3万/μl未満の場合は，免疫グロブリン大量療法あるいは副腎皮質ステロイド薬を投与する。出血症状がある場合は，免疫グロブリン療法あるいは副腎皮質ステロイド薬に加え血小板濃厚液輸血を考慮する。なお，一次治療として免疫グロブリン療法，二次治療として副腎皮質ステロイド薬が推奨される。

免疫グロブリン療法の投与量は1回1 g/kgで，投与後の出血症状や血小板数の推移から反復投与を考慮する。血小板数の増加が得られた場合でも，再度減少することがあることから注意深い経過観察が必要である。

副腎皮質ステロイド薬の投与量は，プレドニゾロンを2 mg/kg/日で，血小板数の推移で適宜漸減する。血小板濃厚液の輸血開始基準は，血小板数3万/μl未満で考慮し，重篤な出血時は血小板数5万/μl以上を維持する。

その他，難治例では，同種免疫性血小板減少症や，他に血小板減少性疾患（先天性血小板減少症やUpshaw-Schulman症候群等）を考慮する。

他ガイドラインとの比較

免疫グロブリン大量療法と副腎皮質ステロイド薬の選択は，欧米のガイドラインにおいても一次治療として免疫グロブリン大量療法が推奨されている[3, 8]。免疫グロブリン大量療法の投与量は，多くは1回1 g/kg[3]である

が他に 2 g/kg[66]等が報告されている。多くは 1 回投与で改善が得られることから，1 回 1 g/kg を投与後，血小板数の推移から反復投与を考慮するとした。

副腎皮質ステロイド薬の投与量および投与期間は，欧米のガイドラインでも明確な記述は少ない[70,71]。わが国では 2 mg/kg/日の 2 週間投与が推奨されているが[72]，多くは 1～2 週間で改善が得られることから[2]，投与期間は適宜漸減するとした。

血小板濃厚液の補充療法開始時の目安は，「血液製剤の使用指針」では血小板数 3 万/μl 未満とされている[73]。英国のガイドラインでは，2 万/μl 未満とするものもあるが[3]，合併症として頭蓋内出血が懸念されていることから，安全性を考慮し，「血液製剤の使用指針」の新生児への血小板輸血のガイドラインに準じて 3 万/μl 未満とした。

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血小板数と血小板形態

Blood platelet count and platelet morphology

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〔臨床検査　59：173-179，2015〕

Point

- 自動血球分析装置の血小板数測定にはさまざまな原理が用いられており，自施設で使用している機器の特徴を把握したうえで評価することが必要である．
- 血小板数測定にはピットフォールが存在し，電気抵抗法で表されるヒストグラムや塗抹標本上の血小板形態の観察は重要である．
- 血小板関連のパラメータには血小板数以外にも平均血小板容積(MPV)，血小板容積分布幅(PDW)などがあり，血小板に関する情報を得ることができる．
- 血小板減少症，増加症には多くの疾患があるが，MPV に表される血小板サイズにも特徴的な疾患が存在する．

Keywords

血小板数，平均血小板容積(MPV)，血小板容積分布幅(PDW)，偽性血小板減少，血小板形態異常

はじめに

現在，血小板数の測定は，自動血球計数装置による報告が主流となっている．しかし，自動血球計数装置の結果で報告できない場合があり，Brecher-Cronkite 法や Fonio 法などを用いて報告している．

血小板数の基準範囲は 15 万～35 万/μL で，5 万/μL 以下に減少すると出血症状が出現し始め，2 万/μL 以下で血小板輸血の対象となることがある．血小板は骨髄中の巨核球が分化，成熟し，その細胞質の辺縁を切断して多数の血小板を放出する．放出された血小板は末梢血液中を 7～10 日間循環して脾臓で寿命を終える．この産生機序に異常が生じると，血小板数の減少や増加，および大きさの大小に変化がみられる．

血小板減少症で出血がみられた場合，脳出血などの重篤な症状を引き起こすこともあり，治療として血小板輸血が行われる．2 万/μL 以下の血小板数では特に精度の高い報告値が求められる．一方，血小板増加症では血栓合併症のリスクも考慮しなければならない．血小板数の正確な測定を行うことは診断や治療経過において重要である．また，自動血球計数装置からは血小板に関するパラ

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メータが測定されているが，検査指標のなかであまり活用されていない．これらのパラメータには平均血小板容積(mean platelet volume：MPV)や血小板容積分布幅(platelet distribution width：PDW)などがあり，さまざまな情報を得ることができる．

本稿では血小板に関する計数値の意義や注意点，さらに血小板に関連する疾患や血小板形態について述べる．

自動血球分析装置の血小板数測定原理

自動血球計数装置に搭載されている血小板数計測の原理は，電気抵抗法や光学的測定法が主流である．電気抵抗法はオームの法則を応用した方法で，電流を通した小孔(アパーチャー)に血球を通過させると血球の容積に比例して電気抵抗の増加がみられ，これを用いて血球を鑑別して血小板を算定する[1]．カウントする細胞数が多いため，再現性に優れている．光学的測定法は，レーザー光を当てて通過する血球により反射した前方散乱光と側方散乱光から細胞の大きさや密度を計測し分類を行う方法で，レーザーの反射情報から血球の内部構造を識別できるため，破砕赤血球や大血小板などの影響を受けにくい．

近年，蛍光標識抗CD61抗体を用いた免疫学的測定法を採用したセルダイン サファイア®(アボットジャパン)[2]や，蛍光色素を用いたフローサイトメトリー法(flow cytometry：FCM)によるPLT-Fチャンネル[3]を搭載したXNシリーズ(シスメックス)も発売され，特に血小板低値域における精度の向上が図られている．自動血球分析装置の血小板数計測には多種の原理があり，特性を正しく理解して使い分けることが大切である．

血小板数の評価におけるピットフォール

自動血球計数装置において，電気抵抗法で測定された血小板の大きさはヒストグラムにて表示される．小赤血球や破砕赤血球が存在すると赤血球の大きさが血小板の大きさに近くなるため，血小板の測定範囲内に入り込み偽高値となる(**図1**)[1]．一方，大血小板さらには巨大血小板が存在すると大きさが赤血球と近くなるために赤血球との区別が難しく，血小板測定範囲内から逸脱して偽低値となる．このような場合のヒストグラムは，正規分布である健常人と異なり，歪な山型や右肩上がりのような形状を示すので注意を要する．また，電気抵抗法と光学的測定法が両方搭載されている装置では，両データに解離がみられることが多く，推測が可能である．

偽性血小板減少が起こる機序には2つあり，1つは抗凝固剤のエチレンジアミン四酢酸(ethylenediaminetetraacetic acid：EDTA)により血小板凝集を起こすEDTA依存性偽性血小板減少症(**図2**)や白血球の周囲に血小板が付着する血小板衛星現象である[4]．EDTA依存性偽性血小板減少症が疑われた患者の血小板数計測には，クエン酸Naやヘパリンなど EDTAとは異なる抗凝固剤を使用して測定を行う方法が一般的であるが，ほかにもEDTA加採血管にカナマイシンなどの抗菌薬を添加して測定する方法や抗凝固剤の入っていない採血管で採血後，直ちに測定する方法などがある．

2つ目の原因は，採血手技や激しい攪拌による血小板凝集である．当検査室では，初回値が血小板数15万/μL以下，または，前回値からの減少幅/前回値と今回値の平均＞40％である場合，血小板凝集やフィブリンの有無を末梢血塗抹標本で確認している．自動血球計数装置によっては，これらに関して警告メッセージ(PLT Clumps? など)を表示し注意を促すこともあり，その場合には血小板粒度分布と標本の確認が必要である．

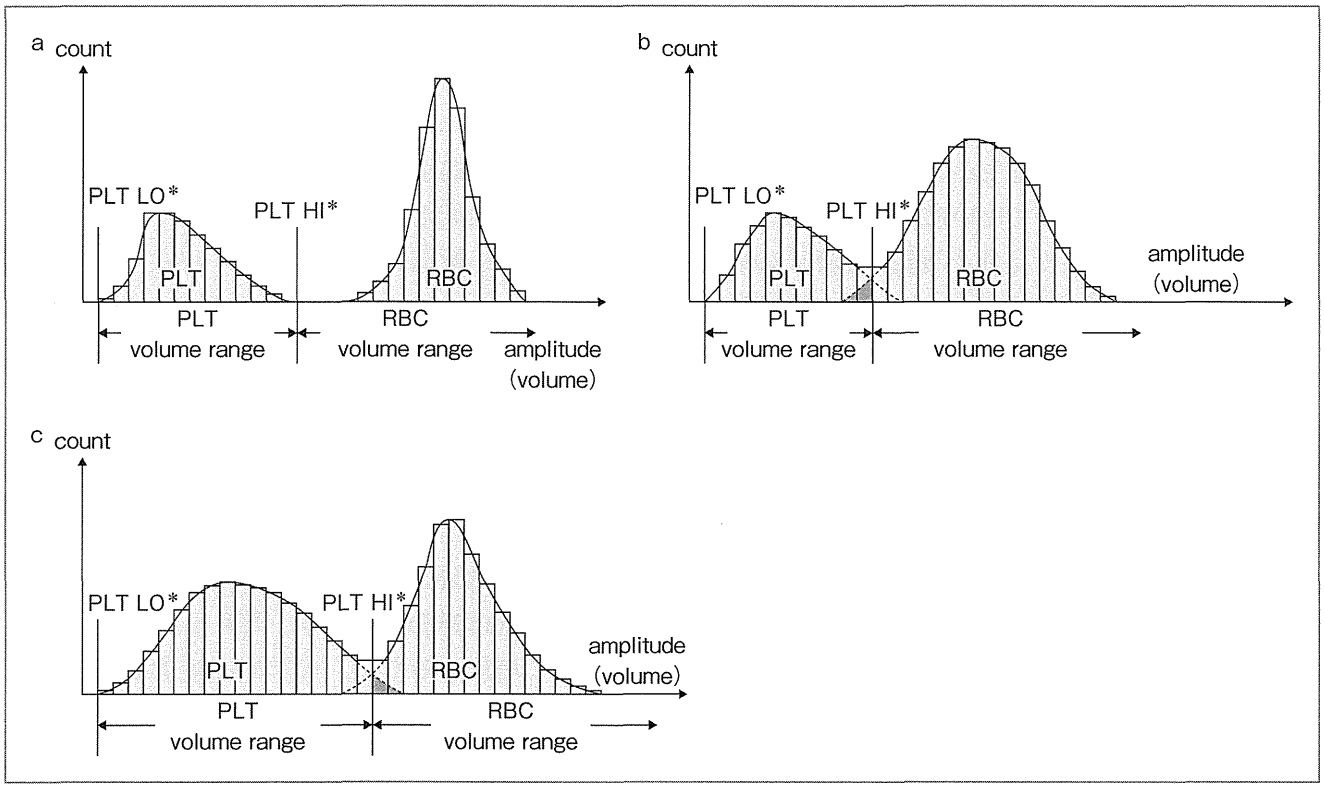

図 1　電気抵抗法による血小板数のヒストグラム

a：normal blood. 血小板(直径 2 μm)と赤血球(直径 8 μm)が明確に分類されている.
b：microcytic blood(microcythemia). 血小板領域に小赤血球，破砕赤血球が入り込んでいる(青色).
c：macro platlet. 大血小板，巨大血小板が血小板領域から逸脱している(青色).
PLT LO*：lower threshold，PLT HI*：upper threshold.
〔杉山昌晃，巽典之：自動血球分析の歴史. 英文対訳　計測技術ティーチング—自動血球分析装置の基本原理(巽典之，血液検査学研究会編)，宇宙堂八木書店，pp32-38，2006 より一部改変して転載〕

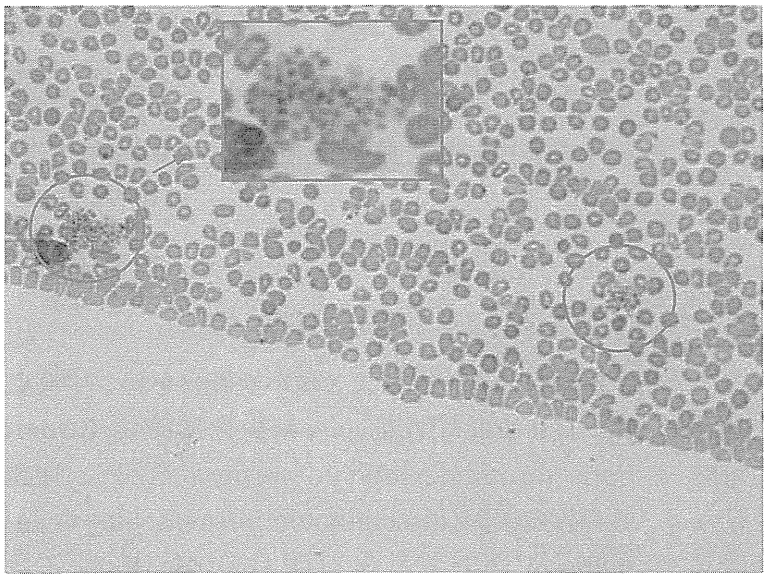

図 2　偽性血小板減少

血小板の凝集が 2 カ所認められる(青丸印). 自動血球計数装置では，これらの血小板がカウントされないために，見掛け上血小板は減少する. 偽性血小板減少症と考えられる.

血小板関連のパラメータ

自動血球計数装置における測定で表示される血小板関連パラメータは，血小板数のほか，MPV，PDW，血小板クリット(plateletcrit：PCT)が挙げられる.

MPV は赤血球での平均赤血球容積(mean corpuscular volume：MCV)に相当し，血小板産生の程度などを推定することができる. 血小板減少症において MPV が利用されており，再生不良性

貧血などの血小板産生低下では小さくなり，特発性血小板減少性紫斑病(idiopathic thrombocytopenic purpura：ITP)のように破壊消費亢進では大きくなる．血小板の産生が亢進している状態では，骨髄での産生後間もない血小板の容積は大きくなるため，健常人では血小板数とMPVの間には逆比例の関係がある[5]．しかし，MPVはEDTA添加により時間とともに血小板が膨張傾向を示すため，採取後なるべく早く測定することが望ましい．松野[6]は，MPVはEDTA添加30分間で増加し，その後2時間までは比較的安定した値をとるが，その後はさらに増大するとしている．厳密にMPVの解析を行うには，採血後30分から2時間に測定した結果を用いるのが望ましい．また，基準範囲は測定機種により測定値が異なるため，施設ごとに設定する必要がある．

PDWは，赤血球での赤血球粒度分布幅(red cell distribution width：RDW)に相当し，ヒストグラムで表した血小板容積分布の程度を数値化したものである．MPVに比べ臨床的意義は低い．また，電気抵抗法にて算出されるため，破砕赤血球が多数出現している試料では偽高値となる場合がある．

PCTは赤血球のヘマトクリットに相当し，全血に対する血小板容積の体積比を示している．個々の血小板容積が小さいため，臨床的有用性は低い．

その他に，シスメックスの分析装置のパラメータには大血小板比率(platelet-large cell ratio：P-LCR)，幼若血小板比率(immature platelet fraction：IPF)がある．P-LCRは12 fLディスクリ以上の大型血小板比率を表しており，血小板凝集や破砕赤血球出現などで起こるオーバーラップの検知，血小板造血機能のモニターに有用とされている．

IPFは，骨髄から産出されたばかりの幼若な血小板を比率で表した数値で，参考基準値は1.1～6.1％である．IPFは骨髄の血小板産生能を反映し骨髄巨核球数と相関する．骨髄機能が正常であれば血小板が増えると巨核球が減り，逆に血小板が減ると巨核球が増えるため，健常人では，IPFと血小板数は逆相関を示す．IPFは血小板回復に先行して増加するため，化学療法や造血細胞移植などの血小板回復予測や血小板輸血適応の判断，血小板減少性疾患での造血不良(再生不良性貧血など)と血小板消費亢進(ITPなど)の鑑別に有用である[7]．ほかにも骨髄検査などの侵襲的検査が困難な新生児における血小板減少症の鑑別や経過観察にも用いられ，活用の幅が広がっている．しかし，骨髄異形成症候群(myelodysplastic syndrome：MDS)には血小板数がそれほど減少していないにもかかわらずIPFが高い“IPF高比率MDS”が存在する．このMDSの特徴には，7番染色体を中心とした予後不良の染色体異常，血小板や骨髄巨核球の形態異常の存在[8]が挙げられている．

血小板に関する疾患や病態

血小板減少症(表1)[9,10]

血小板数が10万/μL以下に減少した場合を血小板減少症という．重大な疾患が隠れている可能性があり，臨床状態と合わせて詳細に検査を行う必要がある．その要因は産生不良，破壊・消費亢進，血管内分布異常の3つに分けられる．

産生不良の疾患は機序によりさらに分類され，そのなかの1つである巨核球の減少は再生不良性貧血などの骨髄不全症や腫瘍細胞の骨髄浸潤，遺伝性血小板形態異常を伴う先天性疾患などで認められる．ほかに，MDSで主に認められる無効造血や血小板産生調節機構の異常がある．

破壊や消費亢進による血小板減少を起こす疾患は，ITPや血栓性血小板減少性紫斑病(thrombotic thrombocytopenic purpura：TTP)，播種性血管内凝固(disseminated intravascular coagulation：DIC)である．ITPは自己抗体による血小板減少，TTPや溶血性尿毒症症候群(hemolytic uremic syndrome：HUS)を含む血栓性微小血管障害(thrombotic microangiopathy：TMA)，DICは微細血管における血栓形成が原因となる．このような無効造血や破壊，消費亢進の病態では巨核球数が増加して血小板の産生サイクルが早くなるため，末梢血塗抹標本上で大血小板が認

表 1　血小板に関する病態や疾患

1. 血小板数の増減
(1) 血小板数減少
a) 産生の低下
再生不良性貧血，骨髄浸潤(癌，白血病など)，放射線・抗癌剤などによる骨髄抑制
先天性疾患(Fanconi 症候群，May-Hegglin 異常，Bernard-Soulier 症候群など)
骨髄異形成症候群(MDS)，ビタミン B_{12} または葉酸欠乏症
b) 破壊・消費の亢進
特発性血小板減少性紫斑病(ITP)，膠原病，周期性血小板減少症，ヘパリン惹起血小板減少症(HIT)，
血栓性血小板減少性紫斑病(TTP)，溶血性尿毒症症候群(HUS)，
播種性血管内凝固(DIC)，新生児血小板減少症，妊娠，感染症
c) 血管内分布異常
Banti 症候群，脾機能亢進症
(2) 血小板数増加
a) 腫瘍性による増加
本態性血小板血症(ET)
b) 反応性による増加(2 次性血小板増加)
慢性感染症，炎症性疾患，溶血性貧血，鉄欠乏性貧血，悪性腫瘍(癌，悪性リンパ腫)，
真性多血症(PV)，慢性骨髄性白血病(CML)，骨髄線維症(MF)
2. 血小板サイズ異常
(1) 小型血小板(MPV の減少)
再生不良性貧血，脾機能亢進症，ビタミン B_{12} または葉酸欠乏症，抗癌剤などによる影響，
Wiskott-Aldrich 症候群
(2) 大血小板・巨大血小板(MPV の増加)
特発性血小板減少性紫斑病(ITP)，慢性骨髄性白血病(CML)，脾摘，
May-Hegglin 異常(MHA)，Bernard-Soulier 症候群(BSS)

MDS：myelodysplastic syndrome，ITP：idiopathic thrombocytopenic purpura，HIT：heparin-induced thrombocytopenia，TTP：thrombotic thrombocytopenic purpura，HUS：hemolytic uremic syndrome，DIC：disseminated intravascular coagulation，ET：essential thrombocythemia，PV：polycythemia vera，CML：chronic myelogenous leukemia，MF：myelofibrosis，MPV：mean platelet volume，MHA：May-Hegglin anomaly，BSS：Bernard-Soulier syndrome.

〔文献 9，10)より作成〕

められ MPV や PDW は高値となるが，血小板数は増加しない．ただし，TMA，DIC では破砕赤血球の出現がみられ，前述した血小板数偽高値の可能性があり注意が必要である．ほかに薬剤により血小板減少や血栓が起こる疾患も存在し，抗生物質や鎮痛剤などは薬物投与 6〜10 日後に現れる場合が多い．特にヘパリンによって引き起こされる疾患はヘパリン起因性血小板減少症(heparin-induced thrombocytopenia：HIT)と呼ばれる．

体内分布異常は，通常 1/3 プールしている脾臓にて血小板が増大し，血中の血小板が減少する状態である．主な原因は脾腫で，悪性腫瘍やうっ血が多い．

正常血小板サイズは約 2 μm に対し，大血小板は 4〜8 μm，巨大血小板は赤血球(約 8 μm)を超える大きさである[11]．血小板の形態異常は，大血小板や巨大血小板がほとんどを占め，MPV は高値となる．このような血小板は ITP や MDS だけでなく先天性血小板減少症にも認められ，代表疾患には May-Hegglin 異常(May-Hegglin anomaly：MHA)をはじめとする MYH9 異常症，Bernard-Soulier 症候群(Bernard-Soulier syndrome：BSS)が挙げられる(**図 3 a**)．MHA は巨大血小板，血小板減少に加え白血球封入体を特徴とする．白血球封入体はデーレ様小体とも呼ばれ，デーレ小体とは好中球以外にもみられる点で異なる．染色性が弱いまたは小型デーレ様小体の場合は見過ごされやすいため，血小板数低値であり，さらに巨大血小板が認められる症例では，顕微鏡の倍率を上げて詳細に観察をするべきである[12]．

血小板の顆粒に異常がみられる疾患としては，α 顆粒が著減する Gray platelet 症候群(**図 3 b**)，巨大 α 顆粒を有する Paris-Trousseau 症候群などがあり，まれではあるが念頭に置いて標本観察を行うことも必要である．

一方，血小板の産生能が低下すると血小板は長期にわたり血管内の循環を繰り返し，小型化する．再生不良性貧血だけでなく先天性疾患の Wiskott-Aldrich 症候群(**図 3 c**)にもみられる．このような血小板は MPV が低値または測定不可となる場合もある．

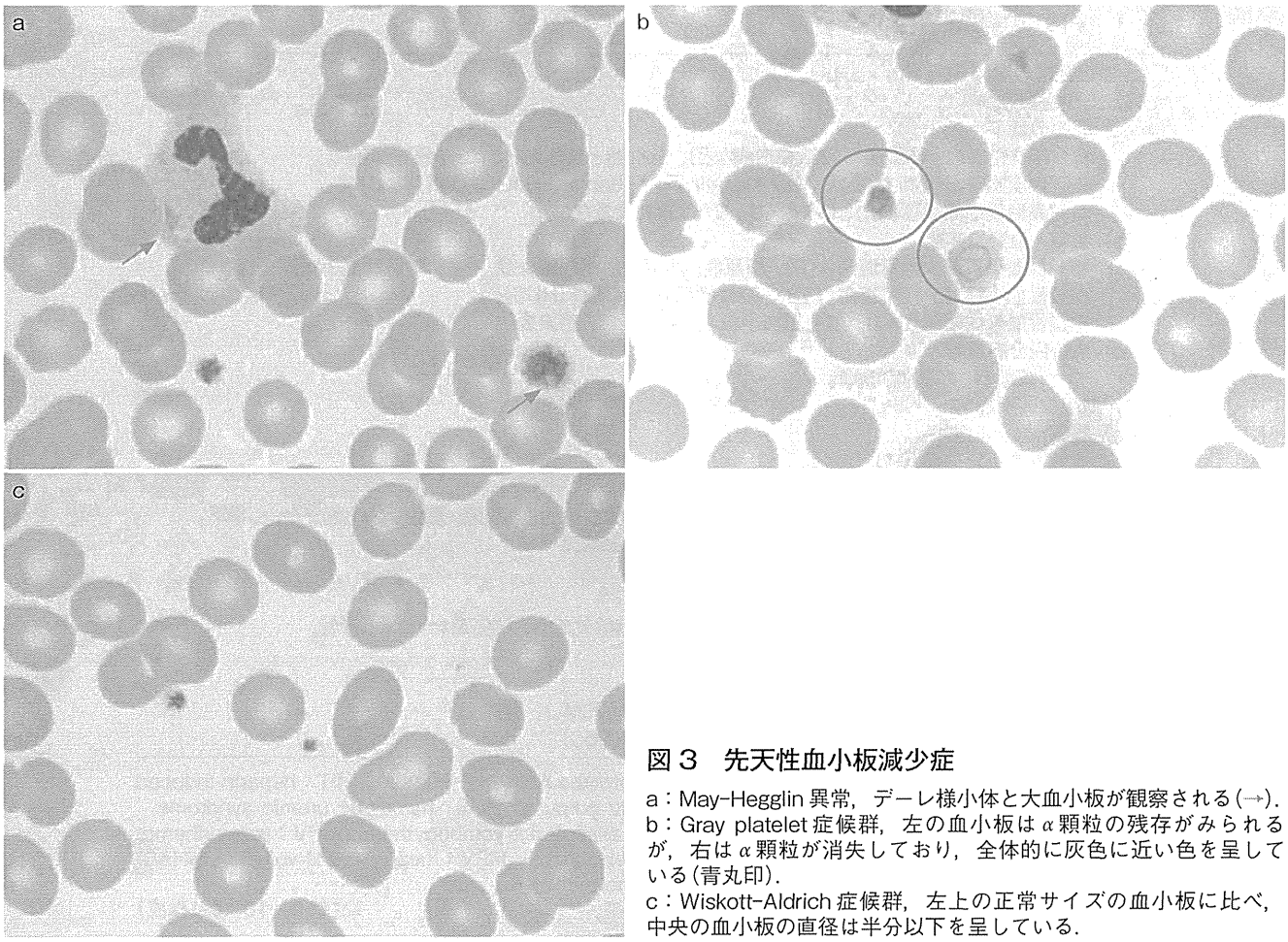

図3　先天性血小板減少症

a：May-Hegglin 異常，デーレ様小体と大血小板が観察される(→)．
b：Gray platelet 症候群，左の血小板はα顆粒の残存がみられるが，右はα顆粒が消失しており，全体的に灰色に近い色を呈している(青丸印)．
c：Wiskott-Aldrich 症候群，左上の正常サイズの血小板に比べ，中央の血小板の直径は半分以下を呈している．

■ 血小板増加症

一般に血小板数が40万/μL以上の場合を指す．血小板増加は骨髄巨核球の増殖により起こり，代表的な腫瘍性疾患は本態性血小板血症(essential thrombocythemia：ET)である．ETは100万/μL以上であることがほとんどであり，血小板機能異常が出現することがある[10]．ほかに血小板増多を起こす疾患には，鉄欠乏性貧血，感染症を含む炎症性疾患，骨髄増殖性疾患，悪性腫瘍などがあり，慢性骨髄性白血病(chronic myelogenous leukemia：CML)ではMPV高値を伴うこともある．これらは一過性であることが多い．

血小板数が高値である血液では，他の測定項目への影響を考慮する必要がある．血液が凝固する過程で血小板は大量のカリウムを放出し，その結果，血清中のカリウムのデータが異常高値となる．この影響を受けずに真のカリウム値を測定するには，測定試料としてヘパリン採血した血漿を用いる方法がある．

おわりに

日常的に行われている自動血球計数装置の血小板測定値からわかる情報を中心に述べた．血小板数だけでなく，同時に測定されたパラメータから得られる情報は多く，さまざまな病態との関係が示唆されていくと思われる．異常値または粒度分布異常のパラメータを活用することで，大血小板や破砕赤血球など干渉の有無の判定，血小板産生回復や予後の予測ができる可能性がある．また，顕微鏡にて血小板形態を観察することも重要であり，それらは臨床的有用性の高い情報となる．

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Original Investigation

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors
A Randomized Clinical Trial

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Editorial page 2503

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IMPORTANCE Prevention of atherosclerotic cardiovascular diseases is an important public health priority in Japan due to an aging population.

OBJECTIVE To determine whether daily, low-dose aspirin reduces the incidence of cardiovascular events in older Japanese patients with multiple atherosclerotic risk factors.

DESIGN, SETTING, AND PARTICIPANTS The Japanese Primary Prevention Project (JPPP) was a multicenter, open-label, randomized, parallel-group trial. Patients (N = 14 464) were aged 60 to 85 years, presenting with hypertension, dyslipidemia, or diabetes mellitus recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007, and were followed up for up to 6.5 years, with last follow-up in May 2012. A multidisciplinary expert panel (blinded to treatment assignments) adjudicated study outcomes.

INTERVENTIONS Patients were randomized 1:1 to enteric-coated aspirin 100 mg/d or no aspirin in addition to ongoing medications.

MAIN OUTCOMES AND MEASURES Composite primary outcome was death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. Secondary outcomes included individual end points.

RESULTS The study was terminated early by the data monitoring committee after a median follow-up of 5.02 years (interquartile range, 4.55-5.33) based on likely futility. In both the aspirin and no aspirin groups, 56 fatal events occurred. Patients with an occurrence of nonfatal stroke totaled 114 in the aspirin group and 108 in the no aspirin group; of nonfatal myocardial infarction, 20 in the aspirin group and 38 in the no aspirin group; of undefined cerebrovascular events, 3 in the aspirin group and 5 in the no aspirin group. The 5-year cumulative primary outcome event rate was not significantly different between the groups (2.77% [95% CI, 2.40%-3.20%] for aspirin vs 2.96% [95% CI, 2.58%-3.40%] for no aspirin; hazard ratio [HR], 0.94 [95% CI, 0.77-1.15]; $P = .54$). Aspirin significantly reduced incidence of nonfatal myocardial infarction (0.30 [95% CI, 0.19-0.47] for aspirin vs 0.58 [95% CI, 0.42-0.81] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; $P = .02$) and transient ischemic attack (0.26 [95% CI, 0.16-0.42] for aspirin vs 0.49 [95% CI, 0.35-0.69] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; $P = .04$), and significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (0.86 [95% CI, 0.67-1.11] for aspirin vs 0.51 [95% CI, 0.37-0.72] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; $P = .004$).

CONCLUSIONS AND RELEVANCE Once-daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

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The World Health Organization estimates that annual global mortality due to cardiovascular diseases (including myocardial infarction and stroke) will approach 25 million by 2030.[1] A recent study of secular trends in cardiovascular disease in Japan indicated that, from 1960 to 2000, the prevalence of smoking decreased and blood pressure control among hypertensive individuals improved significantly. Conversely, a steep increase in the prevalence of glucose intolerance, hypercholesterolemia, and obesity was observed,[2] probably due to the adoption of Western diets and lifestyles. Over this period, a decreasing trend in stroke incidence has slowed, and the incidence of myocardial infarction has not changed.[2] By 2030, it is estimated that 32% of the Japanese population will be 65 years or older.[3] This aging population, combined with the increasing prevalence of well-documented risk factors, means that the prevention of atherosclerotic disease remains an important public health challenge in Japan.

In 2009, the Antithrombotic Trialists' Collaboration (ATTC) reviewed the benefit-risk profile of low-dose aspirin for the primary prevention of vascular disease in a meta-analysis of 6 primary prevention trials. Use of low-dose aspirin was associated with a 12% proportional reduction in serious vascular events compared with no aspirin (annual event rate, 0.51% for aspirin and 0.57% for no aspirin; $P = .001$), mainly due to a reduction in nonfatal myocardial infarction of approximately 20%.[4] Aspirin increased major gastrointestinal and extracranial bleeding compared with control (annual increase, 0.10% for aspirin and 0.07% for control; $P < .001$).[4]

In Japan, the use of aspirin for primary prevention of ischemic heart disease has not been widespread.[5,6] The Japanese Primary Prevention Project (JPPP) was designed to determine whether once-daily, low-dose, enteric-coated aspirin reduces the total number of atherosclerotic events (ischemic heart disease and stroke) compared with no aspirin in Japanese patients 60 years or older with hypertension, dyslipidemia, or diabetes mellitus.

Methods

Patient Selection

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Studies and was approved by the institutional review board of each participating center. Details of the study design and methods have been published previously.[7]

This multicenter, randomized, open-label, parallel-group clinical trial was conducted at 1007 clinics in the 47 prefectures of Japan that routinely offer outpatient care for hypertension, hyperlipidemia, or diabetes. Patients were recruited consecutively at each clinic by primary care physicians between March 2005 and June 2007. The last included patient completed follow-up in May 2012.

Patients were screened when they attended their local clinic on a routine visit if they were aged 60 to 85 years and had not been diagnosed with atherosclerotic disease. Patients were eligible if, at screening, they met Japanese guideline criteria for hypertension (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg),[8] dyslipidemia (total cholesterol ≥220 mg/dL or low-density lipoprotein [LDL] cholesterol ≥140 mg/dL or high-density lipoprotein [HDL] cholesterol <40 mg/dL or triglycerides ≥150 mg/dL; to convert total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113),[9] or diabetes mellitus (fasting morning blood glucose ≥126 mg/dL or any blood glucose ≥200 mg/dL or 2-hour blood glucose ≥200 mg/dL in the 75-g glucose tolerance test, or glycated hemoglobin ≥6.5%; to convert glucose to millimoles per liter, multiply by 0.0555).[10]

Key exclusion criteria were a history of coronary artery disease or cerebrovascular disease (including transient ischemic attack [TIA]), atherosclerotic disease requiring surgery or intervention, or atrial fibrillation (confirmed or suspected). Patients with peptic ulcer or conditions associated with bleeding (eg, von Willebrand disease) and those with serious blood abnormalities (eg, clotting factor deficiencies) were also excluded. In addition, patients with aspirin-sensitive asthma or those with a history of hypersensitivity to aspirin or salicylic acid could not participate, nor could patients who were receiving antiplatelet agents, anticoagulants, or long-term treatment with nonsteroidal anti-inflammatory drugs. The use of antiplatelet (eg, ticlopidine, cilostazol, dipyridamole, trapidil) and anticoagulant agents (eg, warfarin) was prohibited after enrollment.

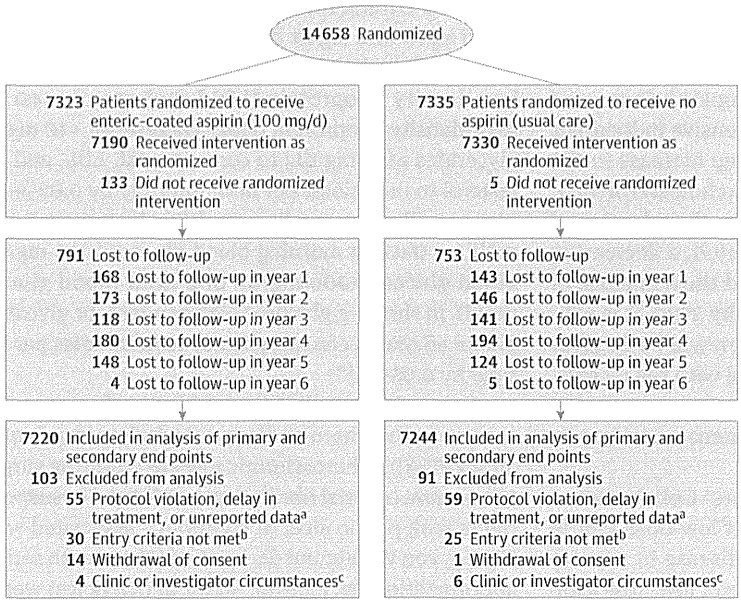
Study Design

Treatment to control hypertension, dyslipidemia, or diabetes (ie, the underlying risk factors for vascular events) was administered to all eligible patients at the screening visit and, in principle, throughout the study, in accordance with Japanese therapeutic guidelines.[9-11]

Approximately 1 month after the screening visit, patients returned for a baseline evaluation and were randomized 1:1 to receive either a 100-mg tablet of enteric-coated aspirin once daily or no aspirin, in addition to any ongoing medication (**Figure 1**). Randomization was stratified by the 3 underlying disease risk factors for atherosclerotic events (hypertension, dyslipidemia, or diabetes). Seven strata were used to account for all the different combinations of the 3 underlying disease risk factors because patients could have single or multiple risk factors (eg, diabetes mellitus, but no hypertension or dyslipidemia; diabetes and hypertension, but no dyslipidemia). The minimization method was applied to balance for sex and age within each stratum (eMethods in the Supplement). Pseudorandom numbers were generated using the Mersenne Twister method with a seed of 4989.[12] The study statistician generated the random allocation sequence using a central computerized system and study physicians were informed of treatment assignments via the study website or by fax.

At baseline and at each annual study assessment, the following variables were evaluated in the clinic when patients met

Figure 1. Flow of Patients Through the Japanese Primary Prevention Project (JPPP)



Data on patients assessed for eligibility are not available.

[a] Protocol violations (aspirin, n=19; no aspirin, n=22); delay in start of treatment (aspirin, n=10; no aspirin, n=15); unreported data by investigators in the clinics (aspirin, n=26; no aspirin, n=22).

[b] Reasons for not meeting inclusion criteria were serious blood abnormalities (aspirin, n = 2), history of prohibited drugs (aspirin, n = 12; no aspirin, n = 18), cerebrovascular disease (aspirin, n = 6; no aspirin, n = 7), atrial fibrillation (aspirin, n = 3), hypersensitivity to aspirin (aspirin, n = 3), peptic ulcer (aspirin, n = 2), atherosclerotic disease (aspirin, n = 1), or long-term use of nonsteroidal anti-inflammatory drugs (aspirin, n = 1).

[c] Clinic or investigator circumstances were closure of clinic and investigator death.

with the study physician: disease outcomes, adverse events, adherence with treatment (self-reported by patients), blood pressure, serum lipids, blood glucose, smoking status, and body weight.

To minimize loss of patients to follow-up, every effort was made to contact patients, including telephone calls, postcards, and visits from a traveling clinical research coordinator. Follow-up of patients ceased in the event of death or withdrawal of consent. If a patient was lost to follow-up because of death but the reason was unclear, the cause of death was established by obtaining the death certificate with permission from the Japanese government; this process was completed in April 2014.

The study was designed and overseen by a steering committee and decisions to amend or discontinue the study were made with advice from an independent data monitoring committee (DMC). Study end points were assessed centrally and biannually by an expert, multidisciplinary event adjudication committee that was blinded to treatment assignments in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) trial design.[13] A placebo-controlled study design was not used because the Japan Pharmaceutical Affairs Law limits the use of placebo in large, physician-led studies of approved products such as aspirin. Members of study committees and details of study clinic locations and investigators are provided in the eMethods in the Supplement.

Study End Points

The primary outcome was a composite of death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. The first secondary end point was also a composite that included the same events as the primary end point, plus TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention. Other secondary end points were death from cardiovascular disease, death from noncardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, TIA, angina pectoris, arteriosclerotic disease requiring surgery or intervention, and serious extracranial hemorrhage requiring transfusion or hospitalization.

Physicians at each study clinic diagnosed myocardial infarction according to the European Society of Cardiology and American College of Cardiology guidelines.[14] Imaging evidence of cerebral infarction or intracerebral hemorrhage accompanied by an acute regional neurological deficit maintained for 24 hours was required for a diagnosis of ischemic stroke.

The main assessment of safety was the secondary end point of serious extracranial hemorrhage requiring transfusion or hospitalization. However, data on the occurrence of the following prespecified gastrointestinal adverse events associated with aspirin were also collected for safety and tolerability analyses: gastrointestinal hemorrhage; gastroduodenal ulcer; reflux esophagitis; erosive gastritis; stomach or abdominal discomfort, pain, or pressure; heartburn; and nausea. The overall incidence of adverse events was not a primary or secondary end point of the study. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), Japanese version 16.0J. Each clinic provided case report forms via the study website or faxed the forms to a central data center for input into the study database.

Statistical Analyses

Based on Japanese epidemiological and interventional studies,[15-23] annual mortality due to cardiovascular causes, nonfatal strokes, and myocardial infarction was expected to be approximately 1.5% to 2% in individuals not receiving aspirin. Accordingly, a sample size of 10 000 patients was determined to be sufficient to provide 80% power to detect a relative risk reduction of 20% in the aspirin group compared with the no aspirin group over a mean follow-up period of 4 years at a 2-sided significance level of $\alpha = .05$. However, a preplanned review at the first annual general examination in July 2006 showed that the incidence of primary outcome events (14 events among 6745 enrolled patients) was much lower than originally estimated.

Therefore, based on the reduced observed event rate, which determined both the sample size and the timing of the final study analyses, the sample size and study duration were reestimated. Assuming that the maximum frequency of events in both groups was 0.79%, it was estimated that enrollment in the study would need to be increased to 14 960 patients for 624 primary end point events to occur over an extended follow-up of up to 6.5 years. The final analyses were to be performed when 624 events had occurred if this was sooner than the maximum follow-up period of 6.5 years. Using these revised assumptions, a reduction in the annual frequency of events from 0.87% with no aspirin to 0.70% with aspirin would be required to detect a 20% difference between the aspirin and no aspirin groups at the $\alpha = .05$ significance level with 80% power.

The primary objective was to test the hypothesis that treatment with once-daily, low-dose aspirin significantly prolongs the time to occurrence of the composite primary end point event compared with no aspirin treatment. Accordingly, the null hypothesis was that the time until such an event does not differ significantly between the 2 study groups. Time until onset of events was estimated using the Kaplan-Meier method in each study group. Between-group differences in the primary end point were assessed using the stratified log-rank test in all patients meeting the inclusion criteria, with stratification for underlying disease (hypertension, dyslipidemia, or diabetes) and a 2-sided significance level of $\alpha = .05$. Hazard ratios (HRs) were calculated using the Cox proportional hazards model and 95% CIs were determined; there was no evidence of violation of proportionality. Adjustment for factors used in the allocation of patients to the study groups and biased background variables were incorporated as needed.

The same statistical methods were used to evaluate between-group differences for each of the secondary end points. Prospectively defined subgroup analyses of the composite primary outcome measure were conducted in subgroups of patients defined by disease and patient demographic risk factors. Interactions between each of the subgroups and aspirin treatment were assessed by the likelihood ratio test in the Cox model. The risk of a primary end point event was also compared between subgroups (eg, in patients with hypertension vs without hypertension) and an estimate of the relative risk of occurrence of a primary end point event (a "parameter estimate") was calculated for each subgroup using Cox regression fitted to the primary end point. A total risk score for an individual patient was then calculated as the sum of the risk factors. Based on the subgroup parameter estimates, men were allocated a rounded risk score value of +1; 70 years or older, +3; smoker, +1.5; hypertension, +1; and diabetes mellitus, +1.5. The primary end point event rate and HR for aspirin compared with no aspirin were then determined in patients with risk score of less than the median value (ie, patients considered at low risk of primary end point events) or more than the median value (ie, high-risk patients).

All primary, secondary, and subgroup analyses were assessed using a modified intention-to-treat population. A modified population was used because a post hoc central assessment had to be performed after randomization to ensure that all randomized patients were eligible for, and actively participating in, the study. As a result of this assessment, the modified intention-to-treat population excluded the following patients: those who were randomized in error (did not meet the study entry criteria or had withdrawn consent), patients who could not be followed up owing to investigator or clinic circumstances (death of investigators or clinical closures), and patients with certain major systematic protocol violations or deviations. Protocol violations included lack of adherence to allocation by the site investigator and patients who had no follow up after randomization and for whom survival status could not be established; protocol deviation was delay in treatment initiation. Patients who were lost to follow-up were treated as censored cases at the last date at which survival had been verified if no primary or secondary end point event had occurred; missing data were not imputed.

The incidence of gastrointestinal adverse events was estimated in the randomized population using the precise CIs determined from the binomial distribution, and between-group differences were tested using the Fisher exact method. All statistical analyses were performed using SAS (SAS Institute), version 9.4.

Interim Analysis and Guidelines for Study Discontinuation

The independent DMC, which included medical experts and a statistician, regularly monitored the results of the trial in a blinded manner. Interim analyses were conducted at yearly intervals between 6 months after the end of patient enrollment and the final study analysis. Following review of each interim analysis, the DMC assessed whether the study should proceed or whether the study protocol should be amended. The study was to be discontinued if a significant difference in favor of aspirin compared with no aspirin was demonstrated for the primary end point at any of the interim analyses time points or if the DMC judged that there was very low likelihood of observing a significant difference if the study was continued.[7] The DMC could also recommend study discontinuation owing to the occurrence of unexpected or serious adverse reactions or an incidence of adverse reactions that was higher than expected, although there were no formal conditions for such decisions. The

other prespecified criteria for discontinuing the study or amending the protocol were publication of similar study results and ethical issues generated by changes in the social environment.

Table 1. Baseline Characteristics for Japanese Patients Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Patient demographics		
Age, mean (SD), y	70.6 (6.2)	70.5 (6.2)
Age, No. (%)		
<70 y	3234 (44.8)	3259 (45.0)
≥70 y	3986 (55.2)	3985 (55.0)
Men, No. (%)	3055 (42.3)	3068 (42.4)
Waist circumference, mean (SD), cm	85.2 (9.9)	84.7 (10.0)
Weight, mean (SD), kg	58.7 (10.4)	58.6 (10.3)
BMI ≥25, No. (%)	2644 (36.6)	2604 (35.9)
Risk factors for vascular events, No. (%)		
HT	6133 (84.9)	6145 (84.8)
DL	5198 (72.0)	5200 (71.8)
DM	2445 (33.9)	2458 (33.9)
HT and DL	4276 (59.2)	4264 (58.9)
DL and DM	1794 (24.8)	1798 (24.8)
HT and DM	1932 (26.8)	1939 (26.8)
HT, DL, and DM	1446 (20.0)	1442 (19.9)
BMI, mean (SD)	24.2 (3.5)	24.2 (3.4)
Blood pressure, mm Hg		
Systolic	137.1 (15.8)	137.2 (15.6)
Diastolic	77.7 (10.4)	77.6 (10.2)
Currently smoking, No. (%)	959 (13.3)	934 (12.9)
Family history of premature CV disease, No. (%)		
No	4058 (56.2)	4086 (56.4)
Yes	1981 (27.4)	1982 (27.4)
Unknown	1181 (16.4)	1176 (16.2)
Laboratory values, mean (SD)		
Cholesterol, mean (SD), mg/dL		
Total	202.9 (32.9)	203.6 (32.5)
Low-density lipoprotein[a]	119.2 (30.5)	119.8 (30.3)
High-density lipoprotein	57.8 (15.8)	58.2 (15.7)
Triglycerides, mean (SD), mg/dL	132.8 (76.0)	131.0 (75.9)
Fasting blood glucose, mean (SD), mg/dL	107.8 (31.2)	107.7 (32.0)
HbA_{1c}, mean (SD), %[b]	6.1 (1.0)	6.0 (1.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CV, cardiovascular; DL, dyslipidemia; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; HT, hypertension.

SI conversion factors: To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

[a] Calculated based on the Friedewald formula and direct measurements.

[b] National Glycohemoglobin Standardization Program method.

Results

Patients

A total of 14 658 patients were randomized between March 2005 and June 2007, and all were included in the safety analyses. For analyses of the primary and secondary end points, 194 patients (1.3%) were excluded from the randomized population owing to protocol violations or deviations (untraceable patients, nonadherence, or delayed start of treatment), not meeting the inclusion criteria, withdrawal of consent, or clinic or investigator circumstances (Figure 1); the remaining 14 464 patients comprised the modified intention-to-treat population.

Baseline characteristics have been reported in detail previously and were balanced between the 2 study groups for patient demographics and disease risk factors.[7] The values reported in **Table 1** differ slightly from those reported previously because the modified intention-to-treat population had not been fixed at the time that the baseline characteristics were originally reported.

Based on the rate of primary end point events at the interim analyses in May 2008 and May 2011, the committee decided that the study was unlikely to show a difference in event rate if follow-up was continued for the maximum of 6.5 years. At the time of the second interim analysis in May 2011, only 290 of the 624 estimated primary end point events (46.5%) had occurred and the estimated HR for aspirin vs no aspirin was 0.95 (99.80% CI, 0.66-1.37). Therefore, the study was terminated prematurely owing to futility; it was judged that statistical power to detect a between-group difference in the primary end point would not be reached and continuing could put participants at unnecessary risk of drug-related adverse events. At the recommendation of the DMC, the final analysis was conducted at the next annual study assessment when patients had been followed up for a median 5.02 years (interquartile range, 4.55-5.33 years); the median follow-up period was similar in the aspirin and no aspirin groups (5.01 years for aspirin and 5.02 years for no aspirin).

Most patients were adherent with aspirin therapy. A total of 88.9% of patients reported that they were adherent in year 1; this value decreased to 76.0% in year 5 (eTable 1 in the Supplement). In the no aspirin group, the proportion of patients who started to take daily low-dose aspirin increased each year from 1.5% in year 1 to 9.8% in year 5. Most patients did not receive medicines (antiplatelet or anticoagulant agents) that had been, in principle, prohibited after enrollment; however, the proportion of patients receiving these prohibited medications increased over time in both the aspirin group (1.3% in year 1, 10.5% in year 5) and the no aspirin group (1.4% in year 1, 10.4% in year 5) (eTable 1 in the Supplement).

Effectiveness

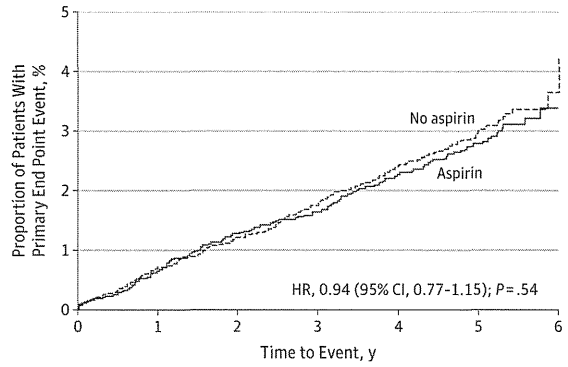
Composite Primary End Point

There was no statistically significant difference between the 2 groups in time to the primary end point—a composite of

Table 2. Fatal and Nonfatal Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Fatal events	56	56
Cerebral infarction	2	7
Intracranial hemorrhage	5	5
Subarachnoid hemorrhage	2	4
Myocardial infarction	7	9
Other fatal cardiovascular events	40	31
Nonfatal events	137	151
Cerebral infarction	83	94
Intracranial hemorrhage	23	10
Subarachnoid hemorrhage	8	4
Myocardial infarction	20	38
Undefined cerebrovascular events	3	5

Figure 2. Time to Primary End Point Composite Event[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin vs No Aspirin (Modified Intention-to-Treat Population)



No. at risk							
Aspirin	7220	7021	6771	6583	6322	3639	169
No aspirin	7244	7073	6861	6645	6359	3711	182

HR indicates hazard ratio. The *P* value was determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). The HRs were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction (**Table 2** and **Figure 2**). The estimated HR for aspirin vs no aspirin was 0.94 (95% CI, 0.77-1.15; *P* = .54). At 5 years after randomization, the cumulative primary event rate was similar in participants in the aspirin group (2.77% [95% CI, 2.40%-3.20%]) and those in the no aspirin group (2.96% [95% CI, 2.58%-3.40%]). Overall, few deaths from cardiovascular causes or nonfatal stroke or myocardial infarction were reported with aspirin (n = 193) or no aspirin (n = 207) (Table 2).

Assessment of the primary end point in subgroups of patients defined by the presence or absence of 8 different disease or demographic risk factors (hypertension, dyslipidemia, diabetes mellitus, male sex, aged at least 70 years, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] of 25 or higher, smoking, or family history of premature cardiovascular disease) did not reveal significant differences between study groups; detailed results from these subgroup analyses are reported in **Figure 3**.

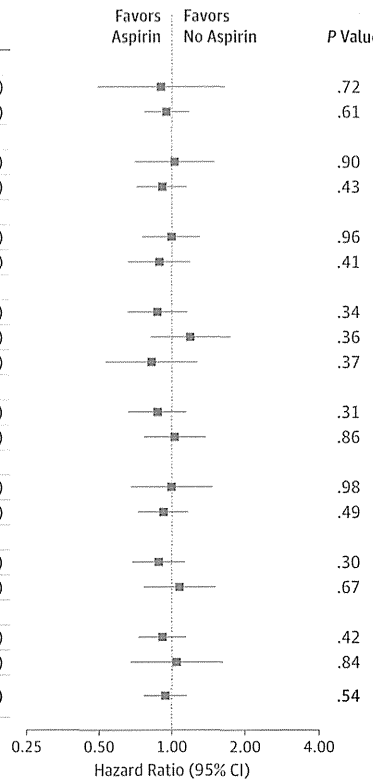
Regression analyses indicated that the risk of a primary end point event was higher in patients 70 years or older vs those younger than 70 years (parameter estimate, 0.92; HR, 2.51 [95% CI, 2.00-3.14]; *P* < .001), in patients with diabetes mellitus vs those without diabetes mellitus (parameter estimate, 0.52; HR, 1.68 [95% CI, 1.38-2.06]; *P* < .001), in patients who were smoking vs nonsmoking (parameter estimate, 0.53; HR, 1.70 [95% CI, 1.31-2.20]; *P* < .001), in men vs women (parameter estimate, 0.34; HR, 1.41 [95% CI, 1.14-1.74]; *P* = .002), and in patients with hypertension vs those without hypertension (parameter estimate, 0.42; HR, 1.52 [95% CI, 1.10-2.09]; *P* = .01). The risk of a primary end point event was not increased in patients with dyslipidemia vs those without dyslipidemia (parameter estimate, 0.13; HR, 1.13 [95% CI, 0.91-1.42]; *P* = .27) or in patients with a BMI of 25 or higher vs those with a BMI lower than 25 (parameter estimate, -0.13; HR, 0.88 [95% CI, 0.72-1.09]; *P* = .24). The risk of a primary end point event was also not significantly lower with aspirin vs no aspirin, irrespective of whether patients had a risk score lower than 4 (1.53% [95% CI, 1.14%-2.05%] for aspirin vs 1.47% [95% CI, 1.08%-1.98%] for no aspirin; HR, 1.09 [95% CI, 0.72-1.63]; *P* = .69) or a risk score of 4 or higher (3.79% [95% CI, 3.21%-4.46%] for aspirin vs 4.19% [95% CI, 3.59%-4.90%] for no aspirin; HR, 0.90 [95% CI, 0.72-1.13]; *P* = .35).

Secondary Outcomes

When TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention were added to the composite primary end point, the difference between the aspirin group (event rate, 4.00% [95% CI, 3.55%-4.50%]) and no aspirin group (event rate, 4.59% [95% CI, 4.11%-5.13%]) remained nonsignificant (HR, 0.89 [95% CI, 0.75-1.04]; *P* = .14) (**Figure 4**). There were also no significant differences between the 2 study groups for time to any cause of death (event rate, 4.29% [95% CI, 3.83%-4.82%] for aspirin vs 4.11% [95% CI, 3.66%-4.62%] for no aspirin; HR, 0.99 [95% CI, 0.85-1.17]; *P* = .93), death from cardiovascular disease (event rate, 0.86% [95% CI, 0.66%-1.12%] for aspirin vs 0.78% [95% CI, 0.60%-1.02%] for no aspirin; HR, 1.03 [95% CI, 0.71-1.48]; *P* = .89), death from causes other than cardiovascular disease (event rate, 3.46% [95% CI, 3.04%-3.94%] for aspirin vs 3.36% [95% CI, 2.94%-3.83%] for no aspirin; HR, 0.99 [95% CI, 0.82-1.18]; *P* = .87), nonfatal cerebrovascular disease (ischemic or hemorrhagic) (event rate, 1.65% [95% CI, 1.37%-1.99%] for aspirin vs 1.64% [95% CI, 1.36%-1.98%] for no aspirin; HR, 1.04 [95% CI, 0.80-1.34]; *P* = .78), angina pectoris (event rate, 0.66% [95% CI, 0.49%-0.89%] for aspirin vs 0.81% [95% CI, 0.61%-1.07%] for no aspirin; HR, 0.86 [95% CI, 0.58-1.28]; *P* = .46), and arteriosclerotic diseases requiring surgery or intervention (event rate, 1.08%

Figure 3. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for the Primary Composite Outcome Measure[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

	Aspirin			No Aspirin				
Disease Risk Factor	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	Hazard Ratio (95% CI)	*P* Value
Hypertension								
No	20	1087	1.74 (1.08-2.80)	23	1099	2.12 (1.40-3.20)	0.90 (0.49-1.63)	.72
Yes	173	6133	2.95 (2.54-3.44)	184	6145	3.11 (2.68-3.60)	0.95 (0.77-1.17)	.61
Dyslipidemia								
No	56	2022	2.89 (2.21-3.78)	56	2044	2.93 (2.26-3.81)	1.02 (0.71-1.48)	.90
Yes	137	5198	2.73 (2.30-3.23)	151	5200	2.97 (2.52-3.50)	0.91 (0.72-1.15)	.43
Diabetes mellitus								
No	107	4775	2.30 (1.89-2.79)	109	4786	2.36 (1.95-2.86)	0.99 (0.76-1.30)	.96
Yes	86	2445	3.70 (2.99-4.58)	98	2458	4.14 (3.38-5.06)	0.89 (0.66-1.18)	.41
Family history[b]								
No	94	4058	2.44 (1.98-3.00)	109	4086	2.72 (2.24-3.30)	0.87 (0.66-1.15)	.34
Yes	61	1981	3.13 (2.42-4.03)	52	1982	2.83 (2.16-3.72)	1.19 (0.82-1.72)	.36
Unknown	38	1181	3.33 (2.41-4.59)	46	1176	4.01 (2.98-5.37)	0.82 (0.54-1.26)	.37
Sex								
Men	99	3055	3.42 (2.80-4.18)	114	3068	3.85 (3.19-4.65)	0.87 (0.67-1.14)	.31
Women	94	4165	2.30 (1.87-2.83)	93	4176	2.32 (1.88-2.85)	1.03 (0.77-1.37)	.86
Age, y								
<70	52	3234	1.67 (1.27-2.21)	53	3259	1.73 (1.31-2.28)	1.00 (0.68-1.46)	.98
≥70	141	3986	3.67 (3.10-4.34)	154	3985	3.98 (3.39-4.67)	0.92 (0.73-1.16)	.49
BMI								
<25	122	4576	2.75 (2.29-3.29)	141	4640	3.21 (2.71-3.79)	0.88 (0.69-1.12)	.30
≥25	71	2644	2.82 (2.22-3.57)	66	2604	2.53 (1.97-3.25)	1.08 (0.77-1.50)	.67
Smoker								
No	150	6261	2.48 (2.10-2.92)	167	6310	2.71 (2.32-3.17)	0.91 (0.73-1.14)	.42
Yes	43	959	4.76 (3.51-6.43)	40	934	4.69 (3.43-6.40)	1.05 (0.68-1.61)	.84
Overall	**193**	**7220**	**2.77 (2.40-3.20)**	**207**	**7244**	**2.96 (2.58-3.40)**	**0.94 (0.77-1.15)**	.54



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared). Data shown for the overall population and for subgroups defined by disease risk factor and by patient characteristics.
The *P* values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

[b] History of premature cardiovascular disease.

[95% CI, 0.86%-1.36%] for aspirin vs 1.24% [95% CI, 0.99%-1.55%] for no aspirin; HR, 0.89 [95% CI, 0.65-1.21]; *P* = .46) (Figure 4). However, compared with no aspirin, aspirin significantly reduced the risk of nonfatal myocardial infarction (event rate, 0.30% [95% CI, 0.19%-0.47%] for aspirin vs 0.58% [95% CI, 0.42%-0.81%] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; *P* = .02) and TIA (event rate, 0.26% [95% CI, 0.16%-0.42%] for aspirin vs 0.49% [95% CI, 0.35%-0.69%] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; *P* = .04). Conversely, the risk of extracranial hemorrhage requiring transfusion or hospitalization was higher with aspirin than with no aspirin (event rate, 0.86% [95% CI, 0.67%-1.11%] for aspirin vs 0.51% [95% CI, 0.37%-0.72%] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; *P* = .004).

Exploratory Analysis

A post hoc exploratory analysis was conducted at the time of study discontinuation (1 year after the second interim analysis) when 400 primary end point events had occurred. It showed that the predictive probability of reaching a significant difference in favor of aspirin over no aspirin was 28% if the study had continued until it was adequately powered (ie, 624 events had occurred).

Safety and Tolerability

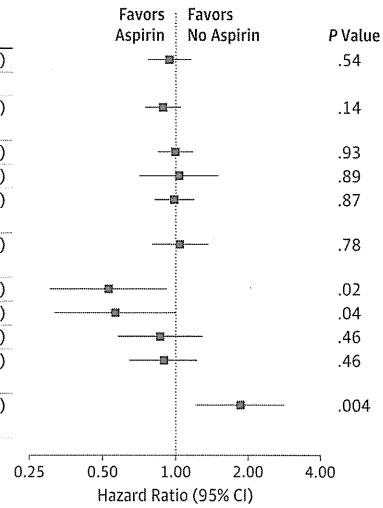
Analysis of gastrointestinal adverse events of interest indicated that these events were reported in a higher proportion of patients receiving daily low-dose aspirin than in those not receiving aspirin (**Table 3**).

Discussion

This study was designed to assess whether primary prevention with once-daily, low-dose aspirin would reduce the combined risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction in Japanese patients (aged ≥60 years) with hypertension, dyslipidemia, or diabetes mellitus. The study was terminated early based on a futility assessment, but an exploratory analysis sug-

Figure 4. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for Secondary End Points Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

End Point	Aspirin (n = 7220) No. of Events	Aspirin (n = 7220) Event Rate Over 5 Years, % (95% CI)	No Aspirin (n = 7244) No. of Events	No Aspirin (n = 7244) Event Rate Over 5 Years, % (95% CI)	Hazard Ratio (95% CI)	P Value
Primary end point[a]	193	2.77 (2.40-3.20)	207	2.96 (2.58-3.40)	0.94 (0.77-1.15)	.54
Secondary end point						
Any atherosclerotic or cardiovascular event[b]	280	4.00 (3.55-4.50)	319	4.59 (4.11-5.13)	0.89 (0.75-1.04)	.14
Any cause of death	297	4.29 (3.83-4.82)	303	4.11 (3.66-4.62)	0.99 (0.85-1.17)	.93
Death from cardiovascular disease	58	0.86 (0.66-1.12)	57	0.78 (0.60-1.02)	1.03 (0.71-1.48)	.89
Death from causes other than cardiovascular disease	239	3.46 (3.04-3.94)	246	3.36 (2.94-3.83)	0.99 (0.82-1.18)	.87
Nonfatal cerebrovascular disease (ischemic or hemorrhagic)	117	1.65 (1.37-1.99)	114	1.64 (1.36-1.98)	1.04 (0.80-1.34)	.78
Nonfatal myocardial infarction	20	0.30 (0.19-0.47)	38	0.58 (0.42-0.81)	0.53 (0.31-0.91)	.02
Transient ischemic attack	19	0.26 (0.16-0.42)	34	0.49 (0.35-0.69)	0.57 (0.32-0.99)	.04
Angina pectoris	46	0.66 (0.49-0.89)	54	0.81 (0.61-1.07)	0.86 (0.58-1.28)	.46
Arteriosclerotic diseases requiring surgery or intervention	75	1.08 (0.86-1.36)	85	1.24 (0.99-1.55)	0.89 (0.65-1.21)	.46
Serious extracranial hemorrhage requiring transfusion or hospitalization	62	0.86 (0.67-1.11)	34	0.51 (0.37-0.72)	1.85 (1.22-2.81)	.004



Data shown for the overall population. The *P* values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

[b] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention.

Table 3. Incidence of Prespecified Gastrointestinal Adverse Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Randomized Population)

	No. (%) [95% CI]		
	Aspirin (n = 7323)	No Aspirin (n = 7335)	*P* Value
Stomach/abdominal discomfort	335 (4.57) [4.11-5.08]	175 (2.39) [2.05-2.76]	<.001
Heartburn	202 (2.76) [2.40-3.16]	137 (1.87) [1.57-2.20]	<.001
Gastroduodenal ulcer	191 (2.61) [2.26-3.00]	91 (1.24) [1.00-1.52]	<.001
Stomach/abdominal pain	168 (2.29) [1.96-2.66]	81 (1.10) [0.88-1.37]	<.001
Reflux esophagitis	160 (2.18) [1.86-2.55]	125 (1.70) [1.42-2.03]	.04
Gastrointestinal hemorrhage	103 (1.41) [1.15-1.70]	31 (0.42) [0.29-0.60]	<.001
Erosive gastritis	89 (1.22) [0.98-1.49]	40 (0.55) [0.39-0.74]	<.001
Nausea	79 (1.08) [0.85-1.34]	50 (0.68) [0.51-0.90]	.01
Stomach/abdominal pressure	31 (0.42) [0.29-0.60]	21 (0.29) [0.18-0.44]	.17

gested a 28% probability of finding a significant difference in favor of aspirin had the study been continued through the planned number of events. Therefore, there remains a possibility that the statistically nonsignificant reduction in the risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction was due to the study being inadequately powered, rather than an absence of beneficial effect of aspirin. However, even if the result had become statistically significant through prolongation of the study, the clinical importance of aspirin in the primary prevention of cardiovascular events would have been less than originally assumed. Therefore, it appears that aspirin is unlikely to show a clinically important benefit in the overall population included in this study. We plan to conduct further analyses to establish whether aspirin had beneficial effects in particular subgroups of patients or if there were beneficial effects with respect to cancer prevention.

Study limitations need to be considered. Assessments of between-group differences in any end point in this study were confounded by a decreasing level of adherence with daily low-dose aspirin in the aspirin group (dropping to 76% in year 5) and increasing uptake of daily aspirin in the no aspirin group (reaching 10% in year 5). In addition, the number of patients lost to follow-up could be considered a limitation of large trials conducted in a real-world setting. However, use of Kaplan-Meier time-to-event analyses limits the effect of missing data, and the proportion of patients lost to